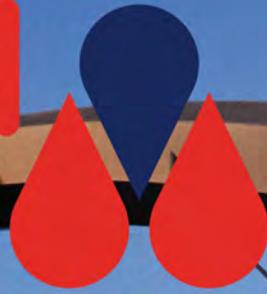


# Blood 2019



## ABSTRACT BOOK

2019 Annual Scientific Meeting  
20 - 23 October  
Perth Convention & Exhibition Centre  
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The combined Annual Scientific Meeting of the:



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O001

## **Haemophilia care – from uncertainty to optimism**

### **Dr John Rowell**

My journey in Haemophilia care started as a new Haematology Consultant at Royal Brisbane Hospital. 1984 was a challenging start with the existing issues of Non-A, Non-B Hepatitis and minimal factor concentrates available. HIV became prominent in Australia for those with inherited bleeding disorders in mid-1984, with the community shocked and disillusioned. But 1984 also saw the identification of the Factor VIII gene and promise of non-plasma based therapies. The Haemophilia community was devastated by HIV and Hepatitis C then and into the future. Further optimism emerged in the 1990s with the advent of recombinant factor VIII and IX concentrates and protease inhibitors and other therapies for HIV. It was not until early 2000s and establishment of Australian Haemophilia Centre Directors Organisation (AHCDO) and National Blood Authority (NBA) that recombinant concentrates were available to all. Over the last few years there has been expanding numbers of treatments including modified factor concentrates with longer half lives and monoclonal antibodies, as mimetics of coagulation factors, or to rebalance haemostasis. These products and with the advent of sustained realistic responses with gene therapy will dramatically change outcomes and quality of life for those affected with Haemophilia.

O002

## **Regulation and blood safety: An unexpected journey**

**Ian Prosser**<sup>1</sup>

<sup>1</sup>*National Capital Private Hospital, Canberra, Australia*

Through her work in blood grouping and genetics, Ruth Sanger was instrumental in improving the safety of blood transfusion in the period following the Second World War. The hazards of blood transfusion have decreased enormously over the past four decades, especially those associated with the transmission of infectious agents, although blood transfusion is never likely to be absolutely safe.

In this oration, I will consider the historical developments in blood safety and risk management that have occurred over the course of my clinical career, and the drivers that have influenced the current governance of fresh blood and blood products in Australia.

Major improvements in transfusion practice have included the evolution of donor screening and selection, implementation of sensitive and selective product testing, robust pathogen inactivation for blood components, substitution of blood-derived products, better patient blood management, use of haemovigilance to detect post-transfusion safety signals and wider adoption of evidence-based methods for determining efficacy and risk.

The evolution of the governance system for blood transfusion has paralleled and arguably augmented these initiatives, with the transformation of the state-based blood services into the national Australian Red Cross Blood Service in 1996 given impetus by the crises of the 1980s. The National Blood Authority was subsequently established in 2003 as a national coordination agency tasked to ensure access to safe and affordable blood products through management of the national supply arrangements.

Regulation of blood by the Therapeutics Goods Administration is a relatively recent development, with regulation of plasma for fractionation from 1992 which was extended to fresh products from 2000. I will reflect on the contribution of regulation to blood safety, how this may evolve in the future and challenges to maintaining a safe and adequate blood supply.

O003

## **A new direction for Australian haematology: Psycho-haematology**

**David Joske**<sup>1</sup>

<sup>1</sup>*Sir Charles Gairdner Hospital, Perth, Australia*

It is a time of enormous, rapid, game-changing advances in the treatment of the blood cancers. The fruits of the molecular biology revolution are arriving at the bedside: witness the tyrosine kinase inhibitors for chronic myeloid leukaemia, ibrutinib and venetoclax for chronic lymphocytic leukaemia and the PD1 checkpoint inhibitors for a variety of haematological and solid tumours. Challenges remain in the T-cell lymphomas and acute leukaemias.

Despite these exciting therapeutic developments, there will always remain the patient experience of the cancer journey from the shock of diagnosis, the rigours of treatment, and what can be a wilderness of after-cancer care. Improved supportive care is now a priority in many health systems and at times has taken on the passion of a social movement. In Australia, policy is being guided by the Optimal Cancer Care Pathways, but the truth is little is being done in the after-treatment phases. The comparison has been made with heart attack and stroke, where there is a recognized need for rehabilitation and resources have been mapped to provide this. Growing and emerging evidence suggests that psycho-social outcomes could be improved in the blood cancers with evidence-based supportive care interventions.

In this oration, I will review my own professional experience and conduct a virtual ward round to examine some of this evidence and make some recommendations to tackle these issues more positively within the Australian Haematological community. A variety of met and unmet needs amongst haematological cancer survivors have been identified. Some of the contentious issues are the role of mental attitude and the mind-body split that occurred in Western medicine, the benefits of exercise, the concept of survivorship, and the need for self-healing amongst health practitioners. There will be diversions in my talk, both haematological and non-haematological, before drawing together some conclusions and ways forward – with the focus as ever, being on what is best for our patients.

O004

## **Randomised controlled trial of freshly irradiated versus standard red cell transfusion for treatment of anaemia of prematurity**

**Maria Saito-Benz**<sup>1,3</sup>, Karen Bennington<sup>1</sup>, William Murphy<sup>2</sup>, Peter Flanagan<sup>2</sup>, Frederica Steiner<sup>1</sup>, Mary Judith Berry<sup>1,3</sup>

<sup>1</sup>Wellington Neonatal Intensive Care Unit, Newtown, New Zealand, <sup>2</sup>NZ Blood Service, Newtown, New Zealand, <sup>3</sup>University of Otago, Newtown, New Zealand

### **Aim**

Gamma-irradiation of leukoreduced red blood cells (RBCs) prevents transfusion-associated graft-versus-host disease, but it also exacerbates storage lesion formation in RBCs. We hypothesized that storage after irradiation decreases the oxygen delivery capacity of transfused RBCs in anaemic preterm infants.

### **Method**

Sixty-four non-urgent transfusion episodes in 42 preterm infants (<34 weeks gestation) were studied in Wellington NICU. Transfusion episodes were randomised to the intervention (RBC irradiated on the day of transfusion, n=32) or control arm (RBCs irradiated and stored as per the ANZSBT guidelines, n=32). Cerebral regional oxygenation (crSO<sub>2</sub>) and fractional tissue oxygen extraction (FTOE) were studied by blinded clinicians using Near Infrared Spectroscopy (Sensmart X-100, Nonin) for 3hrs immediately before, immediately after, 1 and 5 days after transfusion.

### **Result**

We observed a significant increase in crSO<sub>2</sub> (77.4% vs 79.8%,  $p < 0.001$ ) and decrease in FTOE (0.15 vs 0.12,  $p < 0.01$ ) immediately after transfusion in infants who received freshly irradiated RBCs. These effects were sustained up to 5 days after transfusion. There was no difference in crSO<sub>2</sub> or FTOE in infants who received irradiated and stored RBCs (8 ±4 days) at any of the time points.

### **Conclusions**

Our findings indicate that storage after gamma-irradiation has a detrimental effect on the oxygen delivery capacity of transfused RBCs. Further research is required to investigate the safety and efficacy of RBCs prepared as per the ANZSBT guidelines for preterm infants.

## **Red cell transfusion thresholds in outpatients with myelodysplastic syndromes: results of a feasibility and exploratory randomised trial (REDDS-1)**

Simon Stanworth<sup>2,3,4</sup>, Sally Killick<sup>5</sup>, **Zoe McQuilten**<sup>1</sup>, Marina Karakanta<sup>6</sup>, Robert Weinkove<sup>7,8</sup>, Heather Smethurst<sup>2</sup>, Laura Pankhurst<sup>2</sup>, Renate Hodge<sup>2</sup>, Valerie Hopkins<sup>2</sup>, Helen Thomas<sup>2</sup>, Alison Deary<sup>2</sup>, Jeannie Callum<sup>9</sup>, Yulia Lin<sup>9</sup>, Erica Wood<sup>1</sup>, Rena Buckstein<sup>9</sup>, David Bowen<sup>6</sup>

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### **Aim:**

Optimal transfusion support in myelodysplastic syndromes (MDS) has not been established and it remains unclear whether different red blood cell (RBC) transfusion policies could modify clinical outcomes, including quality of life (QoL). We aimed to demonstrate feasibility of recruitment, blinding and follow-up to a trial of different RBC transfusion protocols in MDS patients being treated in an outpatient setting, with an exploratory assessment of QoL.

### **Method:**

Pilot randomised controlled trial comparing a typical restrictive RBC transfusion threshold (threshold for transfusion 80g/L, to maintain haemoglobin concentration between 85 and 100 g/L) with a liberal threshold that maintains a higher haemoglobin concentration (110 - 125g/L). Primary outcomes were measures of compliance to treatment threshold. Other outcomes were exploratory, including QoL EORTC QLQ-C30 and success of participant blinding.

### **Results:**

38 patients were randomised from 12 hospitals (n=20, restrictive; n=18 liberal) in UK, Australia and New Zealand. The compliance proportion for the intention-to-treat population was 86% (95% confidence intervals 75%-94%) and 99% (95%-100%) for the restrictive and liberal arms, respectively. Mean pre-transfusion haemoglobin concentrations for the restrictive and liberal arms were 80 g/L (SD6) and 97 g/L (SD7). Total number of RBCs transfused on study was 82 in the restrictive and 192 in the liberal group. In an exploratory analysis, the five main QoL domains were improved for participants in the liberal compared to restrictive arm. Blinding appeared to be well maintained, with less than a third of participants correctly guessing their treatment arm at three time points: 10/36 (28%), 9/34 (26%), and 9/32 (28%) at day 28, day 56 and day 84.

### **Conclusion:**

Our findings provide new data on the effects of different RBC transfusion thresholds on patient-centered outcomes and blood utilisation. They support the feasibility and rationale of progressing to a definitive trial, and further preparatory work (REDDS-2) is underway.

## **The burden of platelet transfusions in myelodysplastic syndromes: An analysis of platelet transfusion dependency and immune-mediated platelet refractoriness**

**Kathleen Cheok**<sup>1</sup>, Rakchha Chhetri<sup>1,2</sup>, Amilia Wee<sup>1,2</sup>, Simon Mcrae<sup>1</sup>, Deepak Singhal<sup>1</sup>, David Roxby<sup>3</sup>, Devendra Hiwase<sup>1,2,4</sup>

<sup>1</sup>Haematology Department, Royal Adelaide Hospital, Adelaide, Australia, <sup>2</sup>South Australian Health and Medical Research Institute, Adelaide, Australia, <sup>3</sup>Transfusion Medicine, SA Pathology, Adelaide, Australia, <sup>4</sup>University of Adelaide, Adelaide, Australia

**Aim:** Although 40-65% of myelodysplastic syndromes (MDS) patients are thrombocytopenic and require platelet transfusions, there is limited literature on the burden of immune mediated platelet refractoriness (PLT-R).

This retrospective study evaluated the prevalence of thrombocytopenia, platelet transfusion dependency (PLT-TD) and immune mediated PLT-R in MDS patients.

**Methods:** Retrospective analysis of 754 MDS patients enrolled in the South Australian MDS (SA-MDS) registry was performed. Platelet counts  $<100$ ,  $<50$  and  $<20$  ( $\times 10^9/L$ ) were used to define mild, moderate and severe thrombocytopenia respectively. PLT-TD was defined as transfusion of at least one unit of platelets each month for four months. All other patients were classified as transfusion independent (PLT-TI). Immune mediated PLT-R was defined if a patient had HLA-class I or HPA antibodies, poor platelet increments and required HLA-matched platelets.

**Results:** The median age was 73 years (19-97 years) and 106 (14%) patients had moderate to severe thrombocytopenia at diagnosis. During the disease course, 393 (52%) patients required at least one unit of platelet transfusion and 106 (14%) patients were PLT-TD. PLT-TD patients had significantly poorer survival compared to PLT-TI patients (27 vs. 42 months,  $p<0.001$ ).

In total, 30/393 (7%) required HLA-matched platelet transfusions and 20/30 (66%) of PLT-R patients were females receiving disease modifying therapy (DMT). This was substantiated by Cox regression analysis, which demonstrated that female gender (HR=5.2,  $p<0.001$ ), PLT-TD (HR=2.6,  $p=0.03$ ) and DMT (HR=7.59,  $p=0.05$ ) were independent risk factors for PLT-R. Importantly, 20/76 (26%) of female patients who received platelets and DMT developed immune-mediated PLT-R requiring HLA matched platelets.

**Conclusions:** HLA-matched platelet transfusions were required in 7% of MDS patients requiring platelets. Importantly, 1 in 4 female MDS patients who received platelets and DMT also required HLA-matched platelets and contributed to 66% of the total PLT-R patients. Therefore, it is critical to optimise platelet transfusions practices for these high-risk patients.

**Clinical practice improvement can reduce anaemia during pregnancy**

**Corey Markus<sup>1</sup>, Cindy Flores<sup>2</sup>, Ben Saxon<sup>1,2</sup>, Jodie Grech<sup>1</sup>, Elle Knights<sup>3</sup>, Romi Sinha<sup>4</sup>, Angie Yong<sup>3</sup>, Kym Osborn<sup>3</sup>**

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<sup>3</sup>Lyell McEwin Hospital, Elizabeth Vale, Australia, <sup>4</sup>SA Department of Health and Wellbeing, Adelaide, Australia

**Aim:** Iron deficiency (ID) with or without anaemia continues to be a neglected issue in women’s health. Anaemia at delivery is a strong modifiable risk factor for transfusion in women with a postpartum haemorrhage. A **Maternity Blood Management Clinical Practice Improvement (CPI)** was conducted to optimise antenatal haemoglobin and iron stores prior to delivery.

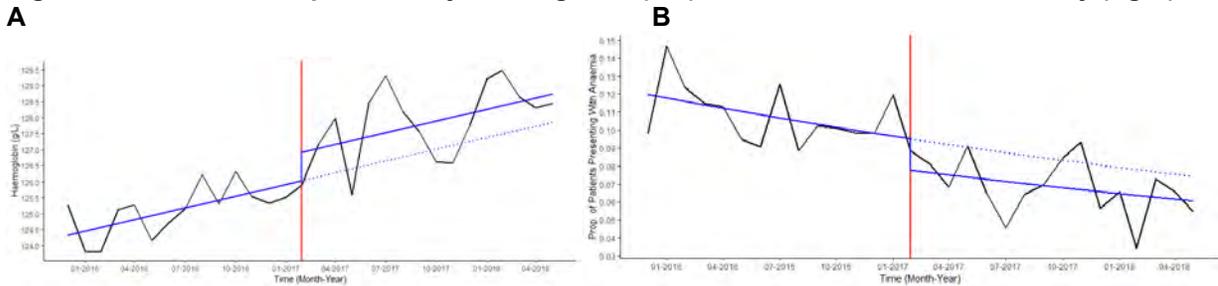
**Methods:** CPI tools (haemoglobin optimisation flowcharts and maternity patient handouts) were introduced at a major tertiary hospital from Nov-2016 to Mar-2017. To assess CPI effectiveness to improve haemoglobin and iron stores, an Interrupted Time Series (ITS) analysis was performed using data collected for all deliveries from Jan-2016 to June-2018. Change point analysis was used to determine CPI impact.

**Results:** There were 11,263 deliveries during the analysis time period. Non-anaemic ID was detected following routine 1<sup>st</sup> trimester ferritin screening (Table 1) rather than relying on haemoglobin alone. A clinically significant increase in the monthly average pre-delivery haemoglobin of 0.9 g/L was found (95% CI –0.4 to 2.2 g/L;  $p=0.16$ ) [Figure 1a]. This corresponded with a reduction in the monthly rate of anaemic patients by 18% (RR0.82, 95%CI 0.6 to 1.1;  $p=0.12$ ) [Figure 1b], and 15.3% reduction of 3<sup>rd</sup> trimester IDA prevalence from baseline (33.9%) to post-pilot (18.6%) [Table 1]. While there was a change in anaemia rates there was no change in rates of non-anaemic ID. Change point analysis showed the statistical properties of Hb changed before and after was on Mar-2017, which coincided the end of the pilot period [Figure 1].

**Table 1. Prevalence of IDA and non-anaemic ID**

	Patients with Ferritin & Hb	Iron deficiency anaemia (IDA) (Hb≤110 & FER ≤30)	Non-anaemic iron deficiency (NAID) (Hb>110 & FER ≤30)	Patients with Ferritin &Hb	IDA (Hb≤110 & FER ≤30)	NAID (Hb>110 & FER ≤30)
	First Trimester			Third Trimester		
Jan-Oct 16 (Baseline)	476	27 (5.7%)	149 (31.3%)	422	143 (33.9%)	169 (40.0%)
Nov16-Mar17 (Pilot period)	235	8 (3.4%)	63 (26.8%)	306	73 (23.9%)	139 (45.4%)
Apr17- Jun18 (Post-pilot period)	840	32 (3.8%)	204 (24.3%)	650	121 (18.6%)	341 (52.4%)

**Figure 1. Time series of pre-delivery haemoglobin (left) and rate of anaemia at delivery (right)**



**Conclusion:** The CPI tools had a clinically relevant but not statistically significant effect in optimising antenatal haemoglobin and decreasing the risk of pre-delivery anaemia. This CPI program demonstrates modification of one risk factor for blood loss and subsequent transfusion in the perinatal period.

## **Whole Blood Use and Patient Outcomes in Critical Bleeding: Results from the Australian and New Zealand Massive Transfusion Registry (ANZ-MTR)**

**Helen Haysom**<sup>1</sup>, Rosemary Sparrow<sup>1</sup>, Neil Waters<sup>1</sup>, Krishna Badami<sup>2</sup>, Richard Charlewood<sup>3</sup>, Kerry Gunn<sup>4</sup>, Dr Bob Ure<sup>5</sup>, Cameron Wellard<sup>1</sup>, Erica Wood<sup>1,6</sup>, Zoe McQuilten<sup>1,6</sup>

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**Aim:** Using Australian and New Zealand (NZ) Massive Transfusion Registry (ANZ-MTR) describe Whole Blood (WB) use in massive transfusion (MT) ( $\geq 5$  RBCs in any 4h period) in NZ and compare transfusion requirements, laboratory parameters and patient outcomes for WB recipients (WB-R) with those receiving only red blood cell (RBC) units RBC-R.

**Method:** All adult MT recipients between 2011 and 2018, at four NZ sites with access to WB, were included in the analysis.

**Results:** 315 of 1947 (16.1%) MT recipients received  $\geq 1$  WB unit. WB was most commonly used in vascular surgery (21%), trauma (17%), gastrointestinal (14%), cardiac surgery (11%). WB-R received a median of 2 (IQR 1, 2) WB units and commenced transfusion sooner relative to time of hospital admission than RBC-R.

WB-R received fewer RBC (9 [6,16] vs 10 [7,15],  $p=0.013$ ), more FFP (6 [2,11] vs 5 [2, 9],  $p<0.001$ ) and more recombinant FVIIa ( $p=0.02$ ) than RBC-R. There were no differences in fibrinogen concentrate, prothrombin complex or other fresh blood products given.

In first 4-hours of MT, WB-R had shorter APTT compared to RBC-R (42 [34, 60] vs 47 [36, 71] seconds;  $p=0.01$ ). Nadir haemoglobin, platelet count and fibrinogen for the two groups were similar.

WB-R had higher in-hospital mortality (31.4% vs 25.3%,  $p=0.024$ ), but similar ICU length of stay and ventilation time. After adjusting for age, sex, number of RBC and FFP units, clinical context and hospital site there was no significant association between WB use and mortality (adjusted odds ratio WB Plasma Reduced 1.19 [95% CI 0.80-1.78] and WB Leucodepleted 1.42 [95% CI 0.94-2.15]).

**Progression of disease within 24 months (POD24) in follicular lymphoma is associated with reduced intratumoral immune-infiltration**

**MK Gandhi**<sup>1,2,3</sup>, Colm Keane, Jay Gunawardana, Peter Mollee, Simone Birch, Thanh Hoang, Justina Lee, Li Li, Mr Li Huang, Valentine Murigneux, Lynn Fink, Nicolas Matigan, Frank Vari, Santiyagu Francis, Robert Kridel, Oliver Weigert, Sarah Haebe, Vindi Jurinovic, Wolfram Klapper, Christian Steidl, Laurie Sehn, Soi Law, Michelle Wykes, Josh Tobin<sup>1,2,3</sup>  
<sup>1</sup>Mater Research, Brisbane, Australia, <sup>2</sup>University of Queensland, Brisbane, Australia, <sup>3</sup>Princess Alexandra Hospital, Brisbane, Australia

**Aim:** Understanding the immunobiology of the 15-30% of patients with Follicular lymphoma (FL) experiencing progression of disease within 24 months (POD24) remains a priority. Solid tumors with low levels of intratumoral immune-infiltration have inferior outcome. It is unknown whether a similar relationship exists between POD24 in FL.

**Methods:** Digital gene-expression profiling (nanoString) was applied to an Australian discovery cohort of early and advanced-stage FL patients (n=132). T-cell receptor repertoire analysis, flow cytometry, multispectral immunofluorescence, and next-generation sequencing was performed. Findings were validated in 2 independent international advanced-stage FL cohorts requiring systemic treatment (BCCA: n=138 R-CVP and GLSG: n=45 R-CHOP), with the latter selected to permit comparison of patients experiencing a POD24 event to those having no progression at ≤5 years.

**Results:** Immune molecules showed distinct clustering of FL samples, characterised by either high or low expression regardless of categorisation as an immune-effector, immune-checkpoint or macrophage molecule. Low PD-L2 was the most sensitive/specific marker to segregate patients with adverse outcome. Results were independent of FLIPI or the International Immune Score. Therefore PD-L2 expression was chosen to distinguish ‘hot’ (high immune-infiltration i.e. high PD-L2) FL biopsies from ‘cold’ (low immune-infiltration i.e. low PD-L2) tumors. Hot tissues were highly infiltrated with macrophages and expanded populations of T-cell clones. Notably, the cold subset of FL patients was enriched for POD24 events (OR 4.32, c stat 0.81, p=0.001) Fig 1A and 1B, validated in the independent cohorts (R-CVP: OR 2.95, c stat 0.75, p=0.011; and R-CHOP: OR 7.09, c stat 0.88, p=0.011). FL mutations were equally proportioned across hot/cold tissues indicating that the degree of immune-infiltration is capturing aspects of FL biology distinct from its mutational profile (Fig 1C).

**Conclusions:** We demonstrate for the first time that assessment of immune-infiltration by PD-L2 expression, is a promising tool to help identify patients at risk of POD24.

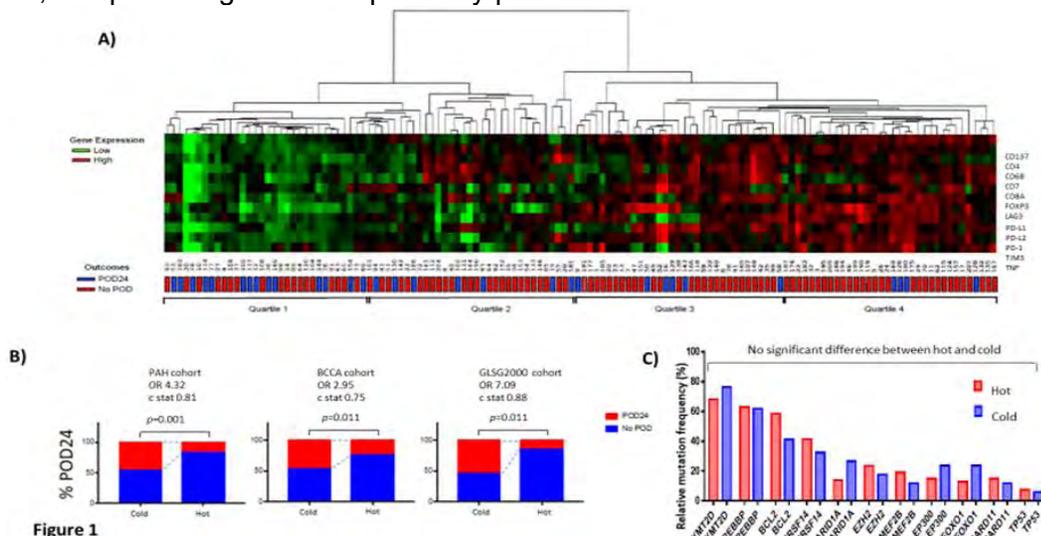


Figure 1

**Administration of third-party virus-specific T-cells (VST) at the time of initial therapy for infection after haemopoietic stem cell transplant is safe and associated with favourable clinical outcomes (the R3ACT-Quickly trial)**

Emily Blyth<sup>1,2,3,4</sup>, Wei Jiang<sup>2,4</sup>, Leighton Clancy<sup>3</sup>, Selmir Avdic<sup>2,4</sup>, David Collins<sup>1</sup>, Gaurav Suttrave<sup>1</sup>, David Bishop<sup>4</sup>, Elissa Atkins<sup>1</sup>, Adrian Selim<sup>6</sup>, Vicki Antonenas<sup>3</sup>, Caroline Bateman<sup>5</sup>, David Ritchie<sup>6</sup>, Peter Shaw<sup>5</sup>, **David Gottlieb**<sup>1,2,4</sup>

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**Introduction**

Partially-HLA matched VST are safe and effective after failure of standard antiviral therapy to resolve viral infection. In this phase I trial, we assessed their safety when administered earlier in the course of viral infection post- haemopoietic stem cell transplant (HSCT).

**Methods**

A cell bank of VST was established from G-CSF mobilised peripheral blood from healthy donors. After stimulation with peptide mixes, VST were selected by expression of CD137 and cultured with cytokines. HSCT recipients were treated with up to 4 doses of  $2 \times 10^7$  of VST/m<sup>2</sup> commencing within 7 days of initial treatment for viral reactivation.

**Results**

A total of 188 doses of VST were manufactured from 7 donors with 12 product manufacturing runs (CMV n=3, EBV n=4 and Adv n=5). Median virus specificity was 75% for CMV, 83% for EBV and 37% for Adv. Thirty HSCT recipient were treated with VST a median of 53 days post-transplant. Data from 24 patients were available for analysis (CMV n=21, EBV n=2, Adv n=1). Median age was 57 (0-71). 17 patients received a single infusion, 6 received 2 and 1 received 4 infusions. There were 3 infusion related adverse events (vomiting, hypertension, fever). There were no cases of de novo acute GVHD of grade 2 or greater post infusion. One patient with previously resolved grade 3 acute GVHD developed grade 4 aGVHD 89 days after infusion as immunosuppression was weaned. 22/24 patients (92%) had complete viral clearance, 2 had a partial response. Median time to best viral response was 20 days. There were 3 deaths (refractory aGVHD, pulmonary VOD/CMV pneumonitis and disease relapse). Overall survival at median 277 days (range 88-620) was 88%.

**Conclusion**

Infusion of third-party donor-derived banked VST early post viral reactivation are associated with a low rate of GVHD and complete viral clearance in 92% of recipients.

## **Genomic findings from targeted next generation sequencing of over 4000 samples referred for investigation of myeloid malignancy**

**Piers Blombery**<sup>1,2</sup>, Ella Thompson<sup>1,2</sup>, Michelle McBean<sup>1,2</sup>, Yamuna Kankanige<sup>1</sup>, Jennifer Lickiss<sup>1</sup>, Georgina Ryland<sup>1,2</sup>, Tamia Nguyen<sup>1</sup>, Shravan Yellenki<sup>1</sup>, Michael Ingbritsen<sup>1</sup>, HweeNgee Goh<sup>1</sup>, Steven Liu<sup>1</sup>, Jessica Diep<sup>1</sup>, Viet Phung<sup>1</sup>, Kate Jones<sup>1</sup>, Paul Yeh<sup>1,2</sup>, Ing-Soo Tiong<sup>1</sup>, Clare Gould<sup>1</sup>, Anthony Bell<sup>1</sup>, Stephen Fox<sup>1,2</sup>, David Westerman<sup>1,2</sup>

<sup>1</sup>Peter MacCallum Cancer Centre, Melbourne, Australia, <sup>2</sup>University of Melbourne, Melbourne, Australia

**Background and Aims:** Detection of genomic abnormalities is central to the diagnosis, prognosis and therapeutic decision making in myeloid malignancy. We describe the aggregated genomic data from targeted next generation sequencing (NGS) in myeloid malignancy from over 4000 samples referred for clinical sequencing to the molecular haematology laboratory at Peter MacCallum Cancer Centre.

**Method:** Genomic data from all samples referred for myeloid amplicon NGS testing from January 2015 to May 2019 were aggregated. Samples were tested using a NATA-accredited (ISO15189) custom 26-gene myeloid amplicon panel targeted sequencing assay (Fluidigm Access Array/Illumina MiSeq) and fragment analysis for detection of *ASXL1* c.1934dup; p.(Gly646Trpfs\*12).

**Results:** Over the study period, 4245 samples (from 4019 patients) were tested with clinical reports issued. Indications for testing included diagnostic categorisation of myeloproliferative neoplasms (MPN) (including resolving MPN overlap syndromes) (54.7%), investigation/prognostication of suspected myelodysplastic syndrome (MDS) (26.0%) and prognostication/therapeutic target identification in acute myeloid leukaemia (15.6%). Pathogenic variants were detected in 46.5% and 48.0% of patients referred for MPN and MDS investigation respectively. Numerous previously undescribed somatic mutations were detected in this cohort including novel mutations in *CALR*, *MPL*, *NPM1*, *U2AF1*, and RAS pathway genes. Other observations from this large cohort include (i) *JAK2/CALR* co-mutation in MPN patients (ii) insights into clonal hierarchy from variant allele frequency analysis and persistence of mutations after therapy (iii) directly targetable mutations (*IDH1/IDH2/BRAF/FLT3*) across the spectrum of myeloid neoplasms (iv) co-occurrence of mutations in common pathways classically described as mutually exclusive (*TET2/IDH1/IDH2/WT1*) and (v) a bias for the presence of multiple clonal *TET2* mutations per case.

**Conclusion:** We have described the clinical utilisation and genomic landscape from one of the largest cohorts to date of patients with myeloid malignancy referred for clinical NGS testing. This cohort highlights the perceived clinical utility of this testing and opportunities for further refinement in testing strategies.

## Early Light Chain Kinetics Is Highly Predictive of Renal Response to Carfilzomib in Myeloma with Renal Impairment- ALLG MM16 trial

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### BACKGROUND/METHODS:

Carfilzomib/Dexamethasone (Cfz/Dex) is a standard of care in relapsed myeloma; renal impairment (RI) confers poor prognosis. MM16 assessed feasibility of treating patients with RI (eGFR 15-40 ml/min) with Cfz/Dex, and determined whether early reduction in serum free light chains (SFLC) ( $\Delta$ LC) predicted renal outcome.

### RESULTS:

Mean age 66.9 $\pm$ 8.3 yr; Stage II/III:4/28. Median eGFR 27 (21-32) ml/min. First 11 patients received Cfz 20/27 mg/m<sup>2</sup>, next 21 received 20/56 mg/m<sup>2</sup>. Twelve patients treatment naïve (TN) (all 20/56, 4 autologous transplant) and 20 relapsed myeloma [median 4.5 (1-8) prior lines]. Median follow-up 5.1 (0.1–26.5) months.

**Disease Response** For patients treated  $\geq$ 4 cycles, 83% achieved  $\geq$ PR. Best responses -TN: sCR 50%, CR 12.5%, VGPR 25%, PR 12.5%; Relapsed: sCR 8.5%, CR 8.5%, VGPR 25%, PR 33%, PD 25%.

**Renal response** After C2, complete and minor renal responses 23% and 27%. D7 eGFR improved in TN vs relapsed (+6.9 vs -1.1ml/min); at D28, greater improvement seen in TN vs relapsed (+19.8 vs +3.2ml/min), and 20/56 vs 20/27 group (+12.8 vs +3.5ml/min).

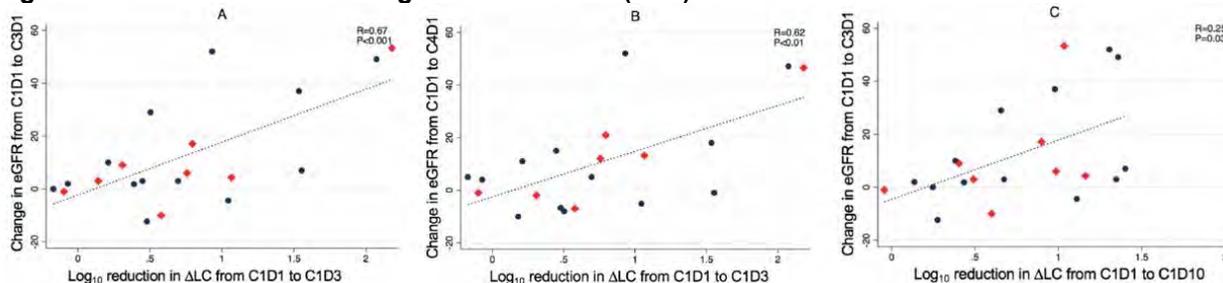
**Early SFLC** Mean reduction in involved SFLC greater in 20/56 vs 20/27 (at C2D1, 81 vs 13%; p<0.001). Early SFLC performed at C1D3 and C1D10:  $\Delta$ LC between baseline and C1D3 predicted eGFR at C3D1 and C4D1 (Fig 1A&B); for every one log<sub>10</sub>reduction in  $\Delta$ LC, eGFR increased 20.0 and 17.4 ml/min at C3&4.  $\Delta$ LC at C1D10 also predicted eGFR at C3 (Fig 1C). Thus  $\Delta$ LC measured early in C1 predicted renal response within 2 cycles.

**Tolerability** Most common  $\geq$ Gd 3 AEs: infection (20%), anemia (13%). AEs of interest: cardiac dysfunction 13% ( $\geq$ Gd 3, 10%), hypertension (Gd 2-3, 13%); tumour lysis (7%); AKI (7%, Gd 2), not attributed to Cfz; thromboembolism 10%. 8/32 died, all relapsed myeloma - myeloma(5), infection(1), respiratory failure(1), chronic kidney injury(1).

### CONCLUSIONS:

In myeloma with RI, reduction in SFLC by 48 hours from therapy commencement accurately predicted subsequent renal response and can indicate the need to intensify treatment. Cfz/dex showed excellent disease and renal responses in TN and relapsed patients.

**Fig. 1 Correlation between change in involved LC ( $\Delta$ LC) and eGFR** • Kappa • Lambda



**Optimal enoxaparin dosing strategies for VTE prophylaxis at treatment for patients at extremes of weight**

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**Background:** Obese patients (BMI > 30kg/m<sup>2</sup>) and morbidly obese patients (MBI > 40Kg/m<sup>2</sup>) are at higher risk of thromboembolism. Because the optimal dosage of LMWHs has not be established for patients with extremes body weight, target anti-Xa levels for LMWHs are not well defined. However some studies. For enoxaparin, some studies suggest a target peak anti-Xa of 0.6-1.0 IU/mL (4 hours after 3 doses of enoxaparin s/c) for a dose of 1mg/kg according actual body weight twice daily in the treatment of VTE and a therapeutic range of 0.2 to 0.5 for the prophylaxis with fixed dose of enoxaparin 40mg BD.

**Aim:** To assess the efficacy and safety of using actual body weight in the treatment and prophylaxis of VTE in obese and morbidly obese patients.

**Method:** At Royal Perth Hospital we conducted a prospective study from 2016 to 2019 using this nomogram (Table 1) for the treatment and prophylaxis of VTE in obese patients. Enoxaparin treatment was given according to actual body weight and adjusted according anti-Xa levels.

**Results:** 87 patients have been enrolled in this study, 39F and 48M. 43 patients received therapeutic therapy: in 23 (53.4%) the therapeutic range of anti-Xa was achieved without any dose-modifications, in 8 patients (18.6%) was necessary a reduction of 20% of the enoxaparin dosage while in 4 (9%) of 10%. A dose-increase was required 8 (18.6%) patients, of 25% in 3 and of 10% in 5 patients. Regarding the complications there were 3 moderate bleeding of which 1 in a patient who required a dose-reduction of 20%. Of the 44 (50.5%) patients in prophylactic treatment for VTE only 3 required a 10% dose increase.

**Conclusions:** In our experience dose adjustments of enoxaparin according to anti-Xa levels seemed to be effective and safe for the therapy of thromboembolism in obese, while regular fixed dosing may not be appropriate.

Table 1 LMWH Nomogram for Treatment doses of Enoxaparin based on anti-factor Xa levels<sup>6</sup>

Anti Xa Level (U/mL)	Hold next dose	Dosage change	Next Anti-Xa level
<0.35	no	increase by 25%	4h after next dose
0.35-0.59	no	increase by 10%	4h after next dose
0.6-1.0	no	no	Day 1, 7, 30
1.1-1.5	no	decrease by 20%	before next dose
1.6-2.0	3h	decrease by 30%	before next dose and 4h after next dose
>2.0	until anti-Xa <0.5U/mL	decrease by 40%	before next dose, q12h until anti-Xa <0.5U/mL

<b>Number of patients</b>	<b>87</b>
<b>Females</b>	<b>39</b>
<b>Males</b>	<b>48</b>
<b>Age (Average)</b>	<b>52.44</b>

VTE prophylaxis	44	Prophylaxis with increased dose	VTE treatment	43	Treatment without dose modification	23	Complications
Trauma	29	10% 3	PE	27	8	Moderate bleeding	4
Sepsi	6		Upper limbs DVT	7	25%		3
Bedbound	5		AF	1	10%		5
Surgery	2		Lower Limbs DVT	8	Treatment with dose reduction	12	
Heart failure	1				-20%		8
Pneumonia	1				-10%		4

## MicroRNA-365a-3p is a potent regulator of tissue factor-dependent thrombin generation

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**Aim:** Elevated oestrogen (E<sub>2</sub>) levels can negatively influence haemostatic balance to provoke hypercoagulability, however the underlying mechanism(s) remains elusive. MicroRNA (miR), miR-365a-3p, is downregulated by E<sub>2</sub> and directly binds tissue factor (TF) mRNA. Moreover, overexpression of miR-365a-3p led to a reduction of both TF mRNA and protein expression. This study aims to determine whether miR-365a-3p affected TF-dependent thrombin generation.

**Method:** HuH-7 hepatocarcinoma cells were transfected with 50nM miR precursors (negative control/NC or miR-365a-3p) for 48h. Cell-based (n=160,000) thrombin generation were assessed using the Ceveron<sup>®</sup> alpha thrombin generation assay (TGA) analyser. TGA was initiated with low phospholipids plus 3-5pM exogenous TF (n=4), or endogenous TF (n=1). The paired *t*-test was performed to analyse statistical significance.

**Result:** Following stimulation using the low TF reagent, prolonged thrombin lag time (29.45 min ± 6.56 min, P<0.05) and time to peak (35.98 min ± 2.95 min, P<0.01) was shown in miR-365a-3p transfected cells, to compared miR-NC controls. Whereas, overexpression of miR-365a-3p significantly decreased peak thrombin (2.30 nM ± 0.51nM, P<0.05) and area under the curve (29.60 nM ± 20.89 nM, P<0.01), but not velocity index (P>0.05). In addition, preliminary data demonstrated a similar trend when endogenous TF was measured without the recombinant TF trigger.

**Conclusion:** Using a HuH-7 *in vitro* model, overexpression of miR-365a-3p resulted in a significant reduction of TF-dependent thrombin generation. Our TGA results strongly suggest a functional role for miR-365a-3p in regulating TF protein expression and its function. Together with our previous findings, we propose that under high E<sub>2</sub> condition miR-365a-3p is downregulated, thus alleviating the suppressive effect it has on TF. This contributes to a hypercoagulable state to promote thrombosis. Conversely, exogenous expression of miR-365a-3p would decrease TF expression and reduce thrombus formation.

O015

## **From phenotype to genotype: Why whole genome sequencing and artificial intelligence are disruptive**

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The diagnosis in hematological diseases is based on cytomorphology, cytochemistry, histology, histoimmunchemistry, immunophenotyping, cytogenetics, FISH and an increasing number of molecular assays. In addition, more and more patients should be followed for measurable/minimal residual disease (MRD) to further guide treatment or to be used as study end points for remission definition.

Many of these diagnostic techniques are based on sophisticated laboratory workflows, need a short turn-around time (TAT), an increasing number of machines and instruments and especially: software applications. Further, most of them are based on phenotypes and that means that the correct readout is based on experience of technicians, doctors, pathologists, cytogenetists, or molecular biologists. As in many circumstances the different techniques needed are not delivered by a single institution, final conclusions are drawn by hematologists sitting next to their patients. Contradictory results can appear.

New techniques such as whole genome sequencing (WGS), whole exome sequencing (WES) and whole transcriptome sequencing (WTS) are now available and are reaching use in clinical routine. These workflows can be accredited, scaled, barcoded and lead to highly reproducible results. However, the readout needs a lot of bioinformatic tools and workflows that so far mostly are not available for routine use. In addition, the final results, mostly delivered by bioinformaticians and molecular biologists need to be translated into languages that can be understood by doctors and patients. On the other hand TAT and reproducibility is close to clinical care and can support unmet needs.

But not only for molecular studies but also for several other techniques - so far based on phenotypes such as morphology or chromosome banding analysis - the implementation of scalable instruments, reproducible workflows and especially the implementation of artificial intelligence for readout and interpretation of data is now possible. Further, the instruments, workflows and software tools driving the complete process can be connected like an internet of things (IoT).

The next step will be to implement the new workflows based on DNA and RNA, software tools, cloud computing and artificial intelligence into clinical routine. Data security and ethical aspects need to be discussed. This can only be feasible and reproducible when the today's gold standards are tested in parallel to the new options and workflows. It will take another five years to do this and during this time, the complete scenario of diagnosis in hematology will change. This for sure can be called disruptive.

O024

## **T cell therapy for post transplant infectious complications and cancers**

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Viral infections are an extremely common and predictable problem in organ and hematopoietic stem cell transplant patients. Antiviral drugs given either prophylactically or as early therapy for patients detected to be shedding virus appears to be an effective strategy for reducing herpes virus infections. However, long-term treatment with these drugs is associated with significant toxicity, expense and the appearance of drug resistance virus isolates ultimately resulting in treatment failure. Over the last few years, there is increasing evidence that cellular immune therapies can reverse the outgrowth of hematological malignancies and can also provide therapeutic benefit against lethal viral infections. While the expansion and adoptive transfer of virus-specific T-cells from the healthy original donor can be an effective strategy to control viral replication, this is not possible when donors are seronegative or are subsequently inaccessible. Studies from our group have demonstrated the successful expansion of human cytomegalovirus (CMV)-specific T-cells from seropositive stem cell transplant recipients of a seronegative graft with active CMV disease and the long term reconstitution of protective anti-viral immunity following their adoptive transfer back into the patients. More recently, we have also developed a single platform technology to extend this immunotherapeutic strategy for multiple pathogens including CMV, Epstein-Barr virus, adenovirus and BK polyomavirus. T cells directed towards multiple pathogens can be rapidly expanded and can be used for adoptive immunotherapy. Finally, in collaboration with an Australian biotech company, Cellestis Inc., we have also developed a novel T cell-based immune monitoring technology (QuantiFERON-CMV<sup>®</sup>) which allows us to identify high risk transplant patients who may develop virus-associated complications post-transplantation and can be offered prophylactic adoptive cellular therapy.

O025

## **Factors impacting outcomes of CD19 CAR-T cells for B cell malignancies**

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Lymphodepletion chemotherapy followed by infusion of T cells that are genetically modified to express a chimeric antigen receptor (CAR) targeted to CD19 is a novel therapy for patients with relapsed and/or refractory B cell acute lymphoblastic leukemia, non-Hodgkin lymphoma, and chronic lymphocytic leukemia. Identification of factors that govern outcomes after CAR-T cell immunotherapy has been hindered in part due to the functional heterogeneity of infused CAR-T cell products. We have conducted the first clinical trial in which CD19 CAR-T cells are manufactured from distinct subsets of T cells and formulated in a defined composition for infusion to patients with B cell malignancies. Clinical responses, toxicities and factors governing outcomes will be presented.

## Machine Learnings Stratification of 2074 cases identifies Novel Prognostic Molecular Sub-Groups in Adults Acute Myeloid Leukaemia

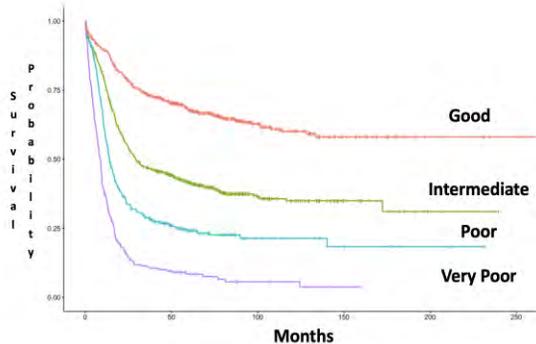
**Shaun Fleming**<sup>1,2,3,5</sup>, Xavier Tsai<sup>4</sup>, John Reynolds<sup>5</sup>, Andrew Wei<sup>1,5</sup>, Hsin-An Hou<sup>4</sup>

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**Background:** Prognosis of Acute Myeloid Leukaemia (AML) is guided by chromosomal and molecular profiling. Standard regression approaches may not be optimal for identifying prognostic gene-gene interactions.

**Aims:** We investigated use of machine-learning by recursive partitioning (RP) and random forest (RF) analysis on two large AML datasets defining prognostic groups. **Methods:** 2074 non-APL AML cases aged ≤70 included from National Taiwan University Hospital (NTUH; n=759) and German AML Study Group (AML5G; n=1315). RP was performed using rpart (4.1-13); RF analysis using randomForestSRC (2.7.0) within R 3.5.1; complexity parameter 0.0007 and minimum-split of 20. Missing data imputed, branch-points without prognostic significance trimmed. Kaplan-Meier and Cox-regression analysis performed utilising survival (2.42-3). **Results:** Median age was 48 (range 15 – 70) years; males 53%. Cytogenetic (CG) risk (ELN-2017) was favourable 13%, intermediate 69% and adverse 17%. Cohorts evenly matched except higher rate of allograft in AML5G (31% vs 18%). Complete remission (CR or CRi) was achieved in 70%; 26% proceeded to allograft in first remission. Median overall survival (OS) for entire cohort was 2.3 years. Machine-learning prognostic decision-tree for OS was based on random 2:1 selection of cases (training-set) validated on remaining cases (validation-set). Each cohort produced similar RP-trees; RF demonstrating similar significant mutations. RP identified groups described in table below, stratifying patients into good (median OS: not-reached), intermediate (median OS: 29.3 months), poor (median OS: 14.1 months) and very poor prognosis (median OS: 8.7 months). The very poor group had a poor outcome even if transplanted. Machine-learning was able to refine AML prognosis and provide individualized risk stratification. The decision-tree approach is simple to use and provides quantitative information regarding frequency of CG and molecular risk subgroups linked to patient outcome. **Conclusion:** By combining large datasets from two AML groups using machine-learning, an AML decision-tree was able to refine the ELN-2017 AML risk classification by providing further prognostic granularity.

Overall survival by prognostic classification



Group Classifier	Additional lesions	Prognostic class
Complex Karyotype	del(7q),-7, TP53 <sup>mut</sup> , -17/abn(17p)	Very Poor
	-5/del(5q)	Poor
	None of above	Intermediate
Inv(16)		Good
CEBPAdmut		Good
Inv(3)/t(3;3)		Very Poor
FLT3-ITD positive	Spliceosome mut	Very Poor
	MLL-PTD, NPM1 <sup>wt</sup> , NPM1 <sup>mut</sup> , DNMT3A <sup>mut</sup>	Poor
	NPM1 <sup>mut</sup> , DNMT3A <sup>wt</sup>	Intermediate
Spliceosome mutation	ASXL1 <sup>mut</sup> , -20/del(20q)	Very Poor
	None of above	Intermediate
NPM1 <sup>mut</sup> FLT3-ITD neg	NRAS <sup>mut</sup> , NRAS <sup>WT</sup> + IDH1 <sup>WT</sup>	Good
	NRAS <sup>WT</sup> , IDH1 <sup>mut</sup>	Intermediate
t(8;21)	KIT <sup>WT</sup>	Good
	KIT <sup>mut</sup>	Intermediate
No group classifier	ASXL1 <sup>mut</sup>	Very Poor
	NRAS <sup>mut</sup> , t(v;11)	Poor
	TP53 <sup>mut</sup> , t(9;11)	Intermediate
	Others	Intermediate

## Clinical utility of next generation sequencing in acute myeloid leukaemia: a real-world experience

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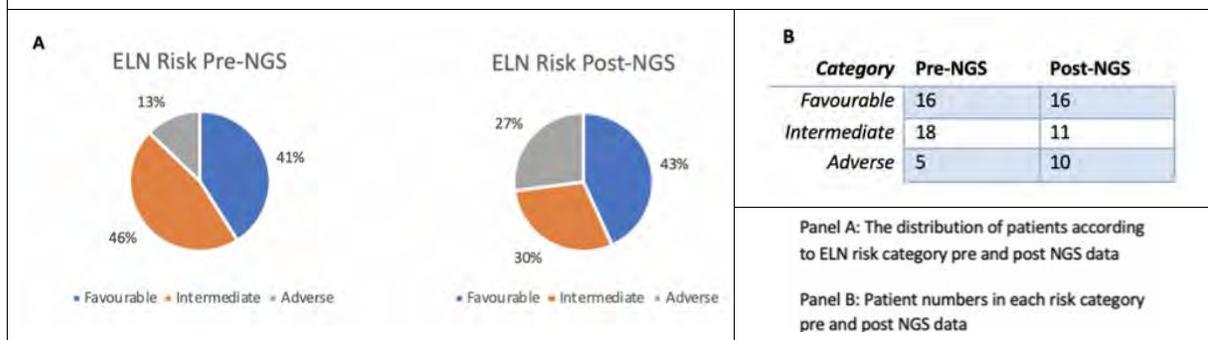
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**Aim:** Acute myeloid leukaemia (AML) is a genomically heterogeneous disease [1, 2]. Advanced molecular techniques, principally next generation sequencing (NGS), are required to analyse the multiple genes of diagnostic, prognostic and therapeutic relevance [3]; yet NGS is relatively expensive, poorly reimbursed and requires expertise for implementation and interpretation [4, 5], resulting in variable access to this technology. The clinical utility of NGS testing in routine care of Australian AML patients is unknown. This study evaluates the impact of NGS in AML management in an Australian tertiary hospital.

**Methods:** Patients (n=45) were retrospectively identified; comprehensive clinical and pathological data was collected from medical records. Clinical utility was defined by a change in diagnosis (WHO classification), prognosis (ELN risk stratification; predicted three-year overall survival calculated by an online multistage prediction tool) and/or therapy (CR1 allograft recommendation; targeted therapy) following addition of NGS results to standard diagnostics.

**Results:** NGS was clinically significant in more than one third of patients (16/45). In the newly diagnosed cohort (n=40), NGS led to changes in WHO diagnosis (1 patient), ELN risk stratification (7 patients), >10% change in predicted overall survival (11 patients) and change to allograft recommendation in first complete remission (2 patients), primarily through the detection of RUNX1, ASXL1 and TP53 mutations in baseline ELN intermediate risk disease. Of particular note is the 39% of patients (7/18) upgraded from intermediate to adverse risk by detection of these mutations. 3 patients received targeted therapy after NGS; one with a novel FLT3 mutation received midostaurin, and 40% of relapsed patients (2/5) received IDH1/2 inhibitors.

**Figure 1:** Impact of NGS analysis on ELN risk categorisation



**Conclusion:** NGS testing is clinically useful in a significant proportion of AML patients, particularly those with ELN intermediate risk and relapsed disease. Funding for NGS as a standard-of-care investigation for AML should be strongly considered; further data supporting the clinical utility of NGS will lend weight to this argument.

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**CPX-351 versus 7+3 in older adults with newly diagnosed AML with myelodysplasia-related changes (AML-MRC): phase 3 exploratory subgroup analysis**

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**Aim:** Patients with AML-MRC (**Table 1**) typically have a poor prognosis after chemotherapy. CPX-351 (Vyxeos®), a liposomal co-encapsulation of cytarabine/daunorubicin at a synergistic ratio, is approved by the EMA and FDA for adults with newly diagnosed, therapy-related AML or AML-MRC. A phase 3 study (NCT01696084) compared CPX-351 versus 7+3 in adults aged 60–75 years with newly diagnosed, high-risk/secondary AML; this exploratory analysis evaluated outcomes in 246 patients who met the WHO 2008 AML-MRC criteria.

**Methods:** Patients received 1–2 inductions with CPX-351 (100 units/m<sup>2</sup> [cytarabine 100 mg/m<sup>2</sup> + daunorubicin 44 mg/m<sup>2</sup>] as a 90-minute infusion on Days 1, 3, 5 [2nd induction: Days 1, 3]) or 7+3 (cytarabine 100 mg/m<sup>2</sup>/day continuously for 7 days + daunorubicin 60 mg/m<sup>2</sup> on Days 1–3 [2nd induction: 5+2]). Patients achieving CR+CRi could receive ≤2 consolidations. Transplantation was permitted per physician discretion.

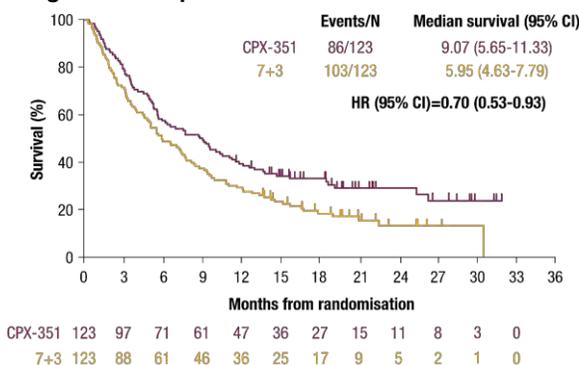
**Results:** Baseline characteristics were similar between arms (CPX-351: n=123; 7+3: n=123); 59.0% had antecedent MDS, 9.3% had antecedent CMML, and 31.7% had *de novo* AML with MDS karyotype. CPX-351 demonstrated longer overall survival (OS) versus 7+3 (**Figure**) and higher rates of CR+CRi (48.0% vs 32.5%; OR=1.83 [95% CI: 1.09–3.09]), CR (37.4% vs 24.4%; OR=1.80 [95% CI: 1.02–3.17]), and transplantation (33.3% vs 24.4%; OR=1.53 [95% CI: 0.86–2.74]). Median OS landmarked from the transplant date was longer with CPX-351 versus 7+3 (not reached vs 10.68 months; HR=0.48 [95% CI: 0.24–0.96]). Serious treatment-emergent AEs in ≥5% of patients were sepsis (CPX-351: 7%; 7+3: 3%) and febrile neutropaenia (4%; 7%). Early mortality rates with CPX-351 and 7+3 were 4.9% versus 8.9% at Day 30 and 13.8% versus 20.3% at Day 60. Prolonged myelosuppression was observed with CPX-351 (**Table 2**).

**Conclusion:** CPX-351 improved OS and CR+CRi rate versus 7+3 in older patients with newly diagnosed AML-MRC, while maintaining a similar safety profile.

<b>Table 1. WHO 2016 criteria for the AML-MRC designation.</b>	
Patients with ≥20% blasts in peripheral blood or bone marrow who meet any of the following:	
Clinical history	A history of MDS or MDS/myeloproliferative neoplasm
Morphological features	Multilineage dysplasia in ≥50% of ≥2 cell lineages in the absence of <i>NPM1</i> or biallelic <i>CEBPA</i> mutations
Cytogenetic abnormalities	An MDS-related cytogenetic abnormality

WHO, World Health Organization; MDS, myelodysplastic syndrome.

**Figure. OS in patients with AML-MRC.**



**Table 2. Time to neutrophil and platelet recovery in patients with CR+CRi after 1 induction.**

n (%)	CPX-351 (n=47)	7+3 (n=24)
Median (IQR) time to neutrophils ≥500/μL	35 days (29–41)	29 days (28–35)
Median (IQR) time to platelets ≥50,000/μL	37 days (29–43)	28 days (27–35.5)

IQR, interquartile range.

## **An antibody drug conjugate against CD300f is promising for minimal toxicity conditioning in haemopoietic stem cell transplantation for acute myeloid leukaemia**

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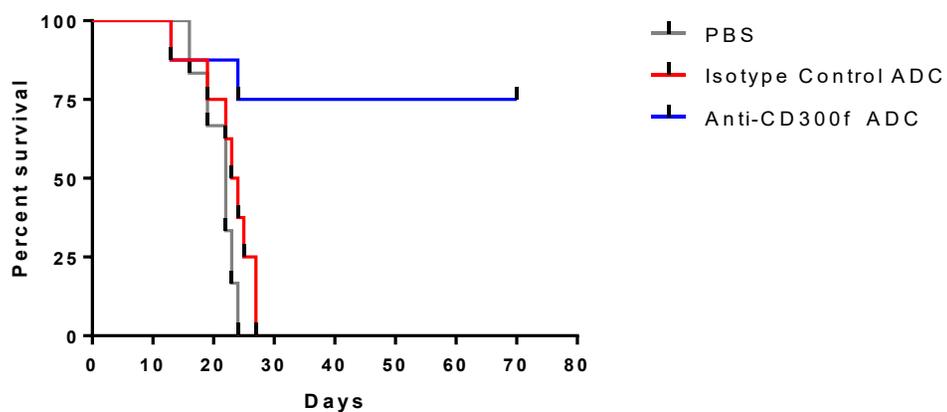
**Aim:** To develop an antibody drug conjugate (ADC) that can be incorporated into current conditioning regimens for haemopoietic stem cell transplantation (HSCT) in acute myeloid leukaemia (AML) with minimal off target effects, which will facilitate further AML depletion.

**Method:** Primary AML (n=35) as well as haemopoietic stem and progenitor cells (HSPC) (n=6) were assessed by flow cytometry for expression of CD300f. Gene expression data from publicly available data sets of primary AML (n=461) and HSPC (n=26) were analysed to compare CD300f expression. The expression of CD300f on healthy HSPC was assessed by colony forming unit (CFU) assay. The ability of our anti-CD300f ADC to target AML cell lines HL-60, U937 and THP-1 as well as non CD300f expressing cell lines was tested with an *in vitro* toxicity assay. The ability to deplete HSPC with our anti-CD300f ADC was assessed via a CFU assay. *In vivo* efficacy of our anti-CD300f ADC was assessed in NOD.Cg-Prkdc<scid>IL-2rg<tm1Wjl>SzJ (NSG) mice engrafted with human AML cell lines.

**Results:** Anti-CD300f antibodies bind to 85% of primary AML samples. CD300f is expressed across all European LeukemiaNet risk groups. CD300f is expressed on all major subgroups of HSPC. Our anti-CD300f ADC depletes AML cell lines *in vitro* with minimal effect on non CD300f expressing cells. CFU formation is inhibited by our anti-CD300f ADC. Anti-CD300f ADC significantly prolongs survival in NSG mice engrafted with human AML cell lines.

**Conclusions:** CD300f is an attractive target for ADC development to enhance HSCT conditioning for AML. Our anti-CD300f ADC has potential either to be incorporated into allogeneic conditioning regimens of patients who are at high risk of relapse post-transplant or replace alkylating agents to reduce early transplant related mortality.

**Survival of HL-60 NSG Mice Treated with ADC (300ug/kg)**



## Gilteritinib significantly prolongs overall survival in FLT3-mutated (FLT3mut+) relapsed/refractory (R/R) acute myeloid leukemia (AML): phase 3 ADMIRAL trial results

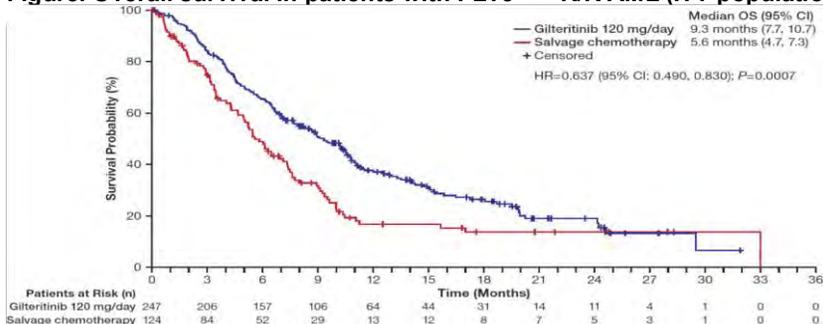
Alexander E. Perl<sup>1</sup>, Giovanni Martinelli<sup>2</sup>, Jorge E. Cortes<sup>3</sup>, Andreas Neubauer<sup>4</sup>, Ellin Berman<sup>5</sup>, Stefania Paolini<sup>6</sup>, Pau Montesinos<sup>7</sup>, Maria R. Baer<sup>8</sup>, Richard A. Larson<sup>9</sup>, Celalettin Ustun<sup>10</sup>, Francesco Fabbiano<sup>11</sup>, Antonio Di Stasi<sup>12</sup>, Robert K. Stuart<sup>13</sup>, Rebecca Olin<sup>14</sup>, Margaret Kasner<sup>15</sup>, Fabio Ciceri<sup>16</sup>, Wen-Chien Chou<sup>17</sup>, Nikolai Podoltsev<sup>18</sup>, Christian Recher<sup>19</sup>, Hisayuki Yokoyama<sup>20</sup>, Naoko Hosono<sup>21</sup>, Sung-Soo Yoon<sup>22</sup>, Je-Hwan Lee<sup>23</sup>, Timothy S. Pardee<sup>24</sup>, Amir T. Fathi<sup>25</sup>, Chaofeng Liu<sup>26</sup>, Xuan Liu<sup>26</sup>, Erkut Bahceci<sup>26</sup>, **Maha Cooney**<sup>27</sup>, Mark J. Levis<sup>28</sup>

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**Aim:** Gilteritinib is an oral FLT3 inhibitor approved as single-agent therapy in patients with R/R *FLT3*<sup>mut+</sup> AML based upon results from the pivotal phase 3 ADMIRAL study (NCT02421939) of gilteritinib vs salvage chemotherapy (SC) in this population. We present final results from the ADMIRAL trial.

**Methods:** Adults with *FLT3*<sup>mut+</sup> AML (*FLT3*-ITD and/or *FLT3*-TKD D835/I836) refractory to induction chemotherapy or in untreated first relapse were randomized (2:1) to continuous 28-day cycles of 120-mg/day gilteritinib or pre-randomization selected SC. Prior treatment with FLT3 inhibitors, other than midostaurin or sorafenib, were excluded. Overall survival (OS) and the combined rate of complete remission/complete remission with partial hematologic recovery (CR/CRh) were co-primary endpoints. Safety/tolerability was also examined. **Results:** A total of 371 patients (median age, 62 years [range, 19-85]) were randomized: 247 to gilteritinib and 124 to SC. Baseline *FLT3* mutations were: *FLT3*-ITD, 88.4%; *FLT3*-TKD, 8.4%; *FLT3*-ITD and *FLT3*-TKD, 1.9%; unconfirmed, 1.3%. Overall, 39.4% of patients had refractory AML and 60.6% had relapsed AML. Patients randomized to gilteritinib had significantly longer OS (9.3 months) than SC (5.6 months; hazard ratio [HR] for death=0.637; *P*=0.0007) (**Figure**); 1-year survival rates were 37.1% and 16.7%, respectively. The CR/CRh rates for gilteritinib and SC were 34.0% and 15.3%, respectively (*P*=0.0001); CR rates were 21.1% and 10.5% (2-sided *P*=0.0106). Common adverse events (AEs) in all randomized pts were febrile neutropenia (43.7%), anemia (43.4%), and pyrexia (38.6%). Common grade ≥3 AEs related to gilteritinib were anemia (19.5%), febrile neutropenia (15.4%), thrombocytopenia (12.2%), and decreased platelet count (12.2%). Exposure-adjusted serious treatment-emergent AEs per patient-year (PY) were less common with gilteritinib (7.1/PY) than SC (9.2/PY). **Conclusions:** In patients with R/R *FLT3*<sup>mut+</sup> AML, gilteritinib resulted in significantly longer survival and higher response rates compared with chemotherapy and was well tolerated. These results establish a new treatment paradigm for R/R *FLT3*<sup>mut+</sup> AML.

**Figure. Overall survival in patients with *FLT3*<sup>mut+</sup> R/R AML (ITT population: N=371)**



Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mut+, mutated; R/R, relapsed/refractory.

O033

**Comparison of ATRA and Arsenic trioxide and ATRA and chemotherapy in Acute Promyelocytic Leukaemia in Western Australia: real world, retrospective, multicentre study.**

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<sup>1</sup>Haematology Department, Royal Perth Hospital, Nedlands, Australia, <sup>2</sup>Fiona Stanley Hospital, Murdoch, Australia

**Background:** ATRA and arsenic have become standard of care in standard risk APML while anthracyclines, Idarubicin is incorporated into treatment regimen of patients with high risk disease. We studied outcomes in APML patients identified across 3 tertiary centres in WA from 2008-2019.

**Methods:** Patients with APML (n=74) with positive cytogenetics/FISH for t(15:17) were included in this analysis. Treatment details were obtained by interrogation of pharmacy and clinical databases.

**Results:** Of the evaluable patients, 30 patients received ATRA and arsenic (ATRA-ATO, as per Lo Coco protocol), while in the ATRA chemotherapy (ATRA-CHT) group: 13 and 21 received the APML3 and APML4 regimens respectively while 10 received induction chemotherapy and ATRA. Patients with standard (WCC <10 at diagnosis) or high risk APML were 60 and 14 respectively. After a median follow up of 41.8 months, the event-free survival, relapse rate, and overall survival at 50 months for patients in the ATRA-ATO versus ATRA-CHT arms were 96.6% v 88.63%, 3.3% v 11.36%, and 96.6% v 79.54%, respectively.

Post induction events included one relapse and one death in CR from CVA with haemorrhagic transformation in the ATRA-ATO arm and 4 relapses after consolidation leading to stem cell transplantations(n=4), and five deaths in complete remission in the ATRA-CHT arm. Three patients in the ATRA-CHT arm developed a therapy-related myeloid neoplasm or other solid malignancy. Molecular CR was seen in 90.9% and 100% of patients in the ATRA-CHT and ATRA-ATO arms. Cox regression hazard model shows that age at diagnosis, treatment significantly affects outcome rather than white cell count at diagnosis or standard risk.

**Conclusion:** Patients on APML3 and had similar outcomes to patients on the Lo Coco protocol. Patients on ATRA plus chemotherapy developed complications like heart failure, infections and secondary malignancy.

## Repurposing Venetoclax and Ruxolitinib to improve stem cell transplant outcomes

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<sup>1</sup>The Royal Melbourne Hospital, Melbourne, Australia, <sup>2</sup>The University of Melbourne, Melbourne, Australia,

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**Introduction:** Allogeneic haematopoietic stem cell transplantation (alloSCT) cures cancer, but is associated with significant side effects such as graft versus host disease (GVHD) and infection. In order to improve patient outcomes, we need to reduce pre-transplant conditioning, promote donor cell engraftment and limit GVHD. Natural killer (NK) cells are important for controlling donor cell engraftment, and are reliant on BCL2 and JAK1/2 pathways for survival. We investigated if NK cells could be depleted from the immune system prior to alloSCT, using the clinically approved BCL2 inhibitor Venetoclax, and the JAK1/2 inhibitor Ruxolitinib.

**Methods:** We used mouse models of acute myeloid leukaemia (AML) to explore the ability of Venetoclax or Ruxolitinib to deplete NK cells in wild-type alloSCT recipients, immediately prior to transplant. AML-bearing mice were treated with drug for 2 days, then given a reduced dose of irradiation, and alloSCT from a MHC-mismatched donor. Mice were monitored for GVHD, donor cell engraftment, and anti-AML response.

**Results:** Pharmacological inhibition of BCL2 or JAK1/2 prior to alloSCT in mice with Venetoclax or Ruxolitinib respectively resulted in rapid depletion of recipient NK cells. A significant proportion (>80%) of alloSCT recipient mice pre-treated with either drug developed full donor cell engraftment after reduced intensity conditioning, did not develop GVHD, and retained potent anti-tumour effects against pre-established AML.

**Conclusions:** BCL2 and JAK1/2 inhibition in alloSCT recipients, in combination with reduced intensity conditioning was:

- 1) well-tolerated
- 2) associated with low rates of GVHD
- 3) resulted in long-term donor haematopoietic cell engraftment
- 4) retained anti-tumour responses in an AML mouse model

Therefore, repurposing clinically-approved drugs to inhibit recipient NK cells may represent a means by which to deliver alloSCT more safely.

## Survival Outcomes in allogeneic haematopoietic stem cell transplant recipients (HSCT) treated for first reactivation of cytomegalovirus (CMV); a multi-centre study

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<sup>1</sup>Bone Marrow Transplant and Cell Therapies Program, Department of Haematology, Westmead Hospital, Sydney, Australia, <sup>2</sup>National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Melbourne, Australia, <sup>3</sup>Department of Infectious Diseases, Royal Melbourne Hospital, Melbourne, Australia, <sup>4</sup>The Peter Doherty Institute for Infection and Immunity, The University of Melbourne and Royal Melbourne Hospital, Melbourne, Australia, <sup>5</sup>Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Australia, <sup>6</sup>Department of Clinical Haematology and Bone Marrow Transplant Service, The Royal Melbourne Hospital & Peter MacCallum Cancer Centre, Melbourne, Australia, <sup>7</sup>Department of Medicine, The University of Melbourne, Melbourne, Australia, <sup>8</sup>Westmead Institute for Medical Research, University of Sydney, Sydney, Australia, <sup>9</sup>Faculty of Medicine and Health, University of Sydney, Sydney, Australia, <sup>10</sup>Sydney Cellular Therapies Laboratory, Sydney, Australia

### Aim

Cytomegalovirus (CMV) reactivation is common after allogeneic haemopoietic stem cell transplantation (HSCT). Pre-emptive treatment is commonly given to HSCT recipients with clinically significant reactivation. Overall survival and causes of death in patients receiving initial treatment for reactivation of CMV are not well described.

### Methods

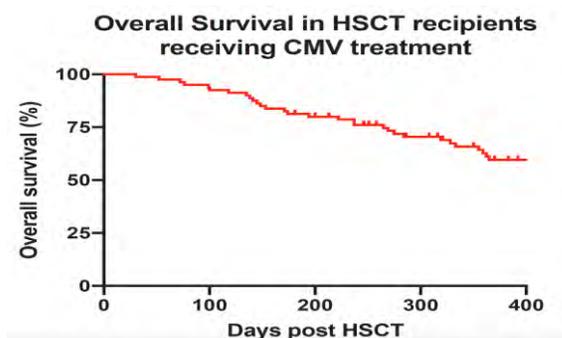
A retrospective study of allogeneic HSCT undertaken at Westmead Hospital between 2010-2011 (to avoid selecting patients treated on CMV directed cell therapy studies) and The Royal Melbourne Hospital between 2015-2017 was performed. Overall survival in HSCT recipients receiving an initial treatment course of anti-CMV therapy was the primary outcome of interest.

### Results

Of the study cohort (n=262, median age 52 years (IQR 42-60)), 80 (30.5%) received an initial course of anti-CMV therapy. These patients were almost exclusively CMV seropositive (98%) and most received reduced intensity conditioning (77%). Ganciclovir either alone or with other agents was commenced in 69% of treated patients. Overall survival was 58% (median follow up 586 days (IQR 369-2155) (Figure 1) and did not differ between those who did and did not receive CMV treatment (p=1.0). Thirty-three of the 80 (41%) patients who received CMV treatment died at a median of 7.4 months (IQR 4.6-10.9). The primary cause of death in these patients was relapse (48.5%). Other causes were infection (18.2%), GVHD (12.1%), graft failure (9.1%), multiorgan failure (6%) and other (6%). There was a trend for worse relapse free survival in patients who received initial CMV treatment compared to those who did not (HR 1.39, 95% CI 0.98 to 2, p=0.07).

### Conclusion

Patients requiring treatment for an initial CMV reactivation post HSCT have a high incidence of relapse. These data provide a baseline for determining whether future interventions in patients receiving initial CMV treatment can reduce mortality. Patients initiating CMV treatment should be carefully monitored for early relapse.



## Infection is the leading cause of death post allogeneic HSCT in Australia: an ABMTRR audit of all-cause mortality 2013-2017

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<sup>1</sup>Royal North Shore Hospital, Sydney, Australia, <sup>2</sup>Australasian Bone Marrow Transplant Recipient Registry, Sydney, Australia, <sup>3</sup>Westmead Hospital, Sydney, Australia, <sup>4</sup>Monash University, Melbourne, Australia, <sup>5</sup>Peter MacCallum Cancer Centre, Melbourne, Australia

**Aim:** To investigate recent infection related mortality in patients undergoing allogeneic haematopoietic stem cell transplant (HSCT) in Australia.

**Methods:** Patients receiving allogeneic HSCT between 2013 and 2017 were identified from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). Types of transplant, demographics and causes of death were extracted from the database and categorised into deaths caused by: primary disease; infection-only; infection-and-GVHD (Graft Versus Host Disease); GVHD-only; and other.

**Results:** Between 2013 and 2017 (inclusive), 2785 first allogeneic HSCTs were performed with 680 (24.4%) deaths at 1-year post HSCT. Infection-only related mortality [28.2% (192/680)] was the highest single cause of transplant related mortality (TRM) and when combined with GVHD-and-infection for any infectious mortality, this was the most common cause of all-cause mortality [37.7% (256/680)]. Other causes of death included relapse of primary disease [36.2% (246/680)]; GVHD-only [12.2% (83/680)]; GVHD-and-infection [9.3% (63/680)]; and other [14.1% (96/680)] (Fig 1). TRM associated with infection appears higher than those reported in international registries, with the Centre of International Bone Marrow Transplant Registry reporting infection related TRM at ~20% of total deaths, however this effect may be due to categorical reporting differences between registries. The annual all-cause mortality at 1-year post HSCT and overall deaths of matched unrelated donor (MUD) versus matched sibling donor (SIB) is given in Fig 2 and 3, respectively. A significantly higher overall proportion of MUDs suffered infection related TRM versus SIBs [7.74% (118/1512) vs 4.96% (51/1029), P<0.05]. GVHD associated TRM was higher in MUDs versus SIBs [3.7% (57/1512) versus 2.1% (22/1029), P<0.05]. 65.6% (124/192) of infection related TRM occurs within 100 days post transplant (Fig 4).

**Conclusion:** Infection in allogeneic HSCT remains a major cause of mortality. Further research and development of infection prevention strategies are warranted in this at-risk patient population.

Figure 1. All cause mortality at 1 year post allogeneic HSCT 2013-17 n=680 (24.4%)

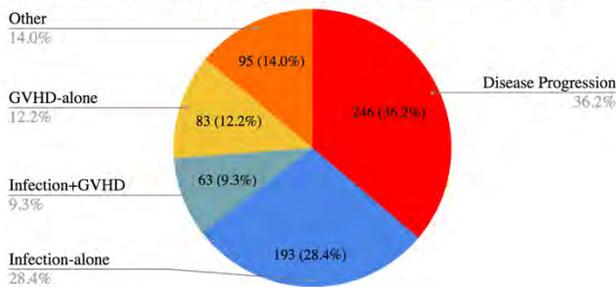


Figure 3. All cause mortality at 1 year post allogeneic HSCT MUDs vs SIBs 2013-17

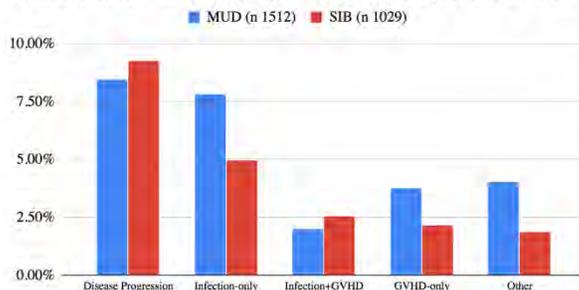


Figure 2. All cause mortality at 1 year post allogeneic HSCT 2013-17 n=680 (24.4%)

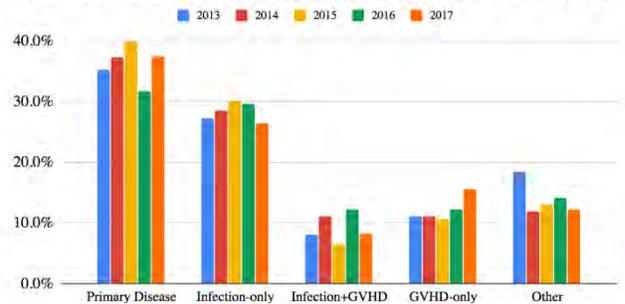
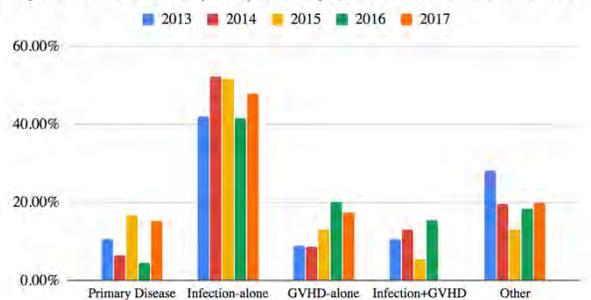


Figure 4. All cause mortality at day-100 allogeneic HSCT 2013-17 n=268 (9.62%)



## Identification of CMV & EBV-specific T-cells following allogeneic blood/marrow transplant is achievable using high-throughput sequencing of T-cell receptor beta loci

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### Background/Aim

We sought to determine whether high-throughput sequencing (HTS) of T-cell receptor beta loci (TCRb) could identify T-cell clonotypes with specificity for CMV and EBV epitopes in the early post-allogeneic blood/marrow transplant (alloBMT) period and assess association with viral-related outcomes.

### Method

DNA was extracted from CD3+ selected peripheral blood samples at Day+30 and Day+60 post-alloBMT from 65 consecutive patients who were donor (D) and/or recipient (R) CMV seropositive. TCRb deep sequencing was performed using LymphoTrack TRB (Invivoscribe). Sequence assembly, annotation and error correction was performed by MiXCR/VDJtools. Epitope specificity was assessed using a curated database of T-cell clonotype specificity (VDJdb).

### Results

CMV-specific clonotypes were identified in 123/125 samples with specificity for p65 (94.33%; 7 unique epitopes), pp50 (4.50%; 1 epitope), IE2 (1.09%; 1 epitope) and IE1 (0.07%; 3 epitopes). A greater proportion of T-cell repertoire comprising CMV-specific T-cells (CMV-Trep%) was associated with D+R+ serostatus (day+60,  $p=0.004$ ), and preceding viraemia (day+30,  $p=0.011$ ; day+60  $p=0.024$ ). Patients with CMV-disease had significantly lower CMV-Trep% at Day+30 compared with those treated for viraemia only (0.075% vs. 0.38%,  $p=0.025$ ).

Patients who demonstrated an increase in CMV-Trep% following viraemia (57%) had significantly lower peak viral load (median 892copies/mL vs. 8714copies/mL,  $p=0.0013$ ) and a trend toward fewer days of antiviral therapy within the first 180 days (21days vs. 29.5days,  $p=0.08$ ).

EBV-specific clonotypes were identified in 118/125 samples. A  $>0.8\log$  increase in EBV-Trep% was observed post-EBV viraemia in 4/4 patients treated with rituximab, without post-transplant lymphoproliferative disorder (PTLD). No increase was observed in the single patient with EBV-associated PTLD, however T-cell repertoire was comprised of highly dominant clones lacking EBV specificity, suggestive of an alternative, possibly non-viral, epitope.

### Conclusion

TCRb-HTS allows for the identification of CMV/EBV-specific T-cells, which appear associated with serostatus and timing of viral reactivation. Monitoring of T-cell response to viraemia is feasible and may provide insights into post-alloBMT viral complications.

O038

## **A Retrospective Analysis on the Outcome of Donor Lymphocyte Infusion (DLI) for Falling Donor CD34 chimerism.**

**Tishya Indran**<sup>1</sup>, Tongted Das<sup>1</sup>, Jenny Muirhead<sup>1</sup>, Bianca Cirone<sup>1</sup>, David Kliman<sup>1</sup>, Sush Patil<sup>1</sup>, David Curtis<sup>1,2</sup>

<sup>1</sup>The Alfred Hospital, Department of Malignant Haematology and Stem Cell Transplantation, Melbourne, Australia, <sup>2</sup>Division of Blood Cancer Research, Australian Centre for Blood Diseases, Melbourne, Australia

### **Introduction:**

We present a retrospective study at The Alfred Hospital on the outcome of DLI following allogeneic haematopoietic stem cell transplant (alloHSCT) in AML or MDS.

### **Methods:**

Using the chimerism database, we identified 19 patients post alloHSCT who received DLI between 2012 – 2018 with measurable donor CD34, CD3 and CD33 chimerism. A cut off <80% donor CD34 chimerism defined relapse [1]. The analysis focussed on the indication for DLI (falling donor chimerism or morphological relapse), the effect on donor chimerism, overall survival and GVHD. The effect of DLI on donor chimerism was tested using the Friedman's test. Wilcoxon Signed Test with Bonferroni correction was used to perform post-hoc comparison. Effect size of the changes were estimated using the Kendall's W coefficient.

### **Results:**

Of the 19 patients, DLI was administered for morphological relapse and falling donor chimerism in 7 patients. 6 of the 7 patients had CD34 chimerism values of <80%. 1 patient with extramedullary disease had donor CD34 chimerism value of 84.5 %.

The remaining 12 patients had DLI for falling donor chimerism alone. 7 patients received DLI for falling CD34 chimerism (with or without CD3). DLI was not effective in 4 of the 7 patients with the lowest CD34 chimerism values (8%, 21%, 59% and 76.5%) who eventually succumbed to disease. The 1 patient with donor CD34 chimerism of 76.5 % at the time of DLI had subsequent extramedullary relapse.

DLI induced acute or chronic GVHD in 14 of the 19 patients. All 5 patients without GVHD died. Statistical analysis of donor chimerism values showed the fall from 60 days to 30 days prior to DLI was statistically significant for CD34 (P=0.0017) but not for CD3 or CD33.

### **Conclusion:**

This small sample size shows that the decline in donor CD34 chimerism, even prior to the cut off 80% is an earlier predictor of relapse. Patients with lower donor CD34 chimerism values at the time of DLI and those without GVHD post DLI did worse. The predictive value of donor CD34 chimerism in extramedullary relapse is unclear.

### **References:**

- 1 Bornhauser, M., et al., *Monitoring of donor chimerism in sorted CD34+ peripheral blood cells allows the sensitive detection of imminent relapse after allogeneic stem cell transplantation.* Haematologica, 2009. **94**(11): p. 1613-7.

O039

## **Time to post-chemotherapy neutrophil recovery does not predict delayed neutrophil engraftment in allogeneic stem cell transplant recipients**

Trung Ngo<sup>2</sup>, David Ritchie<sup>1,2</sup>, **Joanne Tan**<sup>1,2</sup>

<sup>1</sup>Royal Melbourne Hospital, Parkville, Australia, <sup>2</sup>Peter MacCallum Cancer Centre, Parkville, Australia

### **Background:**

Following chemotherapy, patients with acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL) may proceed to allogeneic stem cell transplantation (alloSCT). Neutrophil engraftment following alloSCT may be influenced by stem cell factors and bone marrow stromal microenvironment(1, 2), which may be reflected in delayed post-chemotherapy bone marrow recovery.

### **Aim:**

To determine if there is an association between duration of chemotherapy-induced neutropenia and post-transplant neutrophil engraftment, relapse-free survival (RFS), transplant-related mortality (TRM) and overall survival (OS).

### **Methods:**

72 patients with acute leukaemia who had both their consolidation chemotherapy and alloSCT at the Royal Melbourne Hospital were identified. Time to neutrophil engraftment, RFS, TRM and OS were assessed according to time to neutrophil recovery after the final chemotherapy cycle using the Kaplan-Meier estimate. An independent t-test compared neutrophil recovery times post-chemotherapy to engraftment times following alloSCT.

### **Results:**

48 patients had AML, 21 had ALL and 2 had undifferentiated acute leukaemias. The median age was 46 years. 34 patients had matched related (sibling) donors, 37 had matched unrelated donors, and 1 had a haploidentical donor. 47 patients received myeloablative conditioning and 25 patients received reduced-intensity conditioning. 6 patients did not engraft post alloSCT but were included in the analyses. Using a median time to neutrophil recovery of 22 days as the cut-off, there were no statistical differences in the time to alloSCT engraftment ( $p=0.95$ ) (Figure 1), overall survival ( $p=0.93$ ), transplant-related mortality ( $p=0.93$ ) or relapse-free survival ( $p=0.31$ ).

### **Conclusion:**

The time to neutrophil recovery after the final cycle of chemotherapy is not associated with time to neutrophil engraftment, overall survival, transplant-related mortality or relapse-free survival. Delayed neutrophil recovery following chemotherapy should not impact the decision to proceed to alloSCT.

### **References:**

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## **“Immuno-flowFISH” for the Assessment of Cytogenetic Abnormalities in Chronic Lymphocytic Leukemia**

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**Aim:** We have invented a world-first automated high-throughput imaging flow cytometry method called “Immuno-flowFISH” that integrates fluorescence in situ hybridisation (FISH) on immunophenotyped cells in suspension. We aimed to assess the utility of immuno-flowFISH for the detection of chromosomal abnormalities in chronic lymphocytic leukaemia (CLL), specifically trisomy 12 (+12) and del(17p).

**Methods:** Peripheral blood mononuclear cellss were isolated from the blood of 55 CLL patients (at diagnosis and monitoring). Immunophenotyping was performed with fluorescently conjugated CD3, CD5, and CD19 monoclonal antibodies. Following fixation, cells were permeabilised, double stranded DNA denatured and hybridised with chromosome 12 or 17 enumeration (CEP 12, CEP17) and 17p12 locus-specific FISH probes. Cells were analysed on the Amnis ImageStreamX Mark II to assess the number and percent FISH-positive CD5/CD19-positive CLL cells and the ratio of FISH spot counts for CLL cells to CD3/CD5-positive T cells (FISH “mean spot ratio”).

**Results:** The mean number of cells analysed was 20,000 (range = 10,000 – 50,000). Trisomy 12 was detected in 15% of cases and del(17p) in 8% of CLL cases; there was 100% concordance with standard FISH testing. The number of +12 CLL cells ranged from 0.13 – 45% and del(17p) from 3.5 – 22.8%. The FISH “mean spot ratios” were 1.089 -1.362 for +12 and 0.86 – 0.96 for del(17p).

**Conclusions:** Immuno-flowFISH could detect both +12 and del(17p) in phenotypically identified CD5/CD19-positive CLL cells. Both imagery and quantitative data, including spot count ratio, were used in the analysis. Since a minimum of 10,000 cells were analysed, this was a 100-fold increase compared with standard FISH. Furthermore, the sensitivity and specificity of the FISH result was greater as only cells with the CLL phenotype were analysed. The limit of detection was 1 abnormal cell in 1,000 normal cells.

**TP53 mutation and immunoglobulin heavy chain gene mutation status in Australian FCR (fludarabine/cyclophosphamide/rituximab)-eligible patients with chronic lymphocytic leukaemia**

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**Background and aims:** The presence of *TP53* mutations and/or an unmutated immunoglobulin heavy chain (IGHV) locus are associated with inferior outcomes in patients with chronic lymphocytic leukaemia (CLL) when treated with chemoimmunotherapy (fludarabine/cyclophosphamide/rituximab; FCR). Conversely, the absence of these two molecular risk factors is associated with durable remissions and potential functional cure with FCR. We report herein the immunogenetic landscape from a series of Australian, treatment requiring, FCR-eligible patients with CLL.

**Method:** Clinical *TP53* and IGHV mutation testing was performed in a series of Australian CLL patients referred via a fixed-duration, philanthropically-subsidised testing program. Criteria for inclusion were untreated patients aged under 70 years with CLL meeting conventional criteria for treatment that were being considered for FCR chemoimmunotherapy. *TP53* mutation testing was performed using targeted amplicon sequencing and IGHV sequencing using Lymphotrack IGHV Leader Somatic Hypermutation Assay (Invivoscribe).

**Results:** 164 patients were referred for testing from April 2018 to May 2019, median age 61 years (range 19-81). A high-risk molecular profile (unmutated IGHV [or high-risk stereotype subset] and/or *TP53* mutation) was detected in 47% (n=77). 68 patients had unmutated IGHV, 12 patients had *TP53* mutations (variant allele frequencies 3.4-81.9%) and 12 patients had high-risk stereotype subset usage (subsets #1, #2, #8). Of the 12 patients with *TP53* mutations, four had no detectable del(17p) by FISH and four had multiple *TP53* mutations detected. Biased V-family usage was observed including of V1-69 (21/164), V4-34 (15/164), and V3-23 (11/164).

**Conclusion:** We have demonstrated the potential utility of providing clinically relevant molecular risk stratification of CLL patients. Using these molecular assays, almost half of untreated (but treatment requiring) FCR-eligible patients with CLL in Australia have features identifying that they would not obtain truly durable remission or potential cure with FCR and should be considered for alternative approaches.

**RESONATE final analysis: 6-year follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL)**

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**Aim:** Ibrutinib, a first-in-class, once-daily inhibitor of BTK, is approved in the US for the treatment of CLL/SLL and allows for treatment without chemotherapy. Herein, we report results from the phase 3 RESONATE (NCT01578707) final analysis with up to 6-year follow-up of ibrutinib vs ofatumumab in relapsed/refractory CLL/SLL.

**Methods:** Eligible patients were randomized to receive oral ibrutinib 420 mg/day until PD or intravenous ofatumumab for 24 weeks. Long-term efficacy outcomes were investigator-assessed.

**Results:** In total, 391 patients were randomized (ibrutinib, n=195; ofatumumab, n=196); 86% and 79%, respectively, comprised the genomic high-risk population (del(17p), del(11q), TP53 mutation, and/or unmutated IGHV). Median follow-up on ibrutinib was 65 months (range, 0.3-72) at final analysis. Among patients randomized to ofatumumab, 68% crossed over to ibrutinib therapy. Ibrutinib-treated patients had significant sustained PFS benefits vs ofatumumab, with median PFS 44.1 vs 8.1 months (HR: 0.15;  $P<0.0001$ ). In the genomic high-risk population, median PFS was 44.1 vs 8.0 months, respectively (HR: 0.11). ORR was 91% with ibrutinib (11% CR/CRi). Censored for crossover, ibrutinib conferred better OS versus ofatumumab (HR: 0.64). With median treatment duration of 41 months (range 0.2-71) with ibrutinib, hypertension occurred in 21% of patients (9%, grade  $\geq 3$ ) and atrial fibrillation in 12% (6%, grade  $\geq 3$ ); major hemorrhage occurred in 10%. Most common reasons for ibrutinib discontinuation prior to study closure were PD (37%) and AEs (16%); discontinuation due to AEs occurred in 3%-6% of patients per yearly interval of ibrutinib therapy.

**Conclusions:** Final analysis from RESONATE showed sustained efficacy of ibrutinib with up to 6 years of follow-up in patients with R/R CLL, including in those with genomic high-risk features. Over long-term ibrutinib therapy, rates of discontinuation due to AEs were low, with no new safety signals. These results demonstrate that continuous ibrutinib treatment provides long-term benefits for patients with R/R CLL.

## ASCEND: Phase 3 Study of Acalabrutinib vs Investigator's Choice of Rituximab Plus Idelalisib (IdR) or Bendamustine (BR) in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)

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**Introduction:** Acalabrutinib is a highly selective, potent, covalent BTK inhibitor. In this randomized, global, multicenter, open-label Phase 3 study (CL-309; ASCEND; NCT02970318), the efficacy and safety of acalabrutinib monotherapy was evaluated vs investigator choice of IdR or BR in R/R CLL.

**Methods:** Eligible patient (pts) were randomized 1:1 to receive 100 mg oral acalabrutinib BID until progression vs IdR or BR. Pts were stratified by del(17p), ECOG and prior lines of therapy. The primary endpoint was PFS assessed by independent review committee. Secondary endpoints included OS, ORR and safety. Pts with confirmed progression on IdR/BR could cross over to receive acalabrutinib.

**Results:** 310 pts were randomized to acalabrutinib (n=155) or IdR/BR (n=155 [IdR, n=119; BR, n=36]); median age was 67 y; 16% had del(17p); 27% del(11q); 42% Rai stage III/IV CLL. Median number of prior therapies was 1 (1-8) for acalabrutinib and 2 (1-10) for IdR/BR. Discontinuation due to AEs occurred in 11% pts on acalabrutinib vs 49% Id, 12% R in IdR, 11% B and 17% R in BR.

At a median follow-up of 16.1 mo, acalabrutinib significantly prolonged IRC-assessed PFS vs IdR/BR (median NR vs 16.5 mo; HR 0.31, 95% CI 0.20-0.49, P<.0001); a 69% reduction in risk of progression or death (**Figure**). PFS rates at 12 mo were 88% with acalabrutinib and 68% with IdR/BR. PFS improvement with acalabrutinib was seen across subgroups.

Common all-grade AEs (≥15%) with acalabrutinib were headache (22%), neutropenia (19%), diarrhea (18%), anemia and cough (15% each). AEs of interest were atrial fibrillation (5.2% acalabrutinib vs 3.3% IdR/BR), bleeding AEs (26% vs 7.2%; including major hemorrhage [1.9% vs 2.6%]), Grade ≥3 infections (15% vs 24%), and 2<sup>nd</sup> primary malignancies (excluding NMSC; 6.5% vs 2.6%).

**Conclusions:** Acalabrutinib monotherapy significantly improved PFS with a more tolerable safety profile compared with IdR/BR in pts with R/R CLL.

## **Immune profiling of CLL patients on long-term Venetoclax or Ibrutinib treatment**

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**Introduction:** The advent of targeted therapies, including the BCL2 inhibitor Venetoclax and BTK inhibitor Ibrutinib, for the treatment of CLL has led to improved long-term outcomes. However, patients on these therapies often require continuous treatment for years, and longitudinal immunological follow up studies have yet to be performed. Therefore, this study selected a unique cohort of CLL patients on targeted therapy treatment for a minimum of 1 year, and in some cases, over 3 years.

**Methods:** Immune profiling of CLL patient PBMC samples collected at 3, 6, 9, 12 month, and >1 year time points on treatment, was tested by multi-parameter flow cytometry, and compared to healthy donor age-matched controls. Cell activation and cytokine secretion was tested using overnight anti-CD3/28 bead stimulation, and cytokines measured by cytokine bead array.

**Results:** CLL patients on long-term Venetoclax or Ibrutinib treatment demonstrated a reduction in circulating B cells and restoration of T cell populations comparable to healthy aged matched donors. Treatment with either therapy for more than 1 year resulted in differences in peripheral immune subsets. Venetoclax treatment was associated with an increase in myeloid cell and unconventional T cell frequency, including gd T cells and virtual memory T cells. In contrast, CLL patients on Ibrutinib treatment showed increased myeloid cell frequency, but no change in T cell subsets. Furthermore, unlike Venetoclax, Ibrutinib treatment was associated with decreased T cell function.

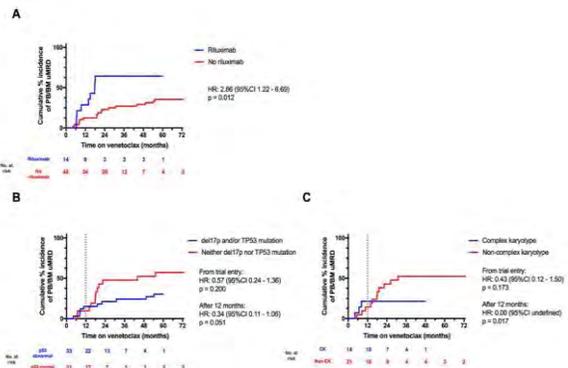
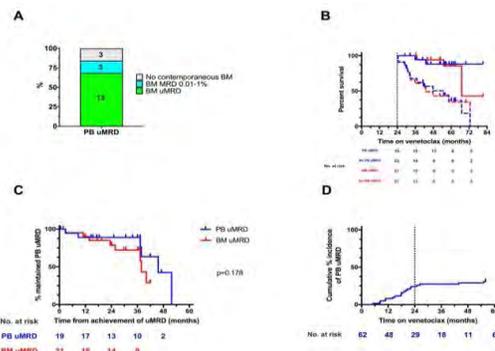
**Discussion:** Longitudinal immune cell profiling indicated that novel targeted therapies can restore immune cell populations in CLL patients similar to age matched donors. However, restoration of immune cell function may be impacted by Ibrutinib treatment. Further studies are warranted to examine this in more detail.

**The attainment of undetectable minimal residual disease (uMRD) in peripheral blood (PB) should be the therapeutic goal of venetoclax (VEN) in chronic lymphocytic leukaemia (CLL)**

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**Aim:** The BCL2 inhibitor VEN achieves deep remissions in CLL, including uMRD (1, 2), an independent predictor of long-term survival (3). We report our institutional experience with VEN in CLL, focusing on: (a) reliability of PB MRD compared to BM; (b) time-to-uMRD; (c) clinicopathological predictors of uMRD; and (d) time-to-MRD recrudescence. **Methods:** MRD status of 62 CLL patients treated with continuous VEN was serially monitored in PB and BM using multiparameter flow cytometry by ERIC methodology (4). Kaplan-Meier methods were used for time-to-event analyses. Associations between clinicopathological variables and rate of uMRD were analysed using the Cox proportional hazard model. **Results:** 16/62 patients achieved PB uMRD and had contemporaneous BM assessments; 13/16 (81%) had uMRD confirmed in BM (Figure 1A). Patients with PB uMRD had time-to-progression (TTP) and MRD recrudescence at least as favourable as those with BM uMRD (Figures 1B-C). Overall, 19/62 (31%) achieved PB uMRD. Excluding 2 patients with PB uMRD confirmed after 4-5 years without prior MRD assessments, median time-to-PB uMRD was 18 (range 5-26) months, with 90% occurring within 24 months (Figure 1D). Median follow-up among patients without disease progression or PB uMRD attainment was 37 (range 4-63+) months. The dominant association with earlier uMRD was concurrent rituximab therapy ( $p=0.012$ ) (Figure 2A). *TP53* dysfunction and complex karyotype were associated with lower rates of uMRD attainment beyond 12 months ( $p=0.051$  and  $p=0.017$ , respectively) (Figures 2B-C). Median time-to-MRD recrudescence was 46 months (Figure 1B). Of the 10 patients with PB MRD recrudescence, median TTP was 17 (range 14-27) months. **Conclusion:** PB strongly correlates with BM uMRD in CLL patients treated with VEN, and is an equivalent predictor of long-term outcome. Most patients who achieve PB uMRD do so by 24 months, with rituximab co-therapy associated with earlier uMRD. Although patients who achieve uMRD have prolonged TTP, MRD recrudescence occurs in most patients.



**Figure 1.** (A) MRD burden in subsequent or contemporaneous (within 3 months) BM assessments of patients who achieved uMRD in PB. (B) Time-to-MRD recrudescence stratified by uMRD achievement in PB and BM. (C) Time-to-MRD recrudescence stratified by time from uMRD achievement in PB and BM. (D) Cumulative incidence of PB uMRD on VEN.

**Figure 2.** (A) Cumulative incidence of uMRD in PB or BM stratified by co-administration of rituximab. (B) Cumulative incidence of uMRD in PB or BM stratified by *TP53* dysfunction. (C) Cumulative incidence of uMRD in PB or BM stratified by complex karyotype.

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**Panobinostat (LBH589) in combination with the  $\beta$ -catenin inhibitor Tegavivint (BC2059) exerts significant anti-myeloma activity both in vitro and in vivo**

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**Introduction:** Panobinostat is approved for the treatment of relapsed multiple myeloma (MM). The Wnt canonical pathway is dysregulated in advanced MM supporting the evaluation of  $\beta$ -catenin inhibition as a potential therapy. We evaluated the anti-MM effect of Tegavivint in combination with Panobinostat.

**Results and Methods:** *In vitro* combination of low doses for 48h was synergistic against OCI-My1 and U266 cells, with combination indices from 0.569 to 0.883 (CI<1: synergism). The combination demonstrated synergistic killing of primary MM tumour cells with synergism quotients from 1.2 to 2 (SQ>1: synergism). The combination rapidly (<24h) decreased the expression of downstream  $\beta$ -catenin targets myc, cyclinD1 and cyclinD2 (immunoblotting). By 20h, the combination decreased both oxidative phosphorylation and aerobic glycolysis as measured by oxygen consumption rate (OCR) and extracellular acidification rate (ECAR), respectively (Seahorse XFe96 analyser). Basal, maximal and ATP coupled OCR were significantly reduced by the combination when compared to vehicle (for OCI-My1 72.45%, 68.54% and 77.82% drop of OCR respectively). Similarly, basal glycolysis and glycolytic capacity were both reduced by the combination (80.02% and 86.09% decrease of ECAR, respectively).

*In vivo*, the combination was superior to either single drug treatment in a murine xenograft MM model. Disease burden was reduced in the combination arm compared to single drug and vehicle arms from day 14 (p=0.02) and until the last bioluminescence imaging (day 49, p<0.001) and translated into significantly prolonged OS (p=0.006). Potential on-target toxicities with BC2059 are a concern as the Wnt canonical pathway is essential for stem cell maintenance in several organs and has a role in bone homeostasis, but the combination did not result in cytopenias nor body weight loss. After euthanasia,  $\mu$ CT demonstrated that neither BC2059 nor the combination negatively affected bone morphometric indices (bone volume fraction, trabecular thickness, connectivity density). Likewise, osteoblastic activity (serum osteocalcin) was unaffected, whereas osteoclastic activity (serum CTX1) was reduced when compared to healthy mice (p=0.008).

**In conclusion** Tegavivint and Panobinostat combination may be a useful therapeutic modality for advanced/refractory MM patients warranting further evaluation.

**ALLG MM17 Trial: A response adaptive salvage strategy with Carfilzomib-Thalidomide-Dexamethasone (KTd) for Multiple Myeloma patients failing front-line Bortezomib**

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**Background:** Transplant eligible newly diagnosed multiple myeloma (TE-NDMM) patients (pts) in Australia are induced with bortezomib-based induction. ALLG MM17 was designed to evaluate an early response adaptive switch to carfilzomib-thalidomide-dexamethasone (KTd) in the 15% of TE-NDMM patients failing bortezomib induction (suboptimal response [SOR] or primary refractory [1REF]).

**Methods:** KTd was K56mg/m<sup>2</sup> on D1, 2, 8, 9, 15 and 16 of each 28-day cycle; T 100mg D1-28; and, d 40mg on D1, 8, 15, and 22 of each cycle. Pts received 4 cycles before re-staging. Those in stringent complete response (sCR) proceeded to a MEL200 ASCT. Those with <sCR received 2 more cycles before ASCT. At day 100 post-ASCT pts received 2 cycles of KTd and then continued Td out to 12 months post-ASCT. EuroFlow minimal residual disease (MRD) evaluation was undertaken sequentially before and after ASCT. The primary endpoint of the study was the overall response rate (ORR) to pre-ASCT KTd.

**Results:** Fifty pts were recruited between 9/2016 and 4/2018. Data cut-off date was November 7, 2018 with the reverse-Kaplan-Meier estimate of the median potential follow-up being 14.8 months (95% CI: 9.7 – 17.8 months). Median age was 50 years (36-71) with 72% males. Median time from initial therapy to KTd was 4 months with disease status at entry SOR in 26 (66%) (< MR n = 13, < PR n = 13) and 1REF in 13 (33%). Median number of pre-ASCT KTd cycles 6 (range 1 to 6). ORR pre-ASCT 78% (95% CI: 64-87%)- sCR 12%, CR 6%, VGPR 38% and PR 22%. On intention-to-treat 32% of pts were MRD neg pre-ASCT, 38% at day 100 post-ASCT and 52% post KTd consolidation. Neither median PFS nor OS have been reached.

**Conclusion:** An intensive KTd salvage approach produces high response rates and MRD negativity in patients failing bortezomib induction.

## Efficacy and safety of carfilzomib and dexamethasone in lenalidomide-exposed and -refractory multiple myeloma patients: combined analysis of carfilzomib trials

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**Introduction:** Once-weekly carfilzomib (K) at 70 mg/m<sup>2</sup> and twice-weekly K at 56 mg/m<sup>2</sup> in combination with low-dose dexamethasone (d) have shown a favourable benefit:risk profile for the treatment of relapsed/refractory MM. This post-hoc analysis assessed the efficacy/safety of Kd in lenalidomide-exposed and -refractory MM.

**Methods:** Individual patient data from the phase 1/2 CHAMPION-1, and phase 3 ENDEAVOR and ARROW studies were pooled to evaluate progression-free survival (PFS), overall response rate (ORR), and safety for those with previous exposure/refractoriness to lenalidomide. Patients were assigned to a group according to prior lines of therapy and previous lenalidomide exposure (Table 1).

**Results:** PFS, ORR, and safety outcomes in the pooled lenalidomide-exposed and -refractory patient populations are shown (Table 1). PFS rates at 18 months: lenalidomide-exposed patients treated with Kd in first relapse, 54.0%; lenalidomide-refractory patients treated with Kd in first relapse, 43.1%; lenalidomide-exposed patients treated in second or third relapse, 57.1%; lenalidomide-refractory patients treated with Kd in second or third relapse, 27.8%. Median K treatment duration (range) was 56.0 (4.0-213.0) months (Kd, 1 prior lenalidomide exposed), 36.6 (1.0-201.1) months (Kd, 1 prior lenalidomide refractory), 36.1 (1.1-210.7) months (Kd, >1 prior lenalidomide exposed), and 34.0 (0.1-198.0) months (Kd, >1 prior lenalidomide refractory). The incidence of treatment-emergent serious adverse events (AEs) and grade ≥3 AEs is shown in Table 1.

**Conclusion:** The Kd doublet is effective and safe in MM patients relapsing on or after treatment with lenalidomide, and for patients who are refractory to lenalidomide. Although data are limited by small sample size, the median PFS of 15.6 months for Kd in lenalidomide-refractory patients treated in first relapse is similar in magnitude to the median PFS reported for novel triplet therapy in this population.

Table 1: PFS, ORR, and safety outcomes in the pooled carfilzomib patient populations.

Population	N	Median PFS, months, (95% CI)	ORR, %	Grade ≥3 AEs, n (%) <sup>a</sup>	SAE, n (%) <sup>a</sup>
Kd, 1 prior len exposed <sup>b</sup>	39	18.3 (14.1–21.0)	89.7	33 (84.6)	20 (51.3)
Kd, 1 prior len refractory <sup>c</sup>	32	15.6 (9.6–NE)	81.3	26 (81.3)	17 (53.1)
Kd, >1 prior len exposed <sup>d</sup>	65	NR (10.3–NE)	76.9	50 (76.9)	33 (50.8)
Kd, >1 prior len refractory <sup>e</sup>	304	8.8 (7.5–11.2)	60.5	225 (74.8)	152 (50.5)

<sup>a</sup>In the 1 prior line group, 39 (len exposed) and 32 (len refractory) patients were evaluable for safety; 65 (len exposed) and 301 (len refractory) with >1 prior line were evaluable for safety.

<sup>b</sup>CHAMPION-1 and ENDEAVOR combined population with 1 prior line of therapy and len exposed but not refractory.

<sup>c</sup>CHAMPION-1 and ENDEAVOR combined population with 1 prior line of therapy and len refractory.

<sup>d</sup>CHAMPION-1, ENDEAVOR, and ARROW combined population with 2–3 prior lines of therapy and len exposed but not refractory.

<sup>e</sup>CHAMPION-1, ENDEAVOR, and ARROW combined population with 2–3 prior lines of therapy and len refractory.

AE, adverse event; CI, confidence interval; Kd, carfilzomib and dexamethasone; NE, not estimable; NR, not reached; ORR, overall response rate; PFS, progression-free survival; SAE, serious adverse event.

**A sequential cohort study comparing KappaMab alone to KappaMab, lenalidomide and low dose dexamethasone in kappa-restricted relapsed/refractory multiple myeloma (AMaRC 01-16)**

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**Aim:** To establish the clinical benefit rate (CBR) of KappaMab alone (Stage 1) and in combination with lenalidomide and low dose dexamethasone (Stage 2). To evaluate safety and survival (PFS, OS).

**Methods:** Investigator initiated, phase IIb, multi-centre, open label sequential cohort study comparing KappaMab alone to KappaMab combined with lenalidomide, dexamethasone in relapsed/refractory kappa-restricted MM, 1-3 prior lines (lenalidomide naive).

Stage 1: KappaMab (10mg/kg IV infusion) weekly for 8/52 (induction), then every 4/52 (maintenance). [One cycle: 28d]. Stage 2: KappaMab dosed as per Stage 1 plus lenalidomide (25mg D1-21) and dexamethasone (40mg weekly). In cycle 1 of Stage 2, lenalidomide and dexamethasone commenced 1/52 prior to KappaMab. [Cycle 1 only: 35d]. Treatment continued until toxicity/progression. This is a planned interim analysis of the primary endpoint (CBR).

**Results:** 54 of planned 60 patients have commenced treatment; however 40 are included in this analysis (Stage 1=19, Stage 2=21). Median 2 prior lines of therapy. 12 patients remain on study (Stage 1=1, Stage 2=11). 20 have progressed (Stage 1=14, Stage 2=6), 5 have died (Stage 1=2, Stage 2=3). Estimated median potential follow-up was 3.7m in Stage 1, and 4.9m in Stage 2.

Stage 1 observed CBR was 5% (1/19, PR=1) compared to 77% in Stage 2 (16/21, VGPR=2, PR=12, MR=2). ORR was 67% for Stage 2.

Median PFS for Stage 1 was 3.7m, compared to 6.2m for Stage 2. Median OS for both stages was not reached. 3/19 patients in Stage 1 had infusion reactions (grade 1 and 2), 4/21 patients in Stage 2 (grade 2).

**Conclusion:** KappaMab combined with lenalidomide and dexamethasone has higher than expected response rates (ORR 67%, median 2 prior lines): ORR after one prior line in the MM-009/MM-010 trials of lenalidomide, dexamethasone was 66.9%<sup>1</sup>. This novel immune-oncology combination may represent a promising new therapeutic option. Trial is ongoing.

**Reference**

E Stadtmauer et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. European Journal of Haematology 2009; 82:426-432

## **Efficacy and safety of daratumumab/bortezomib/dexamethasone (D-Vd) versus bortezomib/dexamethasone (Vd) in first relapse patients with multiple myeloma: two-year update of CASTOR**

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In CASTOR (NCT02136134), after median follow-up of 19.4 months, D-Vd reduced the risk of disease progression or death by 68% versus Vd in relapsed/refractory multiple myeloma (RRMM) patients. The progression-free survival (PFS) benefit of D-Vd was the most pronounced in patients receiving 1 prior line (PL) of therapy. Here, we present an update of CASTOR (2 years post-interim analysis), with a focus on 1 PL. Patients were randomized to receive Vd ± daratumumab. Minimal residual disease (MRD) was assessed at suspected complete response (CR), 6 and 12 months following the first treatment, and every 12 months post-CR. Sustained MRD negativity was defined as maintenance of MRD negativity at  $10^{-5}$  for  $\geq 6$  or  $\geq 12$  months. Median PFS (median follow-up: 31.3 months) was significantly prolonged with D-Vd versus Vd in intent-to-treat (ITT; D-Vd, n = 251; Vd, n = 247; 16.7 vs 7.1 months) and 1PL (D-Vd, n = 122; Vd, n = 113; 20.4 vs 8.0 months). PFS benefits for 1 PL were consistent for patients previously exposed to bortezomib or lenalidomide. Overall response rates (ORR) were significantly higher with D-Vd vs Vd in ITT (ORR: 85% vs 63%) and 1 PL (ORR: 92% vs 74%). MRD-negativity was also significantly higher for D-Vd versus Vd for ITT (14% vs 2%) and 1 PL (20% vs 3%). A greater number of D-Vd treated patients achieved sustained MRD negativity at  $\geq 6$  and  $\geq 12$  months. The most common grade 3/4 treatment-emergent adverse events (TEAEs) with D-Vd versus Vd included thrombocytopenia, anemia, and neutropenia. Rates of treatment discontinuation due to TEAEs were similar between groups. In this 2-year update, D-Vd maintains efficacy benefits in RRMM patients, with greater benefit in 1PL. The safety profile of D-Vd remained consistent. The data suggest that D-Vd for RRMM patients after first relapse may provide the greatest clinical benefit.

## Real-world treatment patterns in relapsed/refractory multiple myeloma in Australia: results from the Myeloma and Related Diseases Registry

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**Aim:** Funding restrictions affect the optimal use of novel therapies in multiple myeloma (MM). We aimed to evaluate real-world treatment patterns in relapsed/refractory MM (RRMM) in Australia.

**Method:** Data from the Myeloma and Related Diseases Registry (MRDR) was assessed for Australian MM patients who initiated a first-line therapy (1L) between 01/01/2011 and 31/12/2017. Clinical trial participants were excluded.

**Results:** Of 887 patients included, 62% were male and median age at diagnosis was 65.7y (IQR 57.6-73.0), with 32%  $\geq 70$ y. At baseline, 27% had high-risk FISH abnormalities, 30% had ISS 3, and 21% had ECOG  $\geq 2$ . Median follow-up from diagnosis was 23.9m.

1L was dominated by bortezomib-based therapy (85%), most frequently VCD (76%). 2L was most commonly thalidomide-based (39%) and lenalidomide-based (30%), with lenalidomide-based regimens becoming predominant from 2018. See Table 1.

Only 5% of 2L incorporated carfilzomib (11% of 2L initiated following reimbursement on Australia's Pharmaceutical Benefits Scheme in January 2018), and 7% of 3L incorporated pomalidomide (8% of 3L initiated post-reimbursement in August 2015).

Following front-line PI use, a switch to an IMiD in 2L was most common (Table 2).

**Table 1.** Treatment regimen by line of therapy. **Table 2.** Treatment sequencing in RRMM.

Therapy, n	1L	2L	3L	4L	5L
Bortezomib +/- non-IMiD	887	310	121	46	20
Bortezomib + IMiD	758	49	20	5	4
Bortezomib + IMiD	13	8	1	0	0
Carfilzomib +/- non-IMiD	4	8	8	7	8
Carfilzomib + IMiD	0	8 <sup>^</sup>	3	4	0
Ixazomib +/- IMiD	0	6	7	1*	1
Thalidomide +/- non-PI	72	121	12	3	0
Lenalidomide +/- non-PI	30	92	54	8	3
Pomalidomide +/- non-PI	0	1	8	10	2
mAb +/- IMiD	0	2	0	3	1
Other regimens	10	15	8	5	1
Excluded due to clinical trial participation, n	58	46	14	5	0

IMiD: immunomodulatory drug  
 PI: proteasome inhibitor  
 mAb: monoclonal antibody  
<sup>^</sup>: 1/8 received pomalidomide concomitantly  
<sup>\*</sup>: 1/1 received pomalidomide concomitantly

1L and 2L		3L					Total No.
1L	→ 2L	NI	PI	IMiD	PI + IMiD	OTHER	
PI	→ IMiD	→ 115	20	48	6	4	193
PI	→ PI	→ 25	3	11	1	2	42
PI	→ PI + IMiD	→ 14	1	5	1	1	22
IMiD	→ IMiD	→ 14	1	2	0	0	17
IMiD	→ PI	→ 6	1	5	1	0	13
OTHER	→ OTHER	→ 15	2	3	2	1	23

OTHER: Other regimens

Autologous stem cell transplant was performed in 71% of patients  $< 70$ y in 1L, 22% in 2L, and 6% in 3L.

Overall response rates ( $\geq$ PR) decreased in later lines of therapy (83% in 1L, 55% in 2L, and 37% in 3L). Median overall survival was 59.3m from 1L initiation, 29.4m from 2L, and 17.4m from 3L.

**Conclusion:** Few Australian MM patients are treated beyond 2L and therefore fail to access newer agents. Given later lines of therapy yield diminishing gains, earlier utilisation of optimal regimens incorporating novel agents for MM is urgently warranted.

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O052

**AML: Next generation game changers**

**Chun Fong**<sup>1</sup>

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The advent and application of next generation sequencing technologies has unlocked game changing opportunities to improve patient outcomes. These technologies have not only identified therapeutic vulnerabilities but have also enabled novel approaches to monitoring of therapeutic efficacy. Furthermore, developments in therapeutic options have fed back as part of translational research to drive scientific discovery. Now, more than ever, we are closer to realisation of personalised precision oncology in AML.

An explosion in the availability of novel therapies has increased the complexity of therapeutic choices in AML. Agents which target aberrant kinase signalling, apoptosis and epigenetic mechanisms of disease along with new agents packaging old drugs and agents harnessing the immune system have come into routine use in the last 5 years. Currently available therapeutic agents in the Australian context will be reviewed and a look forward to upcoming therapeutic opportunities undertaken.

O053

## The molecular landscape of AML

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The last ten years deciphered most of molecular landscape of AML. In addition to well-known techniques such as cytomorphology and immunophenotyping and standard chromosome banding analysis we now learned a lot from molecular investigations. This includes sequencing of single genes, gene panels, exomes, genomes and the use of gene expression profiling including whole transcriptome sequencing (WTS).

All these findings now not only allow us to draw a more or less complete picture of the molecular background of AML but lead to sophisticated investigations at diagnosis and to the situation that more or less every AML patient has his or her own molecular profile. Furthermore, several new treatment options address targets now defined by our diagnostic techniques.

In addition to the well-known example of *PML-RARA* we now can apply specific drugs against *KIT*, *IDH1* and *IDH2*, *FLT3*-ITD and -TKD, *SF3B1* and a lot of antibodies targeting structures like CD33 and others. Many of these drugs have been approved by the FDA in the last five years and can be applied not only in relapse but also in first line treatment making short turn-around times at diagnosis necessary. Furthermore, many of these markers (not only fusions genes) can be used for minimal residual disease (MRD) leading to even more specific guidance in treatment. To answer the question if the patient will benefit from allogeneic transplantation today is therefore much more difficult than ten years ago. Targeted treatment approaches and MRD have to be taken into account before decision making.

This all demonstrates that AML is with its complexity but also with all its options at diagnosis and more and more targeted treatments an important example, how diagnosis and treatment evolved very rapidly in hematology in the last ten years for better treatment and higher cure rates.

O055

## **Evolution of post-transplant maintenance therapy in myeloma**

**Sarah Holstein**

Consolidation with high dose melphalan and autologous stem cell transplant (ASCT) remains a standard of care for younger myeloma patients following completion of induction therapy. While inclusion of ASCT improves progression-free survival, it is recognized that nearly all patients will eventually relapse. The goal of post-transplant maintenance therapy is to prolong time to progression and improve overall survival. In this session, an overview will be provided regarding the data for immunomodulatory drug- and proteasome inhibitor-based maintenance strategies. Inclusion of novel agents such as monoclonal antibodies into the maintenance setting will be discussed.

O057

## **How I treat CRS and neurotoxicity**

**Cameron Turtle**<sup>1</sup>

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Lymphodepletion chemotherapy followed by infusion of T cells that are genetically modified to express a chimeric antigen receptor (CAR) targeted to CD19 is a novel therapy for patients with relapsed and/or refractory B cell acute lymphoblastic leukemia, non-Hodgkin lymphoma, and chronic lymphocytic leukemia. CD19 CAR-T cell immunotherapy can be complicated by severe toxicities, including cytokine release syndrome (CRS) and neurotoxicity. In this session, we will review clinical features and grading of CRS and neurotoxicity and discuss management strategies.

## **Minimal Residual Disease Correlates with Outcome in Previously Untreated Follicular Lymphoma Patients Treated with Obinutuzumab- or Rituximab-Based Immunochemotherapy (GALLIUM)**

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**Aim:** To evaluate the correlation between minimal residual disease (MRD) response at end of induction (EOI) and updated progression-free survival (PFS) data in previously untreated follicular lymphoma (FL) patients treated with obinutuzumab (G)- versus rituximab (R)-based chemotherapy in the GALLIUM study (NCT01332968).

**Methods:** Eligible patients were randomized 1:1 to 6-8 cycles of G (1000mg intravenous on days [D]1, D8, and D15 of cycle [C]1 and D1 of C2-6 or C2-8) or R (375mg/m<sup>2</sup> intravenous on D1) plus chemotherapy (CHOP, CVP, or bendamustine). Responders continued to receive the same antibody every 2 months for up to 2 years, as maintenance. MRD status was assessed by real-time quantitative-polymerase chain reaction analysis at mid-induction, EOI, 4-monthly during maintenance, end of maintenance and 6-monthly during follow-up in peripheral blood; and in bone marrow at only EOI. Investigator-assessed PFS was estimated using Kaplan-Meier methodology (cut-off February 2018).

**Results:** Out of 1202 randomized FL patients, 634 were MRD evaluable at EOI. With 57-months median follow-up, MRD-negative responders at EOI (n=564) continued to have a longer PFS (HR 0.38; 95% CI:0.26-0.56; p<0.0001) in pooled treatment arms. For patients who continued on maintenance treatment, MRD-negative response was observed at EOI in 300/324 (92.6%) patients in the G-arm versus 264/310 (85.2%) patients in the R-arm (p=0.0034). The rate of conversion to MRD positivity was consistent in both G (6.3%) and R (6.1%) maintenance; the majority sustained MRD-negative responses throughout the maintenance period (G: 67.0%; R: 63.2%). Of the MRD-positive patients at EOI who were eligible (according to clinical response) for maintenance, 22/24 (92%) in the G-arm and 36/46 (78%) in the R-arm achieved MRD negativity during maintenance. Twelve patients never achieved an MRD response.

**Conclusions:** In this updated analysis, the prognostic value of MRD status at EOI has been confirmed, in previously untreated FL patients receiving immunochemotherapy.

**Acknowledgment:** This work was funded by F. Hoffmann-La Roche Ltd. Editorial assistance was provided by Joseline Ojaimi, PhD, from Roche Products, Pty. Limited.

## **Baseline SUVmax Did Not Predict Histological Transformation from Follicular Lymphoma to Aggressive Lymphoma in the Phase III GALLIUM Study**

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**Aim:** To assess the relationship between the baseline maximum standardized uptake value (bSUVmax) and histological transformation (HT) into aggressive lymphoma in follicular lymphoma (FL) patients in the GALLIUM study (NCT01332968).

**Methods:** Eligible patients in GALLIUM (n=1202) were randomized 1:1 to receive obinutuzumab (GA101; G)- or rituximab (R)-based immunochemotherapy. Responders continued to receive the same antibody every 2 months for up to 2 years, as maintenance. The primary endpoint was investigator-assessed progression-free survival. The degree of 18-fluorodeoxyglucose (FDG)-avidity measured using SUVmax was an exploratory endpoint and was assessed by an independent review committee for patients with a baseline FDG-positron emission tomography scan.

**Results:** bSUVmax data were available for 522 patients. After a 59-month median follow-up, 13 (2.5%) patients experienced biopsy-confirmed HT to diffuse large B-cell lymphoma or Grade 3b FL. The median age of HT patients was 61 years. HT patients had poorer Eastern Cooperative Oncology Group performance status (ECOG PS 2: 15.4% vs 2.6%) and were more likely to present with a high-risk FL International Prognostic Index (FLIPI) score (61.5% vs 40.3%) and with bone marrow involvement (76.9% vs 52.9%) in comparison to patients without HT. bSUVmax >10 was reported in >65% patients; very few (2.9%) of these patients experienced HT (median [range] bSUVmax: 12.4 [8.14, 27.95] for HT vs 11.8 [3.05, 64.43] without HT). The median (range) baseline SUVrange (bSUVrange), as defined by the difference between bSUVmax of the most and least FDG-avid lymphoma sites, was 6.6 (1.08, 23.91) for HT vs 7.14 (0.00, 59.81) without HT.

**Conclusions:** Although bSUVmax >10 was common in patients with previously untreated FL, it was rarely associated with HT within 6 years of follow-up in the GALLIUM study. bSUVmax and bSUVrange do not appear to predict HT, which questions the benefit of a re-biopsy of lesions to exclude HT prior to initiating therapy.

**Acknowledgment:** This work was funded by F. Hoffmann-La Roche Ltd. Editorial assistance was provided by Joseline Ojaimi, PhD, from Roche Products, Pty. Limited.

O062

## **The use of Bendamustine and infection rates – Retrospective analysis in Western Australia**

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### Introduction:

Bendamustine in combination with monoclonal CD20 antibody is indicated for first-line therapy for indolent lymphoma with superior PFS compared with CHOP. Initial clinical trials suggest improved toxicity profile with reduced infection rates, however a recent study demonstrated increased deaths from infection associated with bendamustine. We reviewed patients in two centres in WA to evaluate the incidence of Infections during treatment with bendamustine for indolent lymphoma.

### Method:

Retrospective analysis of patients receiving bendamustine from 2015 to 2019. Primary outcome was infection requiring hospital admission. Secondary outcomes were types of infection and tolerability of treatment. Statistical analysis was performed with Fisher's exact test.

### Results:

101 patients were included in analysis with median follow-up of 32 months. Median age was 74.5 years. Infection rate was 50.5% (N=51) with half of infection occurring during treatment. Infections were predominantly pulmonary in nature with two patients developing pneumocystis pneumonia. 13 patients did not complete treatment secondary to infective complications. No difference in infection rates between age <70 vs ≥70 (p=0.175) was detected.

### Conclusion:

Overall, bendamustine was associated with high risk of infection requiring hospitalisation without a difference in incidence between age groups, and required treatment cessation in 13%. We recommend careful patient selection when using bendamustine and immunotherapy in treatment of indolent lymphoma.

### References:

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## Interim PET in DLBCL strongly predicts survival outcomes and is independent of clinical prognostic indexes and biological markers

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### Aim

The prognostic value of interim PET (iPET) in DLBCL remains unclear. The optimal timing and PET parameters e.g.  $SUV_{max}$ , Deauville score, and total metabolic tumour volume (TMTV) have not been established. We aim to explore which iPET parameters best predict survival outcomes independent of the clinicopathological prognostic scores.

### Method

In our retrospective study, we included all *de novo* DLBCL cases since 2012 staged with a baseline PET, at least one iPET and 12 months of follow-up. Baseline PET scans were assessed for TMTV. iPET parameters collected were Deauville scores (1-3 vs. 4-5) and reduction in  $SUV_{max}$  from baseline PET (iPET2  $\Delta SUV_{max} >66\%$  vs.  $\leq 66\%$  and iPET4  $\Delta SUV_{max} >73\%$  vs.  $\leq 73\%$ ).<sup>1-2</sup> Clinicopathological data including NCCN-IPI, IHC expression of MYC/BCL2 (DE) and cell-of-origin (COO) by Hans algorithm was also collected.

### Result

196 iPET scans (140 iPET2 and 56 iPET4) were analysed from 152 patients. Median follow up duration was 30.4 months. Estimated 2-year PFS and OS for the whole cohort were 67.1% and 82.5% respectively. At baseline, NCCN-IPI  $\geq 4$  and TMTV  $\geq 298$ ml (cohort's median) but not DE or COO, were prognostically significant on univariate analysis for PFS and OS. In contrast, both Deauville scores  $\geq 4$  and lower  $\Delta SUV_{max}$  at iPET2 and iPET4 were prognostically significant. Patients with residual disease on iPET2 who subsequently achieved complete remission (CR) on iPET4 (n=10) had an estimated 2-year PFS of 100%. Those patients failing to achieve CR by iPET4 (n=29) had 2 year PFS and OS of 41.9% and 52.2% respectively. Baseline TMTV  $\geq 298$ ml and iPET4  $\Delta SUV_{max} \leq 73\%$  were independent prognostic factors on multivariate analysis for PFS and OS (Table 1).

### Conclusion

$\Delta SUV_{max}$  at iPET4 was independently prognostic for both PFS and OS. Patients with residual disease at iPET2 who subsequently achieve CR by iPET4 have excellent outcomes.

**Table 1. Cox Multivariate regression analysis of survival outcomes**

	Progression Free Survival			Overall Survival		
	HR	95% CI	P	HR	95% CI	P
NCCN IPI score $\geq 4$	1.0	0.6 – 4.4	0.994	5.8	1.2 – 27.6	0.028*
Baseline TMTV $\geq 298$ ml	23.5	3.4 – 160.0	0.001*	6.0	1.2 – 29.9	0.028*
iPET2 $\Delta SUV_{max} \leq 66\%$	1.1	0.3 – 3.6	0.921	3.2	0.8 – 12.6	0.101
iPET4 $\Delta SUV_{max} \leq 73\%$	31.0	5.2 – 186.2	0.000*	8.0	1.8 – 35.4	0.006*

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## Deliverability and safety analysis of Australasian Leukaemia & Lymphoma Group NHL29 (IRiC): A phase II Study of Ibrutinib, Rituximab and mini-CHOP, in patients aged $\geq 75$ yrs with newly diagnosed DLBCL

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**Aims:** The optimal treatment strategy for very elderly pts with DLBCL remains unclear. This is a prospective Phase II study of ibrutinib-R-mini-CHOP in pts  $\geq 75$  yrs with newly diagnosed DLBCL conducted at 21 Australian sites. The aims are to assess the safety and efficacy of ibrutinib-R-mini-CHOP measured by deliverability, and 2 yr overall survival. Deliverability results are presented here.

**Methods:** Pts received six 21-day cycles of ibrutinib 560mg daily and R-mini-CHOP (Rituximab 375mg/m<sup>2</sup>, cyclophosphamide 400mg/m<sup>2</sup>, doxorubicin 25mg/m<sup>2</sup>, vincristine 1mg on day 1 & prednisone 40mg/m<sup>2</sup> or 100mg/d x 5) followed by an additional two 21 day cycles of rituximab + ibrutinib (or high dose methotrexate for CNS prophylaxis). Deliverability is measured using Average Relative Total Dose (ARTD), [Average delivered dose of the chemotherapy regimen as a % of the target dose] and Average Relative Dose Intensity (ARDI), [Average delivered dose of the chemotherapy regimen per unit time (week) as a % of the target dose intensity].

**Results:** 80 pts were recruited Nov 2015-Dec 2018, with the last completing 6 cycles by data cut-off 20 May 2019 and median follow-up 13.1 months. One death from sepsis occurred during pre-phase prednisone. 79 are included in the deliverability analysis. Baseline demographics are shown in Table 1. 77% received 6 cycles R-mini-CHOP with ARTD & ARDI presented in Table 2. 30% (24/79) pts discontinued treatment. 62% pts experienced an SAE. Most common AEs were infections & diarrhoea (majority grade 1-2). 28% (22/80) pts have died.

**Conclusions:** In this very elderly cohort, most pts completed 6 cycles of R-mini-CHOP.

A high ARTD and ARDI of both immunochemotherapy and ibrutinib was maintained. With the caveat of notable toxicity consistent with the profile of these agents, ibrutinib in combination with R-mini-CHOP appears deliverable in this pt cohort. We await 2yr follow-up to answer our overall survival endpoint.

Table 1: Baseline Demographics

Sex	Male	39 (49%)
	Female	40 (51%)
Median Age at Registration (years)		81 (Range 75-95)
Ann Arbor Classification	Stage I (bulky)	1 (1%)
	Stage II	14 (18%)
	Stage III	17 (22%)
	Stage IV	47 (59%)
IPI Score	Low Risk (1)	9 (11%)
	Low-Intermediate Risk (2)	20 (25%)
	High Intermediate Risk (3)	23 (29%)
	High Risk (4&5)	27 (34%)
Length of follow-up (months), mean (SD)		14.6 (10.3)
Length of follow-up (months), median (IQR)		13.1 (5.5, 23.0)
Length of follow-up (months), (min, max)		(0.2, 36.9)

Table 2: ARTD and ARDI

Based on 6 Cycles of I-R-mini-CHOP	Median ARTD % (IQR)	Median ARDI % (IQR)	Mean ARTD % (SD)	Mean ARDI % (SD)
Entire Regimen	97.3 (81.9, 99.8)	97.2 (87.8, 99.8)	85.7 (24.3)	93.7 (8.5)
Rituximab	100.2 (93.8, 104.2)	99.5 (94.6, 103.5)	90.6 (25.6)	98.2 (9.3)
Chemotherapy (mini-CHOP)	97.3 (81.9, 99.8)	98.0 (91.6, 100.6)	85.7 (24.3)	95.3 (7.9)
Cyclophosphamide & doxorubicin combined	99.2 (83.5, 101.0)	99.1 (94.0, 101.1)	87.4 (24.4)	96.1 (8.4)
Ibrutinib	97.6 (62.7, 100.0)	97.1 (78.2, 100.0)	77.3 (33.5)	77.7 (53.7)

ARTD: Average Relative Total Dose

ARDI: Average Relative Dose Intensity

## Correlative analyses of cytokine release syndrome and neurological events in tisagenlecleucel-treated relapsed/refractory diffuse large B-cell lymphoma patients

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**Aim:** To report 24mo clinical update and correlations between cytokine release syndrome (CRS)/neurological events (NE) and inflammatory/laboratory analyte markers in JULIET.

**Method:** JULIET is a phase 2 trial of tisagenlecleucel in adult patients with relapsed/refractory diffuse large B-cell lymphoma. Primary endpoint was overall response rate (ORR). Peak ( $\leq 1$  mo of infusion) serum cytokine levels/lab parameters were correlated with rate/grade (gr) of CRS (Penn scale) and NE (CTCAE v4.03) within 8wk post-infusion.

**Result:** As of 11 Dec 2018, 115 patients were infused (99 evaluable for efficacy). ORR remained 54% (complete response [CR], 40%); median duration of response was not reached. Median overall survival was 10.3mo (not reached for patients in CR). Grade 3/4 CRS and NE occurred in 23% and 11%, respectively. 83% patients with NE had CRS; 62% patients with severe NE had severe CRS. Peak cytokine levels within 1mo of infusion were increased in patients with CRS/NE and the trend was more noticeable in patients with severe CRS/NE. Higher CRP, ferritin, interferon- $\gamma$ , IL2, IL6, and IL10 were observed in patients with severe CRS; severe NE showed similar trends of a lesser degree, except for interferon- $\gamma$ . In patients with CRS, cytokines peaked on d6-9, with early increase of IL2, IL6, interferon- $\gamma$  in the first 2d post-infusion with severe CRS. Low platelet count, elevated LDH, and below-normal albumin levels occurred after lymphodepleting chemotherapy; these trends continued in patients with severe CRS. As CRS progressed, hepatic and kidney dysfunction-related analytes trended toward an increase, peaking 2wk post-infusion in patients with severe CRS. Univariate/multivariate analyses correlating inflammatory/laboratory analytes with CRS/NE severity will be presented.

**Conclusion:** With almost 24mo maximum follow-up, tisagenlecleucel continued to demonstrate durable efficacy. Severe NE appeared to correlate with severe CRS. Trends in peak levels of several markers were noted with severe CRS and—to a lesser extent—severe NE.

**Table.** Number of patients with coincidence of CRS and NE in the JULIET trial

	N=115	Any grade NE (n=23/115)	Grade 3/4 NE (n=13/115)
No CRS	49	4	3
Grade 1/2 CRS	40	6	2
Grade 3 CRS	17	6	2
Grade 4 CRS	9	7	6
Any grade CRS	66	19	10

## Utilisation of liquid biopsies in 'functional' high-risk multiple myeloma (MM) demonstrates a unique mutational pattern and extensive spatial heterogeneity

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**Background:** Utilising a targeted amplicon sequencing (TAS) strategy we evaluated liquid biopsies and bone marrow (BM) biopsies to characterise the mutational landscape and extent of spatial heterogeneity (SH) in 'functional' high-risk (HR) MM patients.

**Methods:** 50 patients failing bortezomib-based induction who received carfilzomib-based salvage were studied. DNA from PBMC, BM CD138 enriched plasma cells and plasma(PL)-derived cell free(cf)DNA was evaluated with customised TAS. Mutational fractional abundance (FA) was defined as the relative frequency of a mutant allele at a locus expressed as a percentage. Mutation specific ddPCR was undertaken on cfDNA using commercially available assays. Minimal residual disease (MRD) analysis utilized EuroFlow.

**Results:** 49 patients had evaluable cfDNA (median 3 PL mutations [PLM], range, 0-10) with matched BM from 33 patients (median 4 mutations, range, 0-15). The most prevalent PLM (% patients) were CDC27 (23%), DIS3 (16%), KRAS (16%), PIK3CA (9%) and MAX (9%) with FA from 0.3-50.1% (median 1.25%), with 4 PLM clones with FA>40% (DIS3 50.1%, PIK3CA 46.5%, KRAS 45.2%, CYLD 40.3%). TAS of BM didn't demonstrate 73% of these dominant PLM (including 3 of the 4 clones with FA>40%), consistent with extensive SH. Five patients with RAS PLM who achieved MRD negativity ( $<1 \times 10^{-5}$ ) were tracked with ddPCR - 3 cleared their PLM but 2 had persisting PLM discordant with BM MRD negativity. One developed extra-medullary relapse and rising NRAS Q61R FA (0.1% to 0.9%) 2 months-post-salvage. The other remains clinically in remission with a rising NRAS Q61R FA (0.3% to 0.6%).

**Conclusions:** These data reveal a unique mutational pattern in HR MM including deleterious mutations of CDC27 and targetable mutations of PIK3CA. CDC27 modulates cell cycling via the ubiquitination of CCND1 and its role in HR MM warrants further evaluation. Importantly, extensive SH questions the utility of BM sampling for disease characterization in HR MM.

## **Circulating tumour DNA analysis for NRAS/KRAS/BRAF mutations in Multiple Myeloma**

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### **Background**

Circulating tumour-derived cell-free DNA (cfDNA) is emerging as a powerful non-invasive biomarker of disease status in many haematological malignancies. The most common somatic recurrent mutations found in Multiple Myeloma (MM) have been demonstrated within the NRAS, KRAS and BRAF genes. In this feasibility pilot study, a cross-sectional analysis for tumour related cfDNA(ctDNA) for specific KRAS(Q61H)/NRAS(Q61R) and BRAF(V600E) mutations via digital droplet PCR analysis(ddPCR) was undertaken.

### **Methods**

9mL whole blood EDTA was collected from 48 consenting patients. Plasma separation was completed via two-step centrifugation and within four hours of venous collection. Extraction of cfDNA from 3mL of plasma was completed utilising the QIAamp Circulating Nucleic Acid Kit(Qiagen). The quantitation of specific KRAS/NRAS/BRAF mutations was determined via ddPCR. Matched bone marrow samples were obtained in 12 patients.

### **Results**

64 cfDNA samples were collected from 48 patients with plasma cell dyscrasia at different stages of disease progression (Smouldering MM: n=5; Previously treated MM: n=31; Newly diagnosed MM: n=12). Range of cfDNA obtained varied from 6.8ng/mL of plasma to 627ng/mL of plasma. Interim results are presented: NRAS Q61R mutation was the most prevalent mutation within this patient cohort (10% mutation positive; n=15). BRAF and KRAS mutations were identified at a significantly lower frequency at 3% (1/36) and 2% (1/42) respectively. Bone marrow results were concordant for all samples tested. Sequential ctDNA mutation monitoring was completed in 4 patients; 75% of these patients demonstrated correlation of ctDNA levels with conventional biomarkers. One patient identified with rapidly increasing BRAF mutation levels was otherwise in clinical remission with undetectable conventional biomarkers of disease at time of sampling.

### **Conclusions**

This study adds to the literature supporting utilisation of ctDNA as an additional method for mutational characterisation for MM. In addition, it provides support for ctDNA as an adjunct non-invasive biomarker in treatment monitoring in MM.

## **DNA-repair gene mutations are prevalent in circulating tumour DNA from advanced multiple myeloma patients**

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**Background:** In this study, MM mutational characterisation was performed on bone marrow (BM) MM cell DNA and peripheral blood plasma (PL)-derived circulating tumour(ct)DNA from both newly diagnosed (ND) and relapsed/refractory (RR) patients to investigate if predominant mutations in advanced MM can be identified through PL ctDNA analysis.

**Methods:** Paired (ND = 24; RR = 52) BM MM cell DNA (CD138 selected) and ctDNA was evaluated for mutations in KRAS, NRAS, BRAF and TP53 using the 96-mutation OnTarget™ Mutation Detection (OMD) platform. Correlations between PFS/OS and the number/type of mutations and the tumour burden (expressed as the fractional abundance [FA] - relative frequency of a mutant allele at a locus, expressed as a percentage) were evaluated. These results were validated utilizing targeted amplicon sequencing (TAS) of 36 paired BM and PL samples (ND = 5; RR = 31) for RAS-RAF (KRAS, NRAS and BRAF) and DNA damage-repair genes (DDR) (TP53, ATM and ATR). Statistical analyses were performed with GraphPad Prism V7.

**Results:** OMD analysis revealed that RRMM had more mutations in the PL than NDMM (mean 0.94 vs 0.19, respectively,  $p=0.0002$ ) with 36.5% of RRMM harbouring PL-specific mutations compared to only 8.3% in NDMM. Patients with >2 PL-mutations or a >1% FA had shorter OS ( $p=0.04$  and  $p=0.0006$ , respectively). Patients with PL-specific TP53 mutations had shorter OS compared to patients without PL-TP53 mutations ( $p=0.003$ ). TAS confirmed the presence of PL-specific variants in 91.7% of patients, recapitulating the OMD findings. DDR mutations were more frequent in the PL when compared to RAS-RAF mutations ( $p=0.0095$ ) with 16% of the patients demonstrating PL-specific DDR mutations but only 2.5% of patients with PL-specific RAS-RAF mutations

**Conclusion:** ctDNA analysis captures the spatial heterogeneity and provides prognostic information in advanced MM, and identifies more potentially actionable DDR mutated sub-clones compared to BM analysis.

## **Patient-reported outcome measures in multiple myeloma: real-time reporting to improve care (My-PROMPT) - a pilot randomised controlled trial**

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**Aim:** Multiple myeloma (MM) carries a high burden of disease, which compromises health-related quality of life (HRQOL). Whether using patient-reported outcome measures (PROM) in routine care improves HRQOL in MM is unknown. To design a trial to assess impact of real-time PRO reporting on outcomes, feasibility and acceptability to clinicians and patients of such an intervention needed evaluation.

**Method:** We performed a pilot randomised controlled trial in newly diagnosed MM for this purpose. Intervention patients completed a disease-specific PROM (MyPOS) before 4 clinic visits (T1-4): baseline, 1, 6 and 10 months. Clinicians received a MyPOS summary before visits. Control arm patients completed MyPOS at T1 and 4. Patients completed evaluations of this intervention at T3 and clinicians after T1, 2 and 3. Primary feasibility outcomes were median patient and clinician satisfaction scores. Secondary outcomes included change in HRQOL (T1 to 4) between arms. Descriptive statistics were used to summarise results.

**Results:** We enrolled 32 patients, 16 per arm. Trial arms were well matched other than more males in controls (81 v 25%). Patients' median satisfaction score for MyPOS use was 5 (1=Not at all satisfied, 5=Very satisfied, n=12), and median for 15 clinicians (T1 to 3 visits, n=39) was 85 (1=Not at all satisfied, 100=Very satisfied). Patients: 92% felt MyPOS helped convey concerns to doctors, 75% indicated doctors discussed MyPOS result at visits, 92% felt comfortable answering the questions. Doctors: 80% used MyPOS result to discuss patient concerns, and for 83% it had reduced or had minimal impact on visit duration. There was no significant difference in change in median total MyPOS score between groups, however, the study was not powered to detect this. Males had greater reduction in MyPOS score than females (p=0.015). Median reduction in subscale scores was greater in intervention v controls but not significant.

**Conclusion:** Findings support feasibility and acceptability of real-time reporting of PROM to clinicians and will inform design of a randomised controlled trial powered to assess impact on health benefits and HRQOL.

## Pacific Islanders with multiple myeloma are younger and have inferior survival when compared to other ethnicities: a study from the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR)

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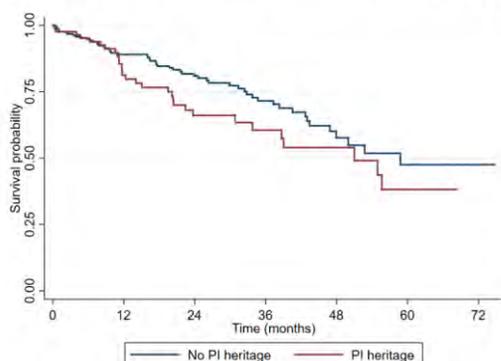
**Aim:** To compare demographics and outcomes of patients with multiple myeloma (MM) in New Zealand (NZ) who have Pacific Islander (PI) ethnicity to the rest of the NZ MM MRDR cohort.

**Method:** PI ethnicity included those with  $\geq 1$  grandparent of Melanesian (including Fijian) or Polynesian (including Maori) heritage. Of 377 NZ MM patients (Sep 2012-Apr 2019), 90 met PI criteria, 59 had unknown ethnicity, leaving 228 controls (mostly European). We calculated overall survival (OS) with Kaplan-Meier methods.

**Results:** PI patients were younger (median age 63 [IQR: 57-72] v 70y [64-77],  $p < 0.001$ ) had poorer ECOG score (ECOG  $\geq 2$ : 17 v 31%,  $p = 0.02$ ) and higher median BMI (32 [27-37] v 27 kg/m<sup>2</sup> [24-30],  $p < 0.001$ ) at diagnosis than controls. Diabetes (22 v 6%,  $p < 0.001$ ) and renal insufficiency<sup>1</sup> (13 v 6%,  $p = 0.04$ ) were more common in PI than controls. PI were more likely to have abnormal karyotype than controls (41 v 22%) including t(4:14) (15 v 7%,  $p = 0.04$ ) and del(13q) (10 v 3%,  $p = 0.04$ ). Fewer PI received anti-myeloma drug therapy (84 v 93%,  $p = 0.01$ ) and there was a trend for shorter OS in PI (HR 1.47 [CI: 0.94-2.29],  $p = 0.09$ ). However, age-adjusted OS was significantly shorter for PI versus controls (HR: 2.0 [1.3-3.2],  $p < 0.001$ ). When adjusted for age and (not) receiving anti-myeloma drugs, PI still had significantly shorter OS (HR 1.68 [1.05-2.71],  $p = 0.03$ ). The same held when non-recipients of myeloma drug therapy were excluded (HR for PI: 1.89 [1.13-2.16],  $p = 0.016$ ).

**Conclusions:** PI patients with MM are younger, more co-morbid and more commonly have adverse karyotype at diagnosis than non-PI MM. Moreover, PI with MM have significantly inferior OS, even after adjustment for age and (not) receiving anti-myeloma drugs. Investigation of modifiable factors to improve outcomes for PI with MM, and to elucidate reasons why MM occurs at a younger age in PI is urgently required.

**Figure 1. Unadjusted graph for overall survival: PI versus Control group.**



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## Patients with Multiple Myeloma over a Large Catchment of 2.5 Million Square Kilometres – A Western Australia retrospective survival review

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There has been concern that patients with malignant disease from regional areas may have adverse outcomes compared with those from cities. Western Australia (WA) with an area of 2,526,786 square kilometres, is one third the size of Australia. It has a population of 2.6 million of which 92% live in the capital city Perth and the southwest corner.

While oral based immunomodulators and alkylators are readily delivered in the regional areas, country patients with multiple myeloma travel to Perth for parenteral chemotherapy and stem cell transplantation. The WA state government subsidizes various support services such as TeleHealth and Patient Assisted Travel Scheme (PATS). A single publicly funded pathology provider, PathWest, services most major district centres in regional WA. Various not-for-profit organisations, such as Leukaemia Foundation and Royal Flying Doctors, also provide accommodations in Perth and medical transfer services.

We retrospectively reviewed the survival outcomes of patients with multiple myeloma in the WA public healthcare system, to gain real-life survival insight of an Australian-based population. Patients diagnosed between 2008 to 2017 were included (n=568). Patients diagnosed and/or followed-up in the private sector were excluded. Overall median survival was 47 months (95% confidence intervals: 42 to 54 months). Median survival of respective R-ISS are stage 1 (n=159) 84 months, stage 2 (n=227) 51 months, stage 3 (n=107) 24 months.

Patients were segregated into either metropolitan or regional areas by their residential address postcodes. No hot spot of incidence has been observed in regional WA districts.

	Metro Perth	Regional WA
N	426 (75%)	142 (25%)
Median survival (95% confidence interval)	51 months (43-57)	42 months (33-56)

Using multivariate Cox proportional hazards model, there is no statistical difference between survival of patients living in regional areas and metropolitan Perth (hazard ratio 0.80, p= 0.08)

## **PDI regulation of Mac-1 function in neutrophils by cleavage of disulphide bonds**

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### **Background/Aim**

Neutrophils are critical to the development of thrombo-inflammation; neutrophil adhesion to inflamed endothelium via cell surface receptors, such as integrin Mac-1, potentiates atherosclerosis whereas neutrophil-platelet aggregates cause microvascular infarction in ischemia-reperfusion injury. Thiol isomerases, including protein disulphide isomerase (PDI), are circulating enzymes, which control neutrophil adhesion to inflamed endothelium and can be potentially targeted to reduce thrombo-inflammation. The aim of this study is to determine the mechanism by which PDI regulates neutrophil function.

### **Methods**

Using mass spectrometry, we measured the redox state of the disulphide bonds in recombinant Mac-1 with or without PDI. Baby hamster kidney (BHK) cells were transfected with wild type Mac-1 or Mac-1 with mutated disulphide bonds. Human neutrophils were isolated from healthy donors, stimulated with fMLF peptide, and subjected to cell adhesion using immobilised fibrinogen without or with PDI inhibitor isoquercetin. Using a transgenic zebrafish line, that stably expresses GFP in neutrophils, wounding assays were performed in zebrafish embryos pre-incubated without or with isoquercetin and the number of neutrophils recruited to the site of injury was determined.

### **Results**

We mapped 21 of the 28 disulphide bonds in  $\beta 2$  subunit of Mac-1 and found that two disulphide bonds near the ligand binding pocket, Cys169-Cys176 and Cys224-Cys264, were -cleaved by PDI. BHK cells expressing Mac-1, with cysteines 169, 176 or 224, 264 mutated to alanines, showed decreased binding to fibrinogen compared to wild type Mac-1. Inhibition of PDI by isoquercetin significantly decreased the velocity of fMLF stimulated neutrophils crawling on fibronectin, under shear rate of 100 s<sup>-1</sup>, *in vitro* and significantly decreased neutrophil recruitment to the site of injury in zebrafish embryos *in vivo*.

### **Conclusion**

Our data indicates that PDI reduction of disulphide bonds 169-176 and 224-264 in Mac-1 enables cell de-adhesion from ligand to promote neutrophil migration during inflammation.

## Diversification of the T cell repertoire following AHSCT is underpinned by thymic derived naïve T cells in patients with aggressive relapsing remitting multiple sclerosis.

Jennifer Massey<sup>1</sup>, Brendan Hughes<sup>2</sup>, Katherine Jackson<sup>3</sup>, Mandeep Singh<sup>3</sup>, Barbara Withers<sup>1</sup>, Sam Milliken<sup>1</sup>, Fabio Luciani<sup>2</sup>, Ian Sutton<sup>1</sup>, David Ma<sup>1</sup>, **John Moore<sup>1</sup>**

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**Aim:** AHSCT is a highly effective immune reconstitution therapy for patients with aggressive relapsing remitting multiple sclerosis (RRMS). It is believed that AHSCT results in an immunotolerant state through deletion of pathogenic clones and regeneration of a diversified T cell repertoire, however data to support these postulations is limited. This study aims to define the T cell subsets driving lymphocyte diversification and uses TREC to determine whether these cells are derived principally from the re-infused graft or develop *de-novo* from a renewed thymus.

**Methods:** This study is part of an ongoing phase 2 trial at St Vincent's Hospital, Sydney (HREC approval - SVH File No. 10/206). Samples collected pre-AHSCT and post-AHSCT were used for high throughput sequencing of T cell receptors in FACS sorted CD45RA+ T<sub>naïve</sub> and CD45RO+ T<sub>memory</sub> CD4+ and CD8+ subsets [n=10]. DNA markers of thymic function - S<sub>J</sub>:b TREC ratio [n=17] were also studied and correlated with clinical response.

**Results:** TCR diversity, as assessed by Shannon diversity, falls in all cell phenotypes in the first 12 months following AHSCT. At 24 months an increase in diversity is detected in all lymphocyte phenotypes; however, only approximates pre-transplant levels in the CD4+ naïve population (Figure 1). A corresponding increase in the proportion of rare clones at 24 months post-AHSCT was detected in the CD4+ naïve population when assessed by clonal homeostasis. Dominant CD4+ naïve clones detected pre-AHSCT are undetectable post-transplant, whilst dominant CD4+ memory, CD8+ naïve and CD8+ memory populations frequently undergo further expansion. S<sub>J</sub>:B TREC ratio remains below baseline at 6 and 12 months, increasing to baseline levels at 24 months and remaining at baseline levels at 36 months, independent of patient age. A trend towards lower thymic output was noted at 24 months in patients who relapsed, suggesting a clinical correlate of this marker.

**Conclusion:** These results suggests that by 24 months post-AHSCT diversification of the T cell repertoire occurs through *de novo* thymic output of naïve CD4+ T cells.

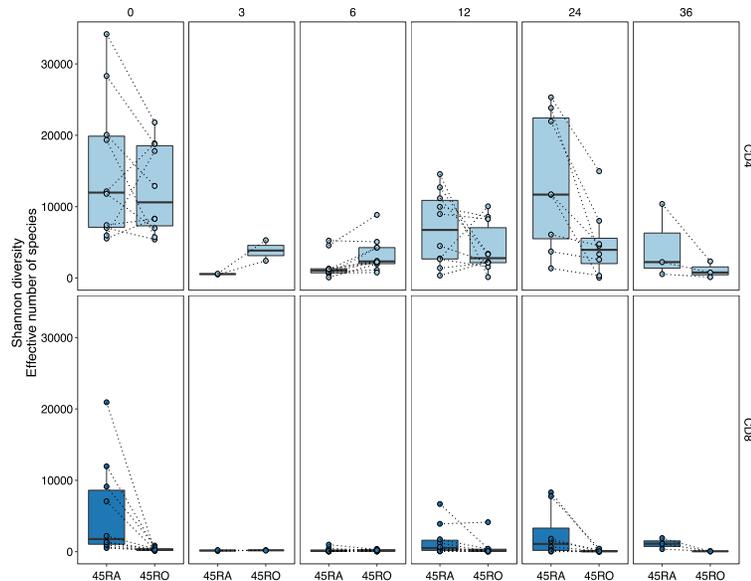


Figure 1. Shannon diversity metrics (y axis, left) of different T cell phenotypes (x axis, bottom and y axis, right) over pre- and post-transplant time points (x axis, top).

## Prognostic value of clone size in paroxysmal nocturnal haemoglobinuria (PNH) for thrombotic events in untreated patients in the international PNH registry

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**Aim:** The association between paroxysmal nocturnal haemoglobinuria (PNH) granulocyte clone size at disease onset and outcomes in patients (pts) with PNH remains unclear. The objective of this analysis was to elucidate this potential relationship in pts untreated with a complement inhibitor and enrolled in the International PNH Registry (NCT01374360). **Method:** Patients untreated with complement inhibitor therapy, enrolled in the Registry as of April 2018, and had  $\geq 12$  months of untreated follow-up after disease onset were assessed. Pts were stratified into 5 cohorts based on clone size at baseline (disease onset, Table). Outcomes included: event rates for TEs and major adverse vascular events (MAVEs); LDH ratio; haemoglobin levels; platelet, absolute neutrophil, and absolute reticulocyte counts at last follow-up. **Result:** The majority of the 2489 pts were female (54.0%) and white (79.2%). Mean age at PNH baseline ranged from 36.4 (cohort 5) to 44.2 (cohort 1) years. Results for the outcomes of interest are summarised in the Table. All cohorts showed a risk of MAVE and TE during follow-up. Although estimated rates of MAVE and TE were highest in the  $>50\%$  clone size cohort, there was no difference in the rate of MAVE or TE during follow-up across the 4 cohorts with clone size  $<50\%$  at disease onset. Pts with clone size  $>50\%$  had lower mean haemoglobin levels ( $P < 0.0001$ ), higher platelet counts, and higher absolute neutrophil counts during follow up. There was a statistically significant difference in reticulocyte count & LDH across the 5 cohorts ( $P < 0.0001$ ). **Conclusion:** All pts with PNH were at risk for TEs and MAVEs, regardless of clone size. Pts with  $>50\%$  PNH clone size had approximately 2-times higher risk of TEs than pts with smaller clones. Event rates for TEs and MAVEs during follow up were similar in pts with small (0.01-5%) and medium sized clones (5-50%) at baseline.

Key Patient Characteristics and Outcomes of Interest

Parameter	Cohort 1 (0.01–1%) n=473	Cohort 2 (1–5%) n=388	Cohort 3 (5–10%) n=185	Cohort 4 (10–50%) n=577	Cohort 5 ( $>50\%$ ) n=866	P Value*
Patients with history of BMD at baseline	n=471	n=387	n=184	n=574	n=860	
n (%)	264 (56.1)	194 (50.1)	91 (49.8)	250 (43.6)	251 (29.2)	
<b>Events during time from baseline to last follow-up</b>						
MAVEs, patients at risk, n	471	386	184	573	857	
No. of events	43	38	25	84	268	
Patient-years	2455.0	2413.5	1289.1	4865.5	8434.1	
Rate (95% CI) per 100 PY	1.8 (1.3, 2.4)	1.6 (1.1, 2.2)	1.9 (1.3, 2.9)	1.7 (1.3, 2.1)	3.2 (2.6, 3.6)	
TEs, patients at risk, n	470	386	184	573	857	
No. of events	17	18	11	50	159	
Patient-years	2453.6	2413.5	1289.1	4865.5	8434.1	
Rate (95% CI) per 100 PY	0.7 (0.4, 1.1)	0.7 (0.5, 1.2)	0.9 (0.5, 1.5)	1.0 (0.8, 1.4)	1.9 (1.6, 2.2)	
<b>Laboratory values at last follow-up†</b>						
LDH ratio	n=316	n=276	n=144	n=434	n=645	
Mean (SD)	1.1 (1.34)	1.5 (1.61)	2.0 (2.05)	2.5 (2.62)	5.1 (3.81)	$<0.0001$
Hemoglobin (g/L)	n=383	n=328	n=164	n=495	n=712	
Mean (SD)	115.9 (27.11)	118.8 (25.68)	117.1 (25.22)	114.4 (26.00)	100.8 (25.24)	$<0.0001$
Platelets ( $\times 10^9/L$ )	n=396	n=332	n=166	n=502	n=718	
Mean (SD)	131.0 (75.61)	128.5 (76.27)	123.5 (68.34)	133.0 (76.11)	148.6 (74.44)	$<0.0001$
Absolute neutrophils ( $\times 10^9/L$ )	n=366	n=310	n=156	n=466	n=647	
Mean (SD)	2.4 (1.63)	2.1 (1.28)	2.3 (1.56)	2.4 (1.58)	2.6 (1.67)	0.0029
Absolute reticulocytes ( $\times 10^9/L$ )	n=166	n=162	n=108	n=296	n=413	
Mean (SD)	62.7 (33.82)	75.3 (46.98)	85.1 (83.93)	88.7 (64.18)	137.4 (93.41)	$<0.0001$

\*P values for laboratory parameters are from an analysis of variance. †Data shown are within 6 months of last follow-up.

BMD, bone marrow disease; CI, confidence interval; LDH, lactate dehydrogenase; MAVEs, major adverse vascular events; PY, patient-years; SD, standard deviation; TEs, thrombotic events; ULN, upper limit of normal.

**Ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal haemoglobinuria: pharmacokinetics and pharmacodynamics observed in two phase 3 randomized, multicentre studies**

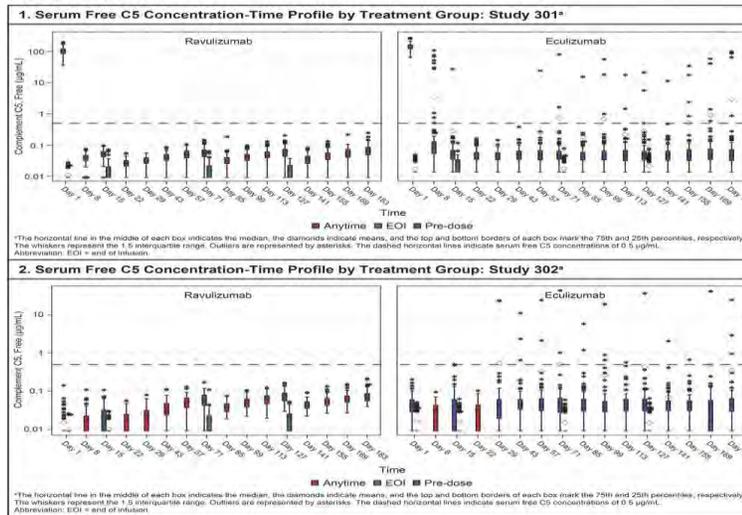
Regis Peffault De Latour<sup>3</sup>, Robert A. Brodsky<sup>4</sup>, Stephan Ortiz<sup>5</sup>, Antonio M. Risitano<sup>6</sup>, Jun-Ho Jang<sup>7</sup>, Peter Hillmen<sup>8</sup>, Aleksandr Kulagin<sup>9</sup>, Rajendra Pradhan<sup>5</sup>, Scott T. Rottinghaus<sup>5</sup>, Rasha Aguzzi<sup>9</sup>, Richard A. Wells<sup>10</sup>, Jeffrey Szer<sup>1</sup>, **James D'Rozario**<sup>11</sup>

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**Aim:** The objective of this analysis was to characterize ravulizumab (ALXN1210, an innovative C5 inhibitor) pharmacokinetics (PK) and pharmacodynamics (PD) when administered every 8 weeks (q8w) in complement inhibitor-naïve or -experienced patients (pts) with paroxysmal nocturnal haemoglobinuria (PNH). Potential PD differences between ravulizumab and eculizumab were also examined to explore a possible mechanistic explanation for results observed. **Method:** Two phase 3, randomized, open-label, noninferiority studies (NCT02946463, study 301, complement-inhibitor naïve; NCT030560040, study 302, clinically stable on eculizumab treatment ≥6mths) included pts ≥18 years with PNH. Pts received weight-based dosing of ravulizumab q8w or eculizumab 900mg q2w (PNH label dosing) for 183 days. Serum samples for PK/PD analyses were collected periodically on study days from 1 through 183. PK/PD outcomes included serum drug concentrations, serum free complement protein C5 and total C5. **Result:** In study 301, 246 pts received study drug (ravulizumab, n=125; eculizumab, n=121); 195 received study drug in study 302 (ravulizumab, n=97; eculizumab, n=98). The ravulizumab PK profile was similar in both studies (Table 1). Mean (SD) post hoc terminal elimination half-life in all 222 pts was 49.7 (8.9) days. Ravulizumab steady-state therapeutic concentrations and complete suppression of free C5 were rapidly achieved following first dose and sustained throughout the 183-day treatment period in both studies (Panels 1 and 2). In contrast, mean free C5 concentrations did not consistently remain <0.5 µg/mL with eculizumab in either study (Panels 1 and 2). **Conclusion:** Ravulizumab q8w led to immediate, complete, and sustained complement C5 inhibition in all pts with PNH irrespective of prior complement inhibitor use, whereas the effect of eculizumab q2w was less consistent. In pts treated with ravulizumab, free C5 suppression below the free C5 threshold was associated with complete inhibition of intravascular haemolysis, providing a potential mechanistic basis for the consistency of the point estimates for all endpoints.

PK Parameter (Units)	Study 301	Study 302
	(N=124)	(N=96)
	Mean ± SD (%CV)	Mean ± SD (%CV)
<i>t</i> <sub>max</sub> (h) <sup>a</sup>	2.5 (2.0, 335.8)	2.4 (2.0, 5.2)
<i>C</i> <sub>max</sub> (µg/mL)	1378.5 ± 275.9 (20.0)	1386.3 ± 268.42 (19.4)
<i>C</i> <sub>through</sub> (µg/mL)	472.7 ± 157.9 (33.4)	500.8 ± 143.2 (28.6)

<sup>a</sup>Values are presented as median (interquartile range). Pharmacokinetic parameters are following the last measurable dose. Abbreviations: AUC = area under the serum concentration versus time curve over the dosing interval; CL = total clearance; *C*<sub>max</sub> = maximum observed serum concentration; *C*<sub>through</sub> = concentrations at the end of the dosing interval; CV = coefficient of variation; SD = standard deviation; *t*<sub>max</sub> = time to maximum observed serum concentration; *V*<sub>d</sub> = volume of distribution at steady state.



## The utility of soluble CD25 and ferritin levels in adult haemophagocytic lymphohistiocytosis

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**Introduction:** HLH is a serious hyperinflammatory condition characterised by uncontrolled immune activation. Diagnosis remains difficult as its presentation is non-specific and can mimic other diseases. Various criteria have been developed to assist diagnosis<sup>1,2</sup>. Ferritin is a diagnostic test frequently performed due to ease of accessibility, but hyperferritinemia has found to be non-sensitive in adults<sup>3</sup>. Soluble CD25 (sCD25), a measure of serum soluble interleukin-2 receptor, is another important test but there is limited primary data comparing sCD25 levels in adult patients with HLH and non haemophagocytic disorders<sup>4</sup>.

**Aim:** To determine the pattern of sCD25 and ferritin levels in adult patients with HLH and non-HLH disorders.

**Method:** We performed a multi-centre case series retrospectively analysing ferritin and sCD25 levels in patients with suspected HLH. Serum sCD25 levels were measured by enzyme-linked immunosorbent assay. To assist with further validation, sCD25 and ferritin levels were prospectively collected on patients with sepsis and malignancy. Statistical analysis was performed using GraphPad Prism 8.

**Results:** Data was collected on 54 patients of whom 19 had confirmed HLH. Median sCD25 levels in the HLH and non-HLH groups were 16944 pg/ml (9522-65791 pg/ml) and 4988 pg/ml (211-35864 pg/ml) respectively. Receiver operating characteristic curve analysis demonstrated that sCD25 was a good diagnostic test with an area under the curve of 0.89 (95%CI 0.81 to 0.97). The optimum threshold for sCD25 was 9000 pg/ml (sensitivity, 100%; specificity, 73%). Median ferritin levels in the HLH and non-HLH groups were 8565 ng/ml (1,067-118,391 ng/ml) and 1734 ng/ml (80 -126,950 ng/ml) respectively. The optimum threshold for ferritin was 1045 ng/ml (sensitivity, 100%; specificity, 34%).

**Conclusion:** sCD25 is a sensitive and specific test in aiding the diagnosis of HLH. Ferritin appears to be less specific than sCD25. There is an intermediate range where both sCD25 and ferritin levels overlap between the two groups which requires further attention.

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O077

## **Making a Difference to Haematology Services in Binh Dinh Province in Central Vietnam**

**Elayne Knottenbelt**<sup>1,2,3</sup>, Kit Norrish<sup>1</sup>, Anne de Bres<sup>3</sup>

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What does it mean to provide assistance to developing countries? How do we measure success? How effective are conferences, medical texts and lectures from visiting speakers?

I have had the opportunity for the last two years to help with diagnostic haematology in Binh Dinh Province in Vietnam, under the New Zealand Vietnam Health Trust (NZVHT). This has been a steep learning curve for me, Kit Norrish (scientist) and the Vietnamese laboratory staff in Binh Dinh General Hospital and the more remote eleven district hospitals.

To make a difference, there must be mutual respect, good relationships with local decision makers and laboratory staff. There needs to be an understanding of the limited access to tests and treatments that we take for granted. There is a lack of qualified personnel and limited resources including appropriate training material. In our experience there is a significantly different spectrum of disease and treatment options.

Making changes towards best practice requires a comprehensive approach that starts with 'hands on' time in the laboratory. This includes good quality control, an accurate complete blood count, the making of a good blood film and interpretation. Diagnosis requires an understanding of haematological disorders with appropriate and practical algorithms for the laboratory staff and clinicians.

The aim is to enable local staff to manage patients safely and appropriately with the resources available, hence reducing the need for unnecessary travel and expensive treatments at a specialist's centre.

I would like to share some of the challenges and what we have learnt from our experience working alongside our Vietnamese colleagues.

O078

## **SynNotch inducible Chimeric Antigen Receptor (CAR) T cells generated with piggybac transposase display specific cytotoxicity in vitro**

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### Introduction

On-target, off-tumour toxicity has limited the utility of chimeric antigen receptor (CAR) T cells outside of lymphoid and lymphoblastic malignancies. The synthetic Notch (SynNotch) system with inducible expression of CAR only in the presence of an additional sensitising antigen could increase specificity and overcome some of the limitations. We generated SynNotch CAR T cells with CD33 as the sensitising antigen with an inducible CAR19. Specificity of the CAR T-cell cytotoxicity against cell lines expressing CD19, CD33 or both antigens was analysed.

### Method

DNA encoding the anti-CD33 scFv fused with murine Notch1 minimal regulatory region and tetR-VP64 artificial transcription factor was cloned into *piggybac* transposon system encoding for CAR19 under the tetracycline response element (TRE3G) promoter control. SynNotch CAR-T cells generated from CD3+ cells from healthy donor peripheral blood are expanded over 3 weeks with IL-15 and irradiated artificial antigen presenting K562 cells. Flow cytometry was used to determine target:effector cell number ratio following co-culture to assess cytotoxicity.

### Results

An 18-fold mean expansion with 82% CAR expression comprising of predominantly naïve and effector T cells was obtained at the end of culture. SynNotch CAR-T cells showed increased CAR19 expression following co-culture with CD33+ sensitising cell lines. CD33+/CD19+ cell lines were significantly reduced following co-culture (mean cell ratio 0.00009 (BV173) – 0.6 (Raji-CD33)) compared with CD33-/CD19+ cell lines (0.4 (Nalm6) – 1.1 (Raji)). Background cytotoxicity against CD33-/CD19+ Nalm6 was observed at high effector:target ratios.

### Conclusion

The *piggybac* transposon system can generate SynNotch CAR-T cells with inducible CAR19 expression in the presence of sensitising antigen (CD33). These cells can preferentially kill cell lines expressing both the sensitising and target antigens (CD33+/CD19+), while sparing cell lines expressing only the target antigen (CD19). SynNotch CAR T-cells could thus reduce off-tumour toxicity especially when single antigen positive healthy tissues are spatially separated from dual antigen positive tumour.

## Targeting control of cell cycle enhances the activity of conventional chemotherapy in chemoresistant acute myeloid leukaemia

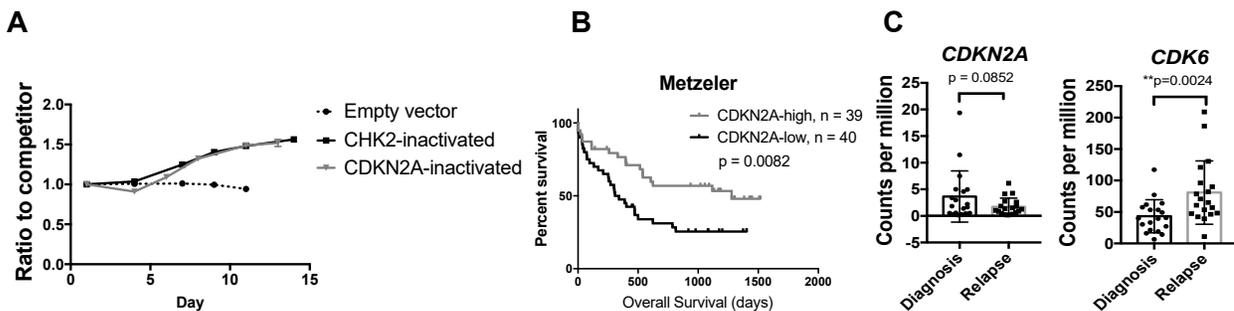
**Victoria Ling**<sup>1,2</sup>, William Godfrey<sup>1</sup>, Sebastien Jacquelin<sup>1</sup>, Jasmin Straube<sup>1</sup>, Leanne Cooper<sup>1</sup>, Claudia Bruedigam<sup>1</sup>, Siok Tey<sup>1,2</sup>, Lars Bullinger<sup>3</sup>, Marco Herold<sup>4,5</sup>, Megan Bywater<sup>1</sup>, Steven Lane<sup>1</sup>  
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**Aim:** Genetic aberrations and clonal evolution underpin chemoresistant and relapsed acute myeloid leukaemia (AML). We used a genome-wide CRISPR knock-out screen to identify genes mediating resistance to Cytarabine (AraC) and Doxorubicin (Dox) in AML. We now present validation of these targets as a novel mechanism to overcome chemoresistance.

**Methods:** Two independent Cas9-expressing human AML cell lines were transduced with the genome-wide, Brunello guide RNA (gRNA) library<sup>1</sup> and treated with synergistic doses of Dox/AraC. Gene representation in resistant populations was identified by next-generation sequencing. 'Hits' were validated in cell lines with CRISPR-mediated gene deletion using individual gRNAs. Relevance to human AML was established by bioinformatic analysis of published patient data.

**Results:** Dominant hits included cyclin-dependent kinase inhibitor 2a (CDKN2A) and checkpoint kinase 2 (CHEK2). CDKN2A and CHEK2 mediate apoptosis and G<sub>1</sub>S cell cycle arrest in response to DNA damage. Functionally, CDKN2A- and CHEK2-inactivated cells demonstrated a selective advantage over empty-vector controls during chemotherapy treatment, confirming their contribution to resistance (Figure A). Mechanistically, this was mediated by evasion of chemotherapy-induced cell cycle arrest, with minimal reductions in apoptosis. Although rarely mutated in AML, CDKN2A reduced expression conferred inferior survival in three cytogenetically normal AML patient cohorts<sup>2-4</sup> (ref. 2 shown in Figure B). In paired diagnosis-relapse AML samples,<sup>5</sup> a trendwise downregulation of CDKN2A and consequent upregulation of CDKN2A's downstream target, cyclin dependent kinase 6 (CDK6) occurred in relapsed AML (Figure C), confirming the adverse influence of deregulated cell cycle. We therefore hypothesised that CDK4/6 inhibitor, palbociclib could enhance Dox/AraC efficacy in AML. Palbociclib induced G<sub>1</sub> arrest in empty vector, CDKN2A- and CHEK2-inactivated cells by 24 hours and synergised with Dox/AraC over longer treatments (4-11 days), demonstrating its potential to improve chemotherapy response in AML.

**Conclusions:** Genome-wide CRISPR screens functionally identify clinically relevant mediators of chemoresistance in AML. Deregulated cell cycle confers inferior prognosis in AML and may be amenable to targeted combination therapies.



References: <sup>1</sup>Doench, et al. 2016, *Nat Biotech*, <sup>2</sup>Metzeler, et al. 2008, *Blood*, <sup>3</sup>Verhaak, et al. 2009, *Haematologica*, <sup>4</sup>Bullinger unpublished, <sup>5</sup>Li, et al. 2016, *Nat Med*.

## Clinical utility of next generation sequencing in the management of myeloid malignancies

**Rishu Agarwal**<sup>1</sup>, Suzanne Svobodova<sup>2</sup>, Wendi Lin<sup>3</sup>, Chun Fong<sup>4</sup>, Chris Hogan<sup>5</sup>, Andrew Grigg<sup>6</sup>  
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**Aim:** Although next generation sequencing (NGS) has helped characterise the complex genomic landscape of myeloid malignancies, its clinical utility remains undefined. This has resulted in variable funding for NGS testing, limiting its accessibility. At our centre, NGS Myeloid panel is offered to all patients with myeloid malignancies, as part of diagnostic workup. Here, we evaluated the diagnostic, prognostic, and potential therapeutic utility of a clinically validated NGS panel in these patients.

**Method:** Peripheral blood/bone marrow from patients referred for diagnostic testing were analysed by a custom designed amplicon based 31-gene targeted NGS panel. Library preparation was done using Fluidigm Access Array System and variant calling was done using reporting software and standardized curation procedure. The mean coverage of the assay was 1000x with a sensitivity of ~3% for variant detection.

**Result:** Mutations were identified in 62% of the patients tested (213/342) with clinical suspicion of myeloid disorders. Amongst myeloproliferative neoplasms, novel variants were identified in 5 patients (2 novel *JAK2*, 2 novel *MPL* and 1 novel *CALR* variants). High molecular risk mutations (*ASXL1*, *SRSF2*, *EZH2*, and *IDH1/2*) were identified in 3 of 15 patients with intermediate risk myelofibrosis, impacting on allograft decisions. A diagnosis of MDS/clonal haematopoiesis was confirmed in 15 of 48 patients with persisting cytopenias (with non-diagnostic morphological features and failed cytogenetics). Amongst 45 AML patients, NGS led to changes in WHO diagnosis (1 patient), ELN risk stratification (7 patients) and change to allograft recommendation in first complete remission (2 patients), primarily through the detection of *RUNX1*, *ASXL1* and *TP53* mutations. 39% of AML patients (7/18) were upgraded from intermediate to adverse risk by detection of these mutations. Targetable mutations were identified as follows: FLT3 (n=12), IDH1/2 (n=13), spliceosome genes (n=20).

**Conclusion:** NGS testing improves the characterisation of myeloid malignancies, establishes diagnosis in morphologically challenging cases, can be integrated in clinical practice as an additional tool to refine decision making for stem cell transplantation, and can identify the candidates for targeted therapeutics.

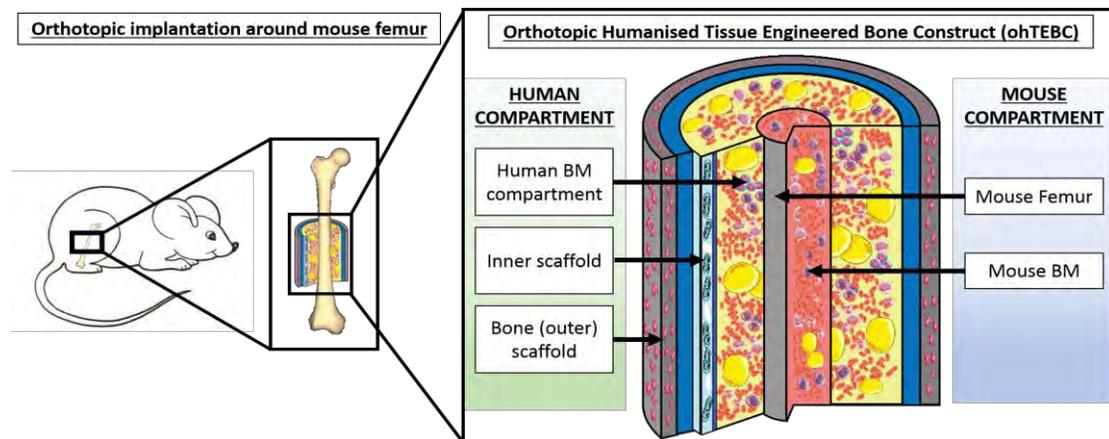
## Tissue Engineering of An Orthotopic Humanised Bone Organ as A Platform for Preclinical Multiple Myeloma Research

**Alvaro Sanchez-Herrero**<sup>1</sup>, Christoph Lahr<sup>1</sup>, Jacqui McGovern<sup>1</sup>, Felipe Prósper<sup>2,3</sup>, Dietmar W. Hutmacher<sup>1,4</sup>

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**Background:** Multiple Myeloma (MM) is a B cell neoplasm that remains largely incurable. Despite numerous efforts to develop new therapeutic strategies for MM, most drugs fail clinical trials, mainly due to the lack of clinically predictable animal models. There is an unmet need to develop a model that mimics key aspects of MM, such as tumour-microenvironment interactions. We sought to address the current lack of reliable preclinical platforms that feature a humanised immune system together with a humanised tumour microenvironment and primary MM cells in order to test immunotherapeutic strategies.

**Methodology:** Here we developed a personalised MM animal model that is able to engraft cancerous cells into an orthotopic humanised tissue-engineered bone construct (ohTEBC) to create a fully functional humanised bone marrow (hBM) niche containing human haematopoietic cells. The ohTEBC was generated from melt electrospun medical-grade polycaprolactone tubular scaffolds and seeded with human bone osteoprogenitor cells, while the hBM niche was engineered with the MM patient's own BM cells in a hydrogel.



**Results:** 6 weeks after orthotopic implantation around the right femur of NSG mice, the ohTEBC formed an organ bone containing a cortical shell infiltrated with human BM that was composed of human cells and extracellular matrix components, with novel blood vessel formation.

Also, we demonstrated that after implantation of aged-patient derived CD34<sup>+</sup>, hCD45<sup>+</sup> cells were found in the mouse BM, human BM compartment, spleen and peripheral blood, reaching levels of as high as 62% by week 7. Moreover, these hCD45<sup>+</sup> cells were also recruited towards the newly formed bone, suggesting the development of new BM tissue.

**Conclusions:** We demonstrated that this tissue-engineered MM model holds the potential as a unique and patient-specific drug testing platform, not only for common drugs but also for immunotherapy, allowing to study interaction with the BM microenvironment as well as the MM effect on a humanised bone.

## **CD45 and CD22 expressing splenic erythroblasts are depleted in two distinct models of stress erythropoiesis**

**Chanukya Colonne**<sup>1,3</sup>, Stuart Fraser<sup>1,2</sup>

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### **Introduction:**

Anaemia induces extramedullary erythropoiesis in the mouse spleen, in a process termed stress erythropoiesis that results in rapid erythrocyte production and splenomegaly. Exposure to toxins, such as phenylhydrazine, is commonly utilised to induce acute anaemia for studying stress erythropoiesis in mice. We hypothesised that pregnancy is a physiological instance of stress erythropoiesis, given the high demand it places on an individual's circulatory system.

We aimed to characterise pregnancy as a physiological model of stress erythropoiesis, and utilise phenylhydrazine and pregnancy as platforms to study the surface phenotype of stress erythroblasts, in the hope of elucidating mechanisms governing stress erythropoiesis.

### **Methods:**

Phenylhydrazine treated and pregnant mice were assessed on haematological parameters, spleen size and surface expression of integrins known to be upregulated in stress erythropoiesis. Flow cytometry was then used to characterise the expression of other cell surface markers on splenic and bone marrow erythroblasts.

### **Results:**

Both phenylhydrazine and pregnancy caused clinical and biochemical signs of anaemia, reticulocytosis, splenomegaly and upregulation of alpha-4 and beta-1 integrins. Steady-state splenic erythroblasts had a unique cell surface phenotype, expressing CD45 and CD22, distinct from their bone marrow counterparts. These CD45<sup>+</sup>CD22<sup>+</sup> splenic erythroblasts were significantly depleted in both models of stress erythropoiesis.

### **Conclusion:**

Pregnancy is a valid physiological model of stress erythropoiesis, and may provide a non-toxic physiological platform for human studies. Stress induced depletion of CD45<sup>+</sup>CD22<sup>+</sup> splenic erythroblasts provides insight into potential negative regulatory roles of these molecules in stress erythropoiesis. CD45 is a tyrosine phosphatase and an inhibitor of JAK2 (involved in the JAK2-STAT5 pathway promoting erythropoiesis), and CD22 is an activator of CD45. Reduced expression of CD45 and CD22, may enable the JAK2-STAT5 pathway unfettered activation, thereby resulting in enhanced erythroblast proliferation during stress erythropoiesis.

O083

## **Cell Free DNA detection and monitoring in Hodgkin Lymphoma**

**Melita Cirillo**<sup>1</sup>, Andreas Engert<sup>2</sup>, Sven Borchmann<sup>2</sup>

<sup>1</sup>Royal Perth Hospital, Perth, Australia, <sup>2</sup>Department of Internal Medicine 1, University Hospital Cologne, Cologne, Germany

### **Aim:**

Biomarkers for disease response in Hodgkin Lymphoma (HL) are an area of unmet clinical need. Additionally, current treatment stratification is based on clinical risk factors due to a lack of a molecular classification. Currently, PET-scans form the basis for interim disease monitoring. However, the predictive value of interim PET is highly influenced by the size of tumour bulk at diagnosis and the choice of therapy. Therefore, we aim to utilize tumour-specific mutations in cell free DNA (cfDNA) as a molecular biomarker for genotyping and response assessment in HL.

### **Method:**

We studied samples collected from patients with early unfavourable and advanced stage HL. We designed a customised gene panel targeting > 670 genes to identify tumour derived mutations in cfDNA of HL patients at diagnosis and in follow-up samples. cfDNA was isolated from plasma, while germline DNA was extracted from white blood cells and sequenced separately. We then identify cfDNA single nucleotide variants (SNV) after exclusion of germline and clonal hematopoietic SNP. A customised bioinformatics pipeline was designed that incorporates error reduction accounting for both random sequencing and position specific errors and allows for high variant calling sensitivity.

### **Results:**

Interim analysis of the first 40 patients will be presented. We will report technical validation studies and mutational profile of cfDNA in this cohort of patient samples. We detected known mutations (e.g. TNFAIP3, STAT6, B2M, NFkB) but also entirely novel mutations using cfDNA in HL patient samples using our platform.

### **Conclusion:**

cfDNA represents an important emerging technique in genotyping and disease response monitoring in malignant lymphoma. We believe that our assay could greatly assist in genotyping, response monitoring and clinical decision making for patients with HL.

## Detection of CD274 (PD-L1) and PDCD1LG2 (PD-L2) abnormalities in cellular and circulating tumour DNA in lymphoid malignancy – a highly clinically relevant target

**Niles Nelson**<sup>1,3</sup>, Satwica Yerneni<sup>1</sup>, Yamuna Kankanige<sup>1</sup>, Jennifer Lickiss<sup>1</sup>, Miles Prince<sup>2,3,4</sup>, Michael Dickinson<sup>2,4</sup>, Mary-Ann Anderson<sup>2</sup>, Simon Harrison<sup>2,4</sup>, Jeff Szer<sup>2,5</sup>, Constantine Tam<sup>2,4</sup>, Michelle McBean<sup>1</sup>, Ella Thompson<sup>1,4</sup>, David Westerman<sup>1,2,4</sup>, Piers Blombery<sup>1,2,4</sup>

<sup>1</sup>Molecular Haematology Laboratory, Peter MacCallum Cancer Centre, Parkville, Australia, <sup>2</sup>Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Parkville, AUSTRALIA, <sup>3</sup>Molecular Oncology and Cancer Immunology, Epworth Healthcare, East Melbourne, AUSTRALIA, <sup>4</sup>Sir Peter MacCallum Department of Medical Oncology, University of Melbourne, Parkville, AUSTRALIA, <sup>5</sup>Department of Medicine, University of Melbourne, Parkville, AUSTRALIA

### Background/Aim

PD-L1 (*CD274*) and PD-L2 (*PDCD1LG2*) overexpression is a mechanism of immune evasion in lymphoid neoplasms targetable by currently available immunotherapeutics. In Hodgkin lymphoma, abnormalities of the *CD274/PDCD1LG2* locus on chromosome 9p24 correlate with response to checkpoint inhibitors. We aimed to perform a next generation sequencing (NGS) based assessment of sequence variants, copy number variations (CNV) and structural variants (SV) of the *CD274/PDCD1LG2* locus in patients with diverse lymphoid neoplasms referred for diagnostic testing at the Peter MacCallum Cancer Centre (PMCC).

### Methods

All samples were assayed using the PMCC PanHaem panel which uses hybridisation-based library preparation targeting approximately 300 genes recurrently mutated in haematological malignancy. In addition, whole genome copy number assessment and analysis of structural variants (SV) involving the IGH locus were performed using GRIDSS and CNspecter.

### Results

254 samples were analysed from patients with lymphoid neoplasms including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, myeloma, peripheral T-cell lymphoma (PTCL) and chronic lymphocytic leukaemia. Genomic abnormalities affecting *CD274* or *PDCD1LG2* were detected in 18 patients including high-level focal amplification (>6 copies)(n=7), translocation with the IGH locus (n=4), other SVs and sequence variants resulting in 3'UTR loss (n=7). Circulating tumour DNA (ctDNA) was available for three patients and all *CD274/PDCD1LG2* abnormalities were detectable in ctDNA. Three of the patients with *CD274/PDCD1LG2* abnormalities (2xDLBCL and 1xPTCL) received checkpoint inhibitor therapy. All patients achieved a complete metabolic response post-therapy. One notable patient had multiply relapsed chemotherapy refractory PTCL NOS with CNS involvement and demonstrated resolution of all systemic and CNS disease (including ctDNA remission) after pembrolizumab.

### Conclusion

Detection of *CD274/PDCD1LG2* genomic abnormalities from cellular and ctDNA is feasible and highly clinically relevant in lymphoid malignancy. It should be considered in all patients with relapsed/refractory disease.

O085

**High proportion of anergic B cells in the bone marrow defined phenotypically by CD21(-/low)/CD38- expression predicts poor survival in diffuse large B cell lymphoma**

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Interaction between the lymphoma cells and the non-clonal immune cells is thought to play a critical role in the pathogenesis of diffuse large B cell lymphoma (DLBCL). While there is considerable literature on the role of T cells in the tumour microenvironment, the prognostic impact of B cell subpopulations remains relatively ill-defined. Our aim was to characterize the proportion of B cell subpopulations in the archived bone marrow (N=47) and peripheral blood (N=54) samples of 75 DLBCL patients at diagnosis using 8 colour flow cytometry panels and study their impact on survival. Anergic B cells in the bone marrow, characterized as having CD21(-/low)/CD38- expression, was found to affect survival with high numbers (defined as >13.9%) being associated with significantly shorter overall survival (67.6 months vs 109.4 months, p=0.020). Cox regression analysis in our cohort of patients established that its prognostic significance was independent of the Revised International Prognostic Index score.

**Sandoz rituximab (GP2013; SDZ-RTX) for the treatment of diffuse large B-cell lymphoma (DLBCL): interim safety results of the prospective, non-interventional, observational, multicenter, open-label REFLECT study**

Manfred Welslau<sup>2</sup>, Norbert Marschner<sup>3</sup>, Julian Topaly<sup>4</sup>, Burkhard Otremba<sup>5</sup>, Thomas Wolff<sup>6</sup>, **Ruchi Bakshi**<sup>1</sup>

<sup>1</sup>Sandoz Pty Ltd, Macquarie Park, Australia, <sup>2</sup>MVZ Onkologie, Klinikum Aschaffenburg, Aschaffenburg, Germany, <sup>3</sup>Onkologische Praxis, Freiburg, Germany, <sup>4</sup>MVZ Klinikum Osnabrueck GmbH, Osnabrueck, Germany, <sup>5</sup>Onkologische Praxis Oldenburg/Delmenhorst, Oldenburg, Germany, <sup>6</sup>Onkologie Lerchenfeld, Hamburg, Germany

**Aim:** SDZ-RTX is approved in Aus/NZ in the same indications as reference rituximab, based on totality of evidence for biosimilarity. REFLECT, a real-world study of SDZ-RTX as curative therapy for treatment-naïve CD20+ DLBCL, represents the first biosimilar rituximab post-approval study in DLBCL.

**Method:** The study includes patients (pts) aged ≥18 years, eligible for R-CHOP therapy. R-CHOP is administered according to product label. Primary endpoint is complete response rate at end of treatment. Secondary endpoints include overall response rate, progression-free survival (12 months), and adverse events (AE). Data are collected at baseline and every study visit for 12 months (efficacy) and ≥30 days after last SDZ-RTX dose (safety). No imputation for missing data is planned; endpoints are summarized descriptively.

**Result:** In an interim analysis (cut off: Sep 6, 2018; recruitment approx. 50% complete), the full analysis set comprised 80 pts: 38 males (47.5%) and 42 females (52.5%), with median age 68.5 years (min 23, max 91); 70% of pts were aged ≥60 years. In total, 6 pts have discontinued. Most pts had little or no restriction in daily activities; >80% had ECOG score of 0 (34%) or 1 (50%). B-symptoms were reported in 15 pts (19%). Extranodal infiltration was observed in 40 pts (50%) and bulky disease was observed in 9 pts (11%). Most pts had early stage (I–IIB: 64%), low to intermediate risk disease (IPI Score 0–2: 61%).

Summary of safety is reported in the Table. AEs were reported in 53 (66%) pts, and 19 (24%) pts had serious AEs. Treatment-related AEs were reported in 13 pts (16%). The most frequent AEs were polyneuropathy (n=10, 13%), anemia (n=8, 10%), and fatigue (n=8, 10%).

**Conclusion:** Interim baseline data are as expected for treatment-naïve pts with CD20+ DLBCL; safety results are as expected for rituximab-based treatment. The study is ongoing.

All patients (N=80) n (%)	All	Treatment-related
AE	53 (66.3)	13 (16.3)
Serious AE	19 (23.8)	2 (2.5)
AE leading to discontinuation	6 (7.5)	1 (1.3)
AE leading to dose interruption	6 (7.5)	2 (2.5)
Death	0	0

## Outcomes of relapsed/refractory Hodgkin's lymphoma with salvage treatment and autologous stem cell transplant in Queensland, Australia: a multi-centre retrospective study

**Stewart Hunt**<sup>1</sup>, Glen Kennedy<sup>1</sup>, Greg Hapgood<sup>2</sup>, Georgina Hodges<sup>3</sup>, Waqas Bokhari<sup>1</sup>

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### Aim:

Primary aim to assess the outcomes of relapsed/refractory Hodgkin lymphoma (HL) in Queensland and assess the impact of post-salvage PET pre-autologous stem cell transplant (ASCT) has on outcomes. Secondary aims to assess the impact of other factors predicting treatment failure and whether intensifying conditioning chemotherapy improves outcomes.

### Method:

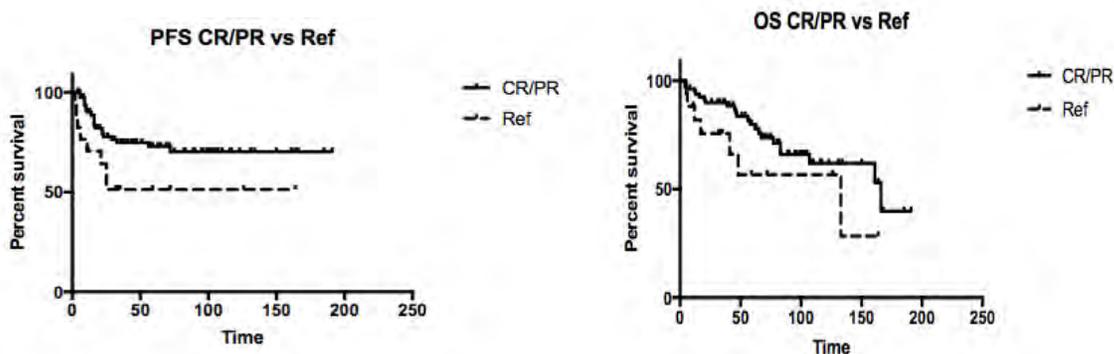
Retrospective multi-centre study included patients aged >16 years with relapsed/refractory HL and ASCT between September 2001-October 2017 across tertiary institutions in Queensland. PET scans were centrally reported. Univariate analysis via Kaplan-Meier curves in Graphpad Prism 8.0 and multivariate analysis via Cox regression in SPSS for statistical analysis.

### Results:

111 patients identified, 10 excluded due to essential data missing. 30% patients had primary refractory disease and majority had early relapse <12months. Platinum-based chemotherapy was used in all patients as salvage with 53.1% complete remission (CR), 29.1% partial remission (PR) and 17.8% refractory. 45 patients had central PET assessment. Majority of patients had BEAM conditioning and 19 patients received more intensive protocols. 82% achieved CR post ASCT. 5-year overall survival (OS) was 76.7% and 5-year progression free survival (PFS) 69% with median follow-up time of 59months. Achieving CR or PR pre-ASCT associated with improved PFS (p0.04) versus refractory. No difference in OS/PFS for CR versus PR. Radiotherapy associated with poorer PFS (p0.04). No significant difference observed in PFS/OS in patients undergoing BEAM conditioning versus more intensive protocols. Multivariate analysis showed high Hasenclever score at diagnosis and presence of extranodal disease at relapse as significant.

### Conclusion:

Salvage chemotherapy and ASCT demonstrated good long-term outcomes. Disease response of at least PR post-salvage is the main determinant of long-term survival. More intensified conditioning regimes may overcome adverse factors. Newer agents such as brentuximab vedotin and check-point inhibitors should be considered in patients who cannot attain at least a PR prior to ASCT.



## The Lymphoma and Related Diseases Registry (LaRDR): A post-pilot update.

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**Aim:** Lymphoid cancer imposes a significant burden for patients and the health system with > 8000 new diagnoses of lymphoma or CLL anticipated in Australia in 2019.

Management approaches are changing with advent of new therapies and there is significant variation in both patient demographics and therapeutic approach across Australia. The Lymphoma and Related Diseases Registry (LaRDR) was established in 2016 to improve quality of care and clinical outcomes for these conditions through systematic data collection, analysis, and reporting for practice improvement and benchmarking purposes.

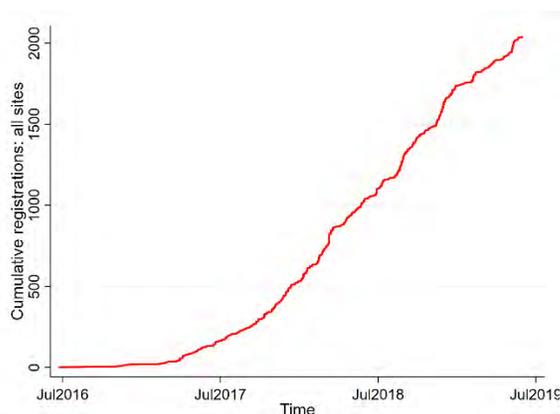
**Method:** LaRDR collects data on diagnosis, co-morbidities, therapy, supportive care and outcomes, on incident cases at participating sites via a secure, web-based database. Following a successful pilot, LaRDR has now transitioned to a fully functioning registry active in all six Australian states and ACT.

**Results:** LaRDR has 19 active sites and 2051 patients enrolled (Figure 1). Median age is 63y (IQR of 48-73), 60% are male. Initial diagnoses show 72.4% of cases have mature B-cell non-Hodgkin lymphoma (NHL), followed by Hodgkin Lymphoma (17.6%), mature T- and NK-cell NHL (5.4%), chronic lymphocytic leukemia (CLL, 4.1%) and post-transplant lymphoproliferative disorders (0.5%). Of the NHL cases 32% of diagnoses are DLBCL subtypes, followed by 16% follicular lymphoma (FL). A specific CLL registry project has been established. LaRDR's current collaborations include a validation study of the WHIMSICAL patient-led WM registry, understanding the prognostic value of GELF criteria for FL (with the Australasian Lymphoma Alliance), a National Blood Authority-funded study of immunoglobulin use and infections, and the International T-cell 2.0 project for PTCL.

**Conclusion:** LaRDR's contribution to understanding lymphoma epidemiology, current practice and outcomes will provide valuable 'real world' data for research, benchmarking and practice improvement. Future work includes pathology review and data validation, provision of hospital reports and linkage with other datasets. Further information is available at [www.lardr.org](http://www.lardr.org).

**Keywords:** Lymphoma, Registries, Quality of care

Figure 1: Accrual of patients across all sites over last three years.



## Therapy-related myeloid neoplasms (t-MN) show a high frequency of rare and predicted deleterious germline variants, mainly in the DNA repair pathway

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**Aim:** Unlike *de novo* AML<sup>1</sup>, little is known about the germline predisposition of t-MN. We report high frequency of deleterious germline variants (DGV) in a previously established t-MN cohort<sup>2</sup>.

**Method:** Clinical and laboratory information on 70 t-MN was collected from the SA-MDS registry. Rare and predicted deleterious somatic and germline variants were identified by sequencing paired bone marrow and germline samples for 240 genes across 11 pathogenic tumour pathogenesis/predisposition pathways using an in-house variant filtration and annotation algorithm and ACMG guidelines.

**Results:** Median age of t-MN diagnosis was 71.5 (21.8-87.1) years. Majority had a prior malignancy (66/70, 94%; lymphoma 26%; breast and prostate cancer 15% each); 49/66(74%) were treated with CT and 17/66 (26%) with RT only. 33 (47%) had high risk cytogenetic abnormalities.

Somatic mutations were present in 87% (61/70) cases, most commonly in *TP53*, *TET2* and *ASXL1*. At a MAF cut-off of  $\leq 0.05\%$ , 98 DGVs were seen in 55/70 (79%) t-MN in  $\geq 1$  major pathways, most commonly in DNA repair (41%, 32/71), drug transporter/metabolism (30%, 21/70) and cell signalling (17%, 12/70). Based on ACMG criteria, 6/98 DGVs were pathogenic, and an additional 12 DGVs were rescued using MAF cut-off of  $\leq 0.2\%$ . 43/55 (78%) had  $>1$  DGV in either same or different pathway. 24% (13/55) of patients had a somatic and DGV in same mechanistic pathway. Of 52/70 (74%) with available family history, positive history of malignancy was present in 31/52 (60%). DGVs in DNA repair and telomere maintenance pathways were common in patients with and without positive family history, respectively.

**Conclusions:** Our results show presence of high frequency of deleterious germline variants in t-MN. Patients with positive family history of cancer have significantly higher frequency of DNA repair pathway variants.

Table 1.

Number of DGVs According to Pathways	Positive history (n=31)	Negative history (n=20)	p-value
Epigenetic modification	2	0	0.505
Cell division	5	2	0.686
Cell signalling	5	5	0.724
DNA repair	20	6	0.012
Drug metabolism	6	4	$>0.999$
Drug transport	2	5	0.113
Splicing	0	0	NA
Telomere maintenance	1	5	0.039
Transcriptional regulation	5	1	0.668
Other	0	0	NA

<sup>1</sup>Maung ZYM, ..., Singhal D et al, Blood Cancer Journal 2018

<sup>2</sup>Singhal D, ..., Hiwase D et al, Leukemia 2019

## **Platelet gene expression in myeloproliferative neoplasms is associated with marrow fibrosis**

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**Aim:** Patients living with myeloproliferative neoplasms (MPN) have up to 20% risk of developing bone marrow fibrosis. The only way to detect fibrosis is through bone marrow examination performed when there are changes in blood counts, appearance on the blood film or development of new symptoms. Megakaryocytes have characteristic abnormalities in MPN, and these progress with fibrosis (i.e. morphological abnormalities; additional megakaryocyte-specific mutations with high allele burden). We therefore aimed to determine whether platelets have any alteration in gene expression with progression to marrow fibrosis.

**Method:** A transcriptome next-generation sequencing approach was used to analyse the expression of >20,800 genes in platelets from 74 individuals. A training cohort of 25 MPN patients and 15 controls were analysed and a fibrosis-associated platelet transcript signature was generated. The signature was then validated using a test cohort of 34 MPN patients. Bone marrow biopsies of all MPN patients were assessed for reticulin content (WHO Grade  $\geq 2$  defined fibrosis).

**Result:** We identified 1,302 and 697 differentially expressed genes (DEGs) in platelets from patients with and without fibrosis, respectively. There was minimal overlap between the DEGs of patients with and without fibrosis. 1,123 of the 1,302 (86%) DEGs in platelets from patients with fibrosis were unique. Of these, 96 DEGs were orthogonally verified by qRT-PCR. A putative 3-gene fibrosis-associated signature was identified and assessed on the test cohort. This verified that the signature could discriminate between patients with and without fibrosis with 88% accuracy (93% negative-predictive value, 71% positive predictive value and area under the ROC curve = 0.82).

**Conclusion:** We have shown there are specific changes in gene expression of platelets in MPN. Further, we have identified a sensitive and specific platelet signature associated with fibrosis. This offers potential for use of a blood-based approach as a surrogate marker for pathological fibrosis in MPN.

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## **Validation and Implementation of a Custom Next Generation Sequencing Myeloid Clinical Assay in a NATA accredited Pathology Laboratory setting**

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**Aim:** Targeted next generation sequencing (NGS) panels to identify genetic alterations in haematological malignancies are increasing becoming an integral part of clinical practice. We report here the design, validation and implementation of a custom 31 gene NGS panel targeted for myeloid malignancies.

Our aim was to develop and implement a NGS Myeloid Panel as a routine NATA accredited pathology test, to assist in the diagnosis, prognosis and therapeutic clinical decisions for patients with haematological malignancies.

**Methods:** A custom amplicon based NGS panel was designed that covers hotspot regions of oncogenes and most of the coding regions of tumour suppressor genes that are known to be clinically significant in myeloid disorders. A total of 59 samples with known mutations and commercially available standards were analysed. This included parallel patient sample testing for the assessment of accuracy, normal blood samples for the assessment of specificity, controls to establish reference ranges, reference standards for the assessment of sensitivity and replicate analysis for precision.

**Results:** For all loci shared by both the Austin myeloid NGS panel and reference methods, there was 99.14% concordance in the variant calls, none of which were false positives. There was one false negative call for a *CSF3R* variant, which was found to be present at a low variant allele fraction (VAF) of 1.4%. This was below the assay sensitivity of 3-5%, established by using reference DNA controls with known mutation allele frequencies as determined by digital droplet PCR. Analytical specificity was assessed by testing samples previously reported as "No Mutations Detected". These samples also provided the data necessary to identify recurrent sequencing artefacts and refine the bioinformatics pipeline for variant calling.

**Conclusion:** This validation has demonstrated that the Austin custom myeloid NGS assay serves as a reliable and effective method to detect somatic mutations in patient's DNA samples and is suitable to implement as a routine assay in a NATA accredited Pathology Laboratory setting.

## **Haemoglobin is an independent predictor of quality of life during disease-modifying therapy for high-risk myelodysplastic syndromes**

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### **Aim**

We aimed to investigate the relationship between haemoglobin and QoL in higher-risk MDS patients over time, including whether change in haemoglobin predicted change in QoL.

### **Method**

Post hoc analysis of two multicentre clinical trials of higher-risk MDS and low blast count acute myeloid leukaemia (AML) patients assigned to azacitidine alone or in combination with thalidomide or lenalidomide. Haemoglobin and EORTC-QLQC30 were collected at study entry, after cycle 4, 12 and study exit. Data were analysed using latent growth curve modelling.

### **Results**

231 patients were included, with median age 70 years and diagnosis of MDS in 170 (74%), CMML 37 (16%) and AML 24 (10%). Higher initial overall QoL and physical functioning were associated with higher haemoglobin ( $p<0.001$  and  $p=0.001$ , respectively) and better performance status ( $p<0.001$ ). Greater increase in QoL and physical functioning were associated with greater increase in haemoglobin ( $p=0.005$  and  $p<0.001$ , respectively) and female gender ( $p=0.023$  and  $p=0.014$ , respectively). Higher initial dyspnoea was associated with lower haemoglobin ( $p=0.001$ ) and worse performance status ( $p=0.001$ ), while greater decrease in dyspnoea was associated with greater increase in haemoglobin ( $p<0.001$ ). Higher initial fatigue was associated with lower haemoglobin, older age, worse performance status ( $p<0.001$ ,  $p=0.045$ ,  $p<0.001$ , respectively) whilst improvement in fatigue was associated with greater increase in haemoglobin, younger age, and better performance status ( $p<0.001$ ,  $p=0.045$ ,  $p<0.001$ , respectively).

### **Conclusion**

In higher-risk MDS/low blast count AML patients undergoing disease-modifying therapy, higher initial haemoglobin and greater increase in haemoglobin, but not disease severity or other cytopenias, were associated with better QoL, physical functioning and less dyspnoea and fatigue. These associations were independent of disease severity, age, gender, performance status, other cytopenias, transfusion dependency and treatment. These findings support the need to further investigate the impact of interventions to improve haemoglobin on QoL in MDS, including RBC transfusion thresholds and novel erythroid maturation agents.

## **An update of Australasian trends in allogeneic stem cell transplantation in myelofibrosis in the molecular era**

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**Aim:** In view of recent advances in the management landscape of myelofibrosis, we aimed to review local practice in transplanting myelofibrosis patients and its outcomes.

**Method:** A retrospective study was conducted using the Australasian Bone Marrow Transplant Registry (ABMTRR) data on patients who received allogeneic stem cell transplantation (alloSCT) for myelofibrosis at an Australian/New Zealand transplant centre between 2006 and 2017.

**Results:** 142 patients underwent alloSCT for myelofibrosis, primary(n =94) or secondary(n=48). Median age was 56 (range:26-69) years. 52% had HLA-identical sibling donors and 78% were given reduced intensity conditioning. JAK2 mutation testing was performed in 74% of patients whilst other mutations (CALR, MPL, EZH2, IDH, SRSF2, ASXL1) were rarely tested (1.4-8.4%). 4.2% had next generation sequencing. Cytogenetic abnormalities were identified in 29% of 120 patients who were tested pretransplant. Before transplant, 16% had splenectomy or splenic irradiation and 38% received JAK2 inhibitors. 42% had intermediate-2 and 23% had high-risk DIPSS+ scores. Median time to neutrophil recovery was 20 days (range:10-43) whereas median platelet recovery was 28 days (range:13-230). Overall survival (OS) was 67% at 1 year and 57% at 5 years. GVHD free progression free survival was 54% at 1 year and 42% at 5 years. The cumulative incidence of non-relapse mortality (NRM) was 16% at 100 days and 25% at 1 year. In multivariate analysis, unrelated donor was the significant independent unfavorable risk factor for OS (HR 2.26, 95%CI 1.17-4.33,p=0.015) and NRM (HR 3.02, 95%CI 1.36-6.71,p=0.007), while splenic irradiation/splenectomy resulted in shortened neutrophil (HR 1.88, 95%CI1.00-3.54,p=0.05) and platelet recovery time (HR 2.13, 95%CI 1.12-4.05,p=0.02). JAK2 inhibitor use has no significant impact on OS or NRM.

### **Conclusion:**

Survival rates were comparable to international studies. Better incorporation of molecular studies in management of myelofibrosis is required. The positive effects of donor type and splenic status need to be assessed further in prospective studies.

## Single centre experience of pegylated interferon alfa-2a in myeloproliferative neoplasms

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### Background and aim:

Pegylated interferon alfa-2a (PEG-IFN) is currently recommended as equal first-line therapy for patients requiring cytoreduction in polycythaemia vera (PV) and essential thrombocythaemia (ET)<sup>1</sup>. Experience with PEG-IFN in patients with myeloproliferative neoplasms (MPN) in Australia is limited as it only received PBS-funding in August 2018. We report on a cohort of patients from a single centre undergoing therapy with PEG-IFN.

### Method:

We conducted a retrospective chart review of all MPN patients on treatment with PEG-IFN in our centre. Data on dosing, tolerability and efficacy after 6 months of therapy was analysed.

### Results:

31 patients were analysed, with a median age of 62 years (range 18-80 years), of which 17 were male and 14 female. MPN subclassification was 16 (52%) ET, 12 (39%) PV, 1 (3%) MPN-unclassifiable, 1 (3%) post-ET myelofibrosis (MF), and 1 (3%) prefibrotic-primary myelofibrosis (PMF). Driver mutations were JAK2 V617F in 21 (68%), CALR in 8 (26%), MPL in 0, and 2 (6%) were triple-negative. All interferon naïve patients commenced PEG-IFN at 45 mcg weekly with dose adjustments depending upon tolerability and efficacy. The median weekly dose of PEG-IFN was 90 mcg (range 22.5-135 mcg). 17 patients (55%) had normalisation of their blood counts and were phlebotomy free, 14 patients (45%) had improvement, but not normalisation, of their blood counts or still required occasional phlebotomies. The most common adverse effect was hepatitis (11 patients – 35%, grade ≤2 91%, grade 3 9%), which spontaneously improved in most patients without requiring dose modification. 3 patients ceased treatment; 2 secondary to patient preference and 1 for allogeneic stem cell transplantation.

### Conclusion:

In our patient cohort PEG-IFN was well tolerated with good response rates. Low dropout rates are likely related to short follow-up, individualised dose escalation and the support of a haematology clinical nurse consultant.

### References

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## Clinical whole genome and transcriptome sequencing in adults with acute lymphoblastic leukaemia

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**Background & Aims:** Recurrent genomic abnormalities are central to risk stratification and determining treatment in acute lymphoblastic leukaemia (ALL). The diversity of these abnormalities, including chromosomal aneuploidies, translocations, altered gene copy number, tyrosine kinase fusions, point mutations and abnormal gene expression, necessitates a complex multi-assay diagnostic work-up (conventional cytogenetics, FISH, microarray, targeted sequencing and TLDA). We aimed to evaluate the feasibility of whole genome sequencing (WGS) and whole transcriptome RNA sequencing (WTS) in patients with ALL to detect genomic abnormalities, to risk stratify patients and identify possible therapeutic targets.

**Methods:** WGS was performed on samples from 16 cases of adult ALL (10 B-ALL and 6 T-ALL) followed by comprehensive analysis of coding and noncoding regions for mutations, structural variants (copy number abnormalities, rearrangements), global mutation signatures and mutational burden using the UMCCR Genomics Platform. WTS was used to verify WGS findings and identify a Ph-like gene expression signature.

**Results:** Clinically relevant and treatment altering genomic lesions were detected across the cohort including (i) B-ALL entity defining genetic abnormalities (*BCR-ABL1* (n=2), *KMT2A*-rearranged (n=2), *TP53* mutated low hypodiploidy (n=1)), (ii) Ph-like B-ALL translocations (n=2; *JAK2-PAX5*, *IGH-CRLF2*), (iii) recently described poor-risk molecular subgroups (n=2; *MEF2D*-rearranged, *ZEB2*<sup>H1038R</sup>), (iv) *IKZF1* and *CDKN2A/2B* deletion, (v) mutational profiles consistent with ETP-ALL (n=2), (vi) hallmark T-ALL translocations (n=3; *TRD-TLX1*, *TRB-HOXA*, *DDX3X-MLLT10*). Assembly of *IGH*, *TRG* and *IKZF1* loci was performed to identify sequences for future MRD monitoring.

**Conclusion:** WGS and WTS is feasible in the clinical setting, comprehensively captures the genomic heterogeneity in adult ALL and can replace multiple conventional testing modalities currently used in this patient group. This approach detected novel and potentially clinically relevant abnormalities that were not detected by conventional testing thereby contributing to optimised prognostication and treatment selection. Preparations are currently underway for clinical implementation of this testing for new ALL patients in Victoria.

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## **Measurable residual disease detection by next generation sequencing in B-cell acute lymphoblastic leukaemia**

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### **Introduction**

Measurable residual disease (MRD), a key prognostic factor in B-cell acute lymphoblastic leukaemia (B-ALL), is traditionally assessed by flow cytometry and/or allele specific oligonucleotide PCR (ASO-PCR). Here we use novel next generation sequencing (NGS) technology to measure MRD. Our aims are to determine the sensitivity of a NGS based assay for MRD and define normalisation techniques for result standardisation.

### **Methods**

Bone marrow samples were analysed using the LymphoTrack® Dx Assay Panel to detect IgH gene rearrangements. The IgH locus was amplified using primers targeted at three conserved framework (FR1-3) regions of the variable gene segments and corresponding joining gene segments. Target genes were sequenced on the Illumina® MiSeq with data analysis undertaken using provided software. Sequence clonality determination was defined as >2.5% of the total reads and >2x the read frequency for the third most frequent sequence. Clinically relevant MRD timepoints were analysed as above in 3 replicates. A 100 cell equivalent spike-in control (LymphoQuant™) was added in each MRD replicate for normalisation. Serial dilution of a commercially obtained known IgH rearrangement was performed to determine the limit of detection of the assay.

### **Results**

Results were concordant (82.86%) between assay methods with the exception of 6 samples. In 5 cases MRD was detected by NGS at a lower level than flow cytometry and ASO-PCR which were negative. MRD positivity by NGS corresponded with poor clinical outcomes in these patients. The dilution series validates the ability of the assay to detect 1 leukaemic cell in 100,000 normal cells ( $10^{-5}$  sensitivity). Replicates of diagnostic samples within and across sequencing runs demonstrate the intra/inter run precision of the assay.

### **Conclusion**

MRD detection by NGS is complementary to standard of care testing using flow cytometry and ASO-PCR. NGS has the added advantage of increased sensitivity, detection of clonal evolution and a rapid turnaround time. Normalisation of MRD levels to cell equivalents is required to suitably compare results with flow cytometry and ASO-PCR.

**MRD predicts survival in an intensive paediatric protocol that is as deliverable in adolescents and young adults as in children with ALL – preliminary results of the ALLG ALL06 Study**

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**Aims:** To assess whether a risk stratified, BFM based protocol (ALL06) could be administered to ALL patients (pts) aged 15-40 yrs in a comparable time frame to paediatric pts (< 15 yrs) (ANZCHOG Study 8) treated using identical induction therapy. The primary outcome was the proportion of pts commencing the next treatment phase, either standard (SR) or high risk (HR) therapy, by day 94.

**Methods:** Pts with de novo Ph-negative ALL were eligible. Treatment consisted of induction phases I and II followed by SR or HR therapy. MRD was assessed using RQ-PCR at day 33 and day 79 of induction. Stratification to HR therapy was based on diagnostic and treatment response criteria.

**Results:** 86 pts were enrolled between 07/12 - 06/18. 4 were ineligible. Median age was 22.7 (16.6 – 38.8) yrs. For the primary objective, 41.5% (95%CI 30.7 – 52.9) of the ALL06 cohort commenced next treatment by day 94 vs 39.3% in Study 8 ( $p=0.77$ ). Induction mortality was 3.6%. With median follow up of 27.4 months, 2 yr DFS and OS was 76.4% and 79.3%. Day 79 MRD negativity rate was 58.6%. Both higher risk and day 79 MRD negativity were associated with 2 yr DFS (HR 3.5, 95%CI 1.1-11.1,  $p=0.013$  and HR 0.23, 95%CI 0.08-0.68,  $p=0.008$  respectively) and OS (HR 6.8, 95%CI 1.5-30.8,  $p=0.013$  and HR 0.14, 95%CI 0.04-0.5,  $p=0.003$  respectively) on univariate analysis. However, only day 79 MRD status remained significant for DFS and OS on multivariate analysis.

**Conclusion:** Day 79 MRD status predicts 2 yr DFS and OS using a BFM style induction protocol which is as deliverable in an AYA population as in children with ALL. Our findings establish ALL06 as a standard chemotherapy backbone that can be used to incorporate novel therapies targeting the unique biology of AYA ALL.

## Disease burden analysis of HRQoL of blinatumomab versus standard-of-care chemotherapy in patients with r/r Ph- B-ALL in the TOWER study

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**Background:** HRQoL between patients with low-versus-high baseline disease burden (bone marrow blast levels; <50% blasts; ≥50% blasts) who received blinatumomab or SOC chemotherapy was assessed in a randomised clinical trial (TOWER).

**Methods:** HRQoL was assessed (EORTC QLQ-C30 Questionnaire) on days 1 (baseline), 8, and 15; on day 29 of cycle 1; days 1, 15, and 29 of consolidation; and at the safety follow-up. The questionnaire included 1 global health status (GHS) scale, 5 functioning scales, 3 symptom scales, and 6 single-symptom items. Time to deterioration (TTD) analyses assessed the treatment effect based on timing from the initiation of treatment to a 10-point deterioration from baseline.

**Results:** 342 patients (blinatumomab; SOC, n=247; n=95) had ≥1 HRQoL result: low blasts, n=87 (n=64; n=23); high blasts, n=255 (n=183; n=72). There was no statistically-significant difference in baseline HRQoL scores between the high and low blasts groups; the high blasts group had worse HRQoL overall. Baseline HRQoL scores were similar between blinatumomab and SOC arms for each group. GHS was improved by blinatumomab regardless of baseline blast level (effect somewhat greater in the low blasts group). When function scores worsened, the extent of worsening was almost always smaller for blinatumomab versus SOC, particularly in the high blasts group. Functioning status scores tended to stay the same or worsen with both blinatumomab and SOC regardless of blast level, except emotional scores, which improved with blinatumomab regardless of blast level (Figure 1). Symptom scores generally improved with blinatumomab but not with SOC, particularly in patients with high blasts (Figure 2). TTD analyses favoured blinatumomab over SOC, particularly in patients with high blasts (Table).

**Conclusions:** Blinatumomab improved HRQoL in patients with r/r Ph- B-ALL and delayed the time to clinically meaningful deterioration in HRQoL versus SOC. Treatment effects of blinatumomab versus SOC on HRQoL were larger among patients with high disease burden.

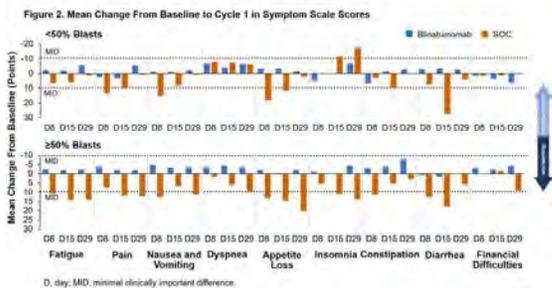
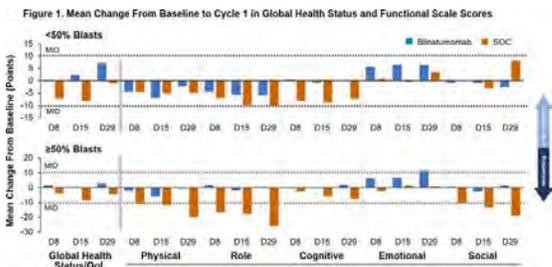


Table 1. HR and Log-Rank P Values of TTD Analyses

	<50% Blasts		≥50% Blasts	
	HR (95% CI)	P <sup>a</sup>	HR (95% CI)	P <sup>a</sup>
Global health status	0.46 (0.23–0.94)	0.023	0.69 (0.46–1.04)	0.063
Physical functioning	1.16 (0.56–2.39)	0.66	0.61 (0.43–0.87)	0.004
Role functioning	0.80 (0.43–1.51)	0.43	0.56 (0.40–0.80)	0.001
Cognitive functioning	0.79 (0.40–1.56)	0.41	0.63 (0.44–0.92)	0.008
Emotional functioning	0.79 (0.40–1.56)	0.41	0.58 (0.36–0.92)	0.017
Social functioning	2.48 (0.93–6.61)	0.056	0.62 (0.43–0.88)	0.005
Fatigue	0.71 (0.37–1.38)	0.28	0.52 (0.37–0.72)	<0.001
Pain	0.54 (0.29–1.03)	0.046	0.52 (0.37–0.74)	<0.001
Nausea and vomiting	0.48 (0.23–1.04)	0.058	0.52 (0.37–0.74)	<0.001
Dyspnea	0.91 (0.30–2.73)	0.86	0.55 (0.35–0.84)	0.004
Appetite Loss	0.60 (0.28–1.27)	0.17	0.37 (0.25–0.54)	<0.001
Insomnia	2.00 (0.84–4.77)	0.11	0.65 (0.44–0.96)	0.022
Constipation	0.60 (0.28–1.26)	0.15	0.43 (0.27–0.69)	<0.001
Diarrhea	0.16 (0.06–0.44)	<0.001	0.38 (0.25–0.58)	<0.001
Financial difficulties	0.71 (0.32–1.61)	0.39	0.86 (0.51–1.44)	0.52

CI, confidence interval; HR, hazard ratio.

<sup>a</sup>Log-rank test stratified by age, prior salvage therapy, and prior alloHSCT; HR <1.0 indicates a lower average event rate and longer survival for blinatumomab versus SOC.

## **Allogeneic stem cell transplant for acute lymphoblastic leukaemia using CD34 selected stem cells followed by prophylactic infusions of pathogen-specific and CD19 CAR T cells**

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### **AIM**

To determine the feasibility, safety and immunological effects of a cellular engineering approach that seeks to simultaneously reduce the incidence of graft-versus-host disease (GVHD), opportunistic infection and disease recurrence after HSCT.

### **METHOD**

We are conducting a pilot study in which patients with acute leukaemia in complete remission (CR) undergo a CD34-selected stem cell transplant (CliniMACS, Miltenyi) followed by two planned prophylactic infusions of donor-derived T cells (one targeting CMV, EBV and Aspergillus, another targeting leukaemic antigens). Patients do not receive peri-transplant ATG or routine post-transplant GVHD prophylaxis.

### **RESULTS**

We have performed matched sibling donor transplants on two patients aged 45 and 27 years with ALL in morphological CR. Conditioning was cyclophosphamide 120mg/kg and TBI 1200cGy. Patients received CD34 selected stem cells (total CD34+ doses 3.5 and 3.6 x 10<sup>6</sup>/kg; total CD3+ cell doses 1.3 and 0.2 x 10<sup>4</sup>/kg). Neutrophil engraftment (>0.5) occurred on days 11 and 12, platelet engraftment (>20) on days 8 and 13. Both patients received planned infusions of pathogen-specific T cells (day 21) and CD19 CAR T cells (days 27 and 21) with no infusion toxicity. CAR T cell expansion persisted in blood for at least 6 weeks in both patients. CRS (grades 1 and 2) and neurotoxicity (grade 1) developed in both patients; the former was treated with tocilizumab, patient 1 also received dexamethasone. Neither patient has developed GVHD. One patient required brief pharmacological treatment for a CMV reactivation and received a second pathogen-specific T cell infusion. The other developed asymptomatic reactivation of HHV6 and BK virus. Neither patient developed invasive fungal infection. At 155 and 147 days post-transplant, both patients are well, GVHD free with no evidence of leukaemia.

### **CONCLUSION**

Infusion of purified stem cells followed by infection and leukaemia-specific T cells has promise for improving leukaemia free survival and minimising infection and GVHD following HSCT.

O101

### **Adult Morphology**

John Giannoutsos<sup>1</sup>, Gemma Crighton<sup>2</sup>, **Surender Juneja**<sup>3</sup>

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& Peter MacCallum Cancer Centre, Melbourne<sup>3</sup>*

In this session the QAP morphology cases sent out in the RCPA haematology September survey will be reviewed by chair of the RCPA-QAP Haematology (Dr John Giannoutsos) followed by interactive presentation of paediatric morphology cases (Dr Gemma Crighton) and the adult morphology cases (Dr Surender Juneja), respectively.

O105

**Imaging flow cytometry for the detection of FISH abnormalities in immunophenotyped CLL cells: “immuno-flowFISH”**

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Imaging flow cytometry is an automated method that enables cells and fluorescent signals to be visualised and quantified. It has proven valuable in research applications and is emerging as a diagnostic tool for the assessment of leukaemia. To date most applications have been based on localisation of cellular molecules (e.g. translocation from nuclear to cytoplasmic compartments as occurs with cNPM in AML *NPM* mutated). Recently we have developed an integrated immunophenotyping and fluorescent *in situ* hybridisation (FISH) method with cellular analysis by imaging flow cytometry. This “immuno-flowFISH” method was established on normal lymphocytes and then applied to chronic lymphocytic leukaemia (CLL). The method requires antibody labelling followed by post-fixation, membrane permeabilisation and denaturation of double-stranded DNA to enable added probe to hybridise. Data for up to 100,000 cells is collected on the Amnis ImageStreamX Mark II imaging flow cytometer. Digital images (x60) and quantitative data (IDEAS software) are used to assess cell morphology, phenotype and FISH probe binding. The “extended depth of field” capability enables FISH probe signals (“spots”) to be localised within the (stained) nucleus of the cells. In addition to automated digital analysis, the imaging capability allows each cell to be visualised: morphology, phenotype and FISH signals. We have successfully detected chromosomes using centromeric probes in phenotyped normal B and T lymphocytes. In CLL we have identified numeric (+12) and structural (del(17p)) abnormalities. Other applications are under development. Immuno-flowFISH increases the limit of detection over slide-based FISH more than 100-fold and allows genotype to be assessed in cells of interest (based on phenotype). The method will be described and illustrated with clinical examples.

H002

**Antimicrobial prophylaxis administration in patients with acute myeloid leukaemia undergoing intensive chemotherapy by haematologists in Australia/New Zealand**

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**Aim:** To study the prescribing pattern of anti-infective measures by haematologists in Australia and New Zealand in patients with Acute Myeloid Leukaemia (AML), who are receiving intensive chemotherapy.

**Method:** A link for an anonymous online survey was distributed to Haematologists via the Australasian Leukaemia and Lymphoma Group (ALLG).

**Results:** Seventy-five haematologists participated in our survey. Antibiotic prescriptions for prophylaxis in AML were very low (only 11%) but almost all the haematologists prescribed anti-fungal agents for prophylaxis (99%).

About 30% of participants reported routine use of Trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis. Users cited a concern about PJP mortality, while non-users cited a lack of evidence.

Routine use of antiviral medications (mainly Valaciclovir) was reported by most of participants (85%). Concerns about serious complications of viral reactivation and its impact on the quality of life of patients was the reason behind this decision.

G-CSF for neutropenia was prescribed by approximately 50% of participants. The neutrophil count at which prophylaxis was ceased was variable; while 36% of haematologists consider at least neutrophil counts above  $0.5 \times 10^9/L$  before ceasing prophylaxis, 47% of them prefer neutrophil counts above  $1.0 \times 10^9/L$  for this purpose. About 11% of haematologists would continue anti-fungal and antibiotics until complete remission is achieved.

**Conclusion:** Prophylactic anti-fungal medications were used by nearly all participant haematologists, reflecting the strong evidence of benefit in the literature. The variability in using other prophylactic measures may reflect the lack of evidence and highlights significant practice variability.

H004

## **NPM1 variant allele frequency does not impact on outcome in de novo acute myeloid leukaemia**

**Oliver Brake**<sup>1</sup>, Anna Ruskova<sup>1</sup>, Helen Moore<sup>3</sup>, Neil Van de Water<sup>1</sup>, Tina Tan<sup>1</sup>, Nikhil Ghallyan<sup>1</sup>, Peter Browett<sup>2</sup>

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**Aim:** In a recent publication Patel et al<sup>1</sup> reported that patients with a high NPM1 variant allele frequency (VAF) have an inferior outcome when compared to those with a lower VAF, however two subsequent studies<sup>2,3</sup> found that NPM1 VAF has no independent effect on prognosis. The aim of this study was to assess the impact of NPM1 VAF in AML patients treated with curative intent at our institutions.

**Methods:** A retrospective review of sequential NPM1 positive AML cases presenting to two tertiary referral units between January 2010 and January 2019 was performed. Demographic, clinical and laboratory data was collated on patients with intermediate risk cytogenetics and NPM1 mutations. NPM1 VAF for each case was calculated and additional mutation analysis of FLT3 and CEBPA, complete remission rates, relapse-free and overall survival (OS) recorded. Patients were treated on UK NCRI AML trial protocols.

**Results:** 113 patients with NPM1 mutated AML were included in the analysis. The median age of the cohort was 60.5 years, with an overall survival (OS) of 19 months at a median follow up of 30 months. Patients who received intensive chemotherapy achieved a median OS of 38 months with a disease free survival (DFS) of 34 months. On univariate analysis NPM1 VAF had no effect on OS or DFS at the lower, median and upper quartile VAF values for the cohort. There was a statistically significant association of NPM1 high VAF with the presence of FLT3 ITD mutations.

**Conclusion:** High NPM1 VAF was not shown to impact DFS or OS in this cohort of sequential NPM1 mutation positive AML patients. An association between high VAF and FLT3 ITD status was observed, and this may contribute to the inferior outcomes seen in patients with a high NPM1 VAF.

### **References:**

1. Patel et al. High NPM1-mutant allele burden at diagnosis predicts unfavorable outcomes in de novo AML. *Blood*. 2018; 131(25): 2816 – 2825.
2. Rothenberg-Thurley et al. NPM1 Variant Allele Frequency and Outcomes in AML. *Blood*. 2018; 132(1): presentation and abstract 1486.
3. Hussein et al. NPM1 mutant variant allele frequency correlates with leukemia burden but does not provide prognostic information in NPM1-mutated acute myeloid leukemia. *Am. J. of Haem.* 2019; 94(6): 158-160.

## Urban-rural survival outcomes in acute myeloid leukaemia patients in Queensland.

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### Aim

Investigate whether there is evidence of an urban–rural disparity in survival outcomes for acute myeloid leukaemia (AML) patients and evaluate if other factors influenced patient outcomes.

### Method

Subjects included 2,784 patients diagnosed with AML from 2000-2015 in Queensland. Data was collected for survival time in months, and patient demographics including residence, socioeconomic status, age group, sex, Indigenous status, and AML sub-type from the Oncology Analysis System created by the Queensland Cancer Control Analysis Team. Kaplan-Meier survival curves were generated and variables with  $P$ -value  $<0.05$  by log-rank test were reported as statistically significant.  $P$ -values  $<0.15$  were included in multivariate Cox regression models to estimate hazard ratios (HR).

### Results

Univariate analysis showed only socioeconomic status, age group, sex, and AML sub-type had significant differences between survival curves ( $P < 0.05$ ). Socioeconomic status curves suggested patients in the disadvantaged group had the poorest median survival of 9 months from diagnosis (7.35-10.65 95% CI), while the affluent group had the highest of 14.4 months (10.23-17.77 95% CI). However, while the HR increased with increasing disadvantage in this group, this was not statistically significant ( $P = 0.11$ ). Age group predictably demonstrated a significant trend of decreasing median survival with increasing age. Differences based on sex were significant in the univariate analysis ( $P = 0.042$ ), but males and females had the same median survival. AML sub-type showed significant differences ( $P=0.000$ ) with median survival lowest for patients with therapy-related myeloid neoplasm at 6 months (2.98-9.02 95% CI).

### Conclusion

This study shows there was little evidence for an urban–rural disparity for AML patients diagnosed 2000-2015, despite published evidence for an urban–rural disparity in the major cancers in Australia. Increased age, AML sub-type, and lower socioeconomic status were factors that significantly contributed to poorer survival.

## Age subgroup analysis of HRQoL of blinatumomab versus standard-of-care chemotherapy in patients with r/r Ph- B-ALL in the TOWER study

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**Background:** Despite the availability of new therapies for acute lymphoblastic leukaemia (ALL), older patients have historically poor responses to treatment and poor outcomes versus younger patients, with 5-year survival rates of approximately  $\leq 20\%$ . In this subgroup analysis, we assessed HRQoL of older patients versus younger patients who received blinatumomab or SOC chemotherapy.

**Methods:** Study design details have been published previously. HRQoL was assessed using the EORTC QLQC30 Questionnaire on days 1 (baseline), 8, and 15, on day 29 of cycle 1; day 1, 15, and 29 of each consolidation cycle; and at the safety follow-up. The questionnaire included 1 global health status scale, 5 functioning scales, 3 symptom scales, and 6 single-symptom items. For global health status and functioning scales, a higher score indicates better HRQoL; for symptom scales/items, a lower score indicates better HRQoL. A 10-point change was viewed as the minimum clinically important difference in EORTC QLQ-C30 (Zikos E, et al. EORTC. 2016). In this analysis, HRQoL in TOWER was assessed using two different age cutoffs:  $<35$  versus  $\geq 35$  years (the randomisation stratification in TOWER) and  $<55$  versus  $\geq 55$  years (the stratification factor for INO-VATE, a phase 3 trial for another therapy in r/r ALL). Analyses included patients with baseline and  $\geq 1$  postbaseline result of any multi-item scale or single-item measure. Time to deterioration (TTD) analyses assessed the treatment effect based on timing from the initiation of treatment to a  $\geq 10$ -point decrease for the functional scales and/or a  $\geq 10$ -point increase for the symptom scales respectively.

**Results:** Mean change from baseline in scores for each scale/item were summarized for cycle 1 (Figure). TTD analyses are shown in the Table.

**Conclusions:** Consistent with the efficacy results, compared with SOC, blinatumomab improved HRQoL and delayed the deterioration in HRQoL regardless of the age group in patients with r/r Ph-BCP ALL.

Table. HR and Log-Rank P Values of TTD Analyses

	<35 Years		$\geq 35$ Years		<55 Years		$\geq 55$ Years*	
	HR (95% CI) <sup>a</sup>	P <sup>b</sup>						
Global health status	0.49 (0.29–0.86)	0.01	0.68 (0.44–1.07)	0.066	0.55 (0.36–0.84)	0.004	0.60 (0.36–0.99)	0.037
Physical functioning	0.49 (0.30–0.80)	0.003	0.87 (0.57–1.33)	0.44	0.59 (0.40–0.86)	0.004	0.60 (0.36–0.99)	0.037
Role functioning	0.49 (0.31–0.77)	0.002	0.69 (0.46–1.03)	0.053	0.59 (0.41–0.85)	0.003	0.59 (0.33–1.03)	0.05
Cognitive functioning	0.51 (0.30–0.87)	0.01	0.78 (0.52–1.17)	0.13	0.63 (0.42–0.94)	0.003	0.70 (0.39–1.23)	0.18
Emotional functioning	0.49 (0.26–0.92)	0.023	0.73 (0.42, 1.27)	0.25	0.48 (0.30–0.79)	0.003	0.90 (0.40–2.00)	0.78
Social functioning	0.59 (0.36–0.95)	0.026	1.05 (0.68–1.62)	0.89	0.72 (0.48–1.07)	0.085	1.05 (0.58–1.90)	0.85
Fatigue	0.47 (0.30–0.73)	<0.001	0.59 (0.40–0.87)	0.004	0.48 (0.33–0.68)	<0.001	0.59 (0.34–1.03)	0.054
Pain	0.45 (0.28–0.71)	<0.001	0.62 (0.41–0.93)	0.013	0.48 (0.33–0.69)	<0.001	0.66 (0.37–1.18)	0.13
Nausea and vomiting	0.20 (0.12–0.36)	<0.001	0.52 (0.32–0.84)	0.008	0.26 (0.17–0.39)	<0.001	0.66 (0.37–1.18)	0.13
Dyspnea	0.66 (0.35–1.22)	0.16	0.54 (0.32–0.91)	0.016	0.67 (0.41–1.10)	0.093	0.41 (0.20–0.85)	0.012
Appetite loss	0.22 (0.12–0.37)	<0.001	0.58 (0.37–0.90)	0.012	0.31 (0.21–0.46)	<0.001	0.70 (0.38–1.32)	0.25
Insomnia	0.37 (0.22–0.62)	<0.001	1.32 (0.82–2.14)	0.28	0.48 (0.32–0.72)	<0.001	2.10 (1.05–4.19)	0.038
Constipation	0.38 (0.21–0.68)	<0.001	0.58 (0.34–0.98)	0.037	0.53 (0.33–0.85)	0.007	2.10 (1.05–4.19)	0.006
Diarrhea	0.27 (0.15–0.47)	<0.001	0.40 (0.24–0.66)	<0.001	0.28 (0.18–0.43)	<0.001	0.53 (0.26–1.10)	0.072
Financial difficulties	0.47 (0.25–0.88)	0.016	1.15 (0.64–2.08)	0.68	0.60 (0.36–0.99)	0.037	1.67 (0.72–3.88)	0.24

CI, confidence interval; HR, hazard ratio

\*The small sample size limited the statistical power in this subgroup.

<sup>a</sup>Log-rank test stratified by age, prior salvage therapy, and prior alloHCT. HR <1.0 indicates a lower average event rate and longer survival for blinatumomab versus SOC.



D, day; MID, minimal clinically important difference.

H007

## **Adult Acute Lymphoblastic Leukaemia in Western Australia: a 10 year review and comparison with historical data**

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**Introduction:** Adult Acute Lymphoblastic Leukaemia (ALL) remains a rare disease with poor prognosis. The overall survival is 30% at 5 years in adults as compared to 90% overall survival in children with ALL. We investigated the changes in demographic, treatment, cytogenetics and overall survival from 2009-2019.

**Method:** Retrospective analysis of patient with cytogenetic diagnosis of ALL in Western Australia (WA) between 2009- May 2019.

**Results:** One hundred thirty two adult patients with ALL were diagnosed in the last 10 years with median age of diagnosis of 50.1 years and a 2:1 male to female ratio. 15% of patients had a white cell count for more than 35 at the time of diagnosis. Cytogenetic analysis of these patients showed t(9,22) abnormality in 23.8% patients, hyperdiploidy (11.2%), hypodiploidy (9%) and normal karyotype (8%). Treatment regimens were Hyper-CVAD in 54% of patients, paediatric based regimen (6%) and enrolment of clinical trial (11%), palliative regimen (17%) and unknown in 11% of patients. 29% of patients received an allogenic bone marrow transplant after achieving remission to consolidate response. This was predominantly with matched unrelated donors (57%) followed by sibling donors (34%) and cord donors (5%). Overall survival was the whole cohort is 50% with a 27.1 month median follow-up period.

**Conclusion:** The demographic remains unchanged in WA in the last 20 years with no improvement in overall survival. Further evaluation is required in the role of monoclonal antibodies in improving the overall survival of adult patients with ALL.

### **References:**

1. Faderi et al Acute Lymphoblastic Leukaemia. Cancer 2010;116:1165-76.

## Over 25 years of Core Binding Factor AML in Western Australia

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**Aim:** Among the AML subtypes, approximately 7-12% have the t(8;21) and inv(16) mutation.[1] with most guidelines suggesting these patients can be treated with chemotherapy alone due to its favourable risk profile.[2] Multicentre group trials have reported the average 5 year OS rates to be 45-66% in this risk group[1] and 44% at 10 years.[3] Furthermore, the 4 year OS in this favourable risk group is 66% compared to 4% in the highest risk monosomy group.[4] We aim to analyse the characteristics and outcomes of patients diagnosed with t(8;21) and inv(16) AML in WA between 1991-2018.

**Method:** Retrospective data from 2 large population based studies evaluating AML in adult patients in (16 years or older) WA between 1991-2005 and 2006-2018 were amalgamated. Patients with t(8;21) or inv(16) were extracted and analysed. Median follow-up was 91 months.

**Result:** 101 patients were identified and 53 were t(8;21) and 48 were inv(16). 76 patients were <60 and 25 patients >60yo with a median age of 50.1. 88% were treated intensively.

Median PFS overall was 15 months. There was no significant difference in t(8;21) vs inv(16) groups (HR 0.88; 95% CI 0.52-1.49), or the era of diagnosis comparing 1991-2005 vs 2006-2018 (HR 1.16; 95% CI 0.68-1.97). Age significantly impacted on PFS with median OS 23 months in ≤60 compared with 8 months in >60 (HR 0.41; 95% CI 0.21-0.82). Of 34 patients who relapsed, 24 received a haematopoietic stem cell transplant (9 autologous, 15 allogenic).

Median OS was 53 months with estimated 5 year survival 49%. There was no significant difference in t(8;21) vs inv(16) groups (HR 0.95; 95% CI 0.53-1.70) or era of therapy (HR 1.10; 95% CI 0.61-1.06). Age was again a significant factor, median OS not reached in ≤60 compared with 11 months in >60 (HR 0.18; 95% CI 0.18-0.77).

**Conclusion:** Our results confirm that t(8;21) and inv(16) AML occurs mainly in younger patients, and most are treated intensively. OS outcomes are consistent with multicenter group trials.

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H009

## **Presentation and clinical progress of a patient with denovo Philadelphia-chromosome positive T-cell Acute Lymphoblastic Leukemia**

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### Background

This case describes the progress of a patient with denovo Philadelphia-chromosome positive T-cell Acute Lymphoblastic Leukemia and reviews the literature of this rare entity.

### Case report

A 22-year old Indigenous male with super-morbid obesity, presented with shortness of breath, pulmonary leukostasis and marked leucocytosis ( $427 \times 10^9/l$ ). The peripheral blood film showed a significant blast population. Blasts appeared medium sized with a high N:C ratio, minimal cytoplasm with some cells showing nuclear indentation and small nucleoli. Flow cytometry of the peripheral blood showed blast population expressing immunophenotype of T-lymphoblasts: positive for CD3, CD2, CD4, CD5, CD7, CD9, CD13, CD1a (20%), and nTdT. Cytogenetic analysis demonstrated the Philadelphia chromosome and RT-PCR showed a BCR-ABL1 breakpoint as E1A2, resulting in the P190 fusion protein.

Despite his age, he was deemed to be not suitable for an intensive paediatric protocol. After receiving 2 cycles of HyperCVAD and Imatinib, he reached morphologic remission but remained MRD positive with a BCR-ABL1 ratio of 0.3. He had a further 4 cycles of HyperCVAD with dasatinib. Unfortunately, he relapsed 8 months later with a T315I mutation, and was switched to ponatinib. Haplo-identical Allogeneic Stem Cell Transplantation is being planned.

### Discussion

The Philadelphia chromosome is the hallmark of Chronic Myeloid Leukaemia (CML), however, it is also present in a subset of patients with denovo acute leukemia. Differentiating CML in T-cell blast crisis from Philadelphia positive T-ALL is a challenge. Due to the rarity of this abnormality in T-ALL, the clinical significance is uncertain but likely represents a poor prognostic factor. Here we present the available literature in this rare disease subtype and present the methods to differentiate CML in blast crisis from denovo Acute Leukaemia with Philadelphia chromosome.

## Impact of minimal residual disease and CR/CR with partial hematologic recovery on survival after gilteritinib therapy in FLT3-mutated relapsed/refractory AML

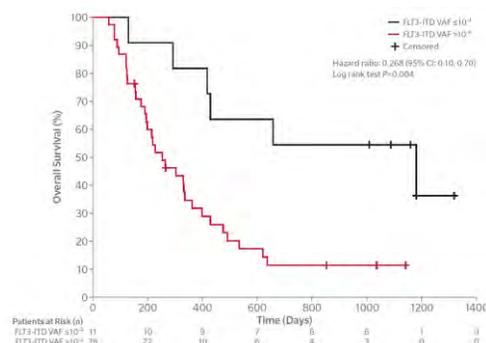
Mark J. Levis<sup>1</sup>, Alexander E. Perl<sup>2</sup>, Jessica K. Altman<sup>3</sup>, Jorge E. Cortes<sup>4</sup>, Catherine C. Smith<sup>5</sup>, Maria R. Baer<sup>6</sup>, David F. Claxton<sup>7</sup>, Joseph G. Jurcic<sup>8</sup>, Ellen K. Ritchie<sup>9</sup>, Stephen A. Strickland<sup>10</sup>, Raoul Tibes<sup>11</sup>, Jason Hill<sup>12</sup>, Matt Rosales<sup>12</sup>, **Maha Cooney**<sup>13</sup>, Erkut Bahceci<sup>12</sup>

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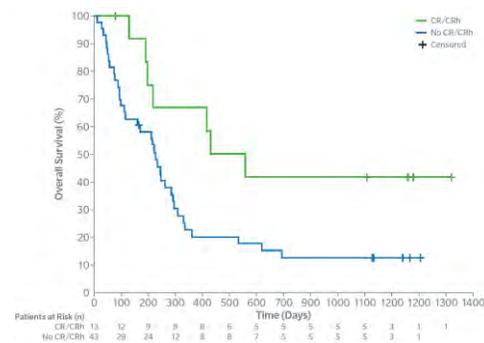
**Aim:** To analyze the impact of minimal residual disease (MRD) and achievement of complete remission/complete remission with partial hematologic recovery (CR/CRh) on overall survival (OS) in patients with FLT3<sup>mut+</sup> R/R AML who received once-daily oral gilteritinib in the phase 1/2 CHRYSALIS study (NCT02014558). **Methods:** Minimal residual disease was assessed by next-generation sequencing (NGS). An ITD variant allele frequency (VAF)  $\leq 10^{-4}$  defined MRD-negative (MRD-) status. Treatment response was evaluated according to the CR/CRh rate. **Results:** Of 108 FLT3-ITD+ patients analyzed for MRD, 95 received  $\geq 80$ -mg/day gilteritinib, which induced maximum FLT3 inhibition and antileukemic response. Of the 95 patients, 82 were MRD-positive (MRD+) and 13 achieved MRD- status at any post-baseline time point; 49 of 95 patients achieved composite complete remission (CRc; ie, CR plus CR with incomplete hematologic or platelet recovery) and 11 were MRD-. Of 46 patients who did not achieve CRc, two were MRD-. Patients who achieved CRc and were MRD- (n=11) had longer median OS (168.7 weeks) than the MRD+ subgroup (n=38; 36.1 weeks;  $P=.004$ ) (**Figure 1**). Of 95 patients who received  $\geq 80$ -mg/day gilteritinib assessed for MRD, 24 achieved CR/CRh, of whom 10 (41.67%) were MRD-. Of the 71 patients without CR/CRh, three (4.2%) were MRD-. Patients in the 120-mg/day cohort were previously shown to have longer survival than other dose cohorts. Of 56 patients who received 120-mg/day gilteritinib, 13 achieved CR/CRh and had a median OS of 70.6 weeks and a 52-week survival probability of 66.7%; the non-CR/CRh subgroup had a median OS of 32.4 weeks and a 52-week survival probability of 20.2% (**Figure 2**).

**Conclusion:** Gilteritinib induced deep molecular responses in patients with FLT3-ITD+ R/R AML, with a potential association between MRD negativity and longer survival. Achievement of CR/CRh appears to be associated with a higher rate of MRD negativity and longer OS.

**Figure 1. Overall survival in patients with R/R AML who had a best overall response stratified by MRD status (FLT3-ITD VAF  $\leq 10^{-4}$  or  $> 10^{-4}$ ) following treatment with  $\geq 80$ -mg/day doses of gilteritinib**



**Figure 2. Overall survival in patients with FLT3<sup>mut+</sup> R/R AML who received 120-mg/day doses of gilteritinib stratified by CR/CRh status**



**Abbreviations:** AML, acute myeloid leukemia; CR, complete remission; CRh, complete remission with partial hematologic recovery; mut+, mutated; MRD, minimal residual disease; R/R, relapsed/refractory; VAF, variant allele frequency.

## Anti-thrombin III Replacement in Patients undergoing L-Asparaginase based Chemotherapy Regimens

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**Introduction:** Reduced anti-thrombin III (ATIII) is one of the mechanisms believed to contribute to the heightened risk of thrombotic events in patients undergoing chemotherapy containing L-asparaginase. The incidence of thrombosis in adult and children receiving L-asparaginase chemotherapy quoted in the literature range between 10% and 35% (Lauw et al, 2013; Mitchell et al, 2003). The THROMBOTECT trial demonstrated that ATIII replacement is effective in reducing thromboembolism during acute lymphoblastic leukemia (ALL) induction in the paediatric population in a randomised controlled setting (Greiner et al, 2019). There is less evidence supporting ATIII use in the adult population.

**Aim:** An audit was undertaken to assess the proportion of thromboses amongst adult patients who received ATIII replacement to evaluate the efficacy of this practice.

**Method:** Anti-thrombin III replacement data available in Liverpool Hospital between 2012 and 2018 were collated. Only adult patients (age>18 years) who presented to the haematology unit and received L-asparaginase based chemotherapy were included.

**Results:** Twenty-two patients who received ATIII replacement were identified. Anti-thrombin III levels were monitored three times a week and ATIII replacement with Thrombol-VF was given to maintain ATIII level above 60%. A total of 260,000IU of Thrombotrol-VF was dispensed for this patient group. Ten patients underwent BFM 2000 protocol for B-ALL or T-ALL, SMILE regimen (7) for NK/T cell lymphoma, CALGB chemotherapy (3) for B-ALL, U-Cal2014 (1) for T-cell prolymphocytic leukemia, and ALL 6 protocol (1) for T-ALL. Four patients experienced thrombotic events (Table 1). Three patients experienced thrombotic events during induction of BFM 2000. All these patients had therapeutic anticoagulation in the form of enoxaparin for between three to six months. All treatments were not delayed due to thrombotic events.

**Table 1: Patient characteristics who experienced thromboembolic events and anticoagulation therapy**

Patient	Age	Sex	Disease	Chemotherapy	Thrombotic Events	Treatment
Patient #1	34	F	T-ALL	BFM 2000	Left cortical vein thrombosis during induction	Therapeutic enoxaparin for six months
Patient #2	30	F	B-ALL	BFM 2000	Bilateral Cerebral cortical vein thrombosis and bilateral upper limb PICC associated deep vein thromboses during induction	Therapeutic enoxaparin for three months
Patient #3	36	M	T-ALL	BFM 2000	Right PICC line associated deep vein thrombosis during induction, pulmonary embolism during induction consolidation	Therapeutic enoxaparin for six months

**Conclusion:** The rate of thromboembolic events in our cohort was 14% (3/22). The cost of 1000IU Thrombotrol-VF is \$1407.20. While ATIII replacement may be effective in the adult population receiving L-asparaginase chemotherapy, other cost effective options may be equally efficacious. Prospective, randomised-control studies similar to the THROMBOTECT study are needed to assess this in the adult population. (Greiner et al, 2019).

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## Relapsed Isolated Myeloid Sarcoma: a therapeutic dilemma

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Myeloid sarcoma (MS) is a rare extramedullary haematological neoplasm occurring with or without bone marrow involvement; most often in the form of acute myeloid leukaemia (AML). The low incidence of MS does not enable prospective clinical trials and the optimal treatment strategy remains unclear. Very few cases of *de novo* MS without bone marrow involvement have been reported (Table 1).

A case of relapsed MS without bone marrow involvement at initial diagnosis, nor at relapse 33 months later, is presented.

A 33-year-old female presented with a nasal mass confirmed to be MS on biopsy in August 2016. Myeloid blasts are of normal karyotype, FLT3 negative, NMP1 positive and IDH2 positive. Bone marrow was not involved. She was treated with 7+3 (cytarabine and idarubicin) induction chemotherapy and three HiDAC consolidations, with complete resolution of the nasal mass. The patient relapsed in May 2019 with a recurrent nasal mass and tissue biopsy confirmed relapse of MS. Bone marrow again showed normal trilineage haematopoiesis.

Aggressive induction chemotherapy such as that used in AML is recommended in *de novo* and relapsed MS. The use of radiotherapy is guided by the tumour site and is of uncertain benefit. Allogeneic haematopoietic stem cell transplant (HSCT) has been proposed as an effective treatment strategy for *de novo* and relapsed MS with or without bone marrow involvement, although limited literature supports this. While early reports suggested inferior prognosis with extramedullary AML, recent expert opinion recommends treatment according to conventional cytogenetic and molecular prognostic features.

This case presents a therapeutic dilemma given the lack of evidence for best treatment approach and historically poor outcomes. This case is presented in order to generate discussion around treatment of extramedullary AML and the role of allogeneic HSCT for this rare haematological malignancy.

Table 1: Summary of recent literature on isolated myeloid sarcoma (MS)

Authors	Year	Study type	Relevant conclusions
Yamauchi <i>et al.</i>	2002	Case report with retrospective case analysis <i>17 cases of de novo isolated MS</i>	Non-leukaemic periods after diagnosis of isolated MS was significantly longer in patients receiving systemic chemotherapy than in those with surgical resection or local irradiation only.
Tsimberidou <i>et al.</i>	2003	Retrospective case analysis <i>21 cases of de novo isolated MS</i>	Overall survival was prolonged in patients treated with combined chemotherapy and radiotherapy compared to chemotherapy or radiotherapy alone.
Chevallier <i>et al.</i>	2008	Retrospective case analysis <i>6 cases of de novo isolated MS</i>	First line allo-HSCT is a valid therapeutic option for MS.
Yilmaz <i>et al.</i>	2013	Systematic review	Most common location for MS is soft tissues. HSCT should be considered in suitable patients with relapsed disease, following reinduction by AML chemotherapy.
Solh <i>et al.</i>	2016	Literature review	Radiotherapy does not confer additional survival benefit compared to systemic chemotherapy alone. Recommend allo-HSCT as consolidation therapy for relapsed extramedullary AML.
Lazaroto <i>et al.</i>	2017	Retrospective case analysis <i>9 cases of de novo isolated MS</i>	Improved overall survival in patients achieving post induction CR and with allo-HSCT.
Kaur <i>et al.</i>	2018	Retrospective case analysis <i>6 cases of de novo isolated MS</i>	Improved overall survival in patients attaining post induction CR. Allo-HSCT may offer long-term remission.

## **A rare case of synchronous lymphoid malignancy in monozygotic twins**

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**Aim:** Concordant and synchronous childhood acute lymphoblastic leukaemia is an uncommon occurrence amongst twins. We present an interesting case of monozygotic twins who presented with Precursor B acute lymphoblastic leukaemia within a day of each other. We review the literature regarding this entity and raise questions for future research.

**Case:** A 2 y.o girl presented with a several week history of fatigue, and pallor. A full blood count (FBC) and blood film revealed pancytopenia. Blasts were estimated at 19%. Immunophenotyping of peripheral blood confirmed pre-B-acute lymphoblastic leukaemia. At the time of diagnosis, her twin had a two day history of fatigue, sore throat and earache. A FBC on the latter twin revealed pancytopenia with a lymphocytosis. Blasts were estimated at 45%, with immunophenotypic expression consistent with that of her twin. Subsequent diagnostic bone marrow aspirates revealed each sister had an abnormal clone containing a translocation between the short arms of chromosomes 11 and 12. Additional cytogenetic abnormalities were identified in one twin.

**Method:** Clinical, pathologic, cytogenetic, and therapeutic data at diagnosis and throughout the course of treatment, will be described.

The literature was examined for clinical, pathologic, cytogenetic and peri-natal features. Comparison and contrast was performed to determine similarities and differences between previously published cases and the current case.

**Results:** To our knowledge this is the first report of childhood acute lymphoblastic leukaemia with synchronous presentation in monozygotic twins harbouring the translocation (11;12) (p11.2;p13).

**Conclusion:** The first report of concordant leukaemia in twin children appeared in 1882. Only 70 monozygotic twin pairs with concordant leukaemia have been reported in the literature. This case offers a unique opportunity to better understand the evolution of mutations and development of childhood leukaemia. The synchronous presentation alludes to the role the cytogenetic abnormality shared by both twins, may have on the “neoplastic biological clock”.

H019

## **When rare meets rarer: acute undifferentiated leukaemia with trisomy 4 and FLT3-ITD mutation**

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Acute undifferentiated leukaemia (AUL) is a subcategory of acute leukaemias of ambiguous lineage (ALAL, WHO 2016) characterised by the lack of expression of lymphoid or myeloid lineage markers. Trisomy 4 as the sole cytogenetic abnormality in acute leukaemia is extremely rare (<1%) let alone in ALAL with only 5 reported cases in literature so far. Mutations in the FLT3 receptor tyrosine kinase has significant prognostic and therapeutic implications in acute myeloid leukaemia, but this has never been reported in AUL.

A 77-year old male was found incidentally with pancytopenia and circulating blasts. Bone marrow examination revealed extensive marrow infiltration with atypical blasts in the absence of significant dysplasia. Immunophenotyping studies were positive for CD34, CD117, CD13, HLA-DR and CD7 (dim). Lineage specific markers cyCD3, MPO, cyTDT and cyCD1a were all negative. Cytogenetic analysis indicate trisomy 4 and next generation sequencing revealed a FLT3-ITD mutation with no other mutations identified.

He underwent palliative induction chemotherapy with low-dose cytarabine (LDAC) and thioguanine but failed to achieve morphological remission, albeit with significant reduction in leukaemia burden. At time of abstract submission, re-induction treatment with LDAC and sorafenib was commenced. His outcomes and other clinical findings will be detailed at the meeting.

We report a rare case of ALAL with trisomy 4 mutation as the sole cytogenetic abnormality, with a concomitant FLT3-ITD mutation that has never previously been described in AUL. Due to the rarity of this disease entity, there is a lack of consensus on the most appropriate treatment approach. The presence of a FLT3-ITD mutation allows for a more targeted approach but further studies are required.

## Double minute chromosomes in acute myeloid leukaemia: a single-centre case series

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### Introduction:

Double minutes chromosomes (*dmin*) are small chromatin bodies that are acentric, atelomeric fragments containing 1-2MB of DNA in multiple copies within a single cell. They are commonly observed in solid tumours but are rare in haematological malignancies (~1%). The presence of *dmin* is often associated with a poor prognosis, rapid disease progression and shortened overall survival. We present four patients with acute myeloid leukaemia (AML) with *dmin* detected on conventional karyotyping, with the amplified region identified by SNP microarray.

### Method:

All cases of AML diagnosed between 2014 and 2019 at ACT Pathology, Canberra Hospital were reviewed. Direct bone marrow culture in addition to 24 and 48 hour synchronised cultures were performed in all samples. SNP microarray was performed on DNA extracted from the bone marrow aspirate and analysed to identify the origin of the *dmin*. Clinical data, including treatment response and outcomes were obtained from medical records.

### Result:

In the 92 cases reviewed, the presence of *dmin* was observed in four patients (incidence: 0.04%). The AML cases consisted of AML with minimal differentiation (n=1), AML with myelodysplastic related changes (n=2) and mixed phenotypic acute leukaemia, B/myeloid (n=1). There were 2 men and 2 women, with a median age of 64.5 (range: 61 to 82 years). None had prior history of cytotoxic therapy or solid organ malignancy. Only 50% had complex cytogenetics. SNP microarray identified *MYC* amplification (n=3) and loss of NF1 (n=1). At time of abstract submission, two patients were deceased and the other two remain in complete remission (5 months and 35 months, respectively).

### Conclusion:

*Dmin* represent gene amplification, which is seen in genomic instability of tumours and often lead to poor treatment outcomes and increase drug resistance leading to a shortened survival. Ongoing studies are recommended to further evaluate their role in haematological malignancies.

## Donor-derived *NPM1mut* acute myeloid leukemia

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**AIM/METHOD:** We report two allogeneic stem cell transplant recipients, who developed *NPM1mut* AML. We performed a literature review to assess management strategies in these patients, in particular whether donor derived *NPM1mut* AML should be treated as a favourable prognosis *de novo* AML or as secondary AML.

### RESULTS

A man was diagnosed with high-risk myelodysplasia with a monosomy 7 mutation at the age of 23 years. One year later, he received a haploidentical transplant. At the age of 41 years, he developed an *NPM1mut* and *TET2mut* AML with normal cytogenetics. He responded to intensive chemotherapy and is minimal residual disease (MRD) negative at 18 months since diagnosis.

The second involved a 65-year old woman who had received a sibling transplant for severe aplastic anaemia and was *NPM1mut* negative in 2013. In February 2019, she developed *NPM1mut* and *WT1mut* AML with normal cytogenetics. She is undergoing intensive chemotherapy, and her *NPM1mut* levels on April 2019 demonstrated a 3.4 log reduction reflecting an excellent MRD response to induction.

Both had DNA chimerism assays of their peripheral blood demonstrating 98-100% full donor chimerism. Their donors have normal peripheral blood counts, and are *NPM1mut* negative.

### DISCUSSION

In a previous multicohort study, donor-derived leukaemia patients had a median survival of 11 months; most patients who received a second allogeneic transplant did so from a new donor.<sup>1</sup> *NPM1mut* status confers a more favourable survival rate in patients with therapy-related AML.<sup>2</sup> *NPM1mut* AML provides a target for MRD monitoring, with excellent outcomes for MRD-negative cases.

### CONCLUSION

The outcome of patients with donor-derived *NPM1mut* AML remains unknown and these cases are illustrative of the therapeutic challenge they provide. In the setting of MRD monitoring and molecular classification it may be viable to treat these patients as *de novo* AML, reserving transplant for molecular progression.

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## Transcriptome analysis in Acute Myeloid Leukemia by NGS sequencing: prognostic and therapeutic implications

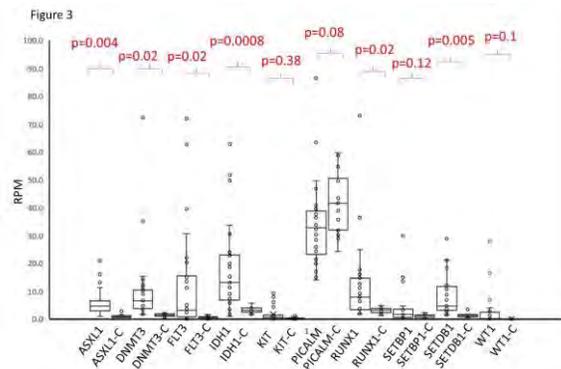
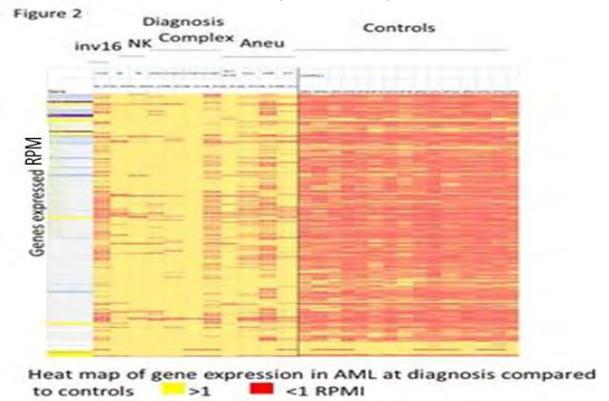
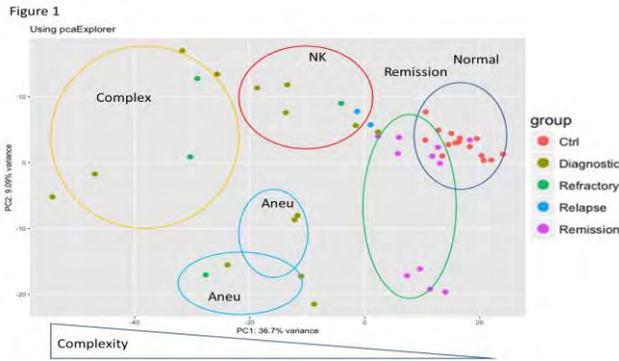
**Annalise Martin**<sup>1,2</sup>, Tony White<sup>2</sup>, Hun Chuah<sup>1,2,3</sup>, Belinda Guo<sup>2</sup>, Richard Allcock<sup>2</sup>, Peter Tan<sup>1</sup>, Michael Leahy<sup>1</sup>, Wendy Erber<sup>2</sup>

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**Background:** AML is a heterogenous disease driven by epigenetic and cytogenetic aberrations within haematopoietic stem cells leading to their uncontrolled proliferation. Here we tested the hypothesis that transcriptome sequencing from platelets can detect the AML signature and can potentially be a platform to characterise AML at diagnosis, during treatment and at relapse.

**Methods:** RNA was isolated from platelets from 25 patients (9 diagnosis-relapse pairs post induction chemotherapy, longitudinal samples of patients treated with hypomethylating agents, decitabine (n=3), Azacitidine (n=3), Azacitidine + IDH1 inhibitor (n=1) and patients in remission (n=9) and healthy controls (n=15). Transcriptome next generation sequencing of platelets was done using Ion AmpliSeq Transcriptome Human Gene Expression Kit. Briefly, RNA was sequenced at a depth of 6-10 x 10<sup>6</sup> reads per sample with median read length of 110bp on an Ion Proton Sequencer. Comparison of transcripts was done using RPM output from Torrent Suite Server and R statistical programme comparing principal component analysis (PCA). Comparison of transcript levels detected within diagnostic and relapsed samples was done using Student T tests, p<0.05 was considered significant. Ethics approval to collect and study patient material was obtained from RPH and UWA.

**Results:** Principal component analysis of variation in transcriptomes derived from healthy controls and AML patients demonstrates clustering of patients based on their cytogenetics at diagnosis compared with healthy controls and patients in remission (Figure 1). Heat map of the transcriptomes shows increased gene expression at diagnosis compared to healthy patients (Figure2). Transcripts are significantly elevated at multiple leukaemogenic loci FLT3, ASXL1, SETDB1 (Figure 3). Gene expression profiles change during treatment and response can be followed longitudinally. **Conclusion:** We were able to identify a changes in AML-associated gene transcripts which may be used to monitor treatment response in patients.



## Azacitidine as upfront therapy improves survival outcomes in elderly patients: a Western Australian retrospective, multicentre study.

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**Background:** Elderly patients with Acute Myeloid Leukaemia present a therapeutic challenge with increased toxicity to conventional induction regimens and presence of other comorbidities.

**Aims:** Front line Azacitidine therapy was compared retrospectively to conventional induction treatment or best alternate therapy (BAT) in AML patients presenting to tertiary hospitals in WA over the age of 60 years, from 2008 to 2018 to assess survival outcomes.

**Methods:** Of 855 patients with newly diagnosed AML, patients over 60 years were studied (n=484). Effect of variables like age, secondary or de novo AML, blast count at diagnosis, cytogenetic risk as per ELN guidelines on survival outcomes was examined using Kaplan Meier survival analysis and Cox regression analysis using Long rank test or Hazard ratios to test for significance. P Value of less than 0.05 was considered significant.

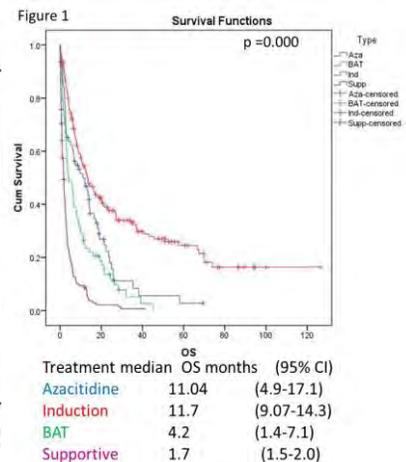
**Results:** Of the treated patients (n=305), upfront Azacitidine, best alternate therapy (BAT) or conventional induction treatment was administered to 73, 69 and 163 patients respectively while 179 received supportive care. Patients received Azacitidine subcutaneously daily over 5+2 days for a median of 5 cycles (range 0.2-23). Number of cycles of azacitidine received influenced outcome with <5 cycles median OS of 2.89 months (1.2-4.4) versus >5 cycles median OS 14.4 mo (10.3-18.6), p=0.009. Patients treated with Azacitidine had a similar OS to patients receiving conventional induction treatment, 11.04 months (4.9-17.1) versus 11.7 (9.07-14.3) and showed a favourable OS compared with BAT 4.2 months (1.4-7.1) p=0.00 or supportive treatment 1.7 months (1.5-2.0) p=0.000 (Figure 1). Secondary AML, high blast cell count at diagnosis, intermediate and poor cytogenetics has a significantly adverse effects on survival (Table 1).

**Conclusion:** Azacitidine in the real world is comparable with clinical trial data AZA-AML-001 trial, and improves OS. Combination therapy

Table 1 Demographic and treatment response in elderly AML population

Covariate	n	Univariate		Multivariate	
		OS (95% CI)	p value	HR (95% CI)	p value
Age median years	69.27 (60.16-89.09)				
Male	197	8.9 (7.07-10.7)	0.179	1.01 (0.98-1.16)	0.33
Female	108	12.03 (7.2-16.7)		0.887(0.67-1.16)	0.38
De novo	165	10.5 (6.7-14.4)	0.002	0.751 (0.56-0.99)	0.048
Secondary	140	8.3 (6.08-10.5)			
Blasts diagnosis median	47			1.006 (1.001-1.012)	0.032
Cytogenetic risk					
Favourable	11	51.1 (29.6-72.5)	0.000	1.49 (0.52-4.2)	0.45
Intermediate	176	12.03 (12.03-14.5)		0.29 (0.11-0.74)	0.01
Poor	114	6.2 (4.0-8.4)		0.66 (0.51-0.86)	0.003
Treatment					
Induction	163	11.7 (9.07-14.3)	0.000	0.57 (0.39-0.83)	0.004
Azacitidine	73	11.04 (4.9-17.1)		0.69 (0.45-1.06)	0.092
BAT	69	4.2 (1.4-7.1)			
NorthShore*	22	3.3 (0.9-5.7)	0.024 (vs Aza)		

Legend 1: 18 patients with t(15:17) were excluded. BAT: Northshore\* (thioguanine and cytarabine) n=22; trial n=15; hydroxyurea n=7; FLICC n=7; etoposide n=4; low dose cytarabine n=9, decitabine n= 6; 6MP n=1. Supportive/palliative n= 179, had a median OS of 1.74 months (1.5-2.0months).



## Geospatial profiling and outcomes of patients with Acute Myeloid Leukemia in Western Australia: a 10year multicentre, retrospective study

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**Background:** Acute Myeloid Leukemia is a heterogenous disease resulting from the acquisition of chromosomal aberration, driver mutations, epigenetic modifications and hence variable response to conventional chemotherapy.

**Aim:** To determine overall survival of patients with Acute Myeloid Leukemia presenting to tertiary hospitals in WA from 2008-2019.

**Method:** We studied 857 patients with AML identified from clinical and cytogenetic, databases. Diagnosis was confirmed on review of bone marrow reports. AML geospatial profiling was done by correlating the incidence rate per 100,000-year (n=841) to their postcodes (total of 177 postcodes in WA) within Tableau 2019.1. Survival outcomes were assessed using Kaplan-Meier method Log rank test was used determine difference in survival outcomes. Cox proportional hazard was used to determine significance on multivariate analysis. P value <0.05 was considered significant.

**Result:** We have identified areas of elevated AML burden around metropolitan Perth (n=635) with clustering of >6 per 100,000-years in 13 areas, compared with a median of 3.7 in 91 areas (p<0.05, using Student T-Tests) Figure 1. Of the patients receiving standard induction chemotherapy (n=529), age at diagnosis, secondary AML, cytogenetics risk and molecular markers like FLT3 and transplantation significantly influenced outcomes in multivariate analysis (Table 1).

**Conclusion:** Clustering of AML is seen in a few postcode areas and may be associated with environmental exposure to petrochemical or other industrial agents. Understanding spatial distribution of disease helps identify social, environmental and biological processes that impacts risk of developing AML in these areas. Survival appears comparable with previously described studies.

Table1. Outcomes in AML in Western Australia

Category	n	OS median months	(95% CI)	p value	Multivariate analysis		
					HR	95% CI	p value
Nil Treatment	310	2.8	2.4-3.3	0.000			
Aggressive	529	24.9	17.3-32.5				
Age median	55.36				1.074	0.852-1.3	0.547
<65 years	124	8.3	5.9-10.6				
>65 years	405	37.4	22.4-52.5				
Gender							
Females	247	24.5	14.9-34.1		1.07	0.82-1.35	0.57
Males	282	25.7	13.6-37.8				
De novo	438	35.04	18.9-51.1	0.000	1.016	1.006-1.025	0.001
Secondary	109	8.05	5.2-10.8				
Cytogenetics	529	24.9	17.3-32.5	0.000	0.125	0.75-0.2	0.000
Favourable	105	NR	NR				
Intermediate	302	23.1	17.0-29.0				
Poor	122	10.0	7.5-12.5				
FLT3-ITD-	200	7.6	18.7-48.9	0.166	1.1	0.7-1.6	0.5
FLT3-ITD+	94	7.7	5.1-35.5		0.71	0.51-0.99	0.048
NPM1+	102	27.1	17.1-37	0.42	1.25	0.88-1.7	0.19
NPM1-	192	35.7	16.6-54.7				

Figure 1



Clustering of AML in WA: increased density around metropolitan Perth

**Outcomes in older adults with newly diagnosed, high-risk/secondary AML who achieved remission with CPX-351 versus 7+3: phase 3 exploratory analysis**

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**Aim:** CPX-351 (Vyxeos®), a dual-drug liposomal encapsulation of cytarabine/daunorubicin at a synergistic ratio, is approved by the EMA and FDA for adults with newly diagnosed, therapy-related AML or AML-MRC. In a randomized (1:1), phase 3 study (NCT01696084) of 309 adults aged 60–75 years with newly diagnosed, high-risk/secondary AML, CPX-351 induction followed by consolidation significantly improved median overall survival (OS; 9.56 vs 5.95 months; HR=0.69 [95% CI: 0.52–0.90]; 1-sided *P*=0.003) and remission rates (CR+CRi; 73/153 [48%] vs 52/156 [33%]; OR=1.77 [95% CI: 1.11–2.81]; 2-sided *P*=0.016) versus 7+3. This exploratory analysis evaluated outcomes in patients achieving CR+CRi after CPX-351 or 7+3 induction.

**Methods:** Patients received 1–2 inductions with CPX-351 (100 units/m<sup>2</sup> [cytarabine 100 mg/m<sup>2</sup> + daunorubicin 44 mg/m<sup>2</sup>] as a 90-minute infusion on Days 1, 3, 5 [2nd induction: Days 1, 3]) or 7+3 (cytarabine 100 mg/m<sup>2</sup>/day continuously for 7 days + daunorubicin 60 mg/m<sup>2</sup> on Days 1–3 [2nd induction: 5+2]). Patients achieving CR+CRi could receive ≤2 consolidation cycles.

**Results:** Median OS was longer with CPX-351 versus 7+3 in patients with CR+CRi (**Figure 1**). Among patients achieving CR+CRi, 40/73 (55%) receiving CPX-351 and 24/52 (46%) receiving 7+3 underwent transplantation (OR=0.71 [95% CI: 0.35–1.44]); median OS landmarked from the transplant date is shown in **Figure 2**. Serious treatment-emergent AEs in ≥5% of patients achieving CR+CRi included febrile neutropaenia (CPX-351: 15%; 7+3: 12%), acute respiratory failure (7%; 2%), ejection fraction decreased (5%; 4%), sepsis (5%; 4%), pneumonia (3%; 6%), and pulmonary oedema (1%; 6%). No patient experienced early mortality within 60 days. Prolonged myelosuppression was observed with CPX-351 (**Table**).

**Conclusion:** Patients achieving CR+CRi with CPX-351 had longer median OS (overall and landmarked from transplant date) and a higher transplantation rate versus 7+3, suggesting deeper responses with CPX-351. The CPX-351 safety profile was consistent with that of 7+3.

Figure 1. OS in patients who achieved CR or CRi.

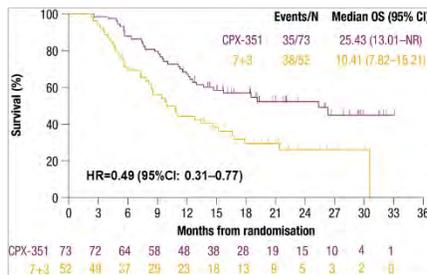
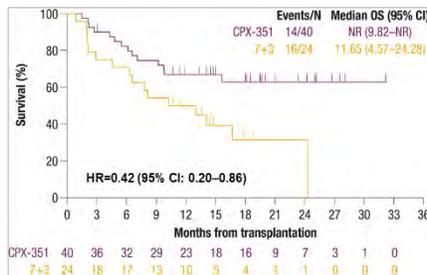


Figure 2. OS landmarked from the transplantation date in patients who achieved CR or CRi.



**Table. Time to neutrophil and platelet recovery in patients achieving CR+CRi.**

	<b>CPX-351 (n=73)</b>	<b>7+3 (n=52)</b>
<b>n (%)</b>		
Median (IQR) time to neutrophils ≥1000/μL	37 days (34–43)	29 days (27.5–35)
Median (IQR) time to platelets ≥100,000/μL	42 days (35–50)	32 days (28–40)
IQR, interquartile range.		

## **Should Myeloid Next Generation Sequence Analysis be incorporated into the risk stratification and management of Paediatric Acute Myeloid Leukaemia? Yes, No or Not yet?**

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### **Aim:**

Myeloid Next generation sequencing (NGS) has been increasingly incorporated into the clinical work up of newly diagnosed or relapsed paediatric Acute Myeloid Leukaemia (AML). A retrospective study was conducted to evaluate the impact of genetic mutations detected on Myeloid NGS panel on treatment and outcome.

### **Method:**

A retrospective study was conducted of patients with de novo AML diagnosed between 2008 and 2018 at a tertiary paediatric hospital. All patients had chromosomal analysis done on diagnostic bone marrow aspirate samples. An exome sequencing based 26-gene myeloid panel was performed on patients diagnosed between October 2014 and December 2018. Data collection consists of demographic information, initial white cell count and CSF involvement, cytogenetic results, mutations detected on the Myeloid NGS panel, chemotherapeutic regimen, disease response after each cycle, transplant in CR1, remission duration, treatment at relapse and overall clinical outcome.

### **Result:**

68 patients were diagnosed with de novo AML between 2008-2018 (median age: 7.61 years; range: 6 weeks - 17.29 years). 46 patients were diagnosed between January 2008–October 2014. 22 patients were diagnosed between October 2014–December 2018. 21 patients had Myeloid NGS analysis performed. 9/21(42.8%) patients had mutations detected on Myeloid NGS analysis. 2/5 patients in favourable risk group had additional mutations detected (1 with 2 *KIT* mutations, 1 with *KIT* and *NRAS* mutations). 3/11 patients in intermediate risk group had additional mutations detected (1 with *FLT3/ITD* mutation, 1 with *WT1* mutation, 1 with *CEBPA* mutation). 4/6 patients in poor risk group had additional mutations detected (2 with *NRAS* mutations, 1 with *FLT3/ITD* mutation, 1 with 2 *WT1* mutations and *NRAS* mutation).

### **Conclusion:**

Myeloid NGS analysis is able to identify additional genetic mutations in paediatric AML patients but its impact on treatment decisions is not yet well defined.

## Unexpectedly diagnosing acute promyelocytic leukaemia - the benefit of taking a broad diagnostic approach with next generation sequencing

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**Aim:** Next generation sequencing (NGS) in haematological malignancy contributes to diagnostic categorisation by detecting diverse genomic lesions. Here we describe the detection of a typical *PML-RARA* gene fusion by NGS in a patient presenting with a myeloid sarcoma, thereby making the unexpected diagnosis of acute promyelocytic leukaemia (APML).

**Method:** Extracted DNA was tested with the Peter MacCallum Cancer Centre PanHaem panel (targeting 300 recurrently mutated genes across haematological malignancies). Sequencing data was analysed with bioinformatic tools to detect sequence variants (HaplotypeCaller), whole genome copy number variation (CNspecter) and structural variants (GRIDSS).

**Results:** A 43 year old man presented with buttock pain and an FDG-PET scan showed an avid sacral lesion. A biopsy showed infiltration by sheets of immature, MPO-positive discohesive cells with granular eosinophilic cytoplasm. A bone marrow biopsy showed no evidence of leukaemia. A diagnosis of myeloid sarcoma was made and the patient underwent induction therapy with cytarabine and idarubicin ('7+3' regimen). There was structural improvement but residual FDG avidity (SUVmax 4.7) after induction chemotherapy, and he underwent one cycle of high-dose cytarabine (HIDAC) consolidation, resulting in complete metabolic remission. NGS performed on the sacral biopsy identified a fusion between exon 6 of *PML* and intron 2 of *RARA* (Figure 1A), confirmed with Sanger sequencing (Figure 1B). NGS also showed mutations in *WT1* and *CALR* and copy number loss involving chromosome 16q. In light of the revised diagnosis of APML, the patient commenced consolidation with ATRA and arsenic trioxide.

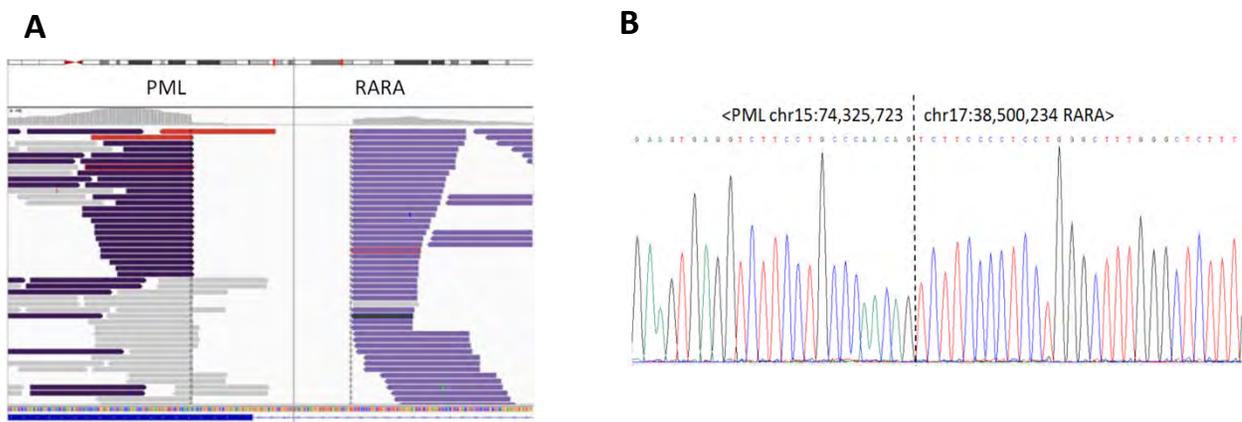


Figure 1. Detection of a *PML-RARA* translocation by (A) NGS and (B) Sanger sequence analysis.

**Conclusion:** We have described a case of occult APML, in which isolated extramedullary presentations are extremely rare. The revised diagnosis has dramatically altered the patient's treatment and prognosis. This case highlights the value of taking a broad NGS-based diagnostic approach in haematological malignancy.

## **Azacitidine In Treatment of Core Binding Factor (CBF) Acute Myeloid Leukemia (AML)**

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**Aim** – We discuss 2 cases of CBF AML successfully treated with the hypomethylating agent, azacitidine.

**Introduction** – CBF-AML includes patients with t(8;21)(q22;22), inv(16)(p13.1q22) or t(16;16). Standard AML therapy utilising combination anthracyclines and backbone of high-dose cytarabine is associated with durable remission in CBF-AML. However, few options are available in patients unsuitable for this chemotherapy regimen. The epigenetic modifying agent, azacitidine, is effective in older patients with AML (Dombret 2015). Its efficacy in CBF-AML remains unknown. We report the outcome of 2 cases of CBF-AML treated with azacitidine.

**Case 1** – A 30-year old female was diagnosed with therapy-related AML (t-AML), karyotype t(8;21) following treatment for Ewing's Sarcoma, with ongoing anthracycline-related cardiomyopathy and several postoperative complications. These precluded standard induction chemotherapies. A complete response (CR) was achieved after 3 cycles of azacitidine. Following improvement in cardiac function, she received induction and consolidation chemotherapy with cytarabine with ongoing CR >2 years.

**Case 2** – A 71-year old female developed t-AML with inv(16), trisomy 9 and ring chromosome, 8 years post-adjuvant anthracycline-based chemotherapy and radiotherapy for breast carcinoma. She received hydroxyurea prior to therapy and subsequently achieved CR following 3 cycles of Azacitidine therapy with <5% blasts on her bone marrow biopsy, ongoing for 6 months.

**Discussion** – There are limited treatment alternatives in CBF-AML with contraindications to chemotherapy or relapsed disease. CBF-AML is found to have epigenetic alterations for silencing gene function (Sinha 2015) including promoter hypermethylation of tumour suppressor genes (Ragon 2017). Hypomethylating agents such as azacitidine may potentially reverse this epigenetic silencing. While these agents are efficacious and less toxic in older adults with AML (Dumas 2017), the use of azacitidine in CBF-AML has not been explored. These cases highlight the potential benefit of utilising targeted therapy in patients with CBF-AML unsuitable for standard chemotherapy.

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H031

## **Etoposide dosing considerations in multi-organ failure**

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### **Aim:**

To describe the pharmacokinetic considerations of etoposide in a critically-ill patient with multi-organ failure.

### **Clinical Features:**

A 57-year-old female presented to hospital to receive consolidation chemotherapy for the treatment of acute myelomonocytic leukaemia. The admission was complicated by prolonged pancytopenia, persistent fevers, colitis and a *C. Glabrata* candidaemia resulting in sepsis and hypoxia requiring an admission to the intensive care unit.

In addition to fevers the patient developed severely deranged liver enzymes, hyperferritinaemia (250,000microg/L), hypertriglyceridaemia (5mmol/L) and a raised soluble-CD25 (17,780microg/L). A bone marrow biopsy was performed and the decision was made to treat for haemophagocytic lymphohistiocytosis (HLH).

The regimen was modelled on the HLH-94 Histiocyte Society Protocol which includes initial treatment with dexamethasone 10mg/m<sup>2</sup> daily and etoposide 150mg/m<sup>2</sup> twice weekly.

### **Literature Review:**

Etoposide and its metabolites are excreted in urine (56 and, 45% unchanged, respectively) and in faeces (44%). Studies of the use of etoposide in renal and/or hepatic impairment are limited and few have evaluated the effect of hypoalbuminaemia which is likely to be significant as etoposide is 97% protein bound. Additionally, hyperbilirubinaemia has been demonstrated to increase the free fraction of etoposide and poses a theoretical risk of toxicity.

### **Pharmacist Interventions, Case Progress and Outcomes:**

The specialist knowledge of the pharmacist was imperative in providing etoposide dosing recommendations. A 75% dose reduction was decided based on available evidence and first principles; in the setting of hyperbilirubinaemia (374microg/L), acute kidney injury (creatinine clearance 44mL/min) and hypoalbuminaemia (16g/L).

The patient's platelets and liver enzymes improved after one dose of etoposide however the patient soon deteriorated after developing posterior reversible encephalopathy syndrome and a worsening kidney injury. Active treatment was subsequently withdrawn and the patient died.

### **Conclusions:**

In the absence of evidence, the pharmacist's knowledge of the principles of pharmacokinetics is critical to optimise dosing of high risk medicines.

## Clinically relevant variation in *FLT3*-ITD quantitation as a function of individual assay conditions and insertion characteristics

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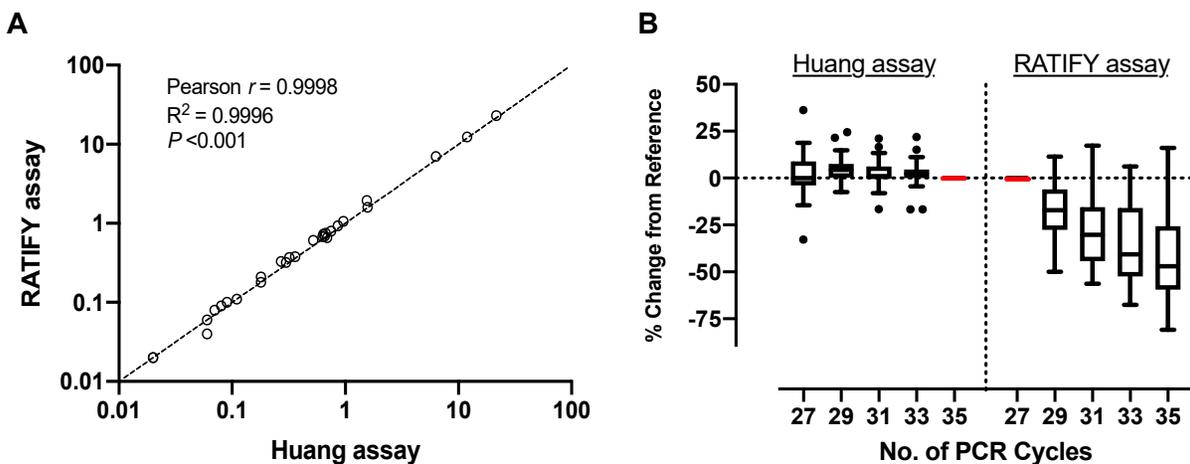
**Background:** *FLT3* internal tandem duplication (*FLT3*-ITD) is routinely incorporated into allogeneic transplant decisions for acute myeloid leukaemia (AML) with high ( $\geq 0.5$ ) allelic ratio (AR) currently considered adverse risk (if *NPM1*<sup>wild-type</sup>) by European LeukemiaNet (ELN) 2017 guidelines. One hypothesised source of variability in *FLT3*-ITD quantitation is the number of PCR cycles used. We aimed to evaluate the effect of PCR cycle number and conditions on the quantitation of the *FLT3*-ITD AR and the potential clinical consequences of any variability observed.

**Methods:** Thirty samples were selected with varying ITD lengths (range 9-187 bp) and AR (range 0.02-21.64). Two *FLT3*-ITD assays were assessed: (i) multiplexed with *NPM1* (Huang 2008 - 35 PCR cycles and peak height AR); and (ii) as measured in the RATIFY trial (Stone 2017 - 27 PCR cycles and area under the curve AR).

**Results:** *FLT3*-ITD ARs obtained by both assays using under standard conditions were highly correlated ( $R^2 > 0.99$ ; Figure A). Using the RATIFY assay ( $n=28$ ), progressive decrease of AR with increasing PCR cycles was observed (Figure B). 4/14 (29%) samples with high AR at 27 PCR cycles would be reclassified as low AR at 35 PCR cycles. Moreover, 2/11 (18%) samples with AR 0.05-0.5 may be reported as negative ( $< 0.05$ ) according to practice in some laboratories, potentially impacting treatment decision in 24% of patients. In contrast, *FLT3*-ITD AR values were stable despite increasing PCR cycles using the Huang assay ( $n=30$ ). The effect of decreasing AR was observed across both shorter ( $< 30$ bp) and longer ( $> 100$ bp) ITDs using RATIFY assay.

**Conclusion:** Concordance of *FLT3*-ITD quantitation between different assays was high using respective standard conditions. However, within an individual assay, variability may be observed as a function of PCR cycle number which may have significant implications for risk stratification and clinical care.

**Figure. (A)** Comparison of *FLT3*-ITD AR (log scale) between two laboratory assays. **(B)** *FLT3*-ITD AR according to number of PCR cycles using Huang and RATIFY assays.



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## Updated results from a phase 1 study of gilteritinib in combination with induction and consolidation chemotherapy in newly diagnosed AML

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**Aim:** The ADMIRAL trial demonstrated that the oral FLT3 inhibitor gilteritinib was superior to salvage chemotherapy as single-agent therapy in patients with *FLT3*-mutated (*FLT3*<sup>mut+</sup>) relapsed/refractory AML. We evaluated once-daily oral gilteritinib combined with front-line chemotherapy in patients with newly diagnosed (ND) AML.

**Method:** This ongoing phase 1 study (NCT02236013) evaluates gilteritinib plus 7+3 induction and high-dose cytarabine (HiDAC) consolidation chemotherapy, and gilteritinib maintenance therapy patients with ND AML. During dose escalation, patients (n=3-6/cohort) received 40, 80, 120, or 200 mg/day of gilteritinib (Days 4-17 [Schedule 1]) and ≤2 induction cycles (cytarabine 100 mg/m<sup>2</sup>/day, Days 1-7; idarubicin 12 mg/m<sup>2</sup>/day, Days 1-3). During dose expansion, patients received the recommended expansion dose of gilteritinib (Schedule 1) plus 7+3 idarubicin induction. Two additional cohorts received gilteritinib on Days 8-21 (Schedule 2) with idarubicin (12 mg/m<sup>2</sup>/day; n=6) or daunorubicin (90 mg/m<sup>2</sup>/day; n=5) on Days 1-3. During consolidation, patients received HiDAC (1.5 g/m<sup>2</sup> q12h; Days 1, 3, 5) and gilteritinib (Days 1-14) at the induction dose for ≤3 cycles. After consolidation or transplantation, patients received gilteritinib (40, 80, 120 mg/day) maintenance.

**Result:** Of the 68 patients enrolled as of October 8, 2018 (median age, 59.5 years [range, 23-77]), 36 (54.5%) were *FLT3*<sup>mut+</sup>. Two patients who received 200-mg/day gilteritinib experienced dose-limiting toxicities (neutropenia, neutropenic enterocolitis); 120 mg/day was established as the maximum tolerated dose and the recommended expansion dose. Common grade ≥3 adverse events were febrile neutropenia (63.6%), thrombocytopenia, neutropenia, decreased white blood cell count, and decreased platelet count (all 19.7%). Composite complete remission rates for evaluable *FLT3*<sup>mut+</sup> patients receiving Schedule 1 (n=22) and Schedule 2 (n=11) were 100% and 81.8%, respectively (**Table**).

**Conclusion:** Gilteritinib can be safely combined with chemotherapy and given as maintenance therapy in patients with ND AML. High response rates were observed in *FLT3*<sup>mut+</sup> patients regardless of anthracycline type or gilteritinib administration schedule.

**Table. Treatment response in patients with *FLT3*<sup>mut+</sup> ND AML who received frontline gilteritinib in combination with intensive chemotherapy**

Response Parameter, n	<i>FLT3</i> <sup>mut+</sup> Patients 120-mg/day Gilteritinib Plus 7+3 Induction			
	Gilteritinib Schedule 1 With 7+3 Idarubicin <sup>†</sup> (n=22)	Gilteritinib Schedule 2 With 7+3 Idarubicin (n=6)	Gilteritinib Schedule 2 With 7+3 Daunorubicin (n=5)	Total (N=33)
CR	16 (72.7%)	2 (33.3%)	4 (80.0%)	22 (66.7%)
CRp	1 (4.5%)	0	0	1 (3.0%)
CRi	5 (22.7%)	2 (33.3%)	1 (20.0%)	8 (24.2%)
CRc <sup>‡</sup>	22 (100%)	4 (66.7%)	5 (100%)	31 (93.9%)

<sup>†</sup>Gilteritinib was initially administered on Days 1-14, but the schedule was later changed to administration on Days 4-17 due to dose-limiting toxicities in the 40-mg/day dose cohort.

<sup>‡</sup>CRc was defined as CR plus CRp plus CRi.

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRc, composite CR; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; mut+, mutated; ND, newly diagnosed.

## Single-centre Australian experience of allogenic haematopoietic progenitor cell transplantation in adult acute T-Lymphoblastic Leukaemia/Lymphoma.

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**Background:** Adult acute T-Lymphoblastic Leukaemia/Lymphoma (T-ALL/LBL) is a rare, aggressive malignancy manifesting as either leukaemia (T-ALL) or aggressive lymphoma (T-LBL). Our local historical practice is for post-induction consolidation with allogenic HPCT in CR1 (T-ALL) or CR2 (T-LBL) (1, 2).

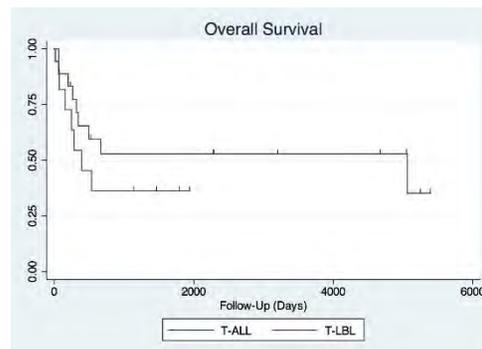
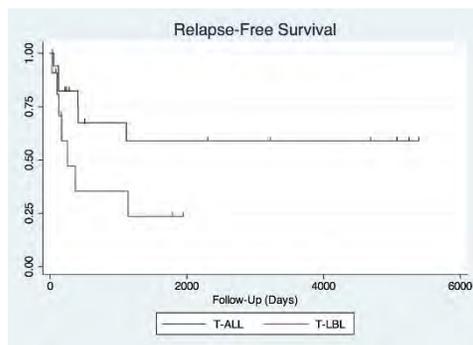
**Aim:** To report local outcomes following allogenic HPCT performed for T-ALL/LBL.

**Methods:** Retrospective audit of adults who underwent allogeneic HPCT for T-ALL/LBL between 2002 and 2019 at our institution. Data collected included: demographic details, disease type (T-ALL or T-LBL), remission status prior to HPCT, incidence of prior autologous HPCT, post-HPCT relapse, and survival. Overall survival (OS) and relapse-free survival (RFS) were calculated using Kaplan Meir analysis and differences between survival assessed using the Log Rank test.

**Results:** 29 patients were included, comprising 20 (69%) T-ALL and 9 (31%) T-LBL. Median age at HPCT was 33 years (17-63 years) with male predominance (n = 20, 69%). Pre-HPCT disease status was CR1 in 15 (52%) patients, and four (14%) patients had active disease. Three patients had undergone prior autologous HPCT.

At a median follow up of 17 months (range 1-175 months) post-HPCT, 13 patients (45%) are alive, and 12 (41%) have relapsed. Disease-free survival (DFS) and transplant-related mortality (TRM) are 35% and 24% respectively. Median OS and RFS for the entire cohort are 22 months and 38 months respectively, with 3-year OS and RFS 46.4% and 55.8% respectively. In the T-ALL cohort, 3-year OS and RFS were 52% and 67.4% respectively; whilst for patients with T-LBL, 3-year OS and RFS were 36.4% and 35.4% respectively. Pre-HPCT disease status and prior autologous HPCT did not significantly affect outcomes.

**Conclusions:** This is the largest case series in Australia of allogeneic HPCT performed for adult T-ALL/LBL over almost 20 years. OS and RFS appear similar to those reported in large international series. HPCT performed at CR1 for T-ALL demonstrates long-term survival similar to that of other high-risk adult ALL, however HPCT for T-LBL remains challenging due to a high incidence of post-HPCT relapse.



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## Veno-occlusive disease after haematopoietic stem cell transplant: reported incidence and mortality in Australasia 2014-2016

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**Aim:** Veno-occlusive disease (VOD) is a potentially life-threatening complication observed after haematopoietic stem cell transplant (HSCT) or chemotherapy without HSCT. Differences in transplant type, stem-cell donor, conditioning regimen, and diagnostic criteria can impact VOD incidence. The aim of this research was to summarise the incidence and mortality rates of VOD in Australasia over the 2014-2016 period.

**Method:** Data on the distribution and characteristics of 6,050 transplants performed in 2014-2016 with reference to VOD from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) was analysed to calculate the incidence and mortality of patients with known VOD status. During this time period, VOD status was available for 93.2% of allogeneic transplants and 49.8% of autologous transplants.

**Results:** Australasian VOD incidence data shows a decreased incidence of VOD diagnosis in 2016 compared to 2014-15 for both allogeneic transplants (estimated 4.5%-4.7% in 2016, 6.0%-6.6% for 2014-15) and autologous transplants (estimated 0.1%-0.3% in 2016, 0.3%-0.6% in 2014-15). This was most notably associated with fewer reported cases of paediatric VOD in 2016. However, the mortality from VOD was higher in 2016 (66%) than the previous 2 years (48% and 52%), associated with increased mortality in patients who had received allogeneic transplants in 2016. A higher VOD incidence was seen in paediatric patients compared with adult patients. VOD associated mortality was higher in adults than in paediatric patients.

Incident cases of VOD and deaths (by age and transplant type)						
	2014		2015		2016	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
0-15 allogeneic	20	8	23	9	10	5
0-15 autologous	4	1	4	3	1	0
16+ allogeneic	18	11	19	12	23	18
16+ autologous	0	0	0	0	1	0
TOTAL (AU/NZ)	42	20	46	24	35	23

**Conclusion:** Ongoing data collection on VOD diagnosis and outcomes will improve the understanding of VOD in the Australasian population.

H038

## **To wash or not to wash? A review of current processing practice**

**Nora Daniel**<sup>1</sup>, Paul Chiappini<sup>1</sup>

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**Introduction:** Depletion of isohaemagglutinins (anti-A or Anti-B) in allogeneic ABO minor mismatched grafts via the Sepax-2 Smartwash process is standard practice within the Bone Marrow Transplant Laboratory (BMTL), Fiona Stanley Hospital (FSH). A review of current practice was performed using a risk based assessment to ensure graft integrity and safety was maintained in the resultant change of practice.

**Aim:** Review of current practice within the BMTL FSH for depletion of isohaemagglutinins in minor ABO mismatched allogeneic grafts using a risk assessment approach.

**Methods:** A comprehensive review of the Sepax-2 Smartwash process currently used for the reduction of Anti-A and Anti-B antibodies in HPC allogeneic grafts was performed using a risk based assessment, as per FACT-JACIE guidelines. The risk assessment evaluated potential insults to the graft during the wash process, including CD34 viability, CD34 and CD3 dose recovery post wash. A literature search guided the generation of an antibody titre cut off point for depletion based on international trends and attitudes. The comprehensive risk assessment was performed by comparing depleted and non-depleted grafts with a risk score assigned to each.

**Results:** The current wash procedure for the depletion of isohaemagglutinins scored higher than un-washed grafts when exclusively comparing the negative effects on the graft. A decision was made by the laboratory medical director to introduce an initial anti-A/B cut off titre where grafts <1:100 do not require depletion. This change in process minimises the potential adverse effect on the graft through over processing whilst ensuring the graft is safe for transplant.

**Conclusion:** This risk-based assessment used to review current practice and improve graft quality allowed for rationalisation and documentation of the change in practice. Collection and correlation of clinical data and evidence to follow.

### Strong correlation between post-processing CD34+ and CFU content in cord blood units volume reduced using the MacoPress®SMART at the Queensland Cord Blood Bank At The Mater (QCBB).

**Barbara Fletcher**<sup>1</sup>, Phillip Johnson<sup>1</sup>, Andrew McCloskey<sup>1</sup>, Elizabeth McKay<sup>1</sup>, Michelle Armitage<sup>1</sup>, Robyn Rodwell<sup>1</sup>

<sup>1</sup>Queensland Cord Blood Bank, South Brisbane, Australia

Contemporary public cord blood banking practice focusses on enhancement of the searchable inventory with high quality cord blood units (CBU). While HLA match, total nucleated cell (TNC) and CD34+ cell dose remains the mainstay in the selection of a suitable CBU for use in transplantation, the CD34+ content represents engraftment potential and is not considered a true measure of biological function/potency.

**Aim:** This study aimed to evaluate the relationship between the routinely quantitated haemopoietic marker CD34+ and the functional, colony forming unit (CFU) potency assay in post-processing, pre-cryopreservation CBU.

**Method:** Retrospective statistical analysis of data obtained from the post-processing, pre-cryopreservation buffy coat samples of 505 CBU processed using MacoPress®SMART (MacoPharma) bottom and top volume reduction (non-HES) by the QCBB between 01/07/2017 and 30/06/2018 was performed.

Samples were tested prospectively using validated assays for CD34+ cells (Beckman-Coulter FC500; CXP Software; StemKit; ISHAGE gating) and CFU (non-lysed, non-washed buffy coat plated in duplicate at a standardised final concentration of  $2 \times 10^4$  WBC/mL onto StemCell Technologies' Methocult GF with EPO H4434 incubated in a saturated (>95% RH), 37°C, 5% CO<sub>2</sub> incubator for 14-days). Colony formation was categorised and scored via microscopy and reported as total CFU-(GM+GEMM)  $\times 10^5$  or total CFU-Erythroid  $\times 10^5$ .

**Results:** Table 1 shows the correlation between each parameter and identifies the strongest relationship between CD34+ and total CFU counts ( $r=0.894$ ).

**Table 1** Correlation between post-processing buffy coat parameters (n=505).

Post-Processing (volume reduced) Buffy Coat	TNC (r)	Total CD34+ (r)	Viable CD34+ (r)	CFU (GM+GEMM) (r)	CFU Erythroid (r)	TOTAL CFU (r)
TNC		0.581	0.580	0.642	0.661	0.690
Total CD34+	0.581		1.000	0.796	0.872	0.894
Viable CD34+	0.580	1.000		0.796	0.872	0.894
CFU-(GM+GEMM)	0.642	0.796	0.796		0.768	0.905
CFU-Erythroid	0.661	0.872	0.872	0.7684		0.964
TOTAL CFU	0.690	0.894	0.894	0.905	0.964	

**Conclusion:** A high degree of correlation ( $r=0.894$ ) between CD34+ counts and total CFU for units volume reduced on the MacoPress®SMART was observed, indicating that the quantitative CD34+ results used in the selection of CBU is a reasonable indicator of graft biological function and engraftment potential.

Our findings suggest that in situations of urgent medical need when treatment cannot be delayed to accommodate a 14-day CFU culture period, the CD34+ content may be an appropriate surrogate for CFU and biological function/engraftment potential.

## **Successful series of salvage lung transplants for severe pulmonary graft vs host disease**

**Mohammad Irhimeh**<sup>1,2</sup>, Michael Musk<sup>2</sup>, Matt Wright<sup>1</sup>, Paul Cannell<sup>1</sup>, Julian Cooney<sup>1</sup>

<sup>1</sup>Department of Hematology, Fiona Stanley Hospital, Murdoch, Perth, Australia, <sup>2</sup>Department of Respiratory Medicine, Advanced Lung Diseases Unit, Fiona Stanley Hospital, Murdoch, Perth, Australia

Bone marrow transplantation (BMT) is an established successful life-saving treatment with high curative rate for haematological and neoplastic diseases. Following HCT, approximately 50% of patients will develop acute GvHD and require systemic treatment. GvHD is a multisystem disorder that if it affects lungs it can lead to chronic respiratory failure usually due to the feared bronchiolitis obliterans (BO).

BO is often refractory to conventional immunosuppressive therapy and has bad prognostic outcomes. Lung transplantation is now an established therapeutic option for patients with end-stage pulmonary failure due to BO. However, there is scarce evidence in the literature for the importance of lung transplantation as a therapeutic option for patients who develop respiratory failure secondary to GVHD post BMT.

We previously found eight isolated case reports in the literature of lung transplantation for chronic respiratory failure after a BMT, and we reported one successful lung transplantation case for severe lung GVHD after allograft for acute lymphoblastic leukaemia. In this study we report two more cases along with the previously reported case that underwent successful lung transplant for pulmonary GvHD.

The three cases are currently 82, 82, and 105 months post SCT and 57, 24, and 6 months post lung transplants, respectively. One case (2) also received a renal transplant from a different donor in 2016. The lung function test for the three cases shows a significant improvement post lung transplant and they continue to be in complete haematological remission (Table 1). Therefore, lung transplant is a treatment option for patients who have end-stage lung disease caused by GvHD after BMT and do not respond to conservative medical treatment.

## Comparison of high dose valaciclovir versus no pharmacological prophylaxis in preventing cytomegalovirus reactivation in allogeneic haematopoietic stem cell transplant recipients

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**Aims:** Primary aim: To determine whether cessation of cytomegalovirus (CMV) pharmacological prophylaxis led to a change in incidence of CMV reactivation or disease within 6 months of allogeneic haemopoietic stem cell transplantation (HSCT).

Secondary aims: To describe the effect on acute graft versus host disease (GVHD), transplant related mortality (TRM) at six months and overall survival.

**Method:** Retrospective cohort study with patients identified from a prospectively maintained transplant database. As per local transplant protocol, patients from April 2013 to 2015 received high dose valaciclovir (2g four times a day). The comparison group was patients from May 2015 to April 2017 when patients received no pharmacological CMV prophylaxis. Data was collected from electronic medical records and statistical analysis was performed using SPSS software.

**Results:** 148 patients underwent transplantation during the study period, seven patients were excluded. Demographics in table one. Cases where the recipient and donor were both serologically CMV negative were excluded from analysis. The prophylactic group had significantly less CMV reactivation ( $p=0.004$ ) and no cases of CMV disease versus four cases in the no prophylaxis group. Multivariable analysis showed that bone marrow source, unrelated donor and higher disease risk were associated with greater likelihood of CMV reactivation. There was no effect on acute GVHD, TRM at six months or overall survival.

**Conclusion:** CMV prophylaxis with high dose valaciclovir decreased the incidence of CMV reactivation and disease within our cohort of patients. The significant pill burden of this regime makes it difficult to institute as standard practice and further research is required to best identify high risk patients who would benefit most from pharmacological prophylaxis for CMV reactivation/disease. With the advent of new anti-viral treatment e.g. letermovir with less of a pill burden and fewer side effects, prophylactic treatment may be more palatable to clinicians and patients who require it.

		Prophylaxis, N = 67	No prophylaxis, N = 74
Age		48 years (17-66)	46 years (19-65)
Gender		66% male	64% male
Type	Related	31 (46%)	26 (35%)
	Unrelated	36 (54%)	48 (65%)
Source	Marrow	4 (6%)	5 (7%)
	Peripheral	63 (94%)	69 (93%)
Recipient CMV status		64% pos	65% pos
Acute GVHD – any		46%	34%
Relapse		23%	22%
Death		45%	32%

## **Incidence of anicteric veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) and defibrotide efficacy following haematopoietic cell transplantation (HCT)**

Selim Corbacioglu<sup>1</sup>, Nancy A. Kernan<sup>2</sup>, Antonio Pagliuca<sup>3</sup>, **Richard Martin**<sup>4</sup>, Robert J. Ryan<sup>5</sup>, William Tappe<sup>6</sup>, Paul G. Richardson<sup>7</sup>

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**Aim:** Hepatic VOD/SOS is a potentially life-threatening HCT complication. Among traditional VOD/SOS diagnostic criteria, hyperbilirubinaemia (bilirubin >2 mg/dL) is compulsory for Baltimore criteria but not modified Seattle criteria. Defibrotide is approved for patients aged >1 month with severe hepatic VOD/SOS post-HCT in the EU, and for adult and paediatric patients with hepatic VOD/SOS with renal or pulmonary dysfunction post-HCT in the US and Canada. This post hoc analysis examined the incidence of VOD/SOS without hyperbilirubinaemia, before and after Day 21 post-HCT, and survival in the defibrotide expanded-access study (T-IND).

**Methods:** The T-IND (NCT00628498) protocol originally required diagnosis of VOD/SOS per Baltimore criteria/biopsy but was amended to allow use of modified Seattle criteria. Patients received defibrotide 25 mg/kg/day, recommended for ≥21 days.

**Results:** Of 991/1000 post-HCT patients with recorded bilirubin at diagnosis, 190 (19%) had bilirubin <2 mg/dL: 57 patients >16 years (49% and 51% diagnosed by and after Day 21 post-HCT, respectively) and 133 patients ≤16 years (80% and 20% diagnosed by and after Day 21, respectively). Overall, Kaplan-Meier–estimated Day 100 survival was 59%; this was 86% for 190 patients with bilirubin <2 mg/dL at diagnosis and 52% for 801 patients with bilirubin ≥2 mg/dL. Among patients with bilirubin <2 mg/dL, 61% had ≥1 treatment-emergent adverse event (TEAE), 18% had ≥1 treatment-related AE (TRAE), and 21% had ≥1 haemorrhagic event. For patients with bilirubin ≥2 mg/dL, 74% had ≥1 TEAE, 22% had ≥1 TRAE, and 31% had ≥1 haemorrhagic event.

**Conclusions:** Adult and paediatric patients had anicteric VOD/SOS, both before and after Day 21. VOD/SOS diagnosis would have been missed in 19% of patients if hyperbilirubinaemia was required. Day 100 survival was higher in patients with bilirubin <2 versus ≥2 mg/dL, suggesting treatment before hyperbilirubinaemia onset may yield better outcomes. The defibrotide safety profile was similar to previous studies.

H044

**Time to complete response with defibrotide in patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) after haematopoietic cell transplantation (HCT)**

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**Aim:** Defibrotide is approved for patients aged >1 month with severe hepatic VOD/SOS post-HCT in the EU, and for adult and paediatric patients with hepatic VOD/SOS with renal or pulmonary dysfunction post-HCT in the US and Canada. Defibrotide 25 mg/kg/day is recommended for ≥21 days and until signs and symptoms of VOD/SOS resolve. Time to complete response (CR), relative to defibrotide initiation, was evaluated in patients receiving defibrotide.

**Methods:** CR was defined as total serum bilirubin <2 mg/dL with resolution of VOD/SOS-related multi-organ dysfunction (MOD). Data were pooled from patients with VOD/SOS post-HCT treated with defibrotide (25 mg/kg/day) in phase 2 (NCT00003966; n=74) and phase 3 (NCT00358501; n=102) studies. Duration of therapy in patients discontinuing due to CR in an expanded-access study (T-IND; NCT00628498; n=1000) was analysed separately due to differences in response assessment.

**Results:** Pooled phase 2/3 studies had 60 patients with CR (n=34 [57%] and n=26 [43%], respectively); median time to CR was 24.5 days (range: 7–123). CR was achieved in 32/60 (53%) and 24/60 (40%) patients beyond 21 and 28 days of treatment, respectively. In T-IND, 390 patients discontinued due to CR (median time to discontinuation=22 days; range: 2–64); 235/390 (60%) and 57/390 (15%) patients discontinued beyond 21 and 28 days of treatment, respectively. In the phase 2/3 studies, 58/176 (33%) patients had treatment-related adverse events (TRAEs), most commonly (≥5%) hypotension (6%), pulmonary alveolar haemorrhage (6%), and epistaxis (5%). In T-IND, 210/1000 (21%) patients had ≥1 TRAE, most commonly pulmonary haemorrhage (5%).

**Conclusions:** Overall, >50% of patients who achieved CR required defibrotide beyond 21 days; a notable proportion required treatment beyond 28 days, highlighting the importance of continuing defibrotide therapy until the signs and symptoms of VOD/SOS have resolved, which may occur beyond the recommended 21-day minimum indicated in the current labels.

## Variability and accuracy of busulfan therapeutic dose modification in matched donor allogeneic haemopoietic cell transplantation (HPCT)

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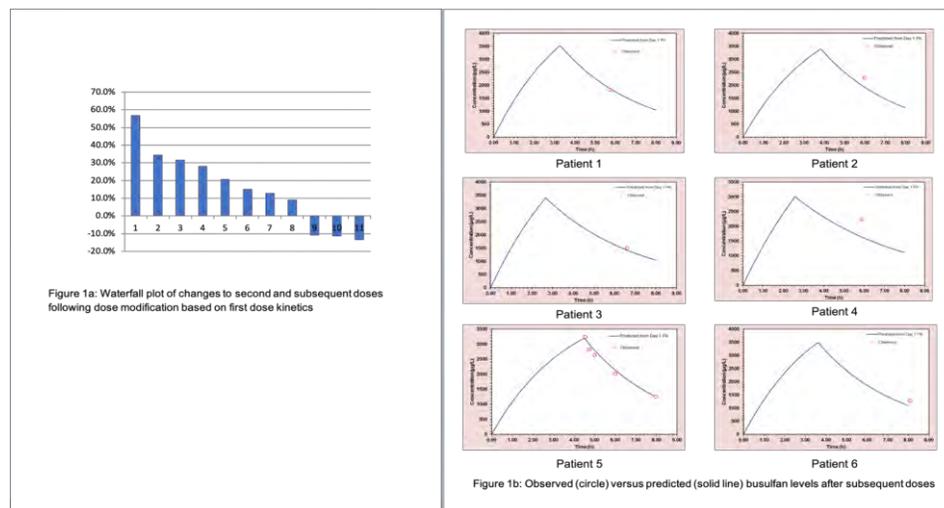
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**AIM:** Busulfan is the backbone of myeloablative conditioning for many allogeneic HPCT. Concerns regarding toxicity and pharmacokinetic variability have led to efforts to optimise dosing for individual patients. We investigated dose variability and accuracy of dose modification made after measurement of first dose exposure and therapeutic dose modification at our centre. Furthermore, we investigated whether busulfan concentrations after final dose would fall rapidly enough to allow stem cell infusion 36 hours later.

**METHOD:** 11 consecutive matched donor HPCT patients received IV busulfan x4 (initial dose 3.2mg/kg of ABW25) with cyclophosphamide 60mg/kg x2 (n=9) or fludarabine 40mg/m<sup>2</sup> x4 (n=2). Busulfan was usually given after cyclophosphamide, per eviQ guidelines, and stem cells infused >48hours post final dose. AUC was calculated from concentrations taken 0 and 15minutes post completion and 4,5,6 and 8hours post start of initial infusion. Subsequent busulfan doses were adjusted to target AUC of 5000mmol.min/L. 6 patients had 'subsequent concentrations' 5-10hr following doses and 7 patients had 'late concentrations' 24-36hr post dose.

**RESULT:** Median initial busulfan AUC was 4388mmol.min/L (range 3182-5790). Median dose change was +15.2% (Figure 1a). Subsequent concentrations were close to predicted in 5 patients, but exceeded prediction by 36% in 1 (Patient 4; Figure 1b). For 7 patients with late concentrations, the median busulfan concentration was 16ug/L, (range 0–144) including one concentration of 115ug/L at 36 hours.

**CONCLUSION:** Drug level monitoring has identified necessary changes to subsequent doses after initial dosing based on ABW25. Observed subsequent concentrations confirmed the accuracy of the model for overall busulfan exposure. However, elevated concentrations up to 36 hours after final dose suggest this model is not adequate for predicting terminal plasma concentrations for some patients. In the absence of further information, we conclude that a 'rest day' between the last busulfan dose and stem cell infusion cannot be omitted.



H046

## **Early outcomes of haploidentical stem cell transplant are not superior to mismatched unrelated donor transplantation**

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<sup>1</sup>Royal Brisbane and Womens Hospital, Herston, Australia

### **Aim**

To evaluate the early transplant outcomes for patients undergoing haploidentical stem cell transplants (Haplo-SCT) with post-transplant cyclophosphamide (PTCy) with comparison to historical mismatched unrelated donor transplants performed at a single institution.

### **Method**

Patients who had undertaken Haplo-SCT between January 2017 and March 2019 were identified from an institutional database. Overall survival (OS), relapse free survival (RFS), relapse rates, non-relapse mortality (NRM) and acute GVHD incidence were determined retrospectively by review of individual patient medical records. All grafts were T-replete and received PTCy. Conditioning regimens included Melphalan/ Fludarabine/Total body irradiation (TBI), Fludarabine/ Cyclophosphamide with or without TBI, Fludarabine/Cyclophosphamide and Fludarabine/Melphalan/Thiotepa.

### **Results**

In total 25 patients underwent Haplo-SCT during the time period under review. Median age was 45yrs (range 22-74yrs). Indication for SCT included AML in 11 patients(44%), B-ALL in 4(16%) MDS/ MPN in 4(16%), NHL in 3(12%) and other indications 3(12%). SCT conditioning included myeloablative protocols in 23(92%) and RIC protocols in 2 (8%). Overall incidence of grade II-IV and III-IV acute GVHD was 46% and 23% respectively, with 17% of patients surviving post D100 developing extensive stage chronic GVHD. At median follow-up for survivors of 13.7mths (range 4.6-33mths) 1yr OS, PFS, and NRM is 75%, 65%, and 18% respectively. On comparison with a historical group of HLA mismatched allogeneic transplants (excluding DQ) and DQ mismatched transplants, there was no significant difference in OS, PFR and NRM.

### **Conclusion**

The early outcomes of Haplo-SCT are similar to our historical cohort of patients undergoing mismatched unrelated donor transplantation. Longer term follow up is required.

H047

**There's no aspergillus in Wellington: a single centre audit of invasive fungal infections in acute leukaemia and allogeneic stem cell transplants.**

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**Aim:** Invasive fungal infections (IFI) are a life-threatening complication of allogeneic haematopoietic stem cell transplantation (alloHSCT). High cost mould-active prophylaxis with voriconazole or posaconazole is used to prevent this in selected patient groups. They are funded for use in New Zealand (NZ) in acute leukaemia induction and severe graft-vs-host disease (GVHD), but our unit has typically chosen fluconazole (no aspergillus activity) as prophylaxis due to a perceived low incidence of aspergillosis in our region. We sought to describe the incidence of IFI in this cohort to aid the decision of which patients ought to receive mould-active prophylaxis.

**Method:** We retrospectively reviewed the medical files of all patients who underwent alloHSCT for any condition or received induction chemotherapy for acute leukaemia between January 2013 and December 2017 inclusive. IFI was defined as described by the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group. Statistical significance was determined using Fisher's exact test

**Results:** 48 acute leukaemia and 128 alloHSCT patients were included in the analysis. There were 11 proven/probable cases (6.25%) of IFI in the total cohort, 8 (6.25%) in the post-transplant population and 3 (6.3%) in the induction chemotherapy group. There was a trend to lower IFI rates in Wellington domiciled patients post-transplant, compared to those domiciled elsewhere, 1.6% compared to 10.8% ( $p = 0.062$ ). This trend was not seen in the induction chemotherapy population, where all IFI cases were in Wellington domiciled patients. Analysis of other risk factors is currently being performed.

**Conclusion:** Despite the perception of low aspergillosis rates in Wellington, our results suggest that overall rates may be higher than expected in the era of routine mould-active prophylaxis. The difference in location of domicile may be a useful finding in local decision making around individual anti-fungal prophylaxis, particularly given the high cost associated with mould-active treatments

H048

## **Factors associated with increased mortality in patients with poor graft function post allogeneic transplantation**

**Ashvind Prabahan**<sup>1,2,3</sup>, Rachel Koldej<sup>1,2</sup>, Lynette Chee<sup>1,2,3</sup>, David Ritchie<sup>1,2,3</sup>

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### **Introduction:**

Poor graft function (PGF), the clinical syndrome of cytopenias in the setting of full donor chimerism, is a serious complication of allogeneic transplantation. While some patients will improve spontaneously without intervention, others die from complications of bone marrow failure. The aim of this project was to identify risk factors for mortality in patients with PGF post- allogeneic transplant.

### **Methods:**

A retrospective analysis of all recipients of allogeneic transplant at our local institution 2000-2016. Patients were defined as having PGF after meeting the following criteria at D30 post-transplant: Platelets  $<100 \times 10^9/L$  and neutrophils  $<1.0 \times 10^9/L$  sustained for 30 days, myeloid chimerism  $>95\%$  and no relapse of initial disease within 100 days of transplant. Univariate analysis was performed to identify risk factors for mortality at 24 months.

### **Results:**

Of 908 transplants, 168 patients fulfilled criteria for PGF. Amongst the PGF patients, 2 groups were compared - those who survived to 24 months ( $n=103$ ) vs those who did not ( $n=65$ ). The PGF patients with early mortality had an older median age (52 vs 43yrs  $p=0.007$ ) had higher rates of Grade II-IV acute GVHD (70% vs 43%  $p=0.0003$ ) and viral infections (excluding CMV) (43% vs 17%  $p=0.0002$ ). Rates of CMV infection between the two groups were not different. ICU admission during the initial transplant admission was more frequent (36% vs 13%  $p=0.0004$ ) in the early mortality PGF group. The median platelet, neutrophil and haemoglobin levels were significantly lower in the early mortality PGF group at D60, 100 and 6 months post-transplant compared to those that survived to 2 years.

### **Conclusion:**

Patients with PGF have a worse prognosis if complicated by 1)GVHD, 2) viral infections (non-CMV related) and 3) history of ICU admission. These factors identify patients at higher risk of death from PGF and who will benefit from the development of prospective interventions.

## **Long term impact of Cytomegalovirus (CMV) viremia on quality of life in allogeneic haematopoietic stem cell transplant recipients (HSCT)**

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There is increasing interest in the indirect effects of cytomegalovirus (CMV) infection following allogeneic haematopoietic stem cell transplantation (HSCT). Its impact on quality of life and fatigue has not been described. We evaluated quality of life measures in recipients of allogeneic HSCT who did and did not experience post-transplant CMV viremia.

### **Methods**

Participants were recruited from the Long Term Follow Up (LTFU) clinic between January 2014 to July 2018. Patients completed the EORTC QLQ-C30, FACT BMT0-148 and FACIT Fatigue Scale questionnaires. Participants were selected if they attended their first clinic visit within the first 2-4 years since HSCT. CMV viremia and treatment were determined by quantitative CMV viral load together with or without commencement of anti-CMV agent. Exclusion criteria were transplantation at another institution.

### **Results**

A total of 140 patients with a median age of 52 years (IQR 40-59) were included in the study. AML (45%) and ALL (11%) were the most common reasons for undergoing HSCT. Of the CMV seropositive recipients, 94% (n=79) experienced CMV viremia of which 66% were treated with an anti-CMV agent. In patients who were younger <50 years of age, the EORTC global quality of life score was significantly lower in patients who received anti-CMV treatment compared to those who did not (67 vs 75 p=0.02) with a higher fatigue score (44 vs 33, p=0.018) and lower social functioning score (67 vs 83, p=0.02). There was a trend towards lower role functioning scores (67 vs 100, p=0.09) but no difference in physical functioning (p=0.5) or financial difficulties (p=0.9). Lower quality of life scores in patients <50years who were treated for CMV viremia were also observed using the FACT BMT0148 (108 vs 124, p=0.02) and BMTS040 (29 vs 31, p=0.07).

### **Conclusion**

There is a significant impact on the long-term quality of life in recipients of allogeneic HSCT who received treatment for CMV infection in fatigue and social functioning. Further studies are warranted to prevent and manage these effects.

## Second haploidentical haematopoietic stem cell transplant from a new donor following graft failure: a case report and literature review.

**Ruwani Rajapaksa<sup>1</sup>**, Paul Cannell<sup>1</sup>, Duncan Purtill<sup>1</sup>

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There is minimal literature on the management of graft failure in haploidentical allogeneic haematopoietic stem cell transplant. An increasing number of haploidentical HSCT with myeloablative conditioning are being performed in Australia for patients lacking suitable HLA-matched donors. We describe our experience managing haploidentical graft failure and review the literature.

A 23-year-old man of Peruvian descent underwent haploidentical transplantation from his brother for acute lymphoblastic leukaemia with high risk cytogenetics in complete remission without detectable minimal residual disease after paediatric-style induction chemotherapy (ALL-06 protocol). Donor specific anti-HLA antibody testing was negative. He received a T-cell replete peripheral blood haemopoietic progenitor cell (HPC) graft ( $3.9 \times 10^6$  CD34+ cells/kg) after fludarabine and busulphan conditioning (targeting a busulphan AUC of  $4500 \mu\text{M}\cdot\text{min} \times 4$  days). Graft-vs-host disease (GVHD) prophylaxis was cyclophosphamide (50mg/kg D+3 & D+5), ciclosporin and mycophenolate mofetil from D+5. He developed fevers on days 0 to 3 and received antibiotics but no corticosteroids. By day +29 there was no evidence of neutrophil recovery and bone marrow biopsy was acellular. Anti-HLA antibodies were not detected. CMV viral load rose transiently to  $[1.37 \times 10^2 \text{ IU/ml}]$  on day 24 and resolved without treatment. Chimerism studies performed on short tandem repeats revealed no evidence of donor DNA. On day 45 from initial transplant, he underwent salvage T cell replete haploidentical HPC infusion from another brother ( $11.19 \times 10^6$  cells/kg), after non-myeloablative conditioning with fludarabine, cyclophosphamide, and total body irradiation (200cGy). GVHD prophylaxis was identical to the first transplant. He achieved neutrophil recovery on day 17 and was discharged home well on day 23 after second transplant.

There are few reports in the literature regarding incidence and management of graft failure following haploidentical transplantation (Table). Our experience of successful non-myeloablative salvage transplant with T-cell replete graft and high stem cell dose adds to the published experience in managing this significant complication.

**Table 1. Initial and salvage haploidentical haematopoietic stem cell graft characteristics and outcomes.**

Patient	HSCT1	Conditioning	GVHD Prophylaxis	CD34+ x10 <sup>6</sup> /kg	DSA	Days to HSCT2	HSCT2	CD34+ x10 <sup>6</sup> /kg	Conditioning	GVHD Prophylaxis	TTNE days	GVHD
Epperla N, Pasquini M, Pierce K, et al. Salvage haploidentical hematopoietic cell transplantation for graft rejection following a prior haploidentical allograft [letter]. Bone Marrow Transplant. 2017 Jan;52(1):147-150.												
60F AML	BM	RIC Flu/Cy/TBI	Cy/MMF/Tacro	2.38	Neg	42	PBSC New donor	4.00	RIC Flu/Mel/TBI	Cy/MMF/Tacro	24	Died – cerebral toxoplasmosis
25M MPAL	BM	RIC Flu/Cy/TBI	Cy/MMF/Tacro	2.94	Neg	37	PBSC New donor	4.00	MA Flu/Bu/Cy	Cy/MMF/Tacro	24	Died – VOD
61M AML	BM	RIC Flu/Cy/TBI	Cy/MMF/Tacro	1.55	Neg	40	PBSC New donor	4.59	MA Flu/Bu/Cy	Cy/MMF/Tacro	17	Acute skin + chronic
Kliman D, Bilmon I, Kwan J, et al. Rescue haploidentical peripheral blood stem cell transplantation for engraftment failure: a single-centre case series. Internal Medicine Journal. 2018; 48: 988-991.												
44F MDS-RAEB	PBSC	RIC Flu/Cy/TBI	Cy/MMF/Tacro	4.6	Neg*	180	PBSC New donor	4.7	MA Cy/Bu/Ritux	Cy/MMF/Tacro	39	Acute - skin & gut Died – relapse
21M SAA	PBSC	RIC Flu/Cy/TBI	Cy/MMF/Tacro	3.6	Pos	55	PBSC New donor	4.1	RIC Flu/Cy/TBI/Ritux/PE	Cy/MMF/Tacro	11	Chronic - skin, oral mucosa, lungs
Nour H, Patil N, Chewning J, et al. Safety of repeated un-manipulated peripheral blood stem cell haploidentical transplant for graft failure [letter]. Bone Marrow Transplantation. 2017; 52, 157–158.												
19M PNH-MDS	PBSC	MA Bu/Flu	Cy/MMF/Tacro	5	Neg	37	PBSC New donor	4.5	Flu/Cy/TBI	Cy/MMF/Tacro	15	Chronic – mouth, liver, lung
33F AML	PBSC	MA Bu/Flu/TBI	Cy/MMF/Tacro	6	Neg	42	PBSC New donor	7	Flu/Cy/TBI	Cy/MMF/Tacro	14	Acute – skin
Bhushan V, Mathews J, Vance E, et al. Salvage therapy for graft rejection with second haploidentical allogeneic stem cell transplantation (Haplo-HCT) from a second related donor. Biol Blood Marrow [abstract]. 2015; 21: S266-S321												
28M PNH-MDS	PBSC	MA Flu/Bu/Cy	Cy/MMF/Tacro	5	Neg	39	PBSC New donor		Flu/Cy/TBI	Cy/MMF/Tacro	19	None
HSCT= Haematopoietic stem cell transplant. GVHD = Graft versus host disease. DSA = Donor specific antibodies. AML = Acute myeloid leukaemia. MPAL = Mixed phenotype acute leukaemia. MDS = Myelodysplastic syndrome. RAEB = Refractory anaemia with excess blasts. SAA = Severe aplastic anaemia. PNH = Paroxysmal nocturnal haemoglobinuria. BM = Bone marrow. PBSC = Peripheral blood stem cells. RIC = Reduced intensity conditioning. MA = Myeloablative. Flu = Fludarabine. Cy=Cyclophosphamide. TBI = Total body irradiation. Bu=Busulphan MMF = Mycophenolate. Tacro = Tacrolimus. Ritux = Rituximab. PE = Plasma exchange. VOD = Veno-occlusive disease. *non-donor specific anti-HLA-antibodies.												

## **Predictors and outcomes of methotrexate and ciclosporin alteration following allogeneic haematopoietic cell transplantation**

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**Aim:** To identify the causes and consequences of omission and/or reduction of methotrexate (MTX) and ciclosporin (CIC) in graft-versus-host disease (GVHD) prophylaxis and to identify an association between pre-transplant patient and disease factors and MTX alteration.

**Method:** Consecutive patients planned to receive standard GVHD prophylaxis of CIC and MTX were evaluated. Multivariate models for landmarked overall survival (OS) and non-relapse mortality (NRM) were generated using proportional hazards modelling and competing risk regression respectively.

**Result:** Of 196 patients; 54 (28%) had MTX alterations and 62 of 188 evaluable (33%) had CIC alterations. No significant associations between MTX or CIC alteration and any of pre-transplant age, anaemia, thrombocytopenia, renal dysfunction, hypoalbuminemia, respiratory impairment or high/very high DRI were observed. MAC was significantly associated with MTX alteration ( $P=0.0012$ ) but not with CIC alteration ( $P=0.5335$ ). MTX alteration remained significantly associated with inferior OS (56% vs 89%) and greater NRM (35% vs 4%) at 12 months. CIC alteration was also associated with inferior OS (60% vs 77%) and greater NRM (24% vs 8%) ( $P < .001$  for both). Patients who had both CIC and MTX altered had inferior survival to patients who had one or none of the two drugs altered. 2y OS in these groups respectively was 40% (95% CI 25-65%), 66% (95% CI 55-79%) and 83% (95% CI 74-91%) ( $P < .001$ ).

**Conclusion:** CIC and MTX dose alterations were associated with reduced OS and increased NRM but pre-transplant biomarkers were unable to predict for these alterations. There remains a group of patients whose tolerability of myeloablative conditioning and therefore likelihood of GVHD prophylaxis alteration, cannot be accurately identified by existing pre-transplant parameters.

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H052

## **Optimal oral cyclosporin dosing with concomitant posaconazole post allograft**

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<sup>1</sup>Olivia Newton-John Cancer and Research Centre, Austin Health, Heidelberg, Australia

### **Aim:**

Cyclosporin, an immunosuppressive agent used in allograft recipients, has a narrow therapeutic range and its metabolism is affected by anti-fungal prophylactic agent posaconazole(1). We reviewed oral cyclosporin-associated clinical toxicity in patients early post allograft on concomitant posaconazole with the intention of defining an optimal initial oral cyclosporin dose which minimises the incidence of toxicity.

### **Methods:**

Retrospective audit of 29 patients undergoing their first matched unrelated or sibling allograft receiving posaconazole at therapeutic levels at the time of transition from intravenous to oral cyclosporin. 72% had received thymoglobulin GvHD prophylaxis. Primary endpoints were the incidence of dose reductions due to cyclosporin-related toxicity (renal impairment, hypertension, hypomagnesaemia, haematological abnormalities and nausea), and a comparison of the cyclosporin dose (mg/kg) at the time points of oral to IV transition, day 40 and day 60. A subsequent audit was performed of 15 patients specifying an initial oral cyclosporin dose of 2.0-2.25mg/kg bd, a dose reduction after the initial audit demonstrated high rates of toxicity at higher transition doses.

### **Result:**

The retrospective cohort had a median initial oral cyclosporin dose of 2.58mg/kg bd (range 1.75–3.95) at median day 18 (14-25). 72% required a dose reduction between transition and day 60. Median doses at day 40 and 60 were 2.20 (1.34–3.33) and 1.46 (0.79–3.33)mg/kg bd respectively. The amended reduction in initial oral cyclosporin dose (median starting dose 2.18mg/kg bd) had little impact on toxicity with the median day 60 dose being 1.31 (1.04-2.08) mg/kg bd. Acute GvHD occurred in 28% of the retrospective cohort and 7% of the amended dose cohort (median grade 2).

### **Conclusion:**

Starting oral cyclosporin doses  $\geq$ 2mg/kg bd are associated with substantial toxicity necessitating dose reductions in allograft recipients receiving concomitant posaconazole. We are now evaluating a starting dose of 1.8–2.0mg/kg bd in T cell depleted allografts.

(1) Atiq F et al., *Converting cyclosporine A from intravenous to oral administration in hematopoietic stem cell transplant recipients and the role of azole antifungals*. European Journal of Clinical Pharmacology, 2018. 47: pg. 767-73

H053

## **Evaluation of haemopoietic progenitor cell parameter on Sysmex XN2000 haematology analyser for timing of peripheral blood stem cell collection**

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Evaluation of haematopoietic progenitor cell parameter on Sysmex XN 2000 haematology analyser for timing of peripheral blood stem cell collection

**Aim:** Adequate number of peripheral blood stem cells (PBSC) are required for a successful transplantation. CD34+ count has traditionally been used to assess timing of PBSC collection. The aim of this study is to evaluate the utility of haematopoietic progenitor cell (HPC) parameter in Sysmex XN 2000 haematology analysers to predict the timing of PBSC collection. This was done by determining the correlation between peripheral blood CD34+ count and HPC count. The cut-off point of HPC for optimum timing of PBSC collection was determined.

**Method:** Single-center prospective study where a total of 31 subjects (12 healthy allogeneic donors and 19 autologous patients) were enrolled and their peripheral blood CD34+ count (enumerated by flow cytometry) and HPC count were analysed prior to PBSC harvesting. SPSS software was used to calculate the cut-off point and to determine correlation between HPC and CD34+ count.

**Results:** We found a strong correlation between peripheral blood CD34+ and HPC with correlation coefficient,  $R=0.810$ . The cut-off point of HPC count for optimum timing of PBSC collection (at the level when  $CD34 + \text{count} > 5 \text{ cells}/\mu\text{l}$ ) is  $31 \times 10^6 \text{ cells/L}$ . If we use this cut-off value of HPC count, it correlates with the current cut-off value of CD34+ count of  $>5 \text{ cells}/\mu\text{l}$  in all our subjects except for one patient. That patient had CD34+ count of  $11.95 \text{ cells}/\mu\text{l}$  which was sufficient for PBSC harvesting but the HPC count was only  $8 \times 10^6 \text{ cells/L}$ . This suggests that when HPC count is low, additionally, CD34+ count should be enumerated to confirm if patient can proceed with harvesting.

**Conclusion:** Our study showed good correlation between peripheral blood CD34+ and HPC count. This supports the clinical utility of HPC parameter as a quicker and cost-effective option in predicting the timing of PBSC collection.

## **Cord allograft outcomes: an Australian Tertiary Centre Experience**

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**Aims:** Allogeneic stem cell transplantation is a proven treatment for haematological malignancies. Cord blood stem cells, as an alternative donor source, may be associated with delayed engraftment leading to increased mortality. Here, we report a consecutive series of patients transplanted at a single Australian Institution between 2009-2018.

**Results:** Twenty-seven patients are included, with a median age of 44 (17-59) years. Indications were: Acute myeloid leukaemia (AML=11, 40%); Acute lymphoblastic leukaemia (ALL=8, 30%); Lymphoma 15%; Other 15%. Myeloablative, and non-myeloablative in 8/27 (30%), 19/27 (70%) patients respectively.

Single and double CBT were used in 16 (62%) and 11 (38%) patients respectively to target TNC of  $>3 \times 10^6$  /kg body weight, Using cord units of at least 5/8 HLA match. Median time to ANC recovery ( $>0.5 \times 10^9$ /L) was 17 days (6-32) whilst platelet recovery ( $> 20 \times 10^9$ /L) was 35 days (13-184). All-cause mortality within 100 days was 5/27. Out of the 22 alive at day 100, 100% donor chimerism was seen in 5/7 MAC and 10/18 NMA CBTs.

Acute graft versus host disease (GVHD) and chronic GVHD was seen in 18/27 (66%) and 8/27 (29%) patients respectively. CMV reactivation was seen in 15/27 (55%).

OS at 1 year was 17/27 (62%), with no difference with respect to conditioning regimen or cord units infused. In comparison, 27 MUDs matched for age, conditioning and disease indication transplanted over the same time period had 1 year OS of 16/27(59%) with similar 100 day all-cause mortality (6/27).

Median overall survival (OS) was 44 months (1.5 to 363.8 months) and at the time of last follow up 18/27 (70%) patients were alive. Causes of death included sepsis (n=3), GVHD (n=2), and relapsed disease (n=3).

### **Conclusion:**

Cord blood as a source of stem cells for allogeneic transplantation has similar outcome as unrelated donors, thus CBT should continue to serve as an alternative donor source.

## Mucositis during Allogeneic Transplantation Determines Post-Transplant Serum Cyclosporin Levels

**Joanne Lay Cheng Tan<sup>1</sup>**, Eric Wong<sup>1</sup>, Radha Ramanan<sup>1</sup>, Andrew BM Lim<sup>1</sup>, Ashish Bajel<sup>1</sup>, David Ritchie<sup>1</sup>

<sup>1</sup>*Bone Marrow Transplant Service, Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Parkville, Australia*

**Introduction:** Intestinal mucosal injury is a common complication following allogeneic stem cell transplant (alloHSCT), especially with myeloablative and TBI-based (total body irradiation) conditioning regimens<sup>1</sup>. Prospective evaluation studies have shown that intestinal malabsorption persists for several weeks following conditioning, beyond visible resolution of mucositis and bowel integrity<sup>2</sup>. Serum cyclosporin levels in the post-transplant period (when patients are taking oral cyclosporin) may be affected by reduced gut absorption and could influence early transplant related outcomes.

**Aim:** To determine the relationship between mucositis severity, cyclosporin levels, and post-transplant outcomes.

**Methods:** 169 patients who received myeloablative (BuCy, CyTBI, EtoTBI) or reduced-intensity (FluMel) allo-HSCT at the Royal Melbourne Hospital were studied. Serum cyclosporin levels were measured at 2 hours post oral dosing. Days of post-transplant total parental nutrition (TPN) were used as a surrogate for severity of gastrointestinal mucositis. To determine degree of renal impairment, creatinine values were recorded at baseline, D+30, D+60 and D+100. The incidence and severity of acute graft-versus-host disease (aGVHD) was recorded before D+100. The incidence of CMV viraemia before D+100 was recorded and analysed according to serum viral load. Patients with disease relapse (<6m versus >6m) were compared with patients without.

**Results:** Linear regression analysis showed an inverse correlation between days requiring TPN with the post SCT 100-day median cyclosporin level ( $p < 0.0001$ ,  $R^2 = 0.23$ ).

Higher median cyclosporin level was associated with a greater percentage increase of creatinine above baseline ( $p = 0.004$ ,  $R^2 = 0.051$ ). There was no significant correlation between incidence ( $p = 0.05$ ) and severity ( $p = 0.47$ ) of aGVHD with lower cyclosporin levels. CMV reactivation was associated with higher cyclosporin levels ( $p < 0.0001$ ). There was no significant difference in cyclosporin levels according to viral copy number ( $p = 0.067$ ). There was no significant difference in cyclosporin levels between disease-relapsed groups and non-relapsed groups ( $p = 0.33$ ).

**Conclusion:** Our data suggest that patients who have significant mucositis have lower serum cyclosporin levels with oral cyclosporin dosing, which in turn impact upon post-transplant outcomes, in particular renal impairment and CMV reactivation.

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## Impact of Pre-Engraftment Cytomegalovirus Viraemia in Allogeneic Haematopoietic Stem Cell Transplant Recipients

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Background: Cytomegalovirus (CMV) reactivation post- allogeneic transplant increases mortality(1). Very few studies have explored the significance of pre-engraftment CMV reactivation on subsequent CMV-related outcomes or therapy.

Aim: To determine the incidence and outcome of pre-engraftment CMV reactivation.

Methods: All consecutive patients transplanted May 2015-Jan 2019 at the Royal Melbourne Hospital were included in this observational retrospective study. Plasma CMV DNA load was monitored by real-time PCR assays twice per week. Pre-emptive CMV treatment was commenced when the CMV viral load was greater than 400 IU/ml. Risk factors for pre-engraftment CMV were assessed by univariate logistic regression analysis. The Mann-Whitney U test was used to compare post-transplant CMV reactivation and time of treatment initiation; the Fisher's exact test was used for CMV disease and acute graft versus host disease (aGVHD); neutrophil engraftment, relapse free survival (RFS) and overall survival (OS) were compared using the Log-Rank Method.

Results: Of the 220 patients, 182 patients had CMV reactivation and pre-engraftment CMV levels available. Of these 182, 102 (56%) had CMV detected on at least one occasion before engraftment (D-10 to D+30). No pre-transplant factors including conditioning type and CMV serostatus were found to be associated with the development of pre-engraftment CMV reactivation. Patients who had pre-engraftment viraemia patients had a shorter time to post-transplant CMV detection ( $p < 0.0001$ ;  $Y = 27.2d$  vs  $N = 36.3d$ ). These patients also had a longer time to neutrophil engraftment ( $p = 0.049$ , median 19d vs 18d). Despite the shorter time to detection, there was no difference in likelihood of commencement of pre-emptive anti CMV therapy ( $p = 0.88$ ), day of CMV therapy commencement ( $p = 0.29$ ) and the total length of treatment ( $p = 0.82$ ). Patients with pre-engraftment viraemia were not at an increased risk of CMV disease ( $P = 0.65$ ) or aGVHD ( $p = 0.87$ ). There was no difference in RFS ( $p = 0.99$ ) or OS ( $p = 0.14$ ).

Conclusion: These results suggest that pre-transplant CMV detection should not affect the decision to proceed to transplant or require earlier initiation of prophylactic or pre-emptive therapy.

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H057

## **Platelet recovery after autologous stem cell transplant in the older patient**

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Platelet recovery post autologous stem cell transplantation (ASCT) has been well documented, with faster recovery associated with the CD34+ dose infused/administered. In patients >65 years there is a perceived risk of delay in recovery time for neutrophils ( $>0.5 \times 10^9/L$ ) and platelets ( $>20 \times 10^9/L$ ) following ASCT, yet investigations have found no difference in neutrophil recovery in this population. Currently there is no consensus on platelet recovery. This study retrospectively looks at platelet dynamics in older ASCT patients.

Method: From 2011 to 2018 there were 235 assessable ASCT patients at Calvary Mater Newcastle Hospital.

Patients were stratified by disease, gender, and age. 134 Multiple Myeloma (MM) patients, 83 male ( $n=32 \geq 65$ ), 51 female ( $n=14 \geq 65$ ). 101 non-myeloma patients (non-MM), 63 male ( $n=13 \geq 65$ ), 38 female ( $n=5 \geq 65$ ). Days to platelet recovery were calculated, and platelet counts at transplant admission, and 12-18 months post-transplant were collected. Statistical significance was ascertained using Pearson correlation (weak, moderate, strong) and by two-tailed T-test ( $P < 0.05$ ) using Excel.

Results: In MM patients all females, and males  $\geq 65$  had faster platelet recovery weakly associated with CD34+ numbers infused ( $r=0.4$ ). In the non-MM group CD34+ dose was moderately associated with platelet recovery only in females  $\geq 65$  ( $r=0.6$ ). Female MM patients  $\geq 65$  had a significantly shorter time to platelet recovery than younger females, and males  $\geq 65$  ( $P < 0.05$ ). Males  $\geq 65$  in both disease groups also had significantly lower platelet counts post-transplant than males  $< 65$  and females  $\geq 65$  ( $P < 0.05$ ). No significant difference in pre-transplant platelet counts could be detected between gender or age groups.

Conclusion: Reported age and gender difference in platelet counts that become significant over the age of 65 years were not observed. Though from our initial findings, males  $\geq 65$  have significantly impaired platelet production after transplant regardless of initial recovery.

H058

## **Education Needs for Haematopoietic Progenitor Cell (HPC) Transplant Recipients**

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<sup>1</sup>*Fiona Stanley Hospital, Murdoch, Australia*

### **Aim**

Each year in Australia approximately 2000 people are the recipients of an haematopoietic progenitor cell (HPC) transplant. It is well documented in the literature that patient education interventions lead to decreased health care costs, better symptom control, improved self-management, and quality of life. Frequently education is delivered through a combination of printed educational materials and face-to-face education within clinics to obtain consent. The aim of this literature review was to identify key areas of education to be included in the pre HPC transplant education program and the best ways to deliver it.

### **Method**

We identified 38 articles, reports, studies, and educational materials through a search of the databases PsychInfo, Embase, Medline, Cochrane, JBI and Proquest. Search terms included bone marrow transplantation, hematopoietic stem cell transplantation, patient education, patient information, transplant, and education session.

### **Result**

Key education themes identified within the literature refer to the basics of HPC transplants, blood cells, donor searches, preparing for the HPC transplant, self-care before, during and after HPC transplant, conditioning regimens, dealing with side effects, psychosocial health, sexual health, nutrition and exercise, complications of HPC transplant, and life after HPC transplant.

### **Conclusion**

Examining the information found within the literature we propose to review current practice in patient education pre autologous and allogeneic HPC transplant. In the future we would like this to include mixed media and delivery formats, with education occurring at structured time intervals leading up to transplant. These include: first visit (initial referral), at time of consent by consultant, and a 1:1 pre-admission education session. Outcomes will be measured via patient satisfaction surveys, evaluation of distress thermometer tools, and staff surveys to assess impact on ward nurses' perceived time taken on bedside education.

## **Clinical Determinants of T Cell Receptor Diversity after Allogeneic Stem Cell Transplantation for Acute Myeloid Leukaemia**

Eric Wong<sup>1,2,3</sup>, Piers Blombery<sup>1,4</sup>, **Jamie Kuzich**<sup>1,4</sup>, Jerick Guinto<sup>4</sup>, Georgina Ryland<sup>4</sup>, Yamuna Kankanige<sup>4</sup>, Rachel Koldej<sup>2,3</sup>, David Ritchie<sup>1,2,3</sup>

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### Background

T-cell reconstitution after allogeneic stem cell transplantation (alloSCT) is critical for protection against infection and to mediate the graft-versus-leukaemia effect against AML. The early TCR repertoire post-alloSCT is oligoclonal. The aim of this analysis was to investigate clinical determinants of TCR diversity after alloSCT.

### Method

Peripheral blood samples were obtained at day 100 (early time-point) from 29 patients who underwent alloSCT for AML. 11 patients had follow-up samples 1-2 years post-transplant (late). T-cells were isolated using immunomagnetic separation. Following DNA extraction, TCR beta loci deep amplicon sequencing was performed using LymphoTrack TRB. Sequence assembly, annotation and error correction was performed by MiXCR. Epitope specificity was assessed VDJdb. TCR diversity was quantified using inverse Simpson's diversity index (1/D).

### Results

TCR diversity was greater in patients who received T-cell replete transplants from matched sibling donors compared with T-cell depleted transplants from unrelated donors (130.1 vs 64;  $P=0.04$ ). Early TCR diversity was reduced in CMV seropositive recipients compared with seronegative recipients (77.5 vs 77.5;  $P=0.01$ ). Early TCR diversity was reduced in patients with CMV viremia within the first 100 days post-alloSCT (83.5 vs 964.4;  $P=0.02$ ). Patients with early CMV viremia continued to have reduced TCR diversity late post-transplant compared with patients who did not have early CMV reactivation (33.2 vs 3868;  $P=0.006$ ). Sixteen patients developed AML relapse at a median of 98.5 days post-alloSCT. There was no significant difference in early TCR diversity between patients who relapsed compared with those who did not (78.4 vs 132.8;  $P=0.22$ ), suggesting that a restricted TCR repertoire early post-transplant is not a mechanism of AML relapse.

### Conclusion

T-cell depletion and CMV viremia are key determinants of early TCR repertoire diversity post-alloSCT, and CMV viremia has persistent and deleterious effects on TCR repertoire late post-transplant. TCR diversity does not impact early AML relapse post-alloSCT.

H060

## **Validation and Comparison of Aerobic and Anaerobic bacteria, yeast and mould detection using the BacT/Alert® 3D™ and Virtuo™ systems for Haematopoietic Progenitor Cells (HPC)**

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### **INTRODUCTION**

The St George Hospital Microbiology department perform bioburden testing of blood products collected from HPC, received from the Cell and Molecular Therapies (CMT) laboratory at RPAH. The Microbiology lab is introducing the new BacT/Alert® Virtuo™ to replace the BacT/Alert® 3D™ system. The Virtuo™ instrument is an automated microbial test system capable of incubating, agitating and continuous monitoring for reduced time-to-detection of aerobic, facultative, and anaerobic microorganism growth from blood and other body fluids. BacT/ALERT® FAN Plus aerobic, anaerobic and paediatric bottles manufactured by BioMerieux are used with both blood culture instruments and the adsorbent polymeric beads and media volume remained unchanged.

### **AIM**

The testing will compare BacT/Alert® 3D™ and BacT/Alert® Virtuo™ monitoring systems and establish that the Virtuo™ is fit for purpose to detect contamination of blood products.

### **METHOD**

A group of 13 fungi, aerobic and anaerobic bacteria were used during validation. The organisms were inoculated into FAN Plus aerobic, anaerobic and paediatric bottles in a seeded bottle trial. The bottles contained human plasma and processed cells collected and processed from patients at RPAH.

### **RESULTS**

In the seeded trial and in the bottles containing patient plasma, all 13 organisms were isolated within the incubation period from at least one of the FAN Plus aerobic, anaerobic or paediatric bottles loaded after inoculation. All expected organisms were isolated from the FAN Plus paediatric bottles containing processed cells with DMSO.

### **CONCLUSIONS**

This validation confirms that the new method using the new BacT/Alert® Virtuo™ instrument and FAN Plus bottles range is able to detect a range of organisms from patients undergoing treatment regimes that include chemotherapy and/or mobilisation regimes (e.g. granulocyte colony stimulating factor), and from processed cells for cryopreservation with the addition of DMSO. It also demonstrates that the 5-day incubation period is sufficient to recover fungi, aerobic and anaerobic bacteria.

## Evaluation of antibody-fluorophore conjugate stability during immuno-flowFISH analysis

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**Aim:** Advances in instrument technology and reagent chemistry have resulted in the development of complex sample preparation protocols designed to maximise data output from small or difficult to obtain samples such as bone marrow, residual tumour or paediatric samples. Immuno-flowFISH is a technique that combines immunophenotyping with fluorescence *in situ* hybridisation (FISH). The protocol involves acid denaturation and high temperature incubations for DNA hybridisation which are essential for accurate FISH analysis but are known to affect fluorophore performance. We aimed to evaluate the performance of commercially available antibody clones with a range of fluorophores in immuno-flowFISH assessment of blood and bone marrow samples.

**Method:** Following red blood cell lysis, nucleated cells were stained with fluorescent conjugated monoclonal antibodies such as CD3, CD4 and CD19. Samples were fixed, permeabilised and treated with an acid solution to denature DNA prior to high temperature FISH probe anneal and overnight hybridisation. Aliquots of the samples were taken after staining, fixation/permeabilisation, acid denaturation and hybridisation, prior to analysis on an AMNIS ImageStreamX mkII imaging flow cytometer. Data was analysed to determine percent of cells positive at each stage of processing and the stain index for each fluorophore.

**Results:** Synthetic polymer-based (BV and BB) fluorophores were more stable throughout analysis. All protein based (APC, PE, FITC) fluorophores and tandem conjugates lost fluorescence after either acid denaturation or hybridisation. Treatment with an amine cross-linker after staining was found to maintain some fluorophores during permeabilisation, acid treatment and FISH.

**Conclusion:** This study found that synthetic polymer fluorophores were more stable than protein-based during immuno-flowFISH analysis. This experiment has improved our understanding of the fluorophore chemistry and expanded the range of fluorophores that we can access for immuno-flowFISH. Validating the use of these fluorophores in the immuno-flowFISH protocol will provide greater flexibility when designing immunophenotyping panels for other applications.

## Real-world Treatment Persistence of New Zealand Chronic Lymphocytic Leukemia Ibrutinib Patients in a Named Patient Program

David Simpson<sup>6</sup>, Shahidul Islam<sup>3</sup>, Richard Doocey<sup>4</sup>, Mark Smith<sup>5</sup>, Ross Henderson<sup>6</sup>, Andrea Puig<sup>1</sup>, Mustafa Acar<sup>1</sup>, **Gene Pateman**<sup>7</sup>, Carlos Amaya-Chanaga<sup>8</sup>, Robert Weinkove<sup>2</sup>

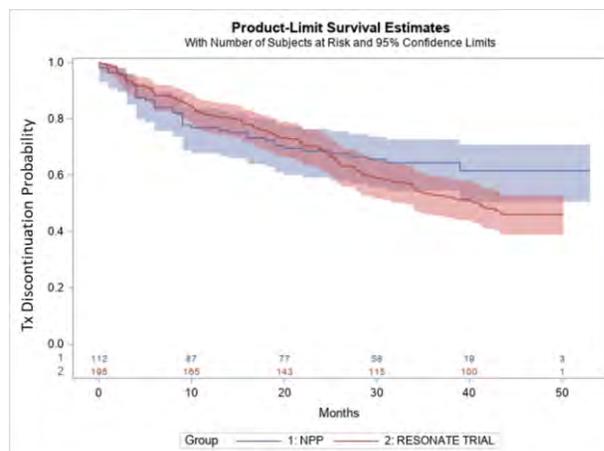
<sup>1</sup>Janssen ANZ, Macquarie Park, Australia, <sup>2</sup>Wellington Blood and Cancer Centre, Wellington Hospital, Wellington, New Zealand, <sup>3</sup>Department of Haematology, Waikato Hospital, Hamilton, New Zealand, <sup>4</sup>Regional Cancer and Blood Services, Auckland City Hospital, Auckland, New Zealand, <sup>5</sup>Haematology Service, Canterbury District Health Board, Christchurch, New Zealand, <sup>6</sup>Haematology Department, North Shore Hospital, Auckland, New Zealand, <sup>7</sup>Janssen ANZ, Auckland, New Zealand, <sup>8</sup>Pharmacoclics LLC, an AbbVie Company, Sunnyvale, United States

**Background:** NPPs (Named Patient Programs) provide access to medicines in response to unsolicited requests by physicians for specific patients before they become commercially available. Janssen New Zealand opened a NPP for ibrutinib for patients with relapsed or refractory Chronic Lymphocytic Leukemia (CLL) from September 2014 to date. This study analyses the duration on ibrutinib treatment for patients with relapsed/refractory CLL enrolled in a New Zealand NPP.

**Method:** A retrospective cohort analysis was conducted using data entered by treating physicians when enrolling patients into the NPP via the Janssen Managed Access Portal (MacWeb). Patient time on treatment was estimated by using resupply requests submitted by physicians. A patient was considered discontinued based on physician declaration, or if no ibrutinib had been resupplied for four months or more. All other patients were censored at the reporting date of 22<sup>nd</sup> May 2019. This real-world estimate of treatment duration was compared to time to treatment discontinuation in the ibrutinib arm of the RESONATE trial, as reported in Hillmen et al. EHA; 2016 (abstract 133196) and Tam et al. EHA; 2018 (abstract 214826). Time on treatment was evaluated descriptively using Kaplan-Meier (KM) curves, and statistical testing was conducted using log-rank testing.

**Result:** 112 patients were included in the analysis and were treated with ibrutinib for CLL. 59% of the population were male, 37% had 3 or more prior lines of therapy before commencing therapy, and 32% had refractory disease. A comparison between patient time on treatment on the NPP and the RESONATE trial showed no statistically significant difference ( $p=0.18$ , HR 0.78, 95% CI: 0.54-1.13).

**Conclusion:** This real-world analysis estimates that patient time on NPP treatment closely tracks time on treatment as observed in the RESONATE pivotal trial. While there are limitations to the NPP data, these findings demonstrate that duration on treatment in a New Zealand real-world setting matches the clinical trial.



H070

## **Allograft and Ponatinib for Primary Refractory CML Blast Crisis: a Case Report**

**Ashlyn Chee**<sup>1</sup>, Duncan Purtill<sup>1</sup>, Julian Cooney<sup>1</sup>

<sup>1</sup>*Fiona Stanley Hospital, Murdoch, Australia*

Background: In the TKI era, transformation of chronic phase CML to acute blast crisis is rare. This case report demonstrates clonal evolution after achievement of early molecular response on Dasatinib at 6 months but subsequently developed blast crisis.

Case presentation: We report a 62 year old male diagnosed with chronic phase CML in June 2018 (46,XY,t(9;22)(q34;q11.2)) who responded to Dasatinib 100mg daily. BCR/ABL levels were 80% at diagnosis, falling to 5.3% and 1.5% at 3 and 6 months respectively. At 8 months post diagnosis, he developed fever and gum infiltration, cytopenias with monocytoid blasts, WCC 106 and BCR/ABL levels rising to 57%. Cytogenetic evolution was confirmed on karyotyping (46,XY,t(9;11)(p22;q23),der(9)t(9;22)(q34;q11.2)del(9)(p21), der(22)t(9;22)(q34;q11.2)). No mutations in the BCR-ABL TK domain were detected. He was refractory to 7-3 induction chemotherapy and underwent salvage with IDA-FLAG and TKI was switched to Ponatinib. A matched sibling peripheral blood stem cell transplant with myeloablative conditioning (Bu/Cy) was performed in morphological remission in May 2019.

Discussion: Traditionally the prognosis of blast crisis CML is very poor after failing TKIs. Patients in blast crisis typically carry multiple mutations, with ongoing BCR-ABL activity and genetic instability and DNA damage however the mechanisms underlying progression to blast crisis is not fully understood.[1,2]

A German CML study group has reported that the median overall survival is only 4 months after the diagnosis of blast crisis.[1] Guidelines recommend allogeneic transplant for best long-term outcomes, with best chance of cure.[2] An EBMT report by Gratwohl et al reported that the 2 year survival after an allogeneic transplant is 16-22%[2] however a retrospective study in Australia has reported that the probability of overall survival was 61% at 5 years post allogeneic transplant and leukaemia-free survival at 5 years post was 45.7%.[3] Inclusion of novel TKIs as adjunctive therapy to allograft may optimise results.

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## A Narrative Review on the Impact of Cessation of Imatinib on the Response Status of Pregnant Women with Chronic Myeloid Leukaemia (CML)

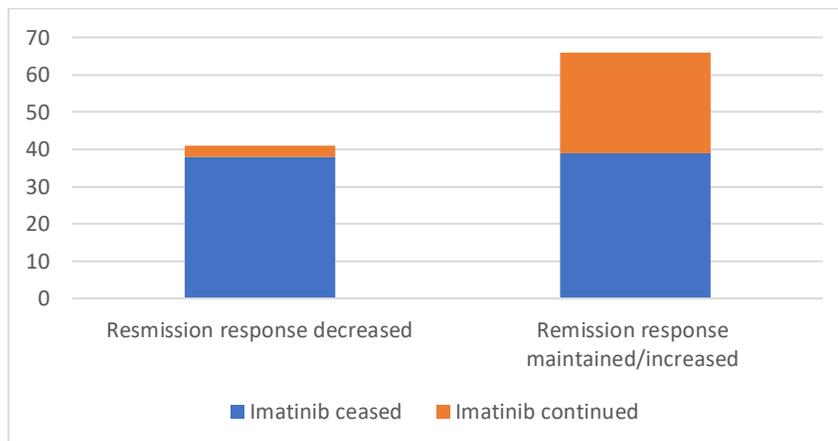
Nandita Kataria<sup>1</sup>, Giselle Kidson-Gerber<sup>3,4,5,6</sup>, David Yeung<sup>7,8</sup>, **Nada Hamad**<sup>1,2</sup>

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**Aim:** Tyrosine kinase inhibitors (TKIs) are used to control the progression of CML, however their teratogenicity in rats have led many to avoid their use in pregnancy, despite there being little information available on the effect this has on response status. This review aims to collate published cases of pregnant women CML being treated with imatinib, and examine the ramifications that continuation or cessation of this therapy has on response status in this population. The study hypothesised that cessation of imatinib would result in loss of response status in pregnant women.

**Method:** Medline, Cinahl and Embase were searched using a combination of keywords that elucidated the concepts of 'pregnancy', 'CML' and 'imatinib'. Publications were selected if they examined a case/s of pregnant women with CML, being treated with imatinib immediately prior to conception, and contained data on duration of imatinib therapy during pregnancy, as well as response status at the onset and cessation of a term pregnancy. Results were presented using a chi square test and odds ratio (OR).

### Results:



**Figure:** Comparison in response status for cohorts with imatinib therapy ceased vs continued in pregnancy

A total of 107 cases from 36 publications were utilised, and an OR of 8.8 was demonstrated between the groups, displaying a significant difference in response status if imatinib was ceased versus if it was continued.

**Conclusion:** Women whose imatinib was ceased during pregnancy were 8.8 times more likely to experience a loss in response status of their CML compared to those who continued treatment. Premature withdrawal of therapy clearly impacts on the remission status in pregnant CML patients, and further research is required to determine the long-term ramifications of this finding.

**First case report of systemic mastocytosis associated with atypical chronic myeloid leukaemia.**

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Systemic mastocytosis (SM) and atypical chronic myeloid leukaemia (aCML) are both rare entities which present diagnostic and therapeutic challenges. Systemic mastocytosis, featuring extracutaneous infiltration of atypical mast cells, can be associated with other haematological neoplasms (SMAHN). We present the first report of SM associated with aCML, a Philadelphia chromosome/BCR-ABL1 mutation-negative disease, morphologically similar to CML, but exhibiting prominent dysplastic granulopoiesis.

The 66 year old presented with bruising, constitutional symptoms and splenomegaly. Bloods showed a marked leucocytosis (white cell count 60 x 10<sup>9</sup>/L), thrombocytopenia, a leucoerythroblastic picture and 2% blasts. Bone marrow aspirate showed markedly hypercellular, left-shifted granulopoiesis, with prominent dysplasia. Blasts comprised 2%, and mast cells <1%. The myeloid:erythroid ratio was 12. FISH did not identify any clonal karyotypic abnormalities such as CHIC2, PDGFRB, FGFR1, JAK2, ABL1 or BCR rearrangements. Molecular markers JAK2, CALR, MPL W515L/K and BCR-ABL1 were negative. The trephine was disorganised and markedly hypercellular with large, fibrotic areas of mixed mast cell infiltrates. The mast cells were immunophenotypically and morphologically atypical. A 23 myeloid gene next generation sequencing (NGS) panel identified c-KIT D816V, supporting the diagnosis of SMAHN. ASXL1, TET2 and KRAS A146T mutations were also found, consistent with aggressive SM.

Treatment of SMAHN requires management of the individual entities. Atypical CML is aggressive with a high rate of leukaemic transformation. It has a dismal prognosis and no established standard of care. Allograft was considered, but declined. We commenced hydroxyurea cytoreductive therapy, with improvement in symptoms, normalisation of blood parameters and resolution of splenomegaly. The patient remains well 8 months later. This report describes the first case of these concurrent haematological rarities, and contributes to the body of knowledge on the treatment of aCML. The NGS panel supported the diagnosis by identifying the driver mutation of SM, but also provided prognostic value and identified other potential therapeutic targets.

## The location of *ABL1* breakpoints in CML is not associated with molecular response

**Kirsty Sharplin**<sup>1,2,3,4</sup>, Susan Branford<sup>1,2</sup>, David Ross<sup>1,2,3,4</sup>

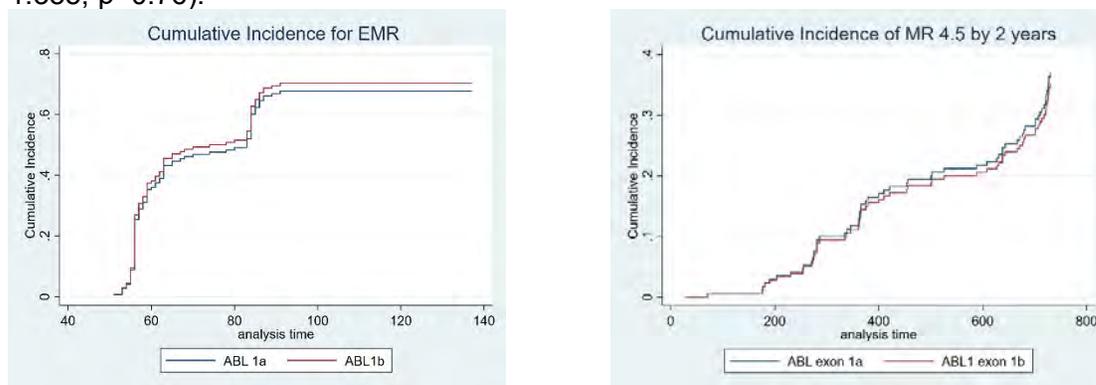
<sup>1</sup>Royal Adelaide Hospital, Adelaide, Australia, <sup>2</sup>University of Adelaide, Adelaide, Australia, <sup>3</sup>SA Pathology, Adelaide, Australia, <sup>4</sup>Flinders Medical Centre, Adelaide, Australia

**Aim:** The advent of tyrosine kinase inhibitors (TKIs) has revolutionised treatment of Chronic Myeloid Leukaemia (CML). There remains however a subset of patients with poor outcomes. Some groups have suggested that the *BCR-ABL1* breakpoint locations or transcript types may be associated with different responses to TKIs. Most work has focussed on *BCR* breakpoint location. We sought to characterise *ABL1* breakpoints and to test whether there is any association with molecular response.

**Methods:** We performed a retrospective analysis of 176 patients treated with either first line imatinib or nilotinib. Several methods, predominantly long-range PCR and next generation sequencing were used to establish the breakpoint locations. To determine breakpoint location, clustering and possible clinical correlation, bed graphs of *ABL1* were analysed. Clinical endpoints were Early Molecular Response (EMR;  $\leq 10\%$  *BCR-ABL1* at 3 months), Major Molecular Response (MMR; *BCR-ABL1*  $\leq 0.1\%$  by 12 months) and MR 4.5 by 2 years, molecular response at a sensitivity level of  $-4.5 \log \leq 0.0032\%$ .

**Results:** Patients had a minimum follow up of 7 years (7-17). There were 82 (46.8%) patients with e14a2 transcripts, 68 (38.8%) e13a2, 25 (14.8%) had both e14a2 and e13a2, and one patient had the rare e13a3 transcript.

Breakpoints within *ABL1* spanned intronic regions only, with the majority in the long intron between exons 1b and 1a (n=96; 55%), between exons 1a and 2 (n=76; 43%), downstream of exon 1b (n=3; 1.7%), and one between exons 2 and 3. There was no association between the *ABL1* breakpoint location and EMR (SHR 1.07, CI:0.78 -1.47 p=0.65) or MR 4.5 by 2 years (SHR: 0.93, CI:0.65 – 1.355, p=0.76).



**Figure 1: Cumulative Incidence of EMR and MR4.5 by 2 years for *ABL1a* and *ABL1b* breakpoints**

### Conclusion:

This study confirms the rarity of breakpoints downstream of *ABL1* exon 1b. We found no association between breakpoint location and molecular response.

## Challenges in clinical management of a rare variant p230 BCR-ABL1 positive case of chronic myeloid leukaemia

**James Yeung**<sup>2</sup>, Dimitrii Minchenko<sup>1</sup>, Francisca Springall<sup>1</sup>, Alberto Catalano<sup>1</sup>, Liane Khoo<sup>1</sup>, Harry Iland<sup>2</sup>

<sup>1</sup>NSW Health Pathology, Camperdown, Australia, <sup>2</sup>Royal Prince Alfred Hospital, Camperdown, Australia

A 78 year old female was referred to the haematology service with a routine full blood count demonstrating leucocytosis to  $38 \times 10^9/L$ , with haemoglobin of 108g/L and platelets  $344 \times 10^9/L$ . Her peripheral blood film showed left-shift, with modest basophilia ( $0.3 \times 10^9/L$ ) and occasional myeloblasts. Apart from 3kg of unintentional weight loss, there were no significant constitutional symptoms or splenomegaly on examination. Her background history included hypertension, hypercholesterolaemia, osteoarthritis, colonic polyps and gastroesophageal reflux. Medications included an angiotensin-receptor antagonist, statin and sustained-release paracetamol. Bone marrow examination confirmed chronic phase chronic myeloid leukaemia, with a 46,XX,t(9;22)(q34;q11.2)[20] karyotype. *BCR-ABL1* qualitative PCR and Sanger sequencing identified multiple splice variants including an in-frame *BCR-ABL1* alternatively spliced e19a2 transcript lacking 45 nucleotides from the 3' end of *BCR* exon 3, *BCR* exons 4 to 18 and 100 nucleotides from the 5' end of *BCR* exon 19.

The patient was commenced on imatinib 400mg daily. She attained a complete haematological response within 10 weeks of treatment and *BCR-ABL1* transcripts continued to be detectable. Serial *BCR-ABL1* monitoring involved qualitative PCR detection of various *BCR-ABL1* splice variants derived from the e19a2 isoform and could not be reported on the *BCR-ABL1* International Scale (IS). At six months post diagnosis a variant in-frame e14a2 transcript was dominant. The patient experienced mild periorbital oedema, subjective palpitations and alternating diarrhoea and constipation which required no intervention. She further developed a pruritic rash three months since starting imatinib, with a subtle scaly rash in the periorbital area and upper forearms. This evolved into a macular rash to the trunk and lower limbs, not responding to antihistamines. A mild eosinophilia ( $0.6 \times 10^9/L$ ) developed corresponding to the drug rash. A skin biopsy confirmed spongiotic reaction, with perivascular lymphocyte and eosinophil infiltrate in the dermis consistent with a drug cause. Imatinib was withheld for two weeks, and prednisolone was commenced. Over the next four weeks, imatinib was restarted and prednisolone was weaned. Complete haematological response was maintained.

## Elderly patients with diffuse large B cell lymphoma - utility of Rockwood Clinical Frailty Score in predicting clinical outcomes and change in functional status

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**Aim:** Elderly patients with diffuse large B cell lymphoma (DLBCL) are more likely to have higher stage disease and mortality rate than younger patients<sup>1</sup>. There is evidence that comprehensive geriatric assessment (CGA) is a useful tool to assess frailty in these patients<sup>2</sup>. We explored the application of clinical frailty scores and functional scores in predicting mortality and detecting functional changes in this population.

**Methods:** A retrospective outcome audit of patients age >60 with DLBCL managed at Northern Health, Melbourne, between 2013-2018 was conducted. Functional assessment tools in current use were reviewed to retrospectively determine patients' Rockwood Clinical Frailty Score (RFS) pre- and post-treatment.

**Results:** 35 patients (mean age 76, 60% female) with DLBCL were analysed. 20 (53%) had aggressive disease with Revised International Prognostic Index (R-IPi)  $\geq 3$ . Overall survival was 68% with a median follow-up period of 718 days, with 90% of mortality disease or therapy related. Factors impacting on survival included: low frailty score at diagnosis, measured both by Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (87% in survivors vs 36% in those who died,  $p=0.001$ ) and RFS 1-4 (92% vs 54%,  $p=0.01$ ), and completion of planned treatment without dose reduction (100% vs 45%,  $p=0.0001$ ). Those who died tended to have poorer mobility (73% vs 21%,  $p=0.003$ ) and were requiring assistance in personal activities of daily living (pADLs) (45% vs 13%,  $p=0.03$ ) at diagnosis (**Table 1**). Amongst the survivors, functional decline – especially decline in mobility – was common. More such patients were identified using RFS than ECOG (33% vs 17%) (**Table 2**).

**Conclusions:** Functional status and frailty, using ECOG and RFS scores appear to be important predictors of survival in elderly patients with DLBCL. Incorporating functional scores such as RFS in prognostic assessment prior to commencing treatment should be considered. Larger prospective studies are needed to confirm these findings.

**Table 1: factors affecting survival in elderly patients with DLBCL**

	Alive (n=24)	Dead (n=11)	p-value
Mean age	74	75.5	0.09
Female gender	12 (50%)	9 (82%)	0.07
Stage III-IV	15 (62.5%)	10 (91%)	0.08
R-IPi 3-5	12 (50%)	8 (73%)	0.2
No dose reduction	17 (71%)	4 (36%)	0.053
All planned treatment completed	24 (100%)	5 (45%)	<b>0.0001</b>
Cycles given (median)	8	3	
ECOG 0-1 at diagnosis	21 (87%)	4 (36%)	<b>0.001</b>
RFS 1-4 at diagnosis	22 (92%)	6 (54%)	<b>0.01</b>
Assisted with mobility	5 (21%)	8 (73%)	<b>0.003</b>
Assisted with pADLs	3 (13%)	5 (45%)	<b>0.03</b>

**Table 2: ECOG vs RFS to measure change in function post treatment**

	ECOG	RFS
Decline in function	4 (17%)	8 (33%)
Gain in function	1 (4%)	1 (4%)
Change in scores	-1 to +1	-3 to +4

Teresa Leung et al (2017) Non-Hodgkin Lymphoma treatment outcomes at Northern Health: focusing on elderly patients with diffuse large B cell lymphoma. Poster presented at Northern Health Research Week, Epping, Victoria

Alessandra Tucci et al (2015) Comprehensive geriatric assessment is an essential tool to support treatment decisions in elderly patients with diffuse large B-cell lymphoma: a prospective multicenter evaluation in 173 patients by the Lymphoma Italian Foundation (FIL), *Leukemia & Lymphoma*, 56:4, 921-926, DOI: [10.3109/10428194.2014.953142](https://doi.org/10.3109/10428194.2014.953142)

## Histological subtyping inaccuracies of grade 3 follicular lymphoma may result in unconventional treatment decisions

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**Background:** Follicular lymphoma (FL) is a heterogenous disease comprising 3 histological grades with grade 3 (G3) subdivided further into grade 3A (G3A) and 3B (G3B). Histologically, G3B can be difficult to distinguish from G3A with 3A having admixed centrocytes (small cells) and centroblasts (large cells) and 3B consisting of centroblasts exclusively with loss of follicular architecture.

Disagreement exists over whether G3B behaves indolently like its lower grade counterparts, or whether it is an aggressive lymphoma, resembling diffuse large B cell lymphoma (DLBCL) which is potentially curable. While conventional treatment for G3B is anthracycline based chemotherapy, G3A can potentially be observed if asymptomatic. This means accurate grading of 3A and 3B FL has major treatment implications.

**Aim:** To assess the diagnostic concordance between 2 blinded expert haematopathologists in Australian cases of high grade follicular lymphoma.

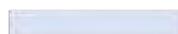
**Methods:** 19 cases of high grade follicular lymphoma from 2003-2019 (G3 unspecified, G3A, G3B and composite G3/DLBCL) were identified using clinical and pathology databases at the Austin Hospital, Victoria and Gold Coast University Hospital, Queensland. The cases were reviewed independently by 2 blinded expert histopathologists.

**Results:** Concordance was seen with 9/19 (47%) of cases. These consisted of 1 G2, 4 G3A, 2 G3B, 1 G3B/DLBCL and 1 G3B/DLBCL. This was in keeping with the original diagnosis on 4 occasions, discordant with the original diagnosis on 2 occasions and could not be compared in 3 cases as the original diagnosis was G3 unspecified. In 1 case the discordant result was histologically downgraded and the other it was upgraded. Discordance between histopathological grading was seen in 10/19 (53%). The results are summarised in **table 1**.

### Conclusion:

There is significant discordance between expert histopathologists with grading high grade follicular lymphoma. New strategies, such as unique molecular signatures, to improve diagnostic accuracy are being investigated.

Original Diagnosis	Reviewer 1	Reviewer 2
3b	3b	3b
3a	3a	3a
3a	3b	3a
3a	3b	3a
3a	3a	3a
3a	3b	3a
3a	3a	2
3a	3b	3a
3a	2	2
3b/DLBCL	3b	3b/DLBCL
3a/DLBCL	3b/DLBCL	3b/DLBCL
3a/DLBCL	3a/DLBCL	3a/DLBCL
3	3a	3a/DLBCL
3	3b	DLBCL
3	3b	2
3	3a	3a
3	3a	3a
3	3a	DLBCL/3a
3	3b	3b

 Discordant results

## Utility of GELF criteria in treatment decisions for follicular lymphoma (FL) treated in clinical practice.

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### Background

The decision to treat patients with FL is often determined by tumour burden, with the majority of low-burden disease treated with initial observation. The Groupe d'Etude des Lymphomes Folliculaires (GELF) developed standardised criteria to assess tumour burden.<sup>1</sup>

Patients must meet  $\geq 1$  criteria to be considered "high" tumour burden:

- Any tumour mass  $>7$  cm.
- At least 3 nodal sites, (each  $>3$  cm)
- B symptoms
- Splenomegaly
- Compression syndrome
- Pleural or peritoneal effusion
- Lymphocytes  $>5.0 \times 10^9/L$
- Cytopenias (neutrophils  $<1.0 \times 10^9/L$  and/or platelets  $<100 \times 10^9/L$ )

The GELF criteria have been widely adopted to assess need for systemic therapy as part of the eligibility for clinical trial enrolment, however outside clinical trial settings, the use and validity of GELF criteria are not well described.

**Aim:** Assess the uptake of GELF criteria to guide clinical decision-making in newly-diagnosed FL

**Methods:** Newly-diagnosed grade 1-3A FL patients (age $>18$ ) were identified from Austin Hospital patient records between 2005-2018. Data collection included baseline characteristics, presence of GELF criteria treatment details and outcomes.

**Results:** 135 cases were included, chemotherapy was administered in 87 (64%) radiotherapy in 21 (16%) and observation in 27 (20%). Of the patients that received chemotherapy, radiation therapy and watch-and-wait, 76%, 57% and 41% respectively had  $\geq 1$  GELF criteria.

**Conclusion:** In FL patients treated in clinical practice, there is poor correlation between the presence of GELF criteria and treatment decisions, suggesting that not all patients with features of high tumour burden require therapy, and not all patients requiring therapy have GELF criteria. Detailed reasons for treatment in GELF-negative patients and outcomes according to number of GELF criteria will be presented. A larger collaborative analysis using the Lymphoma and Related Diseases Registry is ongoing.

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H083

## **A year at a glance in the multidisciplinary Cutaneous Lymphoma Service at Peter MacCallum Cancer Centre.**

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Increasing numbers of patients are presenting to the multidisciplinary Cutaneous Lymphoma Service at Peter MacCallum Cancer Centre, consisting of Haematology, Dermatology, Radiation Oncology, Nursing, Pathology and Palliative Care.

**Aim:** To provide an overview of the activity of the Cutaneous Lymphoma Service, contribution to research, and impact on improving the care of patients living with Cutaneous Lymphoma.

**Method:** A retrospective audit was performed of patients seen from 1/1/2018 to 31/1/2018.

**Results:** During 2018 there were 12 patients seen with new, confirmed diagnoses of primary cutaneous B-Cell lymphoma and 65 with new, confirmed diagnoses of primary cutaneous T-Cell lymphoma (CTCL).

Accompanying the rise in new referrals, we also observed increasing inpatient admissions. 29 patients with Cutaneous Lymphoma required admission; common reasons for admission included sepsis, end-of-life care, skin flare, and management of pruritus with subcutaneous lignocaine and administration of radiolabelled mabthera. The median of inpatient days on the ward was 16.

The National Cutaneous Lymphoma Database at Peter Mac is a unique and valuable resource. As a result of the ongoing clinical service and data collection, multiple papers were generated through collaborative input. Multiple presentations were also given at national and international conferences, providing expert opinions on the multidisciplinary care of cutaneous lymphoma. Patient outcome data was submitted to support the successful PBS applications for Brentuximab vedotin and pralatrexate. In addition, data on 65 patients undergoing extracorporeal photopheresis has contributed to an ongoing TGA submission. Our service continues to participate in collaborative, international research projects such as the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIP1).

**Conclusion:** The multidisciplinary Cutaneous Lymphoma Service at Peter Mac continues to grow, providing patients with super-specialised care. Ongoing research projects are underway utilising the unique and comprehensive National Cutaneous Lymphoma Database.

H085

**Case series: Fingolimod associated Diffuse Large B-cell Lymphoma (DLBCL)**

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**Aim:**

Oral fingolimod is a sphingosine-1-phosphate receptor modulator currently used for treatment of Multiple Sclerosis with superior efficacy for prevention of relapse rate and MRI outcomes. Fingolimod prevents lymphocytes egression from lymph nodes and in mice models blocks immunosurveillance of myeloma and B cell lymphoma by CD4+ T cells. There are case reports of predominantly cutaneous lymphoma associated with fingolimod. We describe a case series with DLBCL whilst on fingolimod.

**Method:**

Survey of the Australasian Lymphoma Alliance identified 3 cases of DLBCL in patients receiving fingolimod. Treating clinicians reported clinical characteristics and outcomes.

**Results:**

Age ranged 52-62 years with all patients on fingolimod 3-8 years for Relapsing Remitting Multiple Sclerosis (RRMS). Clinical presentation was similar, all with intra-abdominal masses causing obstructive symptoms requiring intervention (2 patients with ureteric obstruction and one with bowel obstruction). Histology from all three patients showed a GCB type DLBCL with EBER-ve, cMYC(0–40%), BCL2(30-50%)and BCL6 (30-70%). All three patients had predominantly extranodal disease with IPI>3 and were treated with R-CHOP chemotherapy. Fingolimod was ceased 3-10 days pre-initiation of chemotherapy. Main complications during treatment were infective with one patient requiring prolonged hospitalisation with VZV encephalitis. With short follow-up, outcomes from lymphoma appear favourable with two patients achieving CR and one still undergoing treatment.

**Conclusion:**

This case series suggests possibility of an association between fingolimod and occurrence of GCB DLBCL with extranodal disease. Therapy is complicated by increase infection. Outcomes appear favourable despite high-risk disease. Further investigation of potential mechanisms of oncogenesis and post-marketing surveillance is required.

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Lorvik et al Fingolimod blocks immunosurveillance of myeloma and B cell lymphoma resulting in cancer development in mice. Blood 2012 119:2176-2177

## Western Australian Experience with PD-1 Inhibitors in Hodgkin's Lymphoma

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<sup>1</sup>*Fiona Stanley Hospital, Murdoch, Australia*

**Aim:** Over 80% of patients with Hodgkin's lymphoma (HL) achieve long term remission with first line chemotherapy,[1] however In R/R disease, only 50% are cured with salvage chemotherapy followed by consolidation with an autoSCT.[1] Recently, immune checkpoint inhibitors have been shown to prolong survival in R/R HL in the landmark KEYNOTE 087 study and extended follow up for the CHECKMATE 205 trial. [2,3,4]. In this descriptive study we summarise data from all HL patients who have been treated with PD-1 inhibitors in WA.

**Method:** Inclusive data was collected by electronic and pharmacy records from both private and public systems in WA. We recorded age, gender, subtype of Hodgkin's lymphoma, first line and salvage therapies, autograft and allograft treatment, type of PD-1 inhibitor (nivolumab/pembrolizumab), response and current status.

**Result:** A total of 13 patients were analysed. The median age was 34 years (19-76yo), 9 males and 4 females. 10 patients initially received ABVD and 2 required escalation to BEACOPP halfway. All patients received >3 salvage therapies including BEAM autograft, except for 2 who did not receive an autoSCT due to age. 2 patients had alloSCT post PD-1 inhibitor, with severe GVHD and infective complications in both, with one death; 1 started PD1 inhibitor post alloSCT. 7 vs 5 patients received/due to receive pembrolizumab and nivolumab respectively and 1 switched from nivolumab to pembrolizumab due to subsequent PBS listing.

11 of 13 patients are alive with 5 ongoing remissions. No unexpected side-effects were noted and therapy was well tolerated.

**Conclusion:** This novel class of immunotherapy has been effective in most patients with advanced disease with otherwise poor outlook. Most have continued without allograft and 3 have continuing remission (4-47 months). Earlier utilisation of PD-1 inhibitors in the treatment course may improve outcomes, and allografts remain challenging.

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H087

## **CD71 as a flow cytometry marker for differentiating between aggressive and indolent B-cell lymphomas**

**Laura Chen**<sup>1</sup>, Pranav Dorwal<sup>1</sup>, Helen Moore<sup>1</sup>

<sup>1</sup>Waikato Hospital, Hamilton, New Zealand

**Introduction:** Flow cytometry is a fundamental adjunct in the diagnosis and classification of B cell lymphomas, however differentiating between indolent and aggressive lymphomas by flow cytometry is challenging. CD71 (transferrin receptor) mediates iron uptake into cells, essential for cellular proliferation. We studied CD71 expression on a cohort of patients with B cell lymphomas to assess its usefulness in helping distinguish between indolent and aggressive B cell lymphomas.

**Method:** CD71 was added to our flow cytometry panel for the assessment of B lymphoproliferative disorders. The results were collected and correlated with the final histological diagnosis. We assessed the expression of CD71, the median fluorescence index (MFI) and when available, this was correlated with the Ki-67 index by immunohistochemistry (IHC). The difference in the MFI between aggressive lymphomas (DLBCL, Burkitt lymphoma and high grade follicular lymphomas) compared to more indolent lymphomas was calculated using the student t-test. The sensitivity and specificity for predicting aggressive lymphomas was calculated by taking the histological diagnosis as the true positive and negative.

**Results:** 119 samples were collected and assessed. The difference in mean MFI between the high grade lymphomas and low grade lymphoma was statistically significant. There was also a clear correlation between increasing CD71 expression by flow cytometry with a higher Ki-67 index by IHC. The sensitivity and specificity of CD71 in predicting high grade lymphomas was 91% and 87% respectively.

**Conclusion:** There is a clear correlation between the expression of CD71 by flow cytometry and diagnosis of aggressive B cell lymphomas. There is a high sensitivity (91%) and specificity (87%) in the use of CD71 to predict aggressive B cell lymphoma. This study shows CD71 to be a useful marker in the assessment of B cell lymphoproliferative disorders by flow cytometry.

H088

## **Decision-making in CNS prophylaxis for DLBCL in a single institution**

**Stephanie Clugston**<sup>1</sup>, Dustin Hall<sup>1</sup>, Shane Gangatharan<sup>1</sup>

<sup>1</sup>*Fiona Stanley Hospital, Perth, Australia*

**Aim:** CNS relapse of DLBCL has poorer outcomes than systemic relapse alone. Validated risk scores assist in identifying high-risk populations. A wide variety of CNS prophylaxis methods are considered due to lack of prospective data informing the optimal method. We aim to review the current CNS prophylaxis practice at our institution.

**Method:** Retrospective review of new diagnosis of DLBCL or high-grade B-cell lymphoma identified by lymphoma multidisciplinary meetings, or Lymphoma and Related Disease Registry, 12/11/2016-8/4/2019.

**Result:** 95 patients; median age at diagnosis 69 (range 21-97). 87% had DLBCL (52% GCB, 25% non-GCB, 23% unknown). 23% had transformed disease.

IPI score 0-1, 2-3, 4-5 in 19%, 44%, and 32% respectively. 33 patients had high-risk CNS-IPI of 4-6. CNS-IPI upgraded risk in 11; 3 patients to high risk.

Of 33 patients with CNS-IPI 4-6, 2 were palliated, 2 were refractory to primary therapy, 5 undergoing treatment and one relapsed before CNS prophylaxis. Of 23 who completed treatment 16 (70%) received methotrexate CNS prophylaxis (3 intrathecal, 12 intravenous, 1 both). Of those who did not receive prophylaxis 83% were >70yo and 33% had CrCl <60ml/min.

6 patients with CNS-IPI <4 received prophylaxis; with high risk sites including base of skull, paraspinal, testicular and nasopharyngeal, and one suspected double hit lymphoma.

Overall, 5% did not receive intensive therapy, 12% were refractory/progressed with primary therapy, 74% patients completed therapy, 10% are undergoing treatment. Of patients who completed therapy 5 had systemic relapse and 2 had both systemic and CNS relapse; 1 after prophylaxis (CNS-IPI 5 and triple hit cytogenetics) and 1 before planned prophylaxis (CNS-IPI 4).

**Conclusion:** Multidisciplinary meetings assist in determining CNS relapse risk. Most eligible patients at our institution receive CNS prophylaxis. Our regimen of IV methotrexate does not completely prevent CNS relapse. Prospective studies are required to identify effective CNS prophylaxis strategies.

## Open-label, phase 2 study of blinatumomab as second salvage therapy in adults with relapsed/refractory aggressive B-Cell Non-Hodgkin Lymphoma

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**Background:** This open-label, multicentre, phase 2 portion of an adaptive phase 2/3 study assessed the efficacy/safety of blinatumomab as a second salvage (S2) therapy for patients  $\geq 18$  years with biopsy-confirmed aggressive r/r NHL who have not achieved complete remission or complete metabolic response (CMR) following  $\geq 2$  cycles of platinum-based S1 chemotherapy.

**Methods:** Blinatumomab was given by continuous intravenous infusion for a single 70-day cycle 1 (9  $\mu\text{g/day}$  for 7 days, 28  $\mu\text{g/day}$  for 7 days, and 112  $\mu\text{g/day}$  for 42 days, followed by a 14-day treatment-free interval) and an optional 28-day cycle 2 (9  $\mu\text{g/day}$  for 7 days, 28  $\mu\text{g/day}$  for 7 days, and 112  $\mu\text{g/day}$  for 14 days). The primary endpoint was CMR by central PET. Additional endpoints were objective response rate (ORR [CMR+PMR]), post-response HSCT realization rates, and the incidence/severity of adverse events (AEs).

**Results:** Forty-one patients were enrolled and received blinatumomab. Patient demographics, ORR, best response rates and adverse events are shown in tables 1 and 2. Eight (20%) patients had HSCT in remission, 7 (17%) with autoHSCT (CMR, n=6; PMR, n=1), and 1 with allogeneic HSCT in partial metabolic response (PMR). Thirty-five patients did not have HSCT (n=32) or had delayed HSCT (n=3) due to progressive metabolic disease (PMD) (n=17), lack of CMR (n=4), AE (n=4), patient preference (n=1), no metabolic response (NMR) or unknown (n=1), and other (n=8); 1 patient had missing information. Eight of 9 CMR patients (89%) were alive without relapse, with a median follow up time of 8.8 months. The Kaplan-Meier estimate at 9 months was 51%; median overall survival (OS) was not reached (Table 2).

**Conclusions:** Blinatumomab showed promising efficacy consistent with the efficacy and safety demonstrated in earlier blinatumomab B-NHL trials and potentially offers a treatment option for patients unresponsive to standard salvage regimens.

Table 1: Demographics	N=41	Table 2: Results	N=41
Gender, male	28 (68)	ORR (CMR + PMR), n (%); (95% CI)	15 (37); (22, 53)
Median age, years	56	Best response, n (%)	
Primary disease status, n (%)		CMR	9 (22)
Relapse	13 (32)	PMR	6 (15)
Refractory (no remission)	28 (68)	NMR	5 (12)
Baseline response, n (%)		PMD	12 (29)
NMR/stable disease	5 (12)	No postbaseline assessment	9 (22)
PMR/partial response	9 (22)	Overall survival	
PMD/progressive disease	27 (66)	Median, months (95% CI)	NE (4.5, NE)
Treatment, n (%)		KM estimate at 6 months, <sup>a</sup> % (95% CI)	64 (43,79)
Cycle 1	41 (100)	KM estimate at 9 months, <sup>a</sup> % (95% CI)	51 (28, 70)
Completed	19 (46)	KM estimate at 12 months, <sup>a</sup> % (95% CI)	NE (NE, NE)
Discontinued	22 (54)	Grade $\geq 3$ TEAE, n (%)	24 (59)
Disease progression	17 (41)	Grade $\geq 4$ TEAE, n (%)	10 (24)
AEs	4 (10)	Discontinued due to AEs, n (%)	7 (17)
Death	1 (2)	Neurologic AEs, n (%)	23 (56)
Cycle 2	4 (10)	Grade 3	10 (24)
Completed	3 (7)	Leading to discontinuation	3 (17)
Discontinued	1 (2)	Grade 3 cytokine release syndrome, n (%)	1 (2)
AEs	1 (2)	Other Grade $\geq 3$ AEs, n (%)	
		Infections	8 (20)
		Bone marrow toxicity	7 (17)
		Thromboembolic events	3 (7)
		Hepatic disorders	2 (5)
		Acute pancreatitis	1 (2)

<sup>a</sup>Median (95% CI) time to last follow up was 4.9 (3.5, 9.7) months

<sup>b</sup>Months are calculated as days from randomisation date to event/censor date, divided by 30.5

## PLIMATH: A Phase II study of Pembrolizumab as Frontline Treatment of Patients with Hodgkin Lymphoma (HL) considered Unsuited for ABVD: An Australasian, Investigator-led Trial in Progress

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**Background:** Approximately 25% of patients with HL are greater than 55 years of age. Outcomes following combination chemotherapy are poorer than for their younger counterparts. This is partly due to a higher stage; worse performance status; a higher percent presenting with mixed cellularity disease; and reduced treatment intensity due to poor treatment tolerance. (Evans, 2012) There is no standard induction approach for elderly and frail patients with HL. The PD1 inhibitor, pembrolizumab induces high response rates as a single agent in patients with relapsed/refractory disease with a generally good side effect profile. It is associated with infrequent but idiosyncratic immune adverse events (IAE). We are actively recruiting to a trial of pembrolizumab as a front-line therapy in older patients with HL, or those unfit to receive ABVD.

**Primary objective:** Response rate

**Key Secondary and Exploratory Objectives:** Time-Dependent survival outcomes, subsequent therapy choice, translational studies on peripheral blood CTDNA and tumour biopsies

**Key Inclusion:** Age 18 or above, with either age >64 or considered by the investigator to be ineligible for front-line ABVD combination chemotherapy due to reasons of medical co-morbidity; Measurable disease; Available biopsy sample; ECOG <3,

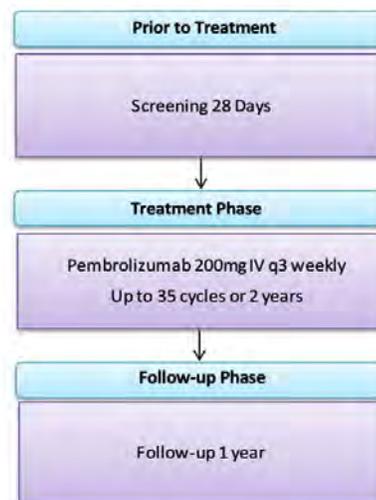
**Exclusion:** Active other malignancy requiring therapy; major organ dysfunction; autoimmune disease

**Intervention:** pembrolizumab 200mg q3w for up to 35 cycles.

**Open treatment sites:** Melbourne, Auckland, Brisbane, Sydney, Perth

**Recruitment:** 25 patients

**Conclusion:** This trial will explore the role of PD1 inhibition in treatment-naïve elderly or chemo-unfit patient group, in an attempt to address an unmet clinical need.



*Main analysis after all patients received 6 cycles of treatment*

## Rapid referral assessment, a key indicator of time to treatment within a phase I haematology clinical trial unit

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**Aim:** To provide referring physicians with a realistic time to treatment when considering phase I clinical trials for patients and to quantify the time between stages of the referral pathway.

**Method:** Data was retrospectively collected for all consecutive haematology patients referred to a phase I clinical trial unit from July 2018 to July 2019. Time to treatment was quantified as the length of time between the initial referral and cycle 1 day 1 (C1D1) in days. If there was a delay due to trial cohort management, this was recorded. Where a patient was unable to receive trial treatment, reasons for this were recorded. Baseline patient characteristics were also collected (*Table 2*).

**Result:** 37 referrals were received, 21 (57%) were successful in receiving treatment. Reasons for patients not receiving treatment included failure to meet initial trial criteria (N=6), screen fail (N=4), patient declined the trial (N=2) or lack of current available cohort slots (N=4). Of the 21 who enrolled, 6 experienced a cohort delay. The median time from referral to C1D1 was 33 days for those without delay and 89.5 days those who were delayed. Overall median time to treatment was 48 days. For those without cohort delays, median time from receipt of referral to first review was 9 days (*Table 1*).

**Conclusion:** Effective and rapid referral triage was the key factor in reducing the time to treatment for patients that enrolled onto a trial given the lengthy but consistent screening period. Majority of the referrals ultimately led to patients receiving clinical trial therapy. This data is informative for physicians who are considering patients for clinical trials as a detailed referral and ongoing communication between referring and trial physicians is key to optimizing the phase I referral pathway.

Table 2 Median Time in days by Cohort Delay

Cohort Delay	N	Referral - Review	Review - C1D1	Referral - C1D1
No	15	9	21	33
Yes	6	62	19.5	89.5
Total	21	24	21	48

Table 3 Patient Characteristics

Characteristics	Successful (N= 21)	Unsuccessful (N=16)	Total (N=37)
Median Age (Years)	62	67.5	65
Sex M/F	10/11	11/5	21/16
Prior Lines of Therapy			
≤2	8	6	14
≥3	13	10	23
ECOG Status at Entry			
0	15	-	-
1	6	-	-
2	0	-	-
Reason for Failure			
Screen Fail	-	4	-
Patient Declined	-	2	-
No Slot Available	-	4	-
Did Not Meet Criteria	-	6	-
Diagnosis			
Waldenstrom's Macroglobulinemia	3	0	3
Follicular Lymphoma	5	1	6
Mantle Cell Lymphoma	1	1	2
Acute Myeloid Leukaemia	1	2	3
Diffuse Large B-Cell Lymphoma	6	7	13
Marginal Zone Lymphoma	2	0	2
Chronic Lymphocytic Leukaemia	2	0	2
Multiple Myeloma	0	5	5
Peripheral T-Cell Lymphoma	1	0	1

ECOG= Eastern Cooperative Oncology Group; ECOG data was not collected for unsuccessful subjects.

## Retrospective review of first-line treatment patterns and clinical outcomes in patients with DLBCL: a single centre experience.

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**Aim:** To describe baseline characteristics, patterns of treatment and outcomes among patients with DLBCL treated at Sir Charles Gairdner Hospital.

**Method:** Retrospective review of patients diagnosed with DLBCL between April 2014 and April 2019. Patients with PCNSL and Richter's transformations were excluded. Data were collected primarily from hospital records.

**Results:** 250 patients were identified: 174 (70%) had *de novo* disease and 76 (30%) had transformed lymphoma. Incidence steadily increased over the study period, from 33 patients in 2015 to 80 in 2018. Baseline characteristics and treatment details are described below.

	De novo (n=174)	Transformed (n=76)
Median age, years (range)	68 (18-93)	66 (44-90)
60 years, n (%)	124 (71)	52 (68)
Males, n (%)	99 (57)	41 (54)
Stage III/IV, n (%)	110 (63)	54 (71)
NOS*, n	141 (81)	71 (93)
HGBL-DH**, n	15 (9)	2 (3)
R-CHOP-based, n (%)	106 (61)	52 (68)
R-miniCHOP-based, n (%)	33 (19)	10 (13)
18-month PFS rate	73.7%	74.6%
18-month OS rate	83.8%	87.3%
*not otherwise specified		
**high grade B-cell lymphoma with rearrangements in MYC and BCL2/BCL6		

Post-treatment responses were available for 215 patients (median follow-up = 18 months). 18/215 died during treatment (most common cause was sepsis). 34/215 were refractory, 12/215 relapsed and 151/215 were in remission. On univariable analysis, age 60, stage III/IV, elevated LDH, ECOG >1 and extranodal sites >1 were associated with inferior PFS, however on multivariable analysis, only stages III/IV (HR 3.4, 95% CI 1.3-8.8, p=0.01) and ECOG >1 (HR 2.0, 95% CI 1.1-3.9, p=0.03) retained association. For OS, age 60, stage III/IV, elevated LDH, ECOG >1, extranodal sites >1 and R-miniCHOP (vs. R-CHOP) were associated with increased risk on univariable analysis, however on multivariable analysis, no variables retained association.

**Conclusion:** In this contemporary cohort of patients treated at a single academic centre, outcomes were favourable and comparable to prospective trials.

### **Adult T cell leukaemia/lymphoma: a rare and unexpected diagnosis**

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Adult T cell leukaemia/lymphoma (ATLL) is a rare lymphoma caused by human T-lymphotropic virus type 1 (HTLV-1) infection, usually seen in populations with endemic HTLV-1. It is rare in Australia where seropositivity is very low, with the exception of Indigenous populations in central Australia<sup>1</sup>. We report a case of a 71 year old Iranian immigrant with a typical presentation of this rare disease: B symptoms, hepatosplenomegaly, widespread lymphadenopathy, a peripheral blood lymphocytosis with floriform nuclear morphology, hypercalcaemia (2.7mmol/L), elevated lactate dehydrogenase (3484U/L), but no skin lesions. Bone marrow aspirate was hypercellular with 10% abnormal lymphocytes which expressed CD2, CD3, CD4, CD5, CD25, T cell receptor alpha/beta and dim CD7. HTLV-1 was positive by ELISA and Western Blot and lymphoid NGS demonstrated a RHOA mutation, consistent with the diagnosis of ATLL. Liver and lymph node biopsies were supportive. He was treated with arsenic, zidovudine and interferon with partial response. However, his course was complicated by peritoneal haemorrhage, sepsis and encephalopathy. He developed multiorgan failure and died 2 months after his initial presentation.

While ATLL is a rare disease in Australia, it should be considered in patients from HTLV-1 endemic regions<sup>2</sup>. Early diagnosis can facilitate introduction of antiviral and chemotherapeutic agents, though acute ATLL is still associated with a dismal prognosis due to inherent chemoresistance and profound immunosuppression<sup>3</sup>.

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**ENABLE: A phase 1 dose escalation trial of third-generation anti-CD19 CAR T-cells incorporating CD28 and TLR2 costimulatory domains for relapsed and refractory B-cell non-Hodgkin lymphomas.**

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Commercially-available 'second-generation' anti-CD19 chimeric antigen receptor (CAR) T-cell therapies lead to high response rates in relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (B-NHL), but only 30 – 40% of recipients remain progression free beyond a year; outcomes among those without early complete response (CR) are particularly poor [1,2]. There is a need for CAR T-cells that elicit higher CR rates. One way to achieve this is to combine co-stimulatory domains, generating 'third-generation' (3G) CAR T-cells.

Activated T-cells express Toll-like receptor (TLR) 2, and incorporation of the TLR2 intracellular signalling domain within CARs enhances cytotoxicity *in vitro*, and leads to improved *in vivo* activity [3]. In a phase I trial in r/r B-cell acute lymphoblastic leukaemia including extramedullary disease, 3G CAR T-cells incorporating CD28 and TLR2 costimulatory domains led to high CR rates, at a lower dose than used for second-generation products [4].

We have initiated clinical-grade manufacture of WZTL-002, comprising autologous 3G anti-CD19 CAR T-cells employing CD28 and TLR2 co-stimulatory domains, within a licensed cell therapy facility at the Malaghan Institute of Medical Research in Wellington, New Zealand.

A single-centre phase I, 3+3 dose escalation trial of WZTL-002 ('ENABLE'; UTN U1111-1216-2053) is being initiated in collaboration with Wellington Zhaotai Therapies Limited. The primary endpoint is safety of WZTL-002; secondary endpoints include manufacturing feasibility, CR rate at 6 months and establishing a recommended phase 2 dose.

Eligible participants have r/r B-NHL lacking curative treatment options, satisfactory organ function, and require no systemic immunosuppression. Bridging chemotherapy is permitted pending WZTL-002 manufacture, product release and treatment scheduling. Lymphodepletion comprises fludarabine (30 mg/m<sup>2</sup>/day × 3d) and cyclophosphamide (500 mg/m<sup>2</sup>/day × 3d), and is followed by a single administration of WZTL-002. Dose limiting toxicities include grade 4 or persistent grade 3 cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. Updated trial progress will be discussed.

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H095

## **Prolonged Response to Venetoclax post Zanubrutinib in Advanced Waldenström's Macroglobulinaemia: A Case Report**

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**Aim:** To present the case of a prolonged response to Venetoclax, first as monotherapy and later in combination with Rituximab, for a patient with advanced and heavily pre-treated Waldenström's Macroglobulinaemia, with previous therapy including two clinical trial agents.

**Method:** The patient's laboratory data and clinical information was reviewed from three teaching hospitals and the patient's local regional hospital, including details from clinical trials, regular patient reviews and routine monitoring investigations.

**Result:** The patient, a 69 year-old man, presented with marked anaemia and splenomegaly in 2006. Clinical features and investigations including serum protein electrophoresis and bone marrow aspirate & trephine were consistent with a diagnosis of Waldenström's Macroglobulinaemia. After initially receiving FCR and obtaining complete response lasting until 2013, he would later experience a series of non-sustained responses to multiple treatments including Bendamustine-Rituximab, Idelalisib, Plasma Exchange and Rituximab, Cyclophosphamide and Dexamethasone, Bortezomib, Thalidomide, and Zanubrutinib (BGP-3111). He experienced adverse effects including multiple infections such as RSV, other respiratory tract infections in the setting of pancytopenia and BK associated cystitis, as well as Idelalisib-associated colitis. He commenced Venetoclax via compassionate access in August 2017 with an impressive response. After twelve months, serum protein electrophoresis demonstrated a gradual but progressive rise in IgM paraprotein accompanied by increasing splenomegaly, which has since stabilised and improved with the addition of Rituximab and increasing the dose of Venetoclax to 800mg daily.

**Conclusion:** Venetoclax, an agent with established efficacy in CLL, has shown efficacy in this case of advanced and heavily pre-treated Waldenström's Macroglobulinaemia, first as monotherapy, and after slow disease progression, in combination with Rituximab. Earlier use of Venetoclax in the treatment of Waldenström's Macroglobulinaemia and possible combination therapy may improve outcomes.

H096

## **Aplastic anaemia secondary to bendamustine**

**Thomas Gleeson<sup>1</sup>**, Philip Choi<sup>1</sup>

<sup>1</sup>*Department of Clinical Haematology, Canberra Hospital, Garran, Australia*

**Aim:** To report two cases of aplastic anaemia attributed to bendamustine in patients with follicular lymphoma, who were treated with rituximab and bendamustine.

**Method:** Retrospective case file reviews.

**Results:** Two patients (aged 76 and 77 years) were diagnosed with follicular lymphoma and treated with six cycles of rituximab and bendamustine. Bone marrow biopsies at the time of diagnosis in both patients were normocellular with normal trilineage haematopoiesis. One demonstrated evidence of marrow involvement with follicular lymphoma at the time of diagnosis. Both patients achieved complete remission post-treatment, however, within two months of completing chemotherapy, both patients developed progressive pancytopenia. Haemolysis screens and viral serologies were negative. Both patients proceeded to bone marrow biopsy which confirmed marrow aplasia without evidence of lymphoma recurrence. The aplasia was attributed to bendamustine and both patients were successfully treated with prednisolone and cyclosporin. These two cases are the first such reported in our institution.

**Conclusion:** Bendamustine may be a rare cause of aplastic anaemia and should be considered in the workup of the pancytopenic patient having been treated with this chemotherapeutic agent.

## Genomic characterisation of the immune evasion landscape in aggressive B-cell lymphoma

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### Background/Aims

Evasion of the immune response is critical to lymphomagenesis in aggressive B-cell lymphoma. Overcoming this immune escape with novel therapies (e.g. PD1/PDL1 inhibitors, chimeric antigen receptor T-cell therapy) is emerging as a highly promising therapeutic approach. We sought to genomically characterise the immune evasion mechanisms in aggressive B-cell lymphoma, which may inform the future stratification of patients who are most likely to benefit from immune-based therapies.

### Method

Gene expression profiling of patient samples was performed using the Nanostring nCounter Human Immunology V2 panel. DNA sequence variants, copy number changes and structural variants were assessed using the Peter MacCallum Cancer Centre PanHaem panel targeting approximately 300 recurrently mutated genes in haematological malignancy.

### Results

128 patients (75 DLBCL, 16 tFL, 26 tMZL, 11 tCLL) with aggressive B-cell lymphoma underwent DNA and RNA analysis. Immune-evasion subgroups were defined by curated DNA-level abnormalities or under/overexpression of relevant genes involved in (i) antigen presentation (AP), (ii) T-cell inhibition (TCI), (iii) T-cell evasion (TCE), (iv) immunosuppressive cytokine generation (ICG) and (v) resistance to apoptosis (RA).

CD40 had the highest frequency of outlier overexpression (24% cases) while HLA DPB1 and FOXP3 had the most frequent outlier underexpression (25%). Outlier over/underexpression was greatest in the ICG subgroup (84%) followed by TCI (68%), AP (55%), TCE (27%) and RA (18%). 87% of patients had gene expression abnormalities in multiple subgroups. DNA abnormalities were elucidated for multiple immune-evasion subgroups including: HLA copy number loss, structural variants involving immune checkpoint genes (e.g. CD274) and missense/truncating sequence variants in AP genes (e.g. B2M).

### Conclusion

In this comprehensive genomic characterisation we observed that a range of immune-evasion mechanisms are exploited in aggressive B-cell lymphoma. These data provide important biological insights into DLBCL and may inform the rational treatment stratification of patients with immune-based therapies.

H098

**Dose adjusted R-EPOCH does not improve outcomes in high grade B cell lymphoma with double expressor status or gain of MYC/BCL2.**

**Prue Hardefeldt<sup>1</sup>**, John Moore<sup>1</sup>, Sam Milliken<sup>1</sup>, Keith Fay<sup>1</sup>, Orlee Lavee<sup>1</sup>, Eleni Mayson<sup>1</sup>, Barbara Withers<sup>1</sup>, Nada Hamad<sup>1</sup>

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**Introduction:**

Diffuse large B cell lymphoma is a heterogenous disease with prognosis known to vary based on histological changes including immunohistochemistry and gene rearrangements by fluorescence in situ hybridisation (FISH). Both immunohistochemical overexpression as well as gene rearrangements in MYC, BCL2 and BCL6 are thought to contribute to poor prognosis. The benefit of high dose chemotherapy is unclear for those with high grade B cell lymphoma with double hit status (DHL) by FISH, double expressor status (DEL) or gain of MYC/BCL2. The purpose of this study was to retrospectively analyse the effect of escalated chemotherapy in this population over a 5 year period.

**Methods:**

All patients with DLBCL treated between 2012-2017 were screened retrospectively for inclusion in the study based on immunohistochemistry and FISH at time of initial diagnosis.

Immunohistochemistry was assessed on formalin fixed, paraffin embedded specimens with BCL2 and MYC considered positive at over 40% and 50% respectively. FISH was assessed using dual colour break apart probe.

**Results:**

135 patients were diagnosed with DLBCL of which 53 patients had immunohistochemistry and FISH at diagnosis confirming either, DEL or gain of MYC/BCL2 status. The mean age was 65 years and median follow up 21 months. The overall response rate in DH treated with DA-R-EPOCH was 57%. There were insufficient cases treated with R-CHOP for comparison. Overall response rates in DEL were 94% for DA-R-EPOCH and 93% for R-CHOP. Overall survival (OS) and disease free survival (DFS) in DHL was 6 months and 2 months respectively when treated with DA-R-EPOCH. There was no significant difference in OS or DFS in DEL treated with DA-R-EPOCH compared with R-CHOP (OS: 42 months vs 38 months respectively ( $p=0.962$ ), DFS 36 months vs 30 months ( $p=0.931$ )). Gain of MYC/BCL2 did not affect OS ( $p= 0.539$ ) or DFS ( $p=0.439$ ) when comparing treatment regimen.

**Conclusion:** DA-R-EPOCH did not improve treatment response rates OS or DFS in patients with double expresser lymphoma or gain of MYC/BCL2. This study also confirms the previously reported poor outcomes associated with DHL

**Updated results: phase-Ib/II study in relapsed/refractory (R/R) DLBCL patients treated with polatuzumab vedotin plus bendamustine with rituximab or obinutuzumab**

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**Aim:** To report updated efficacy, safety and preliminary biomarker data from the multicenter, open-label phase-Ib/II study (NCT02257567) of polatuzumab vedotin (Pola) plus bendamustine (B) with obinutuzumab (G) or rituximab (R) in transplant-ineligible R/R-DLCL patients.

**Methods:** Eligible R/R-DLBCL patients were enrolled in the phase-Ib safety run-in (pola+BR [N=6]), phase-Ib/II expansion (pola+BG [N=27]) or phase-II randomization (pola+BR [N=40] vs BR [N=40]) stages. Patients received pola 1.8mg/kg + B (90mg/m<sup>2</sup>/day x 2 days) and R (375mg/m<sup>2</sup>) or G (1000mg) every 21 days for up to 6 cycles. The randomized cohort was stratified by duration of response (DoR) to last therapy: ≤ vs >12 months. End of treatment responses were assessed by an independent review committee using modified Lugano criteria, with complete response (CR) requiring PET negativity and negative bone marrow biopsy if the screening bone marrow was positive. Primary aims included safety (phase-Ib) and efficacy (pola+BR vs BR) at end-of-treatment (phase-II). Other efficacy measures included investigator (INV) DoR and progression-free survival (PFS); and overall survival (OS). Efficacy by cell-of-origin (COO) was evaluated.

**Results:** Median follow-up (cut-off April 30 2018) was 37.6 months (phase-Ib pola+BR), 27.0 (phase-Ib/II pola+BG), and 22.3 (randomized cohort). Long-term safety was consistent with those previously described. In the randomized cohort, pola+BR patients had significantly higher CR rates (40% vs 18%; p=0.026), and longer INV-DoR (10.3 vs 4.1 months; HR=0.44; p=0.032), median INV-PFS (7.6 vs 2.0 months; HR=0.34; p<0.0001) and median OS (12.4 vs 4.7 months; HR=0.42; p=0.0023), than BR only patients. Pola-BG patients had 30%-CR, 28.4 months-INV-DoR, 5.4 months-median INV-PFS and 10.8 months-median OS. In the randomized cohort, 13 patients had responses lasting >20 months: 7 pola+BR and 6 pola+BG. COO analyses demonstrated improvements in pola+BR in GCB and ABC.

**Conclusions:** Results show that pola+BR improves responses and survival vs BR alone. Pola+BR showed benefit over BR regardless of COO.

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## Intravenous immunoglobulin therapy use in patients with relapsed/refractory diffuse large B-cell lymphoma treated with tisagenlecleucel in the JULIET trial

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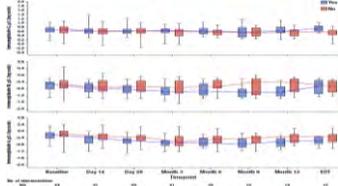
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**Aim:** To evaluate the use and clinical outcomes of intravenous immunoglobulin (IVIg) for hypogammaglobulinemia (IgG <4 g/L) in the JULIET study. **Method:** JULIET is a single-arm phase 2 trial of tisagenlecleucel in adult patients with relapsed/refractory (r/r) DLBCL. IgG, IgM, and IgA were assessed at baseline; day 14, 28; month 3, 6, 9, 12; and end of follow-up. **Result:** At data cutoff (21-May-2018; median follow-up: 19 months), hypogammaglobulinemia was observed in 68/115 patients (59%) following tisagenlecleucel infusion. 37/75 patients (49%) with IgG  $\geq$ 4 g/L prior to tisagenlecleucel subsequently developed hypogammaglobulinemia with median duration of 70 days and median onset of 14 days. CAR-T transgene levels (copies/ $\mu$ g DNA) were comparable between patients with or without hypogammaglobulinemia at all time-points after infusion. Immunoglobulin recovery in the overall population according to IVIg use is summarized in the **Figure**. 38/115 patients (33%) received IVIg following infusion; 25/38 patients received IVIg in the presence of hypogammaglobulinemia, while 13 received IVIg with levels of IgG  $\geq$ 4 g/L. 9/115 patients (7.8%) received IVIg before infusion. Median start of IVIg was 55 days after infusion (range: 5-555). IVIg use in responders vs nonresponders to tisagenlecleucel was 38.3% vs 27.3%, respectively. The frequency of grade 3-4 infections in patients who received IVIg vs those who did not is summarized in the **Table**. IgG levels in patients receiving and not receiving IVIg supplementation were comparable over time. **Conclusion:** Approximately one-third of patients received IVIg following tisagenlecleucel infusion. Use of IVIg was driven by local institutional practice, with heterogeneity in terms of indication, frequency, and duration of treatment. Although our study was not powered to address this question, no clear pattern associating IVIg use with patient characteristics and conditions was observed. Further research is needed to develop guidance for IVIg use following CAR-T infusion in patients with r/r DLBCL.

**Table.** Incidence of grade 3/4 infections over time by IVIg use

Grade 3/4 AEs	< 8 weeks	> 8 weeks to $\leq$ 1 year	> 1 year
Patients who received IVIg, % (n/N)	21 (8/38)	31 (11/35)	15 (3/20)
Patients who did not receive IVIg, % (n/N)	18 (14/77)	11 (7/65)	0 (0/21)

**Figure.** Box plot of immunoglobulin levels over time by IVIg use (yes vs no)



H101

## **Prognostic impact of equivocal MYC / BCL2 double expression in diffuse large B-cell lymphoma**

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### Background

Double expression of BCL2 and MYC in diffuse large B-cell lymphoma(DLBCL) is known to confer worse prognosis. The diagnostic thresholds for BCL2 and MYC on immunohistochemistry(IHC) in the literature are variable and high inter-observer variation exists in quantification of protein expression.

### Objectives

We examined the use of MYC and BCL2 IHC for assessment of prognosis and consider the impact of staining close to the diagnostic cut offs of 40% and 50% for MYC and BCL2 respectively.

### Method

175 lymphoma cases diagnosed and treated with chemotherapy in Nelson and Christchurch were retrospectively reviewed. Diagnostic pathology slides were retrieved and quantified for MYC and BCL2 expression. Cases with equivocal staining were identified and factors contributing to borderline expression were recorded.

### Results

Three groups were formed on the basis of protein expression, 21% were double positive (DP - expression of both MYC and BCL2), 31% were equivocal(either one protein strongly expressed with the other equivocal or both MYC/ BCL2 equivocal) and 48% were double negative(DN - lack expression for at least one protein). DP status was independently associated with shorter PFS ( $p=0.0002$ ) and OS ( $p=0.0003$ ). The equivocal group represented an intermediate group with OS at 6 years of 56.26%(38.51-70.70), compared to 72.68%(57.97-82.96) in DN and 24.68%(9.44-43.64) in DP. Contributing factors to equivocal IHC staining included weak or heterogeneous staining, high T-cell density and poor fixation.

### Conclusion

A significant proportion of DLBCL have MYC and BCL2 expression close to the diagnostic cut off. These cases are have an intermediate prognosis and pose a challenge to reporting pathologists.

## **Primary cutaneous gamma delta T-cell lymphoma: a rare disease entity**

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Primary cutaneous gamma/delta T-cell lymphoma (PCGDTL) is a rare (<1% of lymphoid neoplasm) cutaneous lymphoma with less than 50 cases reported worldwide. Characterised by an aggressive clinical course, PCGDTL responds poorly to polychemotherapy and radiotherapy with allogeneic stem cell transplantation (ASCT) being proposed as the best means of achieving lasting remission.

A 36-year old male with a history of HLA-B27 positive ankylosing spondylitis presented with multiple papules and plaques in his lower limbs which rapidly progressed to involve his trunk. Skin biopsy revealed large atypical lymphoid cells with hyperchromatic and indented nuclei which were positive for CD3, CD8 (weak), CD56 and granzyme B. Beta-F1 T-cell receptor stain was negative and TCR-delta immunostain was strongly positive, confirming a diagnosis of PCGDTL. T-cell receptor gene rearrangement studies were also positive. Staging PET-CT confirmed cutaneous and nodal involvement above and below the diaphragm.

Treatment with cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone (CHEOP) was commenced with apparent disease control after 4 cycles. However, there was early relapse with re-emergence of multiple cutaneous lesions in his lower limbs. Biopsy again confirmed PCGDTL. Salvage treatment with high-dose cytarabine and methotrexate was initiated, and a complete metabolic response was obtained after 2 cycles. He then underwent total skin electron beam radiotherapy prior to ASCT with fludarabine and melphalan conditioning. His immediate outcomes will be presented at the meeting.

We present a rare case of PCGDTL which rapidly relapsed following conclusion of conventional polychemotherapy that responded to salvage chemotherapy. With ASCT, the available data suggests a short progression-free interval, but long-term remissions have been reported, although these numbers remain small. Further studies are required.

## Outcome of Autologous Stem Cell Transplant in first response for de novo presentations of transformed indolent B-cell lymphoma

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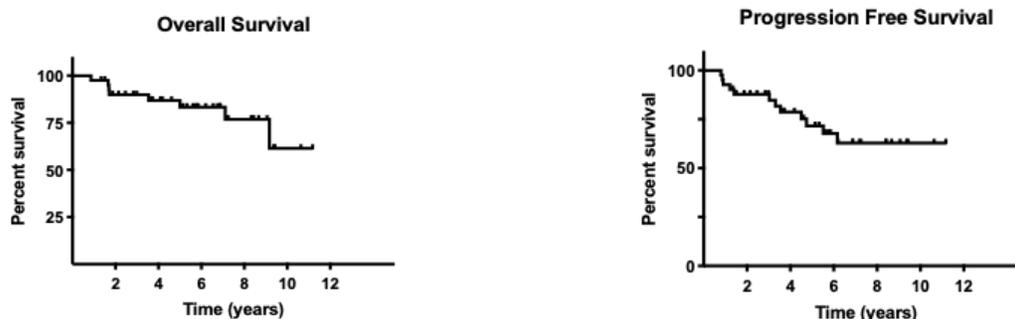
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**Aim:** Transformation of previously diagnosed and treated indolent B-cell lymphoma portends poor survival outcomes. Outcomes and optimal management of patients with *de novo* presentations with synchronous diffuse large B-cell lymphoma and an underlying low-grade lymphoma are still unclear. Our centre adopts the use of high dose chemotherapy and autologous stem cell transplantation (ASCT) as consolidation in CR#1 aiming to prolong survival in this population. We present the outcomes of this treatment approach.

**Method:** A single centre, retrospective case review was undertaken of 41 sequentially treated patients identified from our transplant database over the period 2005 – 2017. The primary endpoints were PFS (by high- or low-grade relapse) and OS. Survival was analysed using the Kaplan Meier method.

**Result:** The median age at diagnosis was 57 (range 29-70) years. 32/41 (78%) had transformed from follicular lymphoma. 21 patients (54%) had discordant marrow disease and 5 (12%) had high-grade marrow involvement. ECOG performance status at diagnosis was 0-1 in 95%. Induction was R-CHOP in 88% and R-DA-EPOCH or R-HyperCVAD in 12%. All patients had achieved a complete metabolic response on CT/PET scan prior to consolidation ASCT (high-dose cyclophosphamide, BCNU, etoposide).

The median follow up time from diagnosis was 6.2 years. Median PFS and OS were not reached. 5 year PFS was 72% (SE, 8%) and 5 year OS was 83% (SE, 6%). There were 10 relapses (24%); 3 with indolent histology, 7 with DLBCL (incl. 1 CNS). Timing of relapse did not differ by histology (high- vs low-grade). Transplant associated mortality was 0% but 4 patients had CTCAE Grade 3-4 toxicity.



**Conclusion:** ASCT of *de novo* presentations of transformed low-grade B cell lymphoma in CR#1 leads to excellent outcomes. Most relapses continue to be with high-grade histology.

## **Novel Immunotherapeutics for the Treatment of Haematological Malignancies: Foetal Outcomes and Mechanism of Teratogenicity**

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### **Aim:**

An aging population and a trend for women to have children later in life has resulted in an increase in the incidence of concurrent haematological malignancy and pregnancy. Novel targeted therapies currently in use in the non-pregnant population which may serve as ideal medications for future investigation, to fulfil the growing demand for treatment options with lower maternal toxicity and foetal teratogenicity. This report aimed to investigate the safety of novel targeted therapies with regard to foetal outcomes.

### **Method:**

A literature review was conducted to identify data on teratogenicity risk and exposure during pregnancy of imatinib, dasatinib, nilotinib, radotinib and rituximab. This search found 61 papers yielding a database of 150 data points with individual foetal outcome information, as well as an additional 515 cases in which only group data was available, including unknown foetal outcomes.

### **Results:**

Rates of spontaneous abortion found in cohort studies were consistent with those found in the general population of 10-20%, specifically, 11% for imatinib (n=206), 13% for dasatinib (n=78) and 22% for rituximab (n=231). Malformation rates found for each agent were 11% for imatinib, 15% for dasatinib and 1% for rituximab. Preterm birth rates were found to be 7% for dasatinib and 14% for rituximab. No exposure during pregnancy data was available for other therapies included in the literature search.

### **Conclusion:**

Overall tyrosine kinase inhibitors appear to potentially have higher associations with congenital malformations. Information on the safety profile of novel agents during pregnancy was primarily in the form of registries of patients with inadvertent exposure during pregnancy, highlighting the importance and need for these registries.

## **THRLBCL-like NLPHL and the importance of repeat biopsy**

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A 31-year-old male presented with 4 weeks of axillary lymphadenopathy, fevers, night sweats, and weight loss. Excisional biopsy of a left axillary lymph node gave a diagnosis of nodular sclerosing classical Hodgkin lymphoma. He had a staging FDG-PET/CT showing Stage IV disease (figure 1a), and received 2 cycles of ABVD (Doxorubicin / Bleomycin / Vinblastine / Dacarbazine) with no clinical improvement. He had a restaging FDG-PET/CT which showed progressive disease (figure 1b).

Given the lack of clinical response a repeat excisional lymph node biopsy was taken from his left axilla. Due to the atypical clinical response and unusual biopsy appearance, the specimen was sent for external review and further immunohistochemistry staining by the reporting anatomical pathologist.

Upon review the diagnosis was revised to nodular lymphocyte predominant Hodgkin lymphoma with THRLBCL-like (T-cell histiocyte-rich large B-cell lymphoma) transformation (figure 2). His therapy was subsequently changed to R-GDP (Rituximab / Gemcitabine / Dexamethasone / Cisplatin) with good clinical response. This will be consolidated with a BEAM (Carmustine / Etoposide / Cytarabine / Melphalan) autologous stem cell transplant.

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) accounts for only 5-10% of cases of Hodgkin lymphoma. Of these cases, a small subset will progress to a THRLBCL-like lymphoma. Histology of THRLBCL-like lymphoma shows features of THRLBCL which are diffuse T-cells and histiocyte-rich infiltrate with only a few tumour cells, as well as at least one typical NLPHL nodule. Typical presentation is a middle-aged male with advanced stage disease. They have poorer outcomes than other subtypes of NLPHL, and comparable to DLCBL<sup>1</sup>.

THRLBCL-like NLPHL is a rare entity that should be considered in patients with Hodgkin lymphoma presenting with advanced stage disease. This case highlights the importance of repeat biopsy and external review for patients with aggressive clinical disease who do not respond as expected to standard therapy.

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## **Hairy Cell Leukaemia arising in a hypoplastic marrow – A case report and review of literature**

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**Introduction:** Hairy Cell Leukemia (HCL) is a rare indolent lymphoproliferative disorder characterized by lymphocytes with cytoplasmic villous (hairy) projections causing diffuse infiltration of the bone marrow and spleen, typically resulting in splenomegaly and development of cytopenias. The diagnosis is made by demonstration of hairy cells in peripheral blood or in bone marrow with a characteristic immunophenotype. Trepine biopsy sections are usually hypercellular while hypocellularity is seen in a minority (~25% of cases)<sup>2</sup>. There are rare case reports of patients with marrow hypoplasia originally diagnosed as Aplastic Anaemia (AA) later found to have HCL.

**Case:** We report a case of a 49-year-old woman presenting with mild neutropenia, thrombocytopenia, monocytopenia and macrocytosis of 18-month duration. She had no hepatosplenomegaly or lymphadenopathy. Bone marrow aspirate was a blood tap and trephine roll preparation did not show cytological dysplasia. There was no abnormal lymphocyte population on flow cytometry. Trepine biopsy was markedly hypocellular without an abnormal cellular infiltrate. This appearance was thought to be Aplastic Anaemia (with a differential diagnosis of MDS). No treatment was given at this time. At 12 months, progression of cytopenias warranted further bone marrow biopsy. The aspirate showed a pauci-particulate, markedly hypocellular specimen with infiltrate of hairy cells with immunophenotype characteristic for HCL. Trepine biopsy revealed a markedly hypocellular marrow with prominent infiltrate of CD20 positive cells which stained weakly for annexin-A1 and BRF-V600E. This case suggests development of HCL in a patient who was originally given a diagnosis of AA

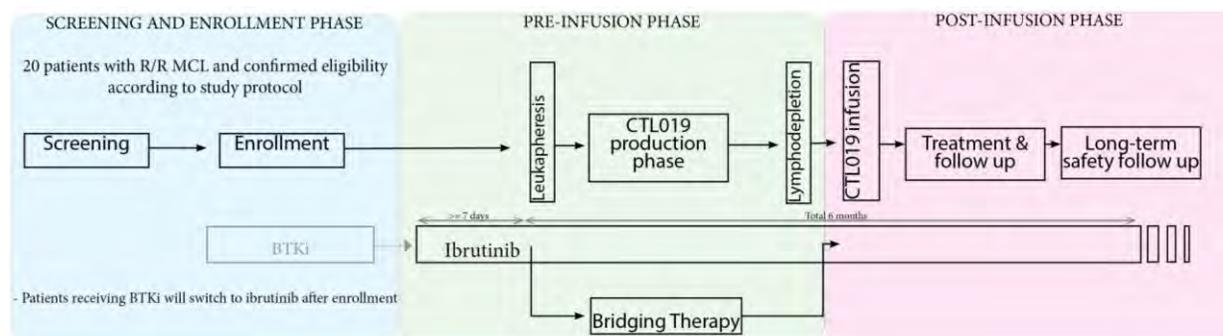
**Conclusion:** This case highlights the difficulty in diagnosis of HCL with hypoplastic marrow. This may lead to an erroneous diagnosis of Aplastic Anaemia. Here we present a literature review showing patient characteristics and morphological features of similar cases.

## TARMAC - A Phase II, Open-Label, Single Arm Trial of the Combination of Tisagenlecleucel and ibrutinib in MANTle Cell Lymphoma: Trial in Progress

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**Background:** Mantle cell lymphoma (MCL) is a clinically and pathogenetically distinct B-cell non-Hodgkin lymphoma that typically presents at a median age of 65 years and in an advanced stage. High dose chemotherapy and stem cell transplantation can achieve durable responses, but most patients relapse. BTKi are active in relapsed MCL but the median PFS is generally less than 2 years. Mutations of *TP53* are associated with refractoriness to chemotherapy and novel agents, and ibrutinib failure is associated with particularly poor outcomes as there is no standard therapy in this population. Allogeneic transplantation is only suitable for a minority of younger, fitter patients who achieve remission to salvage, and has risks of GVHD. Tisagenlecleucel, a CD19 CART (Novartis), has demonstrated efficacy in patients with active DLBCL and ALL. Pre-clinical, and clinical data in CLL suggest combination of tisagenlecleucel with ibrutinib is safe, may increase response rates, and reduce cytokine release syndrome. We are commencing a trial of ibrutinib in combination with tisagenlecleucel in RR MCL, and *TP53mut* pts in <CR after PET2, hypothesising improved outcomes for this poor risk population.



**Primary objective:** Response rate at 16 weeks after tisagenlecleucel infusion

**Key Secondary and Exploratory Objectives:** Adverse events, absence of MRD, genomic correlates, progression free survival

**Key Inclusion:** Age 18 or above, with confirmed relapsed refractory MCL, or *TP53mut* with <CR after 2 cycles of induction chemotherapy.

**Key Exclusion:** Unfit for potential complications of CART; Active CNS disease, Active other malignancy requiring therapy; major organ dysfunction; autoimmune disease

**Intervention:** Ibrutinib to commence pre-apheresis; tisagenlecleucel infusion; ibrutinib maintenance time limited to 6months in those with MRD-negative CR.

**Initial sites:** Melbourne, Sydney

**Recruitment:** 20 patients

**Conclusion:** This novel combination of cellular therapy and BTKi may represent an important treatment option for patients with relapsed/refractory/ *TP53mut* MCL.

## Updated results from the Phase III GALLIUM study in patients with untreated follicular lymphoma

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**Aim:** Significant improvements in investigator-assessed progression-free survival (PFS) with obinutuzumab- versus rituximab-chemotherapy (G-/R-chemo; median follow-up=34.5 months) was demonstrated in the primary analysis (PA) of the GALLIUM study (NCT01332968). We here report updated results from GALLIUM.

**Methods:** Eligible patients were randomized 1:1 (G-chemo:R-chemo) and stratified by chemotherapy regimen (chosen by participating centers). Complete and partial responders received maintenance every 2 months for 2 years with the same antibody. Data cut-off: February 2018.

**Results:** A total of 1202 patients (median age 59 years) were enrolled (n=601 each arm). Median follow-up was 57.3 months. Incidence of any grade adverse events (AEs) was comparable across treatment arms (G-chemo, 99.8%; R-chemo, 99.5%), as was incidence of AEs leading to discontinuation (G-chemo, 16.3%; R-chemo, 14.6%). Grade 3-5 AEs (79.2% vs 71.2%) and serious AEs (48.7% vs 42.2%) were observed more frequently in the G-chemo arm. Grade 3-5 second malignancies (6.9% vs 4.4%), grade 3-5 infections (22.2% vs 18.6%), and grade 3-5 neutropenia (48.4% vs 41.4%), were numerically higher in patients receiving G-chemo versus R-chemo, consistent with PA. Investigator-assessed PFS was significantly improved with G-chemo versus R-chemo (4-year PFS rate=78.1% [95%CI: 74.4%, 81.3%] vs 67.2% [95%CI: 63.1%, 71.0%]; HR=0.73; 95%CI: 0.59, 0.90; p=0.0034). Four-year OS rates were comparable across the G- and R-chemo arms (92.6% [95%CI: 90.1%, 94.4%] vs 90.3% [95%CI: 87.6%, 92.5%]; HR=0.88; 95%CI: 0.61, 1.27; p=0.49); data remain immature. Mortality was similar for G-chemo (n=54 [9.1%]) and R-chemo (n=61 [10.2%]). Patients receiving G-chemo demonstrated an improvement in time to next treatment (TTNT) versus R-chemo (4-year TTNT rate=84.2% [95%CI: 80.9%, 86.9%] vs 76.7% [95%CI: 73.1%, 80.0%]; HR=0.70; 95%CI: 0.54, 0.90; p=0.0046).

**Conclusions:** These updated analyses further support the role of G-chemo in previously untreated FL patients, providing clinically meaningful and durable responses relative to R-chemo. Safety data are consistent with those from the PA.

**Acknowledgment:** This work was funded by F. Hoffmann-La Roche Ltd. Editorial assistance was provided by Joseline Ojaimi, PhD, from Roche Products, Pty. Limited.

## Cisplatin induced acute kidney injury in the treatment of mantle cell lymphoma, a single centre retrospective series

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**Aim:** Our primary objective was to determine the rate of cisplatin induced acute kidney injury (AKI) in patients undergoing treatment with R-DHAP for mantle cell lymphoma (MCL) at the Royal Brisbane and Women's Hospital. Secondary objectives included the requirement for dose reductions in subsequent cycles and impacts on Overall Survival (OS) and Progression-Free Survival (PFS),

**Method:** Patients receiving DHAP as part of therapy for MCL from 2014 to 2018 were identified from an institutional database. Data including baseline demographics, treatment dosing, cycle number, renal function prior, during and following therapy and patient outcomes were collected from medical records. Time dependent covariate were analysed by Kaplan Meier method using log rank test and categorical variables were analysed by fisher exact test.

**Results:** 12 patients were identified with a median age of 64.5 years (range 49-70yr), Eight received the R-CHOP/DHAP protocol whilst the rest received DHAP as salvage therapy. 10 out of 12 patients (83%) developed an AKI (Figure 1). Nine patients experienced an AKI with the first cycle. Peak AKI occurred day 7-9 of treatment. No patients required renal replacement therapy. In patients experiencing an AKI, no patients renal function returned to baseline. Only 1 patient received the planned total treatment dose of cisplatin across all cycles. With a median follow up of 48 months the median OS was 43 months. The only factor associated with OS and PFS was the MIPI score. Proceeding to auto SCT was associated with a trend towards improved OS ( $p=0.08$ ). AKI was not associated with OS noting only 2 patients were free of AKI (Figure 2).

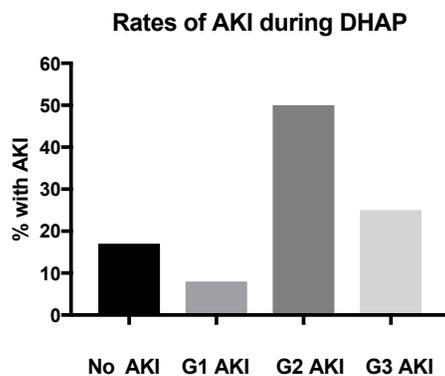


Figure 2

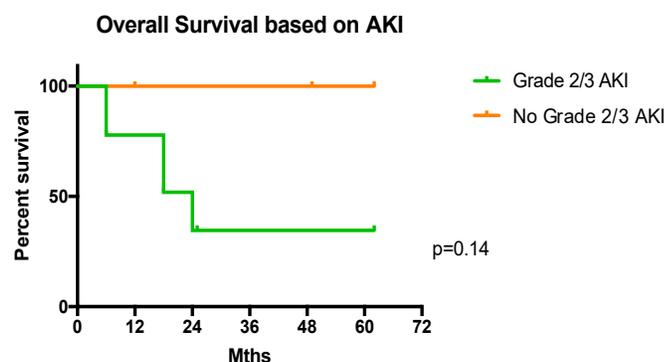


Figure 3

**Conclusion:** In a real-world population of patients with MCL receiving therapy incorporating DHAP, rates of AKI are high and permanent despite pre-hydration strategies. Alternate non-cisplatin, high dose cytarabine containing regimens maybe more appropriate as frontline therapy.

## Outcome of alternating R-CHOP and R-DHAC induction chemotherapy followed by autologous stem cell transplantation in mantle cell lymphoma: a single institutional review over 10 years

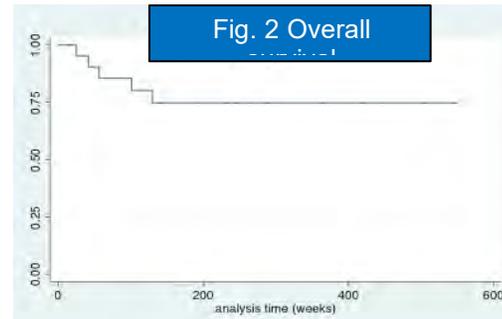
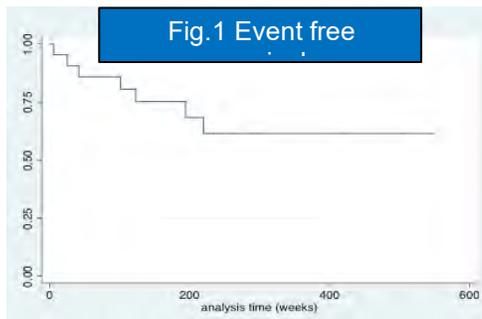
**Omali Pitiyarachchi**<sup>1,2</sup>, Lindsay Dunlop<sup>1,3</sup>, Nicholas Viiala<sup>1,4</sup>

<sup>1</sup>Liverpool Hospital, Liverpool, Australia, <sup>2</sup>Chris O'Brien Lifecare, Camperdown, Australia, <sup>3</sup>Western Sydney University, Campbelltown, Australia, <sup>4</sup>University of New South Wales, Kensington, Australia

**Aim:** Since 2008, the preferred treatment regimen for newly diagnosed transplant eligible patients with Mantle Cell Lymphoma (MCL) at our institution has been alternating cycles of R-CHOP/R-DHAC (6 cycles in total) followed by autologous stem cell transplantation with BEAM conditioning. Carboplatin was used for ease of administration and avoidance of renal toxicity associated with cisplatin. We aim to present our outcomes using this regimen and provide comparison with other published protocols.

**Method:** A retrospective search of the medical records between January 2008 and May 2019 was undertaken to identify all newly diagnosed MCL patients, selecting those commencing the above regimen. Data was collected on patient and disease characteristics, response to induction, survival, disease relapse and progression.

**Results:** 28 newly diagnosed transplant eligible patients were identified, with 6 patients who received alternative regimens excluded. Of the 22 patients in this study, the majority were male (86%), median age 62 (range 37-73), and were stage IV (77%) at diagnosis. All were ECOG 0-1. MIPI score was low (32%)/intermediate (32%)/high risk (36%). Blastoid/pleomorphic features in 3 patients (14%). Majority (90%) completed the regimen (n=1 patient declined transplantation, n=1 disease progression following cycle 2). Overall response (combined CR + PR) after induction was observed in 21/22 patients (95%). Median follow up was 213 weeks. 4 patients have relapsed. 5 patients have died (including 2 deaths following BEAM ASCT). 5-year EFS was 61% (Fig.1) and OS was 75% (Fig.2).



**Conclusion:** Although a small cohort, our data for using R-CHOP/R-DHAC as induction for transplant eligible MCL patients compares favourably to reported rates of overall response, PFS and OS by Nordic MCL2<sup>1</sup>, LyMA<sup>2</sup> and GELA<sup>3</sup>, and present an effective equivalent treatment option. There is potential to improve outcomes further with the use of Rituximab<sup>2</sup> maintenance, or use of a more potent anti-CD20<sup>4</sup> antibody.

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## Diagnosis of Chronic active Epstein-Barr Virus Infection (CAEBV) by FACS of fixed peripheral blood mononuclear cells and EBV DNA by PCR

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**Aim:** CAEBV is a rare NK/T cell LPD characterised by protracted infectious-mononucleosis-like symptoms which is often progressive and fatal. The pathological hallmark of CAEBV is infection of T- or NK cells by EBV. Our patient is a 28 year old male of Vietnamese origin who presented with a 3 month history of malaise and weight loss. Clinical findings included fever, lymphadenopathy, splenomegaly, CN III palsy, liver dysfunction and EBV viraemia. Lymph node core and excisional biopsies showed an abnormal polymorphous infiltrate, however immunohistochemical characterisation was difficult and EBER-ISH stained only a small subset of cells. Due to the suspicion of CAEBV, an alternative diagnostic strategy was sought. Kimura et al first described a method of fractionating peripheral blood mononuclear cells (PBMCs) using an immunobead method, with cell fractions analysed by either quantitative EBV PCR or EBER1-ISH<sup>1</sup>. We posited whether we could use FACS to sort fixed PBMCs into lymphocyte subsets and successfully extract DNA for EBV PCR.

**Method:** Testing was conducted at the Peter MacCallum Cancer Centre and Royal Melbourne Hospital Pathology. 32mL of EDTA whole blood was collected. PMBCs were separated by Ficoll Hypaque. White cell count was obtained and volume adjusted to stain with BD Multitest antibody panel – CD45 PerCP-Cy5.5, CD3 FITC, CD16/56 PE, CD4 PE-Cy7, CD19 APC, CD8 APC-Cy7, followed by a lysis step (which includes paraformaldehyde fixation) and washing step. The sample was reconstituted with PBS for sorting. Boolean gating strategy was used to perform a 4 way sort of T-helper cells (CD3+CD4+CD8-), T-Suppressor cells (CD3+CD4-CD8+), NK cells (CD3-CD16/56+) and  $\gamma\delta$ T cells (CD3+CD4-CD8-) on a BD FACS Aria II. A normal control (CD3-CD19+ B-cells and CD3+CD19- T-cells) was subjected to the same method. Sorted cell populations then underwent DNA extraction using the QIAamp® DNA FFPE Tissue Kit and EBV PCRs run on an Abbott® Realtime EBV assay.

**Result:** Cell numbers obtained and corresponding EBV DNA as shown below:

Cell type	Cell Count	EBV DNA (IU/mL)	EBV DNA Log (IU/mL)
Patient CD3+CD4+ T helper	3.9 x 10 <sup>6</sup>	906	2.96
Patient CD3+CD8+ T suppressor	1.7 x 10 <sup>6</sup>	155	2.19
Patient CD3+CD4-CD8- $\gamma\delta$ T cells	1.7x10 <sup>5</sup>	Detected, <40	Detected, <1.60
Patient CD3- CD16,56+ NK cells	6.06 x 10 <sup>5</sup>	50,768	4.71
Patient plasma	N/A	6,921	3.84
Control CD19+ B cells	2.1 x 10 <sup>4</sup>	Not detected	Not detected
Control CD3+ T cells	5 x 10 <sup>4</sup>	Not detected	Not detected

These results confirmed a diagnosis of NK cell type CAEBV.

**Conclusion:** This study indicates that FACS of fixed PBMCs, a DNA extraction method suitable for formalin fixed cells, and EBV PCR is a viable method for the diagnosis of CAEBV.

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A single institution's experience validating a flow cytometric assay for the diagnosis of breast implant associated anaplastic large cell lymphoma

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<sup>1</sup>*Sullivan Nicolaidis Pathology, Bowen Hills, Australia*

**Aim:** To evaluate a cocktail for the detection of Breast Implant Associated – Anaplastic Large Cell Lymphoma (BIA-ALCL) – CD30 T-cell positive lymphocytes, in breast FNA/Tissue samples. Due to an increase in requests from Histology/Cytology for “Flow cytometry to exclude ALCL – T-cell panel including CD30” a specific tube which includes CD30 would be useful as a screening tube. The lymphoma cells in BIA-ALCL commonly reside in light scatter regions typical for monocytes and granulocytes and they show frequent loss of T-cell antigens including CD3, retain expression of CD4, which is not only a T-lineage associated marker but also a monocyte lineage associated marker<sup>1</sup>. These properties can make it difficult to distinguish these cells from normal monocytes and may pose a diagnostic challenge. With the addition of CD14, these large cells falling in the monocyte gate can be identified as monocytes and excluded from the population of interest. If a CD30 positive T-cell population is identified or there is suspicion of an abnormal T-cell population, a full extended T-cell panel workup needs to be performed to further type and confirm the presence of anaplastic T-cells. A report will be generated for these requests to state that CD30 has been tested. The same methodology, instrumentation and software in current operation will be used.

**Method:** Breast specimens from the daily runs were run with the current extended T-cell panel (addition of drop-in CD30 PE) in parallel with the proposed ALCL tube with the following fluorescent antibodies (already in use within the laboratory):

Antibody	Quantity
<b>Alpha Beta TCR FITC</b>	20uL
<b>CD30 PE</b>	20uL
<b>CD3 PerCp</b>	20uL
<b>HLADr PE-Cy7</b>	5uL
<b>CD7 APC</b>	5uL
<b>CD4 APC H7</b>	5uL
<b>CD14 v450</b>	5uL
<b>CD45 v500</b>	5uL

Samples were acquired on the FACSLytic flow cytometers. All data was analysed using the current software, FCS Express.

The dot plots and percentages of target cell percentages were compared between the extended T-cell panel (where available) and the ALCL tube.

Kesler MV, Paranjape GS, Asplund SL, McKenna RW, Jamal S, Kroft SH. Anaplastic large cell lymphoma: A flow cytometric analysis of 29 cases. *Am J Clin Pathol* 2007;128:314–322.

## **EBV-associated diffuse large B cell lymphoma arising within atrial myxoma in an immunocompetent patient: case report and literature review**

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### **Aim**

Primary cardiac lymphoma is rare, and often associated with poor prognosis.<sup>1</sup> Several cases of composite tumours of diffuse large B cell lymphoma (DLBCL) arising within atrial myxoma have been reported, the majority of which are Epstein-Barr Virus (EBV) driven. Growing evidence suggests that despite aggressive histological features, these tumours exhibit indolent clinical behaviour.

### **Methods and Results**

We report the first Australian case of EBV-positive DLBCL arising with atrial myxoma and review the literature for fifteen similar cases. This immunocompetent 52-year-old male presented with dizziness, altered sensation and dysarthria. Transthoracic echocardiogram revealed a 6x2.2cm left atrial mass, which was resected. Histological, immunohistochemical and molecular analyses confirmed an EBV-associated CD20+ DLBCL within atrial myxoma. Staging imaging and bone marrow biopsy did not reveal any other evidence of disease. The patient remained in complete remission following surgical resection, without the need for chemoradiotherapy. There was no evidence of recurrence four years following diagnosis.

The majority of existing cases were associated with EBV infection, showing pattern of type III latency. Six patients were treated with chemotherapy, with one patient dying of complications at five months.<sup>2</sup> Of the nine patients who did not receive chemotherapy, seven were healthy at follow-up, with two deaths from unrelated causes. The longest documented length of survival without recurrence in those receiving surgery alone is 10 years.<sup>3</sup>

### **Conclusion**

This case contributes to a small series of patients with EBV-associated DLBCL arising within atrial myxoma who exhibit a clinically indolent phenotype. Our literature review suggests that a 'watch-and-wait' approach following complete surgical resection is appropriate to avoid unnecessary toxicity of systemic treatment. The association with EBV positivity and type III latency in immunocompetent hosts implies that there are mechanisms of local immunosuppression, likely mediated by IL6. Early diagnosis and resection remains imperative and regular surveillance is critical to ensure sustained response.

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## Is upfront Autologous Stem Cell Transplant required in Mantle Cell Lymphoma?

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<sup>1</sup>Department of Haematology, University Hospital, Geelong, Australia, <sup>2</sup>Deakin University School of Medicine, Waurn Ponds, Australia, <sup>3</sup>Clinical Haematology, Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, Australia, <sup>4</sup>Sir Peter MacCallum School of Oncology, University of Melbourne, Melbourne, Australia

**Aim:** Mantle cell lymphoma (MCL) has a variable disease course. It is most commonly treated with intensive chemoimmunotherapy, such as R-hyper-CVAD and the Nordic protocol. Uncertainty surrounds the question of consolidative autologous stem cell transplant (ASCT). Our standard institutional practice is to use minimal residual disease (MRD) guided therapy with R-hyper-CVAD and to omit ASCT in MRD negative patients. MRD is assessed using PET/CT and bone marrow examination. We have previously published data suggesting excellent long-term outcome in patients treated with this approach. We aim to compare the outcomes of our cohort of patients with a similar cohort treated with consolidative ASCT at a second institution.

**Method:** We performed a retrospective analysis of MCL patients treated at two institutions with intensive chemoimmunotherapy with and without consolidative ASCT. We compared the overall (OS) and progression-free survival (PFS) of two cohorts: those at our institution who achieved MRD negativity and did not receive ASCT (group 1) and those at a second institution who underwent consolidative ASCT in first complete remission (group 2).

**Result:** 31 patients were analysed: 15 patients in group 1 and 16 patients in group 2. Patients in group 2 received ASCT conditioning with either BEAM or BuMel. There was no significant difference in OS or PFS between the two groups. Importantly, patients in group 1 had an excellent long term outcome, with 5-year OS and PFS of 100% and 90% respectively, compared with 68% and 48% for patients in group 2. There was no treatment related mortality for patients in group 1.

**Conclusion:** These results in a small patient cohort suggest that MCL patients achieving MRD negativity following intensive chemoimmunotherapy have excellent long-term outcomes and may reasonably avoid consolidative ASCT. The results also highlight the benefit of MRD assessment to guide treatment decisions in MCL.

Figure 1

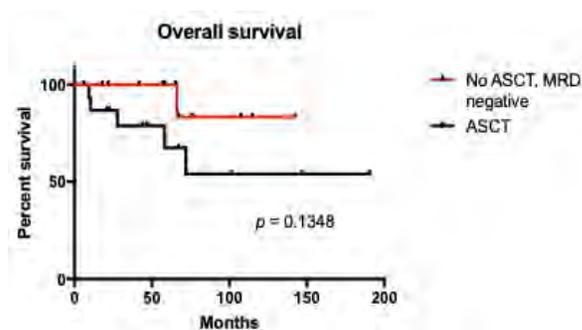
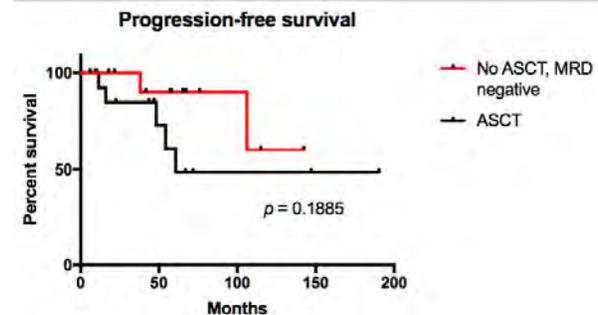


Figure 1



**Epstein-Barr Virus infection mimicking DLBCL - a diagnostic and therapeutic dilemma: a report of two cases**

**Yih Seong Wong**<sup>1</sup>, Yang Liang Boo<sup>1</sup>, Zuliana Jamli<sup>1</sup>, See Guan Toh<sup>1</sup>, Soo Min Lim<sup>1</sup>, Adrena Abdul Wahid<sup>2</sup>, Ming Yen Lee<sup>2</sup>, Noraida Khalid<sup>2</sup>

<sup>1</sup>*Department of Haematology, Hospital Sultanah Aminah Johor Bahru, Ministry of Health Malaysia, Johor Bahru, Malaysia,* <sup>2</sup>*Department of Pathology, Hospital Sultanah Aminah Johor Bahru, Ministry of Health Malaysia, Johor Bahru, Malaysia*

**Aim:** Acute EBV infections are typically diagnosed based on clinical and laboratory findings. Lymphadenopathy is an atypical presentation, and when biopsied may reveal a histological picture resembling lymphoma. The two diagnostically challenging cases described highlight the potential pitfalls of misdiagnosing EBV infections as lymphoproliferative disorders.

**Case descriptions:** Case 1 describes a 24-year-old female who initially presented with nasal congestion for two weeks duration. A nasopharyngeal mass was detected via nasopharyngoscopy and contrast enhanced CT scan, and a biopsy of the mass revealed a diagnosis of diffuse large B-cell lymphoma, non-GCB subtype. The patient then defaulted further follow up, and represented seven months later due to an unrelated illness. A repeat biopsy of the same nasopharyngeal lesion and a separate adenoid biopsy revealed no evidence of malignancy. The original biopsy sample was then re-evaluated and additional EBER ISH staining confirmed the diagnosis of an acute EBV infection. Case 2 describes a 17-year-old male who presented with a one week history of fever and night sweats. A right cervical lymph node biopsy was done, and the preliminary diagnosis of diffuse large B-cell lymphoma was made based on morphological and immunohistochemistry evaluation. The patient was commenced on standard R-CHOP chemotherapy while awaiting a second histopathological opinion of his biopsy sample. Due to difficulties obtaining a definite diagnosis, the patient was further misdiagnosed as NK/T-cell lymphoma before finally arriving at the diagnostic conclusion of acute EBV infection. Unfortunately, the patient had by then almost completed the entire course of R-CHOP chemotherapy.

**Conclusion:** An extreme course of EBV infection has the potential to be confused for a lymphoproliferative disorder, both in terms of clinical presentation and morphological evaluation of biopsied lymphoid tissue. A high index of clinical suspicion supported by perceptive use of immunohistochemical stains offers the best chance of avoiding such misdiagnosis.

## Plasmablastic Lymphoma in Western Australia

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<sup>1</sup>University of Western Australia, <sup>2</sup>Royal Perth Hospital

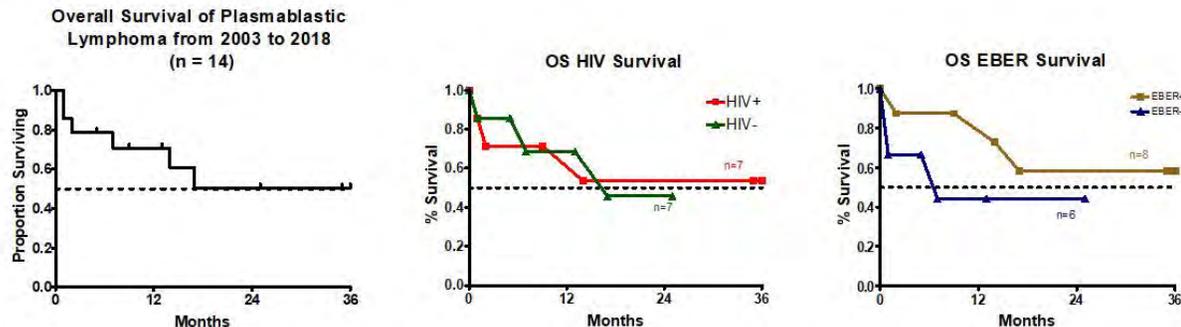
**Aim:** Plasmablastic Lymphoma (PBL) is rare lymphoma seen in patients with HIV infection. It is difficult to distinguish from other diffuse large B cell lymphoma (DLBCL), hence it is commonly clustered with other subtypes of DLBCL. PBL has a poor prognosis, but recent data from the MD Anderson Cancer Center has demonstrated improved responses with dose-adjusted EPOCH in combination with bortezomib.<sup>1,2</sup> Our study aim is to identify these cases in Western Australia and review their survival outcomes.

**Method:** Cases were identified via COBRA auditing software by using ICD-10 code C833 for DLBCL together with M97353 plasmablastic lymphoma. Kaplan-Meier statistical analysis was performed using GraphPad Prism software.

**Result:** We identified 14 cases between 2013 to 2018. Seven cases were HIV-related, one case of post-transplantation lymphoproliferative disorder and the remaining six did not have co-existing immunodeficiency disorder.

Treatment was varied and included mini-CHOP/CHOP, HyperCVAD and DA-EPOCH with/without radiotherapy. Rituximab were given if CD20-positive. Two patients had upfront BEAM autologous stem transplantation and remain in remission following treatment.

Median survival of the cohort is 37 months with a median follow-up duration of 14 months. HIV-positive patients have a longer median survival than those without HIV (median survival 37 vs 17 months), but this is not statistically significant by log-rank analysis due to cross-over of Kaplan-Meier curves (Hazard ratio 1.28, 95% CI 0.28-5.7, p-value 0.74). Patient who are EBER-negative by immunohistochemistry (n=6) have a median survival of 7 months, but it is not statistically significant (hazard ratio 0.46, 95% CI 0.05-2.2, p-value 0.26).



**Discussion:** We present a case series of a rare aggressive lymphoma. Statistical analyses are limited by the small numbers found but we observed similar trend to international case series where HIV-negativity has worse outcomes.<sup>3</sup> However, EBER-negativity also implies a worse prognosis that is not previously described in the literature.

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## **Angioimmunoblastic T-cell lymphoma followed by isolated central nervous system B-cell lymphoproliferative disorder**

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<sup>1</sup>*Liverpool Hospital, Liverpool, Australia*

### **Introduction**

We present a case of angioimmunoblastic T-cell lymphoma (AITL) who subsequently developed an isolated CNS B-cell lymphoproliferative disorder (B-LPD) after completion of chemotherapy for AITL.

### **Case Presentation**

A 66 year old woman presents with proximal muscle weakness, lymphadenopathy, hepatosplenomegaly and constitutional symptoms. She was hypercalcaemic with significant renal impairment. An excisional biopsy of a supraclavicular lymph node demonstrated features of AITL with an accompanying EBV-associated lymphoplasmacytic proliferation, with further testing demonstrating monoclonal TCR-beta and TCR-gamma gene rearrangements with polyclonal IgH gene rearrangement. Staging PET scan demonstrated stage IV disease and she was commenced on CHOEP chemotherapy with plan for autologous stem cell transplant following six cycles. Interim PET after four cycles confirmed complete metabolic response. Therapy was complicated by probable fungal chest infection and cryptogenic organising pneumonia resulting in deferment of stem cell mobilisation.

Whilst awaiting resolution of her lung lesions she developed a left cranial nerve VI palsy with large abnormal lymphocytes with prominent nucleoli and irregular cytoplasmic projections seen on CSF. A monoclonal B-cell population with CD11c+ was identified which was suspicious for marginal zone lymphoma or atypical hairy cell leukaemia (aHCL) however this could not be confirmed with TRAP and BRAF testing. Her cranial nerve palsy resolved following intrathecal chemotherapy. The monoclonal B-cell population was absent on both peripheral blood and bone marrow aspirate samples and she remained in complete metabolic response in terms of her AITL.

### **Discussion**

AITL is a rare disorder primarily of malignant monoclonal T-cells, occasionally with a concurrent B-LPD. However an isolated B-LPD on background of treated AITL in remission has not been previously described to our knowledge. Although a diagnosis of aHCL could not be confirmed, this case was also suspicious for CNS involvement with aHCL which is exceedingly rare with only a few cases reported. The pathophysiology to explain a potential link between these two rare LPDs remains unclear from our current understanding of the disease process.



## **Poor yield from bone marrow cytogenetic in Myelofibrosis in WA 2009-2019**

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**Introduction:** Myelofibrosis is a myeloid malignancy characterised by extramedullary haematopoiesis as well as progressive marrow failure with median survival of 5 years. Cytogenetics plays a key role in the prognostication of myeloid malignancies such as Acute Myeloid leukaemia. However cytogenetic results in patients with myelofibrosis can be difficult to obtain due to low yield marrow aspirate samples given fibrotic nature of the marrow. In the presence of circulating myeloid precursors, peripheral blood can be considered an alternative sample source without major discordance of results.

**Method:** Retrospective analysis of patients diagnosed with primary and secondary myelofibrosis in Western Australia between 2009-2019 using the pathology reporting system (ULTRA) and cytogenetic laboratory data base.

**Results:** Sixty four patients were identified with either primary or secondary myelofibrosis. Only 14 patients (21%) had cytogenetic results from a bone marrow biopsy. The rest of the patients had no samples available for cytogenetic analysis or no dividing cells seen during analysis.

**Conclusion:** Cytogenetic yield from bone marrow sampling remains low due to difficulty in obtaining an adequate sample. Peripheral blood sampling will now be considered routine practise for patients with diagnosis of primary/secondary Myelofibrosis to improve cytogenetic yield and thus the prognostication of these patients. Further evaluation between concordance of results between bone marrow and peripheral blood sample will be required.

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## **A lesson not to judge a book by its cover**

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**BACKGROUND:** Polycythaemia refers to an abnormal elevation of haemoglobin (Hb) and/or haematocrit in the peripheral blood. Current World Health Organisation definitions are Hb > 165 g/L in men (Hb > 160 g/L in women) or haematocrit > 0.49 in men (>0.48 women). Stratification between primary and secondary causes determines the diagnostic approach and generally relies on serum erythropoietin and the presence of a JAK-2 molecular mutation. Where serum erythropoietin levels are normal or high evaluation for secondary causes and in particular exclusion of a paraneoplastic EPO producing tumour are recommended.

**CASE:** The case involves a 42-year-old normotensive male with BMI 24 who was referred for further investigation and management of an incidentally detected and persistently elevated haemoglobin 199 g/L with a PCV 0.63 and iron deficiency of 20 mcg/L. He was an ex-smoker with no evidence of chronic obstructive pulmonary disease. Serum erythropoietin (EPO) was elevated at 33.2 U/L. JAK-2 V167F and JAK-2 exon 12 molecular mutations were not detected. CT, MRI and PET imaging for an underlying EPO secreting tumour were negative. On further review there was no evidence of a high affinity haemoglobinopathy, normal energy levels and no day time somnolence. A sleep study showed severe obstructive sleep apnoea (OSA). Serum bicarbonate was elevated at 37 mmol/L in response to the severe hypercapnoea of 52 mmHg and hypoventilation caused by upper airway obstruction.

**CONCLUSION:** Polycythaemia is a frequent incidental finding and accounts for a substantial number of clinical haematology referrals. This case highlights the beneficial role of serum erythropoietin in classifying cases as primary or secondary. Whilst OSA is more common in obesity, non-obese patients can also have severe OSA related to their upper airway anatomy. Patients with severe OSA may not necessarily report typical symptoms.

## **Concomitant essential thrombocythemia with MPL positive mutation in a patient with chronic myeloid leukaemia: a case report**

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<sup>1</sup>Nepean Hospital, Kingswood, Australia, <sup>2</sup>Nepean Cancer Care Centre, Kingswood, Australia, <sup>3</sup>Crown Princess Mary Cancer Centre, Westmead, Australia

Myeloproliferative neoplasms (MPN) are chronic haematological conditions associated with clonal proliferation in one or more elements of the myeloid lineage. In the last few decades, the utility of molecular testing in aiding the diagnosis and treatment of these disorders has been increasingly recognised. While BCR-ABL translocation in chronic myeloid leukaemia (CML) and Janus kinase (JAK2)/ calreticulin (CALR)/ myeloproliferative leukaemia virus oncogene (MPL) mutations in Philadelphia negative MPNs are normally thought to be mutually exclusive cases, there have been few case reports of such co-occurrences in the present literature. In particular, there are virtually no reports on CML associated with MPL positive essential thrombocythemia (ET), with the mutation being the rarest with a cited incidence of 2-5% for ET.

We describe what is possibly the first reported case of CML and MPL-positive ET: a Fijian man in his late thirties initially presenting with his first attack of gout with incidental left-shift neutrophilic leucocytosis on a routine blood test. He was subsequently diagnosed with chronic phase CML on further workup, and had responded favourably to a tyrosine kinase inhibitor as demonstrated by molecular response on peripheral blood. However on several follow-ups, persistent thrombocytosis was noted despite normalisation of other cell counts. Myeloproliferative neoplasm gene panel were then performed, which was positive for a MPL W515L mutation. A bone marrow biopsy demonstrating megakaryocytic hyperplasia and clustering confirmed the diagnosis of ET with resolution of granulocyte hyperplasia from the CML.

This case illustrates the diagnostic challenges of the hybrid MPN in which CML may mask underlying ET. Although rare, the association of BCR-ABL1 rearrangement and MPL mutation warrants investigation in patients with suspected concomitant MPNs. As genetic testing is traditionally not done within our institution, the addition of specific molecular panel studies invites additional costs - an issue that our report will address.

## **A unique case of refractory malignant histiocytic sarcoma**

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Histiocytic sarcoma is a rare, aggressive malignancy usually presenting with mass lesions, skin changes and constitutional symptoms. The *BRAF*<sup>V600E</sup> mutation is increasingly recognised as a driver mutation in histiocytic sarcoma and may be targeted in some instances. Given the rarity of histiocytic sarcoma, no standard of care exists and median overall survival is six months.

We describe a case of primary refractory histiocytic sarcoma in a 45-year-old man. He presented with progressive abdominal distension, early satiety and weight loss. CT scan demonstrated a large, poorly-demarcated left upper quadrant mass. With inconclusive fine needle biopsy, histiocytic sarcoma was confirmed after extensive primary surgical resection. Immunohistochemical staining for *BRAF*<sup>V600E</sup> was negative.

After prolonged recovery from complications of surgery, radiotherapy was delivered to the operative bed and to a nearby lymph node demonstrating PET-avidity. Multifocal progression was identified on re-staging PET post-radiotherapy. Due to poor performance status he received three cycles of CHOP, however progressed, and ICE salvage was unsuccessful. Gemcitabine/vinorelbine led to partial response. Autologous stem cell transplantation was undertaken 18 months after initial diagnosis with further partial response. During this time tissue referred to the Molecular Screening and Therapeutics clinical trial did not identify any targetable mutation.

The patient became significantly malnourished as a result of extensive intestinal resection, chemotherapy and stem cell transplantation. Given the sustained response and case reports in the literature, thalidomide was commenced as maintenance therapy.

Relapsed disease was confirmed after one cycle of thalidomide, presenting with intractable nausea and abdominal pain, and the patient died 24 months after initial diagnosis. His long survival was unexpected given his refractory disease and the incredibly poor prognosis of histiocytic sarcoma. This case highlights the difficult diagnostic and management issues of this rare and aggressive disease, with limited treatment options.

## **Proteasome inhibitors are associated with improved immune reconstitution and progression free survival in newly diagnosed myeloma; a retrospective analysis**

**Shivam Agrawal**<sup>1</sup>, Peter Presgrave<sup>1</sup>, Pauline Warburton<sup>1</sup>, Shrinivas Desai<sup>1</sup>, Kylie King<sup>1</sup>, Gurdeep Parmar<sup>1</sup>

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### **Aims**

Immunoparesis in myeloma is defined as suppressed levels of uninvolved polyclonal immunoglobulin (Ig). The primary goal of our study was to assess whether novel agents including proteasome inhibitors (PIs) and immunomodulatory imide drugs (IMiDs) when used as first line treatment in patients with immunoparesis at diagnosis had an influence on Ig reconstitution and survival.

### **Methods**

Data of newly diagnosed myeloma patients (between 2010 and 2016) treated at the Illawarra cancer network were collected. 48 patients who presented with immunoparesis and were treated upfront with novel agents were included in this analysis. Timing of the analysis facilitated at least thirty months of follow up. Multiple Ig levels at landmark timepoints post therapy initiation were included to explore the role of Ig recovery as a dynamic variable.

### **Results**

32/48 patients were treated with a PI up-front (exclusively Bortezomib). 16/48 patients were treated with up-front non-proteasome inhibitor (non-PI) therapy (mostly IMiD regimens). 70% of patients in this cohort received an up-front autograft. Interestingly, 6/32 (19%) patients in the PI group achieved complete immune reconstitution during the follow-up period compared to only 1/16 (6%) patients in non-PI group. Furthermore, the median PFS was noted to be significantly higher ( $p = 0.0089$ ) in the PI group (46 months) compared with the non-PI group (27 months). The overall survival was not different between the two groups. Infection rates in the first 6 months, and out to 60 months after treatment initiation were not significantly different between the two groups.

### **Conclusion**

Patients with immunoparesis at diagnosis showed improved immune reconstitution rates and PFS when treated with PI based therapies. Upfront PI use however did not confer to reduction in infections rates in our analysis. Further research is required to explore the beneficial role of PI based therapies in patients with immunoparesis.

## **Velcade, cyclophosphamide, and dexamethasone (VCD) as front-line treatment for systemic AL amyloidosis (AL): An updated analysis of a real-world experience at a single centre**

**Yee-shuen Chong**<sup>1</sup>, Felanita Hutani<sup>1</sup>, Masa Lasica<sup>1</sup>, Stephen Ting<sup>1</sup>, James Hare<sup>2</sup>, Simon Gibbs<sup>1</sup>

<sup>1</sup>Eastern Health, Box Hill, Australia, <sup>2</sup>Alfred Health, Prahran, Australia

### **Aim**

“VCD” as first-line treatment for AL was reported to have excellent clonal responses. We sought to undertake a “real-world” local analysis of VCD in this setting.

### **Method**

We conducted a single-centre, retrospective, observational study of response rates and overall survival (OS) for patients undergoing VCD frontline treatment for AL between September 2014 and May 2019.

### **Results**

Thirty-eight patients were identified. Median age was 63.5 years. Revised Mayo Staging System was Stage I in 13.2% of total subjects, II in 21.1%, III in 31.5%, and IV in 34.2%. Amyloid organ involvement included cardiac in 28 (73.6%), renal in 12 (31.6%), and gastrointestinal in 2 (5%). Median follow-up was 24.5 months (range 2-53 months).

Overall haematological response (PR or better) was observed in 35 (92.1%), VGPR or better in 26 (68.4%), and CR in 14 (36.8%). A VGPR was achieved in 25 (65.8%) after two cycles of VCD.

Cardiac response (NTproBNP >30% decrease) occurred in 14/28 (50%) and renal response (proteinuria >50% decrease) in 3/12 (25%).

Median PFS was 17.8 months in 33/38 patients who did not undergo planned autologous stem cell transplant. OS after 12 months was 90.3%. Median OS was 29 months. Ten patients died: 90% had cardiac decompensation; 5 had Stage IV disease; 2 were non-responders. Median NTproBNP at diagnosis was 638pmol/L in the deceased cohort vs 393pmol/L in patients still alive.

There was no difference between median OS for patients who achieved a VGPR by cycle 2 and for those who did not (28.9 vs 28 months) ( $p=0.59$ ).

### **Conclusion**

VCD was an excellent frontline treatment for AL with impressive clonal and moderate organ responses. Patients with early stage cardiac disease had a better prognosis. Although VCD did not confer long term PFS, our study suggested the treatment offered brisk clonal responses to stabilise the initial disease phase.

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**Innovation in autologous stem cell transplants for multiple myeloma, redesigning the model of care.**

**Jessica Demajo**<sup>1</sup>

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**Aim:** The feasibility of mixed inpatient and outpatient delivery of autologous stem cell transplants (AUSCT) for multiple myeloma patients at a tertiary city hospital. Thirty transplants are performed each year, with an average inpatient length of stay (LOS) of 18 days. Model of care changed to 8 days as an outpatient, with planned admission on day +7. Projected savings of \$9,926 per patient.

**Method:** A dedicated expert haematology nurse created an outpatient AUSCT guideline and patient education resource. The project nurse also educated hospital in the home (HITH) and cancer day unit (CDU) clinicians on caring for patients post-transplant. An outpatient AUSCT care plan was created to guide HITH nurses and grade symptom severity. Patients and their carer opted-in to the outpatient model of care and attended a transplant dedicated education session. Dieticians were involved pre and post-transplant to ensure optimal nutrition throughout. The project nurse coordinated all care for these patients.

**Result:** Seven patients participated in an outpatient AUSCT over a 10 month period. A total of \$56,549.08 was saved, with an average of \$8,074.44 per patient. Forty-six inpatient bed days were relinquished with an average inpatient LOS of 11 days. The increased utilisation of current services broadened HITH and CDU clinicians' scope of practice.

**Conclusion:** The success of the pilot program has led to the mixed outpatient and inpatient model of care being adopted as the standard model of care for all eligible patients. Due to the strict criteria to be eligible for the outpatient model of care we are looking at ways to expand outpatient options, particularly to include out large regional population. Further research to include assessing the impact the outpatient model has on patients and their carer's quality of life and if this model of care reduces infection rates.

## **Superiority of cytoplasmic immunoglobulin (clg) selected FISH for abnormality detection in plasma cell dyscrasias**

**Marcus Dickey**<sup>1</sup>, Mark McKinley<sup>4</sup>, Tukten Rolfe<sup>1</sup>, Adayapalam Nandini<sup>4</sup>, Bronwyn Telford-Herdman<sup>4</sup>, Sarbjit Riyat<sup>4</sup>, Katherine Tania Budgen<sup>4</sup>, Mu-Su Chen<sup>4</sup>, Hugh Smith<sup>4</sup>, Susan Clarke<sup>4</sup>, Peter Mollee<sup>3</sup>, Joel Collins<sup>1,2,3</sup>

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### **Aim:**

International guidelines recommend that FISH be performed on selected plasma cells rather than whole marrow in patients with plasma cell dyscrasias. In 2015 Pathology Queensland introduced a cytoplasmic immunoglobulin (clg) selected FISH method, whereas previously only unselected FISH and standard karyotyping was utilised for plasma cell cytogenetic analysis. An audit was conducted to assess the utility of the clg FISH method.

### **Method:**

The modified clg FISH protocol described by Gole *et al* was adopted by the laboratory. This method involves kappa/lambda antibody staining of plasma cells to easily distinguish them during the FISH process. The technique is easily incorporated into the standard cytogenetic workflow. To audit the outcomes of the new method, all bone marrow samples collected between 2011 and 2018 where "myeloma FISH" was requested were identified via the laboratory information system. This data was then collated and subsequently analysed via SPSS.

### **Result:**

There were 770 bone marrow FISH samples available for analysis. 355 samples were subjected to clg FISH testing, and 415 underwent unselected FISH analysis. The mean patient age for both clg and unselected FISH was 67 years, with 59.0% of clg FISH patients being male, vs 60.2% for unselected. The median marrow aspirate plasma cell burden was 12% for clg FISH vs 22% for unselected FISH.

Overall, clg selected FISH analysis yielded a superior detection rate. Specifically, clg selected detection of TP53 abnormalities was 26.5% (n=92) vs 9.4% (n=38) unselected ( $p<0.001$ ), chromosome 13 abnormalities, clg 46.8% (n=161) vs 19.2% (n=77) unselected ( $p<0.001$ ), IGH abnormalities, clg 56.8% (n=192) vs 17.8% (n=72) unselected ( $p<0.001$ ). Chromosome 1 abnormality testing did not reach statistical significance, though revealed a clg detection rate of 47.1% (n=164) vs 36.0% unselected ( $p=0.079$ ).

### **Conclusion:**

Bone marrow cytoplasmic immunoglobulin (clg) selected FISH outperforms unselected FISH for detection of prognostic cytogenetic abnormalities in plasma cell disorders and can be easily adopted into the standard cytogenetic laboratory workflow.

Gole, L., Lin, A., Chua, C., Chng, W (2014). *Cancer Genetics* (207) pp 31-34.

**Implementation of the Velcade at Home program at Peter Mac Callum Cancer Centre.  
Lessons learnt so far....**

**Emma-Jane Furphy**<sup>1</sup>, Hayley Beer<sup>1</sup>, Nella Combe<sup>1</sup>, Trish Joyce<sup>1</sup>, Colin Wood<sup>1</sup>, Alison Drosdowsky<sup>1</sup>, Jo Phipps-Nelson<sup>1</sup>, Mei Krishnasamy<sup>2</sup>, Simon Harrison<sup>1</sup>

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Background: With the change in mode of administration of Velcade from intravenous to subcutaneous, evaluation of the patient's Velcade administration experience was conducted. 85% of respondents stated they would prefer home based care, leading to the development of the Velcade at Home program.

Method: The program designed gave patients the option to be taught how to self administer their Velcade, have administration via their local GP or with Peter Mac at Home. This program does not replace delivery via chemotherapy day unit. Sterility testing of the reconstituted Velcade was undertaken allowing an extended expiry time of 14 days enabling every second weekly dose to be administered in the community. Eligibility and an intense education and training package for the patient and GP was developed and delivered by the Myeloma Nurse Consultants. Eligibility is reassessed after the first 4 weeks of training. Weekly telehealth or phone contact, assesses toxicities and provides opportunity to reassess technique. Patient experience questionnaires and the EORTC QLQ-MY20 are collected throughout the first four months of treatment and disease response is tracked.

Results: Of the 46 patients screened over a 9 month period, 12 were eligible and willing to self administer, 3 eligible and willing to have GP administration, 14 patients chose Peter Mac at Home and 17 commenced treatment with chemotherapy day unit. 6 patients who self administer have completed the four month pilot program with none needing to revert back to standard care. 1 patient required further counselling as they failed to self administer a dose.

Discussion: Less learnt so far; patient compliance/honesty, courier reliability, GP engagement, communication pathways between Myeloma Nurse Consultants, pharmacy and cytostatic. With these problems rectified, focus will be on increasing patient numbers and analysing the data collected with the view to implement this program as standard of care.

Disclaimer: This research was supported by Janssen through an unrestricted educational grant. The company had no role in analysing the data developing the program or preparing the abstract.

**A review of follow-up and treatment patterns of elderly, regional patients with MGUS/multiple myeloma.**

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**Aim**

To identify the treatment and follow up patterns of elderly patients (≥65y) living in regional Australia with a diagnosis of MGUS or myeloma. To gain insight into the additional burdens faced by this patient group, given the challenges Australia's geography poses and concentration of haematology services in metropolitan centres. To assess whether this influences treatment choices and follow up patterns.

**Method**

Retrospective chart review of patients ≥65y reviewed in the preceding three months in three regional centres.

**Results**

95 patients were identified. Median age 77 years (range 65-95y). Sixty-percent of patients were male. The most common diagnosis was symptomatic myeloma (42 patients/44%). Thirty-two patients (34%) had MGUS; 20 (21%) smoldering myeloma and one patient (1%) plasma cell leukaemia.

Median distance travelled to clinic 34km (range 1-388 km). Fifty-five patients (58) were currently being observed only. Twenty-three patients (24%) are on either subcutaneous or intravenous therapy requiring day unit attendance. Ten patients (11%) were on oral therapy. One patient (1%) had declined treatment. Telehealth was utilised for follow up in only two patients.

**Conclusion**

There are many barriers facing the elderly population in regional areas to receive specialist care. Travel in particular is an issue, as many patients and their carers can no longer drive and public transport is minimal. We identified many patients with symptomatic disease, requiring treatment and frequent review. We will compare our population with current published epidemiology and treatment data to assess whether geography and travel time influence treatment decisions.

## **Bortezomib Self-injection is time-saving, cost-neutral and well received by patients with Myeloma or AL amyloidosis: Results from the “SUBLIME” Study**

**Afshan Kajani**<sup>1</sup>, Masa Lasica<sup>1,2</sup>, Josephine Foo<sup>3</sup>, Katrina Wragg<sup>1,2</sup>, Lesley Turner<sup>1</sup>, Stephen Ting<sup>1,2,4</sup>, Simon Gibbs<sup>1,2,4</sup>

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### **Introduction:**

First-line treatment for myeloma (MM) and systemic AL amyloidosis (AL) consists of subcutaneous bortezomib, with oral cyclophosphamide and dexamethasone (VCD). Patients can spend several hours each week travelling into hospital or waiting for Hospital in the Home (HITH) nurses for one subcutaneous injection.

### **Aim:**

To assess the feasibility of a Self-administration of subcutaneous Bortezomib in multiple myeloma and AL-amyloidosis at home (SUBLIME) program. We sought to determine the money, patient travel and waiting times saved, and quality of life (QOL) impact.

### **Method:**

Patients undergoing VCD for MM or AL were included. Exclusion criteria included poor dexterity/vision, non-compliance or mental illness including significant anxiety. Cycle one was administered in the Day Oncology Medical Unit (DOMU), during which time, patients were taught subcutaneous administration, cytotoxic handling and disposal by the SUBLIME nurse. Once deemed safe, subsequent injections were administered by patients or carers at home. Patients were reviewed by the haematologist and SUBLIME nurse at the start of each cycle. The SUBLIME nurse telephoned patients after each self-injection.

### **Results:**

28 patients were identified from December 2018 to June 2019 inclusive. 11 patients were ineligible, 6 refused enrolment. 11 patients consented; 8 self-administered, three received injections from carers.

Program feasibility was confirmed with 84 injections administered safely without adverse outcomes. 3 hours of DOMU chair time or HITH nurse travel time were saved per patient per cycle.

4 cycles of bortezomib administered in DOMU costs \$2180, by HITH \$2023, and by SUBLIME \$1805, thus confirming SUBLIME is cost effective. Patients reported positive experiences, but formal QOL analysis will be completed at the end of the program.

### **Conclusion:**

The SUBLIME bortezomib self-administration program is safe, cost-effective, reduces patient travel time, and frees up nursing time for more complex therapies. Such a program may be applicable to other subcutaneous chemotherapies, such as cytarabine.

## **Outcomes of bortezomib induction followed by autologous stem cell transplant for treatment of multiple myeloma – a single centre study**

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<sup>1</sup>Gold Coast University Hospital, Gold Coast, Australia, <sup>2</sup>Griffith University, Gold Coast, Australia

**Background:** There is an evolving therapeutic landscape in the treatment of multiple myeloma. Autologous stem cell transplantation (ASCT) is the standard of care for transplant eligible patients with newly diagnosed multiple myeloma. Triplet therapy with immunomodulatory drugs and proteasome inhibitors has yielded deeper, more durable haematologic responses and improved survival compared to other regimens. However, these combinations are not available for induction in Australia and instead most transplant eligible patients receive triplet therapy based on a proteasome inhibitor, alkylator and steroid.

**Aim:** To evaluate outcomes of patients undergoing bortezomib, cyclophosphamide and dexamethasone (VCD) induction followed by ASCT +/- thalidomide maintenance, in the first line setting.

**Method:** This is a single centre retrospective analysis of newly diagnosed myeloma patients commencing treatment at Gold Coast University Hospital between 2012-2017.

**Result:** There were 52 patients in total. 22 were female, with a median age of 61 years (range 41-73 years). Patients received 3-5 cycles of VCD prior to ASCT, and 13 (25%) received thalidomide maintenance. Response to VCD pre ASCT was 8 (15%) CR, 9 (17%) VGPR, 31 (60%) PR and 4 (8%) SD. Response at 3 months post ASCT was 21 (40%) CR, 10 (19%) VGPR and 18 (34%) PR. The median progression free survival (PFS) from commencement of VCD induction was 27 months. The median PFS for those who received thalidomide maintenance was 34 months and 27 months for those who did not. Median OS for the cohort was 40 months. There was one case of transplant-related mortality. The median follow-up time for the cohort was 48.5 months.

**Conclusion:** This single centre study highlights outcomes following induction with triplet therapy with a proteasome inhibitor, alkylator and steroid, without availability of lenalidomide maintenance. Our outcomes are comparable to other published international studies [1,2] using a similar induction regimen and without lenalidomide maintenance.

### **References**

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Leiba M, Kedmi M, et al. Bortezomib-Cyclophosphamide-Dexamethasone (VCD) *versus* Bortezomib-Thalidomide-Dexamethasone (VTD) -based regimens as induction therapies in newly diagnosed transplant eligible patients with multiple myeloma: a meta-analysis. *Br J Haematol* 2014

## **Transformation to Anaplastic Multiple Myeloma whilst on Lenalidomide**

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Anaplastic Myeloma (AMM) is an aggressive morphological subtype of Multiple Myeloma (MM). This extremely rare variant has been described in previous case reports which all highlight the poor prognosis and treatment resistant nature of this disease.

This poster presents a case of AMM whilst on lenalidomide for relapsed Kappa light chain myeloma (LCM). A 72-year-old man was initially treated with bortezomib, cyclophosphamide and dexamethasone after the diagnosis of multiple myeloma (R-ISS Stage 1). He achieved a stringent Complete Remission, which was maintained for two years. Kappa light chains then began to rise with a repeat bone marrow examination showing 30% plasmacytosis. Treatment was started with lenalidomide and dexamethasone. He achieved a Partial Remission after four months of therapy with a 50% reduction in his kappa free light chains.

Rapid deterioration occurred during his fifth cycle of lenalidomide with fatigue, weight loss, anaemia and an elevated Lactate Dehydrogenase of 1410U/L. Bone marrow examination revealed 50% large, abnormal anaplastic cells with multiple and prominent nuclei. Cytogenetics revealed hypotetraploidy (70-108 chromosomes) with a complex, composite karyotype including clonal and non-clonal structural and numerical abnormalities. PET CT was described as a "myeloma superscan" with extensive osseous involvement. Given his poor functional status and the aggressive nature of his disease, the decision was made for palliation and he died one week later.

A Literature Review of the topic including all case reports with clearly described anaplastic morphology is included in this poster. There is a focus on the similarities between available cases, including cytogenetics, immunohistochemical staining and clinical features. The morphological similarity of AMM to Plasmablastic Lymphoma is also discussed. Previous case reports have shown limited therapeutic success with novel myeloma treatments but some response seen with conventional Lymphoma treatments.

**Post-ASCT consolidation/maintenance strategies for multiple myeloma – a single centre experience**

**Phillip Nguyen**<sup>1</sup>, Jenny Muirhead<sup>1</sup>, Anna Kalff<sup>1</sup>, Krystal Bergin<sup>1</sup>, Patricia Walker<sup>1</sup>, Sushrut Patil<sup>1</sup>, Andrew Spencer<sup>1</sup>

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**Aim:** Post-ASCT therapy for MM enhances progression free survival (PFS) and overall survival (OS). We conducted a retrospective analysis at our transplant centre to determine the impact of different post-ASCT strategies in our unit over a 10-year period

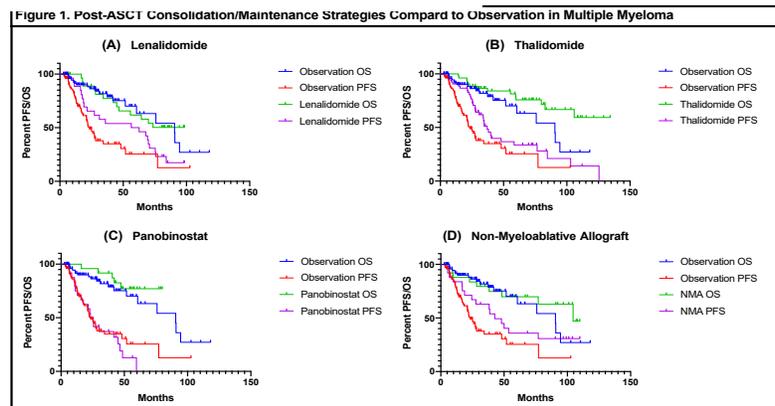
**Method:** Consecutive patients undergoing a first ASCT and surviving >90 days post-ASCT between January 2008 to December 2018 were evaluated. PFS and OS curves were constructed using the Kaplan Meier method. Statistical analysis was performed using the log rank test.

**Result:** 278 patients were included and 5 different approaches evaluated: observation only (n=79), lenalidomide (n=29, treatment until progression), thalidomide (n=54, maximum 12 months treatment), panobinostat (restricted to patients failing to achieve a CR post-ASCT) (n=24), and non-myeloablative allograft (NMA) (patients with =>2 high-risk disease features) (n=25). 67 patients receiving a variety of other approaches were not evaluated further. Patient characteristics are shown below (**Tab 1**). Median follow-up was 43 months (range 3-134). Lenalidomide patients demonstrated a trend in better median PFS compared to observation (62 vs 23 months, p=0.09), but no benefit in OS (**Fig 1A**). Thalidomide consolidation improved median PFS (37 vs 23 months, p=0.02) with a trend in better OS (HR 0.52, p=0.08) (**Fig 1B**). Panobinostat patients had similar PFS and OS compared to observation (**Fig 1C**). Patients with NMA post-ASCT demonstrated a trend in improved median PFS (43 vs 23 months, p=0.13) but no difference in OS (**Fig 1D**).

**Conclusion:** In this retrospective analysis we show that both thalidomide and lenalidomide prolong PFS following ASCT. Importantly, panobinostat and NMA overcome sub-optimal therapeutic responses and high-risk disease features, respectively.

Characteristics	Observation N = 79	Lenalidomide N = 29	Thalidomide N = 54	Panobinostat N = 24	NMA N = 25
Age (median)	61	60	60	57	52
Male	42	18	36	12	14
Female	37	11	18	12	11
ISS					
Stage I	26	8	18	7	4
Stage II	25	13	19	8	8
Stage III	24	8	15	10	12
Unknown	4	0	2	1	1
<b>Results</b>					
Median follow up (range)(mo)	28 (3-118)	70 (7-98)	62 (3-134)	48 (16-80)	58 (5-109)
Progression free survival					
Median (mo)	23	63	37	24	43
Hazard ratio (95% CI)	NA	0.61 (0.34-1.07)	0.58 (0.36-0.93)	1.21 (0.71-2.07)	0.63 (0.35-1.15)
P value	NA	0.09	0.02	0.49	0.13
Overall survival					
Median (mo)	91	*	*	*	105
Hazard ratio (95% CI)	NA	0.92 (0.44-1.91)	0.53 (0.26-1.07)	0.58 (0.21-1.61)	0.72 (0.32-1.67)
P value	NA	0.82	0.08	0.30	0.45
Alive at 6 years	63%	54%	76%	77%	70%

\*Median OS not reached



## Cell surface glucose-regulated protein 78 (GRP78) is upregulated in plasma cells of patients with multiple myeloma compared to monoclonal gammopathy of uncertain significance

**Slavisa Ninkovic**<sup>1,2,3</sup>, Lenny Straszkowski<sup>3</sup>, Anupa Dey<sup>1</sup>, Constantine Tam<sup>1,2,5</sup>, Harshal Nandurkar<sup>4</sup>, Simon Harrison<sup>5,6</sup>, Louise Purton<sup>2,3</sup>, Hang Quach<sup>1,2</sup>

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### Background:

Glucose-regulated protein 78 (GRP78), an endoplasmic reticulum molecular chaperone, is upregulated at times of cellular stress and limits proteotoxicity to promote cell survival. Translocation to the cell surface (csGRP78) and interaction with cell signalling and survival pathways is emerging as a critical step providing tumour cells with a survival advantage. csGRP78 is of interest as both a prognostic marker and a therapeutic target in multiple myeloma. We aim to objectively quantify the cell surface expression of GRP78 in plasma cells (PC) and cells of the TME in patients (pts) with MGUS, newly diagnosed (NDMM) and relapsed/refractory MM (RRMM).

### Method:

Bone marrow trephines from pts with MGUS (n=14), NDMM (n=21) and RRMM (n=21) were stained for CD138 and GRP78 by multiplex immunofluorescence histochemistry using the Opal™ workflow. Data was extracted using inForm® software with multispectral images scored based on membrane expression of CD138 and GRP78. Patient demographics, disease characteristics, and treatment outcomes were extracted from medical records. Descriptive statistics and ordinary one-way ANOVA were applied as appropriate.

### Results:

There was no difference in the total number of nucleated cells (NCs) assessed across the 3 cohorts; p=0.459. CD138+ve PCs (% of all NCs; mean±SD) in the MGUS, NDMM and RRMM cohort were 7.5±5.0 vs 32.2±22.6 vs 22.6±25.1 respectively (p=0.0052). Overall csGRP78 expression (% of all NCs; mean±SD) was highest in NDMM pts (30.6±23.8, 49.6±25.3, 23.7±21.7; p=0.0027). PC csGRP78 expression (CD138+, GRP78+) was highest in NDMM pts [60.3±29.3 vs 36.6±29.2 (MGUS; p=0.0341), vs 34.9±21.9 (RRMM; p=0.0090)]. csGRP78 expression in non-plasma cells (GRP78+ CD138-) was increased in MGUS pts [91.4±6.3 vs 62.3±24.6 vs 63.7±30.5; p=0.0017].

### Conclusion:

This study is the first to demonstrate upregulation of csGRP78 expression in plasma cells of pts with NDMM compared to MGUS, and a downregulation of csGRP78 in the cells of the TME, suggesting a potential role for csGRP78 in the tumorigenesis and progression from MGUS to MM. These results are intriguing and warrant further, larger-scale exploration.

**Long-term proteasome inhibition in newly diagnosed multiple myeloma (NDMM): US MM-6, a real-world study transitioning from bortezomib to ixazomib**

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**Aim:** Long-term (LT) proteasome inhibition (PI) improves outcomes in NDMM vs non-PI based therapy. However, efficacy improvements in clinical trials are often not achieved in real-world (RW) settings; duration of PI-based therapy is typically shorter in RW patients vs clinical trials. US MM-6 is a RW US community-based Phase 4 study investigating transitioning from a parenteral (bortezomib) to an oral (ixazomib) PI in NDMM with the goals of increasing treatment adherence and duration, maintaining quality of life (QoL), and improving outcomes.

**Methods:** US MM-6 (NCT03173092) is enrolling ~160 non-transplant patients with ≥stable disease after 3 cycles of bortezomib-based induction. Patients receive IRd (ixazomib 4mg, days 1, 8, 15; lenalidomide 25mg, days 1–21; dexamethasone 40mg [20mg for patients >75 years], days 1, 8, 15, 22; 28 day cycles) until progression/toxicity. QoL and adherence are assessed via electronic patient-reported outcomes (ePROs). Patients use wearable digital devices and smartphones to record adherence and actigraphy (average steps and sleep). Primary endpoint: progression-free survival; secondary endpoints: response, duration of therapy, ePRO compliance, overall survival, safety. We report preliminary data for the first 25 patients.

**Results:** Overall, 80% of patients were ≥65 years, and 43% had ISS stage III disease. Comorbidities included renal/urinary disorders (48%), peripheral neuropathy (28%), and cardiac disorders (24%). Patients received a median of 5 cycles of IRd (+3 cycles of pre-enrollment bortezomib-based therapy). Average ePRO compliance was 92%. Mean (SD) number of steps/day and sleep time were 3236 (3540) and 8.35 (3.21) hours.

**Conclusion:** Duration of PI-based therapy is similar to previous reports of LTPI; US MM-6 patients are older with higher rates of advanced-stage disease vs previous LTPI studies. Yet, actigraphy/ePRO data demonstrate high compliance rates and adherence to an all oral triplet regimen. US MM-6 will provide useful data on patient/disease characteristics and outcomes for IRd-treated NDMM RW patients receiving LTPI.

## Association between bortezomib cumulative dose and treatment-free interval in transplant ineligible patients with previously untreated multiple myeloma

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**Aim:** Higher cumulative bortezomib doses [combined with melphalan-prednisone (VMP)] are associated with improved overall survival for multiple myeloma patients ineligible for stem cell transplantation vs melphalan-prednisone (1). Our aim was to determine whether higher cumulative bortezomib doses are associated with longer treatment-free interval (TFI), or lower cumulative incidence (CI) of subsequent therapy.

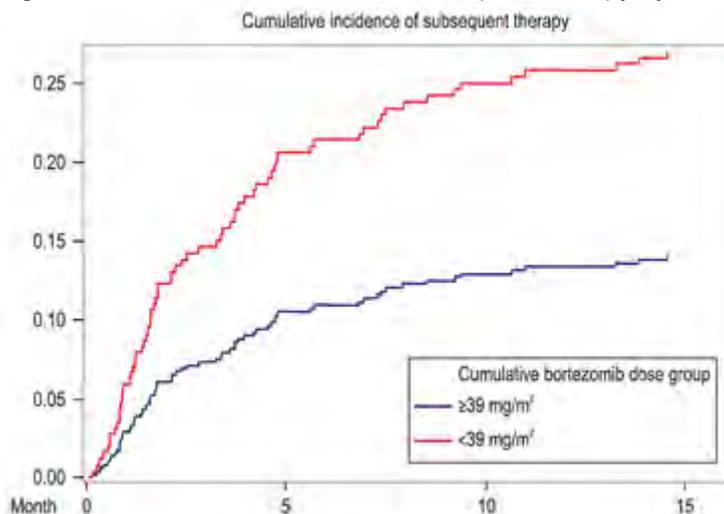
**Method:** This was a post-hoc analysis of patients treated with VMP in phase 3 VISTA (2). Baseline characteristics and clinical outcome (TFI, time from the last dose of study drug to the start of subsequent treatment) were analysed based on median cumulative bortezomib dose. For subjects who were not known to have died, survival time was censored at the date last known to be alive. Multivariate competing risks hazard ratios (HR), and estimates of CI of subsequent therapy, were computed using the Fine and Gray proportional hazards model for sub-distributions. HR<1 favours higher bortezomib cumulative group.

**Result:** Median cumulative dose of bortezomib was 39 mg/m<sup>2</sup> (median follow-up: 25.9 months). Patients in higher cumulative bortezomib dose group (n=170) were significantly younger (70.8±4.6 vs. 73.6±6.2, P<0.0001) vs lower group (n=170). No major differences between groups are identified. Only 44 (25.9%) and 24 (4.1%) patients in the lower and higher dose group had documented subsequent therapy. Overall, 39 (22.9%) and 10 (5.9%) patients died in lower and higher dose group. TFI did not reach the median for either dose group, though it was significantly longer in the higher vs lower dose group (HR:0.48, P=0.004; age-adjusted HR:0.49, P=0.009). The CI at month 12 for subsequent therapy was 0.134 for higher dose group vs 0.258 for lower group (Figure 1).

**Conclusion:** With relative short follow-up, higher cumulative bortezomib dose was associated with significantly delayed subsequent therapy. Further studies are warranted to understand the relationship between cumulative bortezomib dose and clinical outcomes.

**Keywords:** bortezomib, multiple myeloma, overall survival, treatment-free interval

**Figure 1:** Cumulative incidence of subsequent therapy by bortezomib dose group



### References

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## Comparing cytogenetic assessment techniques in patients with Plasma cell neoplasms

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**Background:** Cytogenetic abnormalities (CA) including immunoglobulin heavy chain (IgH) translocations, 17p deletion, 1p deletion, and 1q amplification, are of prognostic importance in Plasma cell neoplasms. Conventional cytogenetic analysis is typically associated with low diagnostic yield in these cases, whereas interphase fluorescence in-situ hybridisation (FISH) has been recognised as a more effective technique for routine detection of CA. Single nucleotide polymorphism (SNP) array is a more sensitive technique with emerging use. Our laboratory routinely performs conventional cytogenetics, interphase FISH on specific request, and has recently commenced performing SNP array in place of conventional cytogenetics on cases referred from two referral centres.

**Aim:** To compare the diagnostic yield of conventional cytogenetics, interphase FISH, and SNP array when applied to bone marrow samples of patients with Plasma cell neoplasms.

**Methods:** Retrospective audit of laboratory records from May - October 2018. All cases referred for conventional cytogenetics, FISH or SNP array where the primary diagnosis was a Plasma cell neoplasm were included. Relevant additional clinical, biochemical, and morphological data were collected.

**Results:** Eighty cases were referred for conventional cytogenetics, 40 for FISH, and 19 for SNP array. CA were demonstrated in 17.5%, 87.5%, and 84% of cases referred for karyotyping, FISH, and SNP array, respectively. High risk CA were found in 12.5%, 42.5%, and 63% of cases referred for karyotyping, FISH, and SNP array respectively.

**Conclusions:** Conventional cytogenetics resulted in the lowest diagnostic yield of CA. We found FISH to be the most sensitive technique for detection of Revised International Staging System (R-ISS) defined high risk CA, i.e. deletion of 17p and high risk IgH translocations. SNP array was especially sensitive for detection of chromosome 1 abnormalities.

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## **Patterns and outcomes of infection in multiple myeloma patients managed with next-generation therapies**

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### **Aim:**

Infections are a leading cause of early morbidity and mortality in patients with multiple myeloma (MM). The increased risk for infection can be attributed to several patient-, disease-, and treatment-related factors. Recent advances in treatment have transformed the care of MM through use of novel agents including next-generation immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies. However, minimal data exists regarding infection risk and outcomes in patients treated with newer agents.

The study aims to assess the epidemiology, risk factors and outcomes of infections in MM patients managed with next-generation therapies.

### **Methods:**

This study is a retrospective record review of MM patients treated with next generation therapies at Peter MacCallum Cancer Centre between January 2013 and December 2018. Clinical and microbiology patient records were reviewed to capture patient demographics, myeloma characteristics and infection episodes (type, severity, outcomes). Logistic regression was performed to identify clinical predictors associated with infection risk and outcomes

### **Results:**

48 myeloma patients were followed for a median of 13 months (IQR: 7.13-23.90). This cohort had a median of 5 lines of therapy (IQR: 4-7). A total of 143 infection episodes were identified with 46.2% as clinically defined, 35.7% as microbiologically defined and 18.2% as fever of unknown focus. Incidence rate of infection was 2.25 infections per patient year of follow up. Rates of invasive fungal disease was 8.3%. Respiratory infections were most commonly observed (53.8%) with 6 episodes associated with ICU admissions (4.2%) and 4 episodes associated with death (30-day mortality) (2.8%). No independent clinical factors associated with infection (by type, by severity) were identified on multivariate analysis.

### **Conclusion:**

Infections are commonly seen in myeloma patients. In this heavily treated MM patient cohort, no clinical risk factors were identified. Novel approaches to infection risk assessment such as immune profiling should be evaluated.

**Sustained minimal residual disease (MRD)-negativity in relapsed/refractory multiple myeloma (RRMM) patients treated with daratumumab plus lenalidomide/dexamethasone (D-Rd) or bortezomib/dexamethasone (D-Vd)**

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In phase 3 studies, RRMM patients treated with D-Rd or D-Vd rapidly achieved MRD negativity and demonstrated prolonged progression-free survival (PFS) versus MRD-positive patients. MRD assessment is under investigation as a potential surrogate for endpoints such as overall survival (OS), and sustained MRD-negativity may provide a more robust assessment of disease control. Here, we evaluate sustained MRD negativity with D-Rd and D-Vd and its association with PFS/OS in RRMM. Patients in POLLUX and CASTOR studies received  $\geq 1$  prior line of therapy and were randomized (1:1) to receive Rd or Vd, respectively,  $\pm$  daratumumab. MRD was assessed via next generation sequencing at  $10^{-5}$  at suspected complete response (CR) and 3 and 6 months post-CR in POLLUX, suspected CR and 6 and 12 months following the first treatment dose in CASTOR, and every 12 months post-CR in both studies. Sustained MRD negativity was defined as maintenance of MRD negativity in the bone marrow confirmed  $\geq 6$  or  $\geq 12$  months apart. Median follow up was 39.5 months in POLLUX (D-Rd, n=286; Rd, n=283) and 31.3 months in CASTOR (D-Vd, n=251; Vd, n=247). At  $\geq 6$  and  $\geq 12$  months, significantly more patients in the intent-to-treat (ITT) population achieved sustained MRD negativity with D-Rd versus Rd ( $\geq 6$  months: 16% vs 0.7%,  $P < 0.0001$ ;  $\geq 12$  months: 13% vs 0.4%,  $P < 0.0001$ ) and D-Vd versus Vd ( $\geq 6$  months: 9% vs 1%,  $P = 0.0001$ ;  $\geq 12$  months: 3% vs 0%,  $P = 0.0074$ ); similar trends were observed in  $\geq CR$  patients. Sustained MRD negativity was associated with longer PFS and OS at  $\geq 6$  and  $\geq 12$  months for daratumumab-containing regimens versus patients without sustained MRD negativity (ITT). Daratumumab plus standard-of-care regimens enable significantly more patients to achieve deep and durable responses of  $\geq CR$  and MRD negativity at  $10^{-5}$ . Durable MRD negativity is associated with prolonged survival, suggesting sustained MRD negativity should be a treatment goal for RRMM patients.

## **Real world outcomes post novel agent induction and autologous stem cell transplant (ASCT) in newly diagnosed multiple myeloma**

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### **Aim:**

Novel agent induction followed by high-dose melphalan and ASCT is the standard of care for eligible patients with newly diagnosed multiple myeloma (MM). We sought to analyse our local outcomes with this therapy and evaluate the influence of pre- and post-ASCT factors.

### **Method:**

The RBWH transplant database was interrogated for all patients who underwent novel agent-based induction and ASCT as part of frontline therapy for MM. Patients who were transplanted in relapse or with incomplete data were excluded. Baseline characteristics, response and survival data was collected and analysed using comparative statistics.

### **Results:**

Between January 2007 and December 2017, 197 patients underwent SCT and 124 met criteria for analysis. The median age at SCT was 59 years and 65% of patients were male. Induction agent included thalidomide in 53/124 (43%) and bortezomib in 69/124 (56%). High-risk cytogenetic abnormalities (HR-CA) including t(4;14), t(14;16) and del(17/17p) by FISH were identified in 10%, and were unknown in 13%. Post-ASCT maintenance was given in 21 patients (17%).

Day 100 ORR was 96% and  $\geq$ VGPR was 75%. Regression analysis revealed no association with age, HR-CA, ISS stage or novel induction agent. Median follow-up was 56 months. Median progression free survival (PFS) was 42 months with the median overall survival (OS) not reached. The 4-year OS was 84%. Factors associated with inferior OS on univariate and multivariate analysis were HR-CA (HR 5.41, 95% CI 1.46-20.01, p=0.01) and >1 line of therapy pre-ASCT (HR 3.54, 95% CI 1.49-8.38, p=0.004). Of the latter group, the majority had less than a partial response (<PR) to first-line therapy.

### **Conclusion:**

Response and survival outcomes post-ASCT in our cohort appear similar to published experience from other centres. Similarly, the strongest predictor of inferior survival was HR-CA. These results will be used for future analyses to evaluate the real-world impact of tandem ASCT and lenalidomide maintenance in this patient group.

## Targeted next generation sequencing of liquid biopsies in multiple myeloma

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Multiple myeloma (MM) is a haematological malignancy characterised by the clonal proliferation of plasma cells within bone marrow (BM). Traditionally, MM diagnostic and prognostic markers are identified by various tests including cytogenetics using bone marrow aspirates (BMAs) and serum studies using peripheral blood (PB). However, BMAs are invasive and are sampled from a single site, introducing sampling bias due to the spatially distributed nature of MM lesions in patients. There is increasing interest in liquid biopsies (LB) in MM as a less invasive and more accessible alternative to BMAs. LB refers to cell-free DNA (cfDNA) and circulating tumour cells (CTCs) extracted from PB. Previous research suggests that LB can overcome the sampling bias associated with MM as cfDNA and CTCs can originate from multiple lesions. However, previous research has typically analysed data obtained from either cfDNA or CTCs with varying availabilities of matched BM samples. Additionally, only two studies have analysed matched cfDNA, CTC and BM samples from four and 23 patients. The current project aims to i) collect matched cfDNA, CTCs and BMAs from 24 MM patients at diagnosis, ii) design and apply a custom next generation sequencing panel to identify genetic changes with validated prognostic significance in the cfDNA, CTCs and BMAs as there is currently no commercially available panel and iii) investigate the genetic concordance between LB and BMAs. It is hypothesised that cfDNA and CTCs together will show the same changes as identified in BMAs, in addition to changes not seen in the BM. Matched diagnostic BMAs and PB samples have been collected from 24 patients. This project will expand on the feasibility of LB as a less invasive, less biased and more accessible alternative to BMAs in MM diagnosis and prognostication.

## MYC - containing double minutes in plasma cell myeloma: A case report

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Double minute chromosomes (*dmin*) are commonly observed in solid tumours and have also been reported in haematological malignancies, particularly myeloid neoplasms. However, the presence of *dmin* has rarely been reported in plasma cell myeloma (PCM).

A 76 year old female presenting with back pain was found to have anaemia, hypercalcaemia and an L3 lesion on computer tomography. Core biopsy revealed a plasmacytoma. Subsequent bone marrow biopsy confirmed advanced PCM, with protein studies confirming oligosecretory disease. Conventional karyotyping showed a complex, hyperdiploid karyotype with *dmin*. FISH studies identified gains of ATM with no other abnormalities. Microarray analysis showed amplification at 8q24 containing the MYC and PVT1 genes. NGS identified a heterozygous 12bp deletion in TP53 which is predicted to result in premature termination and loss of function due to nonsense mediated decay.

Treatment for her Stage II R-ISS PCM included triplet therapy of bortezomib, cyclophosphamide and dexamethasone which resulted in a biochemical stringent Complete Remission (sCR) after 6 cycles and normalisation of anaemia. However, she soon developed worsening cytopenias with repeat bone marrow biopsy confirming primary refractory PCM. A palliative approach was sought and she soon succumbed from her disease.

We present the case of a 76 year old patient with primary refractory R-ISS Stage II PCM who had otherwise standard risk cytogenetic features as defined by IMWG. We postulate that the presence of MYC and PVT1-containing *dmin* and concomitant TP53 sequence variant may have contributed to her poor risk profile and overall survival.

## Does Age Matter in Autologous Transplant for Multiple Myeloma?

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### **Aim**

Autologous stem cell transplant (ASCT) remains a standard treatment for multiple myeloma (MM). Our centre treats many older MM patients (>65 yrs) including use of ASCT. This study examines the impact of age on ASCT in our MM cohort.

### **Methods**

From 01/2001–07/2018, 290 MM patients received ASCT and 315 transplants were performed in our centre. Patients were stratified by age, as <65 yrs (group A), 65–69 yrs (group B) and >69 yrs (group C). The success of stem cell collection and post-ASCT outcomes has been compared across these age groups.

### **Results**

For entire cohort, median age at transplant was 62 (33-76) yrs. 60.6% were male. Median follow-up was 3.2 (0.03-15.2) yrs. 62.9% (198/315) of transplant recipients were in group A, 30% (85/315) in group B and 10.2% (32/315) in group C. Stem cells collected were significantly lower in Group B and C patients than in Group A patients, total median collected CD34+ cells in group A, B and C were 7.8, 5.6 and 5.8 x10<sup>6</sup>/kg, p= 0.01. Patients who had received >1 lines chemotherapy also had reduced CD34+ cell numbers, median total collection CD34+ cells after 1 line chemo and >1 lines chemo were 7.5 and 5.7 x10<sup>6</sup>/kg, p=0.01. However gender, disease stage and status at transplant did not significantly affect CD34+ cells collection. In post-transplant outcomes, ISS/R-ISS significantly affected relapse rate, 5yr DFS and OS (p= 0.001, 0.007 and 0.002, multivariate analysis). Patients receiving >1 lines chemo had higher TRM and shorter 5yr OS (p= 0.003 and 0.008 multivariate analysis). Surprisingly, there were no significant differences in post-transplant outcomes across the 3 age groups.

### **Conclusion**

In our single centre study, we found that ASCT is feasible in many patients over 65 yrs. Age did not affect post-transplant outcomes but did reduce numbers of CD34+ cells mobilized.

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**Assessment of haematopoietic stem cell mobilisation (HPC) outcome by retrospective analysis of 5mg/kg twice daily (bd) with 10mcg/kg daily G-CSF in patients with myeloma (MM) or AL amyloidosis.**

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The optimal G-CSF dosing schedule ie bd vs daily dosing for HPC is uncertain.

We conducted analysis of MM and AL amyloidosis patients undergoing their first HPC mobilisation with G-CSF alone comparing 10mcg/kg daily (2017 collections) to 5mcg/kg bd (2018/19 collections). Collection proceeded if pre-collection CD34 $\geq$ 14x10<sup>6</sup>/L. Eighty patients were included: 40 in each arm. 36 per arm gave a power of 0.8 and alpha error of 0.5 to detect a 1.4 X10<sup>6</sup>/kg difference in CD34. Collection target was 2-3x10<sup>6</sup>/kg/transplant. T-test/Kruskal Wallis were used to compare medians.

Patient characteristics:

GCSF	Diagnosis MM/ALAmyloidosis	Age (Median years)	Radiotherapy	G-CSF treatment days
daily	30/6	64 (46-73)	2	5
bd	31/5	62 (34-74)	6	5.5
P value	0.990	0.091	0.260	0.001

Collection data:

	Pre collect CD34x10 <sup>6</sup> /L	Collectio n day WCC	Day 1 bag CD34x10 <sup>6</sup> / kg	Total CD34x10 <sup>6</sup> / kg	Collectio n days	Volume processe d(L)	Collectio n efficiency
daily	29	36	5.26	5.70	1.5	14.65	66
bd	34	47	3.14	4.98	2	17.55	56
p	0.012	0.005	0.305	0.237	0.904	0.969	0.001

\*medians provided

Induction therapy was VCD (34/36) in each arm. Pre-collection CD34 and total white cell count (WCC) were higher in the bd group. This did not result in a better day 1 or overall CD34 collection yield. The number of patients with insufficient CD34(<2x10<sup>6</sup>/kg) for one transplant was similar: 3/36 (daily) and 2/36 (bd). Collection efficiency (or the cell separator collection success) was lower with bd dosing. There was no difference in the cryopreserved product volume, number of bags stored or CD34 viability between the two arms.

Although bd G-CSF resulted in a higher pre-collection CD34, there was no difference in the final CD34 product yield. The higher pre-collection WCC may have contributed to the lower collection efficiency. Our cohort showed no advantage to bd dosing for stem cell mobilisation in patients with MM and AL amyloidosis.

## **Paediatric cyanosis an uncommon cause**

**Jacquie Anderton**<sup>1</sup>, Hayleigh Wallace<sup>1</sup>, Janine Campbell<sup>1</sup>, Song Chen<sup>1</sup>, Tina Yen<sup>1</sup>, Chris Barnes<sup>1</sup>  
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### **Background**

Gamma globin haemoglobinopathy is an uncommon disease usually with no clinical significance and self-resolving when Hb F reaches adult level after 2 years of age. However, some rare gamma globin variants can cause severe clinical phenotypes in the neonatal period resulting in a diagnostic dilemma and difficult management. Here, we report a case of Hb F-M Toms River variant in a newborn.

### **Case**

A term neonate developed central cyanosis 2.5 hrs after birth. Initial evaluation excluded congenital cardiac malformation and primary pulmonary disease. Treatment for possible sepsis failed to improve oxygen saturation. Discordant blood gas analysis and pulse oximetry readings prompted consideration of a less common cause for the cyanosis. Measurement of oxygen saturation by pulse oximetry (SpO<sub>2</sub>) is based upon a normal oxygen-haemoglobin dissociation curve. The consistently reduced SpO<sub>2</sub> values suggested the presence of a dysfunctional variant haemoglobin. Haemoglobin analysis by capillary electrophoresis revealed no abnormality. Further testing by DNA analysis was warranted when paternal history revealed a similar clinical course of hypoxia during the first 6 months of life. The patient was found to be a carrier of a gamma globin haemoglobinopathy, Hb F-M Toms River a mutation in the gamma2-globin gene. The amino acid substitution causes an altered heme pocket resulting in oxidative instability and lowered oxygen affinity leading to cyanosis and anaemia. The patient required blood transfusion and oxygen support for the first few months of life.

### **Discussion**

Clinical diagnosis and management of neonatal central cyanosis is a medical emergency necessitating prompt assessment to determine the causative agent. The significance of discordant blood gas results and serial family history was critical in detecting the presence of a rare variant haemoglobin, which is important for prognostic assessment and further management. Investigation and genetic counselling are warranted for future pregnancies.

## **Anaemia in general medicine inpatients: an overview of the prevalence, recognition and management**

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**Background:** Anaemia in surgical inpatients has been researched extensively, but little is known about the prevalence of anaemia in an Australian medical inpatient setting.

**Aims:** To determine the prevalence of anaemia and its associations in medical inpatients; to characterise the current state of recognition, investigation and management of anaemia.

**Methods:** A retrospective, cross-sectional study of all admissions to the acute medical unit of Royal Perth Hospital, a large tertiary hospital in Perth, Western Australia during September 2017. The final sample size was 800 patients. Descriptive statistics, univariate regression and multivariable logistic regression were utilised for data analysis.

**Results:** Of 800 patients, 330 (41.25%) were anaemic on admission. Independent predictors of anaemia were older age ( $p < 0.001$ ), male sex ( $p = 0.005$ ), Aboriginal or Torres Strait Islander ethnicity ( $p = 0.003$ ), diabetes ( $p = 0.018$ ), chronic kidney disease ( $p < 0.001$ ) and proton pump inhibitor therapy ( $p = 0.012$ ). Anaemia was most commonly mild (49.1%), normocytic (82.1%), chronic (62.7%) and unrelated to the admission diagnosis (87.3%). Anaemia was recognised or possibly recognised in 137 (41.5%) of 330 anaemic patients. Of 137 patients, 120 patients (87.6%) had further investigations and 53 patients (38.7%) had a management plan. No significant difference in the proportion of patients recognised was found in patients  $>65$  years compared to  $<65$  years ( $p = 0.460$ ). There was a significant difference in the proportion recognised by severity level ( $p < 0.001$ ) and mean cell volume ( $p = 0.048$ ). Significantly more anaemic females were investigated than anaemic males ( $p = 0.011$ ).

**Conclusions:** Anaemia is highly prevalent in medical inpatients yet is poorly recognised, investigated and managed. Although the admission diagnosis is often the focus in acute medicine, hospitalisation is an important opportunity for anaemia to be investigated and corrected, especially in patients who do not regularly seek medical care.

## Safety and efficacy of self-administered romiplostim in patients with ITP: results from an integrated analysis of five clinical trials

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**Background:** Self-administration (SA) by patients/caregivers can offer time/cost savings to providers and is convenient for patients. This analysis examined the safety and efficacy of romiplostim SA in adults with immune thrombocytopenia (ITP).

**Methods:** Data were pooled from 5 romiplostim clinical trials. Patients who achieved a stable dose for  $\geq 3$  consecutive weeks ( $\geq 4$  weeks in 3 trials;  $\geq 3$  weeks in 2 trials) could self-inject romiplostim (or have it administered by a caregiver). The SA analysis group included patients who ever self-administered romiplostim in any of these 5 trials. To provide a meaningful comparator, an HCP-dosed subgroup of patients from the 5 trials were included in the analysis. These patients were required to have received the same stable romiplostim dose for  $\geq 5$  consecutive weeks with platelet response and with all doses administered by an HCP. Patients in the HCP group may have been eligible for SA provided they had received physician approval and adequate training. In the SA group, the analysis index date was the 1st day a patient self-injected romiplostim. In the HCP group, the index date was the date of the 5th consecutive stable dose. Safety parameters were adjusted for differences in romiplostim treatment duration in the SA and HCP groups (duration-adjusted values reported herein). Statistical analyses were descriptive.

**Results:** Baseline characteristics are shown in the table. Duration-adjusted event rates were numerically lower in the SA vs HCP group for all treatment-emergent adverse events (TEAEs), bleeding TEAEs, Grade  $\geq 3$  bleeding TEAEs and serious bleeding TEAEs (table). Adjusting for the duration of treatment, the romiplostim dose adjustment rates/100 subject-weeks were 1.24 vs 1.60 in the SA vs HCP groups, respectively.

**Conclusion:** Romiplostim self-administration appears well tolerated and effective in eligible patients with ITP who have stable platelet counts  $\geq 50 \times 10^9/L$  for  $\geq 4$  consecutive weeks and have undergone training.

## Implementation of a linked electronic healthcare delivery system in a rural outpatient haematology setting

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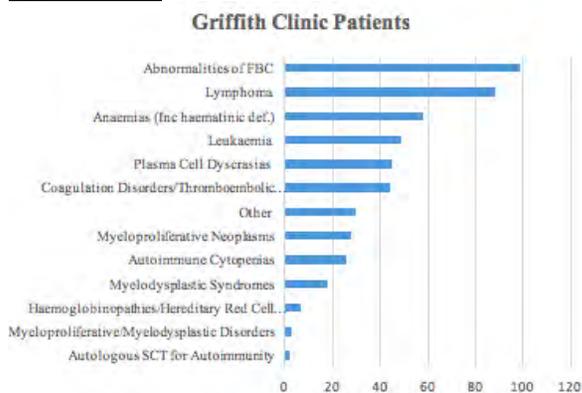
**Aim:** To integrate the electronic healthcare delivery systems at a metropolitan hospital and a rural outreach haematology clinic to facilitate streamlined and safe outpatient care.

**Method:** The MOSAIQ v2.64 [Elekta] system utilized at St Vincent's Hospital, Sydney, was introduced at a linked rural outreach haematology clinic in Griffith, a city in the Riverina region of New South Wales. MOSAIQ is a comprehensive practice management system incorporating all relevant patient notes and results along with administrative capabilities. The two systems were consolidated into one with patient information accessible from both sites.

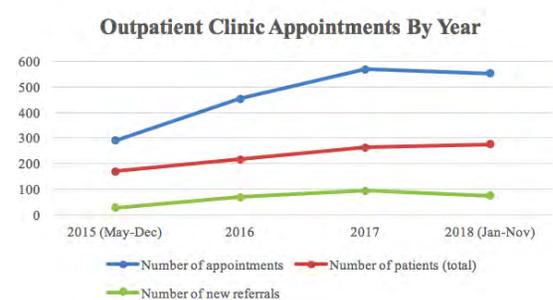
**Result:** The electronic systems were successfully linked between the two sites in October 2017. As of November 2018 there were 497 patients registered with the service with the breakdown of diagnoses shown in Figure 1, with lymphoma found to be the most common haematological diagnosis. Service activity over time including clinic appointments and patient numbers is shown in Figure 2. Nine chemotherapy regimen types encompassing 2174 overall treatments were delivered at the service over the fifteen months since implementation, the most common being R-CHOP [Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone] followed by azacitidine. The linked system has improved streamlined care during patient transitions between the two hospitals with enhanced continuity of documentation and management. Chemotherapy prescribing has transitioned to electronic at the Griffith site and is guided by inbuilt, pharmacist-reviewed protocols allowing for safer and flexible prescribing remotely which has standardized management of haematology patients across both hospitals.

**Conclusion:** Our study provides a novel example of the successful implementation of a centralised electronic healthcare record and chemotherapy prescribing system in a haematology setting shared between a metropolitan service and a rural outreach hospital clinic. This has positive implications for the safety and efficiency of healthcare delivery at the rural site as well as allowing data collection to assist future planning of the service.

**Figure 1: Griffith Haematology Clinic Outpatients Diagnoses.**  
**Appointments.**



**Figure 2: Griffith Outpatient Clinic**



## **Jadenu transition study: Has Jadenu improved chelation adherence in transfusion dependent thalassaemia?**

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**Aim:** To evaluate whether the transition from Exjade (dispersible deferasirox tablets) to Jadenu (film-coated deferasirox tablets) impacts chelation adherence and side effects experienced by patients with transfusion-dependent thalassaemia and haemoglobinopathies. Exjade production is being discontinued and will no longer be available for supply in Australia. Exjade requires dispersion in water or juice prior to administering to allow adequate absorption. Side effects and difficulty swallowing the mixture reduces compliance in some patients. Jadenu is the replacement formulation that can be swallowed whole.

**Method:** The compulsory transition from Exjade to Jadenu was studied in all patients in our Thalassaemia and Sickle Cell service. There were 46 patients, aged 19 to 54 years. Assessments include change in serum ferritin, assessment of compliance by direct questioning and analysis of dispensing records. Furthermore, a questionnaire examined tolerability, adverse events, ease of administration and self-reporting of missed doses of chelation medication.

**Results:** Impact on adherence and serum ferritin, a surrogate measure of iron stores, will be presented. Patient perception will be presented – their experience and subsequent ongoing self-motivation and quality of life are important factors in their ownership over management of their chronic disease.

Side effects experienced upon commencement of Jadenu, including renal function and impact of dual chelation versus single agent chelation will also be discussed. The psychological impact associated with the transition to a new medication was not predicted within this group of long term iron chelators and will be discussed.

**Conclusion:** This study will describe the patient-centred outcomes of the transition from a dispersible tablet to film-coated tablet and provide a greater understanding of this patient group with long term healthcare requirements. Greater understanding of the impact of this change will help inform future therapeutic choices in this cohort.

## **Update from the Australian Aplastic Anaemia Registry: diagnostic challenges in a diagnosis of exclusion**

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**Aim:** The differential diagnoses of bone marrow failure (BMF) are broad and aplastic anaemia (AA) remains a diagnosis of exclusion. The objective of the Australian Aplastic Anaemia Registry (AAR) is to capture the clinical features of, therapeutic approaches for and outcomes of all Australian patients with AA. It aims to describe the diagnostic challenges in this patient group and inform strategies to overcome this significant barrier to optimising patient care.

**Method:** The comprehensive national dataset in the AAR was interrogated to examine patient demographics and national practices in diagnosis of AA.

**Result:** At June 2019, 160 patients were enrolled and 39 sites approved for patient recruitment. Median age at diagnosis was 39 years (range 2 – 94 years) with bimodal diagnostic peaks observed between 11-20 and 61-70 years of age. There was no sex predilection observed (male:female ratio 1:1.03). 124 patients had a diagnostic bone marrow report available. 48 (39%) had features sufficient to result in a diagnosis of AA alone. In all other patients, hypocellular myelodysplastic syndrome, inherited bone marrow failure (IBMF) or alternative conditions were identified as possible diagnoses. Dysplastic features were observed in 58 patients (47%). 4 patients were subsequently diagnosed with occult IBMF as the cause of the BMF. Reticulocyte count was not available for 21%, precluding assessment of AA severity by Camitta criteria and potentially reflecting a perceived lack of clinical utility of this test. Paroxysmal nocturnal haemoglobinuria testing, telomere length assessment and chromosomal fragility studies as recommended by international guidelines were not always performed.

**Conclusion:** The substantial array of differential diagnoses in BMF contribute to diagnostic uncertainty and challenge optimal management. Broad screening investigations are recommended to narrow diagnostic possibilities however are performed inconsistently. Examination of national practices by the AAR has the potential to identify mechanisms by which diagnostic precision may be optimised.

## Findings and utility of targeted gene panel testing for heritable bone marrow diseases

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**Aim:** Building on the Melbourne Genomics Health Alliance bone marrow failure (BMF) flagship, Peter MacCallum Cancer Centre has implemented ongoing testing for patients with suspected inherited bone marrow diseases (IBMD). We aim to describe the findings of targeted next generation sequencing in the first 100 consecutive patients referred to this new diagnostic service.

**Method:** 100 consecutive patients referred for germline assessment underwent targeted testing with the Peter MacCallum Cancer Centre 40-gene IBMD panel.

**Result:** Patients were referred for testing between September 2018 and May 2019. Median age was 31 years (range 1 month – 84 years) and 32 patients were less than 18 years old. Forty-two patients had a suspected inherited BMF or haematological malignancy predisposition syndrome. Thirty patients had a diagnosis of acquired BMF (including aplastic anaemia, paroxysmal nocturnal haemoglobinuria and hypocellular myelodysplastic syndrome) in whom the treating team wanted to exclude occult inherited BMF. Twenty-eight patients had BMF that was unable to be definitively classified as inherited or acquired before testing.

Twelve patients had a pathogenic or likely pathogenic variant detected (in SBDS, CSF3R, TINF2, GATA2, RPL11, RPS19, RPL35A, DDX41 and ANKRD26) thought to be causative of the observed phenotype. Four patients had variants of uncertain significance detected (in RPS26, TERT and GATA1) which were considered likely candidates for the observed phenotype. Of the 16 patients in whom a causal or suspicious inherited variant was detected, 14 had a working diagnosis of an IBMD prior to testing. No patients with a working diagnosis of an acquired BMF had an occult germline cause detected.

**Conclusion:** There is significant clinical demand for genomic testing to investigate IBMD and patients with a high suspicion of an underlying inherited cause have the highest incidence of identified abnormalities. Refinement of testing criteria in those with suspected acquired disease is an area of ongoing research need.

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## **Losartan reduces the albuminuria of patients with sickle cell disease**

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### **AIM**

To evaluate the effects of losartan, an angiotensin receptor blocker, on albuminuria associated with sickle cell anemia.

### **METHODS**

8 males and 4 females, mean age  $18.8 \pm 3.0$  years, with sickle cell anemia and proteinuria (urinary protein,  $\geq 0.5$  g per day) and serum creatinine concentrations of less than  $177 \mu\text{mol}$  per liter ( $2.0$  mg per decilitre), received losartan for 3 weeks. After 3 weeks of treatment, 24-hour urinary protein excretion were measured again. Treatment was then discontinued, and the same study was performed a third time three weeks later.

### **RESULTS**

The rate of urinary protein excretion decreased in all 12 patients at the end of the three -week period of treatment with losartan ( $P < 0.001$ ). The mean decrement was 47 percent below base line (range, 23 to 67 percent). When measured again three weeks after treatment with losartan was discontinued, the mean protein excretion was 80 percent of the base-line value.

### **CONCLUSIONS**

Our results demonstrate that losartan reduces albuminuria in all sickle cell patients suggesting that glomerular capillary hypertension may be a pathogenic factor in sickle cell nephropathy. After discontinuation of the drug, however, the albuminuria tends to increase again. Whether long-term therapy with angiotensin receptor blocker can lower protein excretion persistently and prevent the development of renal insufficiency remains to be determined.

## Gain of novel CSF3R mutation leading to acute myeloid leukaemia (AML) complicating homozygous glucose-6-phosphatase catalytic subunit 3 (G6PC3) mutation related severe congenital neutropenia (SCN)

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**Background:** Severe congenital neutropenia (SCN) secondary to homozygous G6PC3 mutation is an autosomal recessive disorder characterised by recurrent severe infection from infancy and a heterogeneous phenotype of congenital abnormalities. The syndrome, first described in 2009, includes recurrent infection, urogenital malformations, structural heart defects, prominent superficial veins and chronic thrombocytopenia<sup>1</sup>. Although SCN due to more common mutations has an increased propensity towards leukaemic transformation<sup>2</sup>, this has not been consistently described with G6PC3 mutation. We describe the third reported case of AML complicating SCN due to G6PC3 mutation, and the second case to be successfully treated by haploidentical haematopoietic stem cell transplant (HSCT).

**Case Discussion:** Our patient, with consanguineous parents, was homozygous for G6PC3 mutation causing SCN. Her syndromic features included profound neutropenia with severe recurrent infections, renal dysplasia with vesicoureteral reflux, atrial septal defect and prominent superficial veins. There was progressive thrombocytopenia from age 6 years. By age 18, annual bone marrow surveillance demonstrated increased marrow fibrosis, left shifted myelopoiesis and worsening cytopenias. She subsequently developed AML ten years after commencing G-CSF treatment (2.5mcg/kg/day). Gene sequencing revealed a novel somatic mutation of the CSF3R gene, c.2296C<T, not previously described in the literature. The patient was successfully treated with azacitadine chemotherapy followed by HSCT from her haploidentical mother. Post-transplant she maintains a normal neutrophil count without G-CSF treatment, suggesting a curative treatment option.

**Conclusion:** Ten years after G6PC3 mutation causing SCN was described we report the second case of progression to AML with successful haploidentical transplant. In this case, chronic G-CSF treatment and somatic gain of novel CSF3R mutation implicates G-CSF signalling in the pathophysiology of leukaemic transformation. As with other genetic causes of SCN, predisposition towards malignancy should be evaluated in patients with G6PC3 mutation. G-CSF treatment should be maintained at minimal effective dose and surveillance for AML should be routine.

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## **Establishment of a National Clinical Haematology Education Programme**

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### **AIM**

To develop an easily deliverable, widely accessible standardised clinical haematology teaching programme aimed at advanced trainees to supplement the existing laboratory haematology education programme.

### **METHODS**

Responses from a survey conducted of 48 haematology advanced trainees who attended the 2017 HAA trainees day indicated the need for a dedicated clinical haematology teaching programme. Many felt ill-equipped to manage acute haematological conditions in their first year of training and those in their final years lacked confidence in the outpatient setting, due to a lack of structured teaching in busy clinical rotations.

A SWOT analysis identified opportunities for developing an interactive online programme, delivered by experienced clinicians to complement rapidly evolving evidence-based practice, relevant to an Australasian context. A curriculum proposal was drafted by a committee of haematologists and advanced trainees and has been endorsed by the Committee for Joint Training in Haematology (comprised of curriculum development personnel of the RACP and RCPA), as well as the Haematology Society of Australia and New Zealand.

A steering committee was formed and partnered with MD briefcase, an online continuing medical education provider. MD briefcase has independently sourced industry funding to support the development of the program. Interactive modules incorporating lectures, case studies and multimedia elements will be written by a nationwide consortium of haematologists in collaboration with MD Briefcase. The programme will be provided to trainees at no cost, and as an approved continual professional development activity. Delivery is expected to commence in the latter half of 2019, with ongoing evaluation and reporting of participant feedback and usage patterns to inform continuous improvement.

### **CONCLUSION**

A national, standardised, accredited clinical haematology education programme has been developed based on trainee identified educational needs and will be piloted and evaluated using online usage data analytics.

## **Rituximab for autoimmune haemolytic anaemia: audit of clinical practice at the Royal Hobart Hospital**

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**Background:** Autoimmune haemolytic anaemia (AIHA) is an uncommon disease entity. Rituximab in low dose can be an effective treatment of AIHA. This treatment is convenient, minimises likelihood of adverse effects and may be cost effective compared to alternative treatments.

**Aim:** To determine the response to low dose rituximab in a population of patients with autoimmune haemolytic anaemia at the Royal Hobart Hospital between 2012 and 2018.

**Method:** Data was collected from all patients treated with low dose rituximab for AIHA between 2012 and 2018. Treatment consisted of a 100mg infusion of rituximab once weekly for four weeks. Parameters included response, time to response, duration of response, relapse rate, relapse free survival, reported side effects and complications of treatment.

**Results:** There were a total of 15 individuals treated, with 18 courses of treatment included. The average age of patients treated was 71 years old, with a range from 21 to 89 years. 10 patients were female, 5 were male. The vast majority of cases (n=13) were treated for warm autoimmune haemolytic anaemia (WAIHA), with one case of cold agglutinin disease (CAD), and another of antibody negative haemolytic anaemia. 67% of patients achieved a complete response to treatment (haemoglobin >120g/L), and a further 17% achieved a partial response (haemoglobin 100-120g/L or >20g/L increase), with an overall response rate of 83%. Average baseline haemoglobin was 85.7g/L, increasing to an average maximum haemoglobin of 129.4g/L following treatment. Mean time to response was 28 days from beginning of treatment, although peak haemoglobin concentration occurred up to 2 years following treatment. 6 cases relapsed, and of these 2 were effectively re-treated with rituximab.

**Conclusion:** These results show that treatment with low dose rituximab can be effective as a second line treatment for AIHA. Results were comparable to past studies of low dose rituximab, confirming its safety and efficacy.

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## No Difference between clinical outcome of patients with Intracranial Bleeds on Direct Oral Anticoagulants vs. Warfarin

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### Background

Anticoagulation, using direct oral anticoagulants (DOAC) and warfarin, is used for ischaemic stroke prophylaxis in patients with atrial fibrillation. Bleeding, particularly intracranial bleeds, is a major and sometimes life threatening complication. DOAC have revolutionised anticoagulation, and is currently the preferred anticoagulant of choice. However, the lack of a reversal agent particularly with Factor Xa inhibitors, have led to clinical concern regarding our ability to effectively treat patients with intra-cranial bleed. To further understand this, we performed an audit to understand the outcomes of intracranial bleeding in the DOAC era.

### Methods

A retrospective analysis of all the patients at the Northern Hospital with an intracranial bleed from 2014 – 2018 was conducted. The presentation, management and outcomes of patients on warfarin (n = 31) was compared to those on DOACs (n = 19).

### Results

	DOACs (n=19)	Warfarin (n=31)
Type of DOAC	Rivaroxaban 3 (15.8%) Apixaban 12 (63.2%) Dabigatran: 4 (21.1%)	NA
Age (years)	79.5	78.2
Gender	Females: 9 (47.3%) Males: 10 (52.6%) (n = 19)	Females: 15 (48.4%) Males: 16 (51.6%) (n = 31)
Indication	AF: 18 (94.7%) CVA: 1 (5.3%)	AF: 21 (67.7%) DVT/PE: 6 (19.4%) Mechanical valve: 6 (19.4%) Coronary stents: 3 (9.7%) CVA: 1 (3.2%)
Deaths	6 (31.6%)	12 (38.7%)
Days in Hospital (excluding deaths)	12.1	20.9
Transferred for neurosurgical intervention	2 (10.5%)	6 (19.4%)
Mean Rankin scores (excluding deaths)	Admission: 4 DC: 4 Follow-up: 3	Admission: 4 DC: 3 Follow-up: 3

The proportion of patients that died on DOACs and warfarin was similar. There is no difference in the proportion of patients accepted for neurosurgical intervention between the groups and no significant difference in Rankin scores on discharge and on follow-up. This suggests outcomes are similar between the groups despite a lack of reversal agent for DOACs.

### Conclusion

Patients on DOACs are likely to have similar outcomes to those on warfarin after intracranial haemorrhage. The lack of reversal agent does not appear to impact on the outcomes of these patients.

## Clinical predictors of pulmonary embolism for inpatients: are computed tomography pulmonary angiograms being requested appropriately? – retrospective analysis

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**Background:** Pulmonary embolisms (PE) are a major cause of morbidity and mortality amongst hospital inpatients. The clinical presentations are often heterogeneous and there is significant practice variability with risk of over-requesting Computed Tomography Pulmonary Angiograms (CTPAs). Current clinical predictors for PE, including Wells' criteria and Pulmonary Embolism Rule-out Criteria (PERC), have predominantly focused on outpatient and Emergency Department populations.

**Aim:** To determine the clinical indicators for ordering inpatient CTPAs and the predictors of positive scans for PE.

**Methods:** Three hundred and twelve consecutive inpatient CTPAs (scans performed >24hours after admission) performed in a one year period (2017-2018) were retrospectively reviewed. Variables including baseline characteristics, vital signs and risk factors for venous thromboembolism were extracted.

**Results:** The average age of the inpatients was 67 years, with 46% being male. The average time to CTPA request was 7 days and 36 CTPAs were positive for PE (11.5%). Clinical indicators associated with positive scans were hypoxia (OR 2.45; CI 1.18 – 5.1), recent surgery or immobilisation (OR 2.68; CI 1.24 – 5.76), S1Q3T3 pattern on ECG (OR 7.31; CI 1.86 – 28.83), and right bundle branch block pattern on ECG (OR 5.22; CI 2.02 – 13.45). Tachycardia, tachypnoea, hypotension, fever and malignancy were not significant. The average Wells' Score was 4.7 for positive scans and 2.8 for negative scans with a negative predictive value (NPV) of 95.8% (Table 1). Only 12 of 312 negative scans did not score any PERC criteria with its NPV being 100%.

Table 1: Positive Predictive Values and Negative Predictive Values of Wells' Criteria and PERC rule

	Positive Predictive Value (%)	Negative Predictive Value (%)
Wells' Criteria	27.0 (95%CI 21.97 to 32.69)	95.8 (95% CI 92.73 to 97.55)
PERC	12.0 (95% CI 11.74 to 12.27)	100

**Conclusion:** Inpatient CTPAs appear to be over-requested and can potentially be rationalised based on a combination of clinical predictors such as hypoxia, recent surgery or immobilisation and certain ECG changes as well as Wells criteria and/or PERC rule which have high negative predictive values. Further prospective studies are needed to develop accurate clinical decision tools targeted towards inpatients.

H174

## **The role of exome sequencing in haemophagocytic lymphohistiocytosis (HLH) secondary to infection – a case report**

**Pratheepan Puvanakumar**<sup>1</sup>

<sup>1</sup>*Peter MacCallum Cancer Centre, Melbourne, Australia*

HLH is increasingly recognised in adults secondary to infection, malignancy, and auto-immune disease in immunocompromised patients. However, the role of genomic testing has gained prominence highlighting molecular defects predisposing to disease in absence of conventional triggers. Here, we discuss a case of primary EBV-driven HLH in an immune competent individual and use of whole exome sequencing (WES) to guide future management.

A 30-year-old woman presented to ED after seeing her GP with a prodrome of pharyngitis, fevers and malaise for one week. Given a diagnosis of tonsillitis, the patient was commenced on empirical antimicrobials but showed progressive clinical deterioration with new abdominal pain and jaundice. This precipitated her presentation to hospital with suspected biliary sepsis.

Following presentation, the patient developed multi-organ impairment with acute liver dysfunction, anuric renal failure, overt coagulopathy with pancytopenia. In combination with positive monospot test, a detectable EBV viral load and markedly elevated ferritin, this supported a clinical diagnosis of HLH.

Despite early identification and treatment including rituximab, etoposide and corticosteroids, the patient had a tempestuous course requiring ICU support for haemodynamic instability, coagulopathy and haemofiltration. Despite the end-organ complications, the patient made a remarkable clinical recovery.

Conventional investigations did not yield an underlying pathology to explain her fulminant presentation. WES has been requested with results pending at time of writing. Molecular testing may guide risk of recurrence and need for maintenance treatment including allogeneic stem cell transplantation.

This case illustrates a ubiquitous virus with a common presentation culminating in a cytokine storm in an apparently healthy person. WES may shed novel insights into molecular pathogenesis in these patients and identify promising targetable mutations for therapeutic intervention. Incorporation of exome sequencing should be considered as part of workup for HLH of unclear aetiology.

H175

## **Two cases of morphological red cell abnormalities as a consequence of treatment with Alectinib**

**Sonia Raj**<sup>1</sup>, Allison Black<sup>1</sup>, Tracey Batt<sup>1</sup>, Nick Murphy<sup>1</sup>, Sam Hitchins<sup>1</sup>, Archana Sharma<sup>1</sup>

<sup>1</sup>*Royal Hobart Hospital, Hobart, Australia*

Alectinib is a potent second-generation tyrosine kinase receptor inhibitor which inhibits anaplastic lymphoma kinase (ALK). ALK gene abnormalities result in expression of oncogenic ALK fusion protein which results in increased cellular proliferation in tumours that express ALK fusion protein. Alectinib inhibits ALK phosphorylation and decreases tumour viability.

Alectinib, in the clinical trials have been shown to cause anaemia. There is no comment on the cause of anaemia which occurs in 25% of patients. There has also been no report in the literature of the blood film findings of spherocytes and acanthocytes which we describe in these 2 cases at our institution both of which had normal blood counts and blood films prior to commencement of Alectinib.

### **Case 1:**

77 year old female with Stage IV ALK mutated, signet ring cell lung cancer resulting in liver and bone metastasis. She commenced Alectinib following development of asymptomatic brain metastasis while on crizotinib.

11 months following the use of Alectinib:

**Results:** Hb 132g/L, MCV 92fL, reticulocyte count 36/nL, haptoglobin 0.50 (normal) and blood film showed marked acanthocytosis with spherocytes. Direct Antiglobulin test (DAT) was negative.

### **Case 2:**

71 year old female with ALK mutated metastatic lung adenocarcinoma with metastasis to bone. She achieved complete metabolic response on Crizotinib but switched to Alectinib 600mg bd due to toxicities.

6 months following use of Alectinib.:

**Results:** Hb 94g/L, MCV89 fL, reticulocytes 101/nL (high), haptoglobin 0.10 (low) and blood film showed marked acanthocytes and spherocytes. DAT was negative. Creatinine 109 umol/L and liver function was normal.

Ongoing mild anaemia is possibility due to low grade haemolysis and, spherocytosis with spiculated spherocytes and acanthocytes are an ongoing feature of her blood film.

We report these two cases of red cell abnormalities with Case 2 slightly more severe with DAT negative low grade haemolysis leading to mild anaemia.

These indicate that there are likely to be off target effects of Alectinib on red blood cells which are useful for Haemtologist and Oncologists to be aware of.

## Haematological complications related to copper and Wilson's disease

**Sonia Raj**<sup>1</sup>, Archana Sharma<sup>1</sup>, Sam Hitchins<sup>1</sup>

<sup>1</sup>Royal Hobart Hospital, Hobart, Australia

Wilson's disease is an inherited genetic abnormality that leads to impairment of cellular copper transport. Copper is known to play a role in haematopoiesis. Both deficiency and excess of copper can result in haematological complications. We described one of each case seen at our institution.

### **Case 1**

26 year old female with Wilson's disease was found to be pancytopenic on elective admission.

**Results:** FBE showed haemoglobin 73g/L, MCV 90fl, MCH 26pg, WCC  $1.5 \times 10^9/L$ , neutrophils  $0.7 \times 10^9/L$  and platelet count  $115 \times 10^9/L$ . Bone marrow examination revealed a normocellular marrow with dyserythropoiesis, sequential myeloid maturation and increased megakaryocytes. Erythroid and myeloid precursors showed vacuoles in the cytoplasm. There were prominent iron positive inclusions in the plasma cells in the iron stain.

These bone marrow findings have been classically described in copper deficiency. Zinc therapy prevents copper absorption. The patient was on long term Zinc supplementation (220mg three times a day). Her serum zinc level was 19.2umol/L(high), serum copper 0.1 umol/L(low) and ceruloplasmin 0.02 g/L(low).

**Conclusion:** Overtreatment with zinc induces copper deficiency leading to cytopenias with characteristic bone marrow appearance. Recognition is important as copper deficiency can cause neurological deterioration.

### **Case 2**

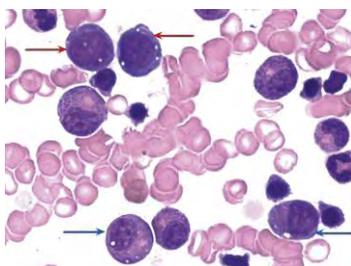
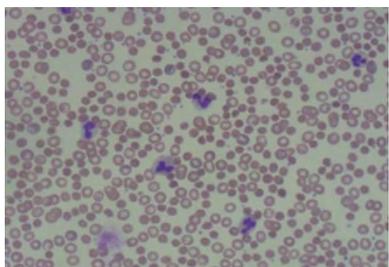
24 year old female with Wilson's disease with fulminant hepatic failure in the setting of non-adherence to copper chelation therapy.

**Results:** Hb 97g/L, MCV 114fl, WCC 28, reticulocyte count 221/nL, platelet count 288. Bilirubin 496umol/L, 369umol/L conjugated, creatinine 199umol/L, AST 262, haptoglobin <0.1g/L. Blood film revealed moderate number of spherocytes, burr cells and polychromasia. (Figure 2).

Direct antiglobulin (DAT) was negative. Serum caeruloplasmin 0.08g/L (low) and serum copper 14.1umol/L (normal)

Features were in keeping with DAT negative spherocytic haemolysis. She underwent plasmapheresis as rapid copper chelation and transfer to a liver transplant facility. She underwent an orthotopic liver transplant and the histopathology of the native liver was consistent with copper toxicity.

**Conclusion:** DAT negative haemolysis is a rare complication of Wilson's disease and copper excess and is an indication for urgent rapid removal of copper or a liver transplant.



## Relationship between mean cell volume and development of arthritis in HFE Haemochromatosis

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### Introduction

HFE Haemochromatosis (HH) is a genetic disorder attributed to homozygous C282Y mutation. Arthritis is a common manifestation of HH. Previous studies have demonstrated that HH subjects exhibit elevated mean cell volume (MCV) and mean cell hemoglobin (MCH) compared with those without HH.[1]

### Aim

To evaluate the relationship between erythrocyte parameters and the presence or absence of arthritis in HH subjects compared to a control group of non-HH subjects with arthritis.

### Method

Consecutive HH subjects aged between 20 and 70 years with C282Y homozygosity were included (n=119). Out of these 66 subjects exhibited arthritis. MCV and MCH values were collected and compared. For comparison, MCV and MCH values were collected from randomly selected non-HH subjects with rheumatoid arthritis (n=100) and osteoarthritis (n=100), consisting of equal numbers of men and women.

### Results

All data are presented as mean  $\pm$  SEM values. Analysis of variance was used to analyse differences between the groups using Brown-Forsyth and Welch's tests. Statistical significance was assigned for  $p < 0.05$ . MCV values were significantly higher in HH subjects exhibiting arthritis (mean MCV  $95 \pm 0.56$  fL) than HH subjects without arthritis (mean MCV  $92.75 \pm 0.50$  fL) with  $p = 0.004$  (Figure 1). HH subjects, with or without arthritis, demonstrated a higher MCV when compared to the two control groups of non HH rheumatoid arthritis (mean MCV  $90.94 \pm 0.57$  fL,  $p < 0.001$ ) and non HH osteoarthritis (mean MCV  $90.12 \pm 0.46$  fL,  $p < 0.001$ ). MCV values of non HH rheumatoid and osteoarthritis groups were similar. There were no statistically significant associations of MCH with any of the groups.

### Conclusion

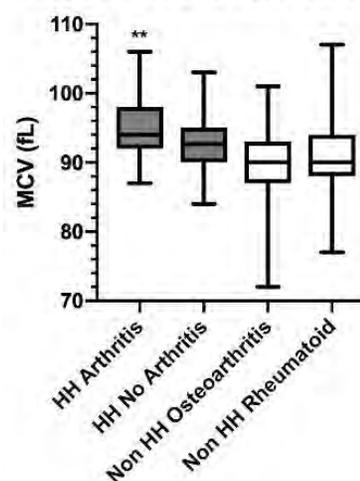
This study has shown a relationship between elevated MCV and development of arthritis in HH subjects. Whether perturbations of erythrocyte size may reflect iron deposition in tissues, including synovium, and thus predispose to arthropathy, warrants further investigation.

### References

[1] Adris et al. Detection of HFE Haemochromatosis in the clinic and community using standard erythrocyte tests. *Blood Cells, Molecules and Diseases* 74 (2019) 18–24.

**Figure 1**

### MCV in HH and non-HH Arthritis



## Acute Q fever and the full blood count: A North Queensland review

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### Background:

Q fever is a zoonotic infection caused by *Coxiella burnetii*, leading to acute or chronic disease with protean clinical manifestations. Presentations can range from flu-like illnesses with varying degrees of pneumonia, hepatitis and other multi-system involvement which are rarely life-threatening. Given the wide variation in presenting features and delayed presentation, diagnosis of acute Q fever can be difficult and is frequently overlooked.

Haematological manifestations of acute Q fever are poorly described. The most common abnormality reported is thrombocytopenia in 25% of patients. Other less commonly reported haematological manifestations of Q fever include haemolytic anaemia, antiphospholipid antibodies and an increased incidence of Non-Hodgkin Lymphoma (NHL).

### Aim:

The aim of this study was to assess all acute Q fever cases at our institution for haematological manifestations and report severity of cytopenias.

### Method:

A retrospective cohort study was conducted for all patients diagnosed with acute Q fever at The Townsville Hospital between 1997 and 2019. Patients were identified by searching laboratory databases for positive Q fever serology.

### Results:

102 patients (75.5% male; median age 52 years) with acute Q fever were identified. 65% developed thrombocytopenia (platelets  $<400 \times 10^9/L$ ) of any grade during their presentation; 6% grade 4, 12% grade 3, 20.5% grade 2 and 24.5% grade 1 (CTCAE definition). The median time to platelet nadir was 1 day following presentation. 72% of patients developed lymphopenia (lymphocyte count  $<1 \times 10^9/L$ ). Other haematological manifestations in our cohort include positive antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) and one case of haemophagocytic lymphohistiocytosis. No cases of NHL were identified.

### Conclusion:

Thrombocytopenia and lymphopenia may be more prevalent in acute Q fever than previously reported. These findings may prompt earlier diagnosis and treatment.

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## **Outcomes of allogeneic bone marrow transplantation for severe aplastic anaemia - a single institution experience**

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**Background:** Allogeneic haematopoietic stem cell transplantation (HSCT) from a HLA matched sibling or matched unrelated donor remains the therapeutic modality of choice for younger, physiologically fit individuals with severe aplastic anaemia (sAA). Data on the optimal conditioning, graft vs host disease (GVHD) prophylaxis and long term outcomes in adult recipients is lacking.

**Aim:** To review the local, single institutional experience of HSCT for sAA with an emphasis on describing long term outcomes

**Method:** A retrospective analysis on HSCT patients for sAA at Westmead Hospital, Sydney between 2012 and 2018.

**Results:** A total of 27 HSCT were performed for sAA in 23 individual patients with a median age of 30 years (range 18-66). Fully HLA matched siblings (40.7%) were the most common donors, followed by 10/10 HLA matched unrelated donors (37%), with the majority donating bone marrow stem cells (70.4%). At a median follow up of 30 months (range 4-82), 2-year overall survival was 96.3%, with no differences seen between different donor types. Grade II-IV acute GVHD occurred in 18.5%, with grade III-IV acute GVHD in 7.4%. Chronic GVHD occurred in 25.9%, with moderate to severe chronic GVHD in 14.8%. Infectious complications were not uncommon, with invasive fungal infections in 11.1% and CMV reactivation requiring treatment in 29.6%. Mixed T-cell chimerism occurred in 48.1% of patients, all of whom underwent conditioning with fludarabine/cyclophosphamide/alemtuzumab. Primary graft failure occurred in 7.4%, however all these recipients were successfully salvaged with a second HSCT at a median of 59 days (range 56-62 days) following their first stem cell infusion.

**Conclusion:** Adults undergoing HSCT for sAA have favourable survival outcomes with tolerable morbidity from GVHD and infectious complications, even when utilising alternative donors. Further investigation is required to determine optimal conditioning and GVHD prophylaxis regimens to minimise toxicity from HSCT in this cohort of patients.

## Recombinant FVIIa use in two Sydney tertiary hospitals over the last decade

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**Background:** Recombinant activated FVIIa (rFVIIa; NovoSeven™) previously enjoyed widespread popularity as an off-label haemostatic agent in the non-haemophiliac critical bleeding setting, as published by the Australian and New Zealand Haemostasis Registry with data spanning 2000-2009.<sup>1</sup>

**Aim:** To review data on rFVIIa use within two tertiary Sydney hospitals between January 2010 - December 2018 inclusive.

**Method:** Retrospective review of demographic data, context of bleeding, rFVIIa administration and laboratory results were collected in a de-identified manner. Outcome measures collected include thromboembolic adverse events and 28 day mortality.

**Results:** Interim results for a single institution over the last decade are currently presented; rVIIa was prescribed in 128 cases for 107 patients over this time period (median age: 60 (Range: 17-87), 65% male). There was a convincing and steep decline in rVIIa use over the decade studied; 24 patients prescribed rVIIa in 2011 with gradual decline to 5 patients prescribed in 2018.

Data presented here spans the entire time period but excludes 2011. Clinical indications included: cardiac surgery (44%), other causes (24%), obstetric haemorrhage (17%), medical bleeding (8%) and trauma (7%). The median dose dispensed was 7mg and 83% of patients received a single dose. 28 day survival was 61%. pH strongly correlated with outcome measures e.g. pH<7.20 correlated to a mortality of 88% whilst pH>7.30 was associated with a mortality of 17%. Overall, thromboembolic events occurred in 14% of patients prescribed rVIIa.

**Conclusion:** We confirm there is declining popularity for rFVIIa use in the non-haemophilia setting over the last decade. Mortality outcomes remain strongly correlated to pH. Thromboembolic complication rates are similar to previous reports.<sup>1</sup>

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**Activation of the platelet P2X7 receptor releases free mitochondria which can initiate vascular inflammation**

**James Wiley**<sup>1</sup>, Joelyn Wong<sup>1</sup>, Harry Teoh<sup>2</sup>, Ben Gu<sup>1</sup>, Malgorzata Krupa<sup>2</sup>, Mastura Monif<sup>3</sup>, Mark Slee<sup>2</sup>

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Human blood contains many circulating microparticles (MP), mainly derived from platelets, which play a role in coagulation but can also mediate inflammatory effects. Our aim was to identify the specific MP causing inflammation. We examined the expression of the P2X7 receptor on human platelets, as much data from monocyte/macrophages links P2X7 with assembly of the NALP3 inflammasome and production of interleukin-1 $\beta$ . Expression of this receptor on platelets and MPs was shown on flow cytometry by binding of P2X7 mAb and confirmed by Western analysis of platelet and MP lysates. We then studied the ability of gel-filtered platelets (GFP) to form a P2X7 mediated pore since pore opening and K<sup>+</sup> efflux is required for NALP3 assembly, but our results showed that P2X7 is not coupled to pore opening in platelets. Could P2X7 link to NALP3 by a different mechanism?

Inflammation can also be caused by release of superoxide anion from mitochondria, so we looked for this organelle in ambient medium of platelet-rich plasma (PRP) and GFP by staining with MitoTracker dyes. A single well-defined population of mitochondria was evident on two-colour flow cytometry. The number of MitoTracker-positive mitochondria was measured in platelet-free plasma of 15 normal donors and counts ranged between 0.1 and 11.3 x10<sup>6</sup>/mL with a skewed distribution. In human platelets, we measured the additional release of mitochondria after incubation of PRP with the selective P2X7 agonist BzATP. The release of mitochondria increased with increasing BzATP concentration between 1.0 and 500  $\mu$ M with no sign of a plateau. In contrast PRP with genetic loss of P2X7 function showed complete absence of any mitochondrial release after incubation with BzATP. Finally, cryo-electron microscopy images showed that mitochondria released from platelets by BzATP were free while those released by thrombin were predominately enclosed within a vesicle. Our data suggest that the inflammatory effects of platelets is initiated by their P2X7 receptor causing release of free mitochondria and these organelles may cause inflammation in the vascular wall.

## **Retrospective review of patients with newly diagnosed portal vein thrombosis**

**Ghassan Zammar**<sup>1</sup>, Elora Bartlett<sup>1</sup>, Stephanie P'Ng<sup>1</sup>, Dominic Pepperell<sup>1</sup>

<sup>1</sup>*Fiona Stanley Hospital, Perth, Australia*

### **Aim:**

To assess the risk factors, management and outcomes of patients with newly diagnosed portal vein thrombosis (PVT) at a tertiary hospital in Western Australia.

### **Method:**

Patients admitted between January 2017 to April 2019 with a new diagnosis of PVT were retrospectively reviewed. Seventy-three patients were identified. Electronic medical records were reviewed to identify risk factors for PVT, their management and outcomes.

### **Result:**

Of the 73 patients identified (mean age 62 years, range 22-90 years), 28 had liver disease, 27 had a solid organ malignancy and 30 presented with an acute inflammatory condition or sepsis. Seven patients (9%) had no provoking factors for portal vein thrombosis. Twenty patients died during admission or within 3 months following admission.

Fifty (68%) patients were anticoagulated (average duration 5.9 months) with 13 patients requiring longterm treatment. The most common initial anticoagulant used was Enoxaparin (72%) followed by Heparin (22%) and DOAC (10%). For ongoing treatment over 1 month, warfarin was preferred (48%) followed by Enoxaparin (22%), Apixaban (18%) and Rivaroxiban (12%).

Of the 50 people treated, 38 were followed up for resolution of PVT. Of these, 63% patients achieved recanalisation within 6 months, 37% patients had ongoing occlusive thrombus despite active anticoagulation, with 31% patients developing cavernous transformation.

Twenty-one patients of the patient treated were followed up by the haematology department for assessment, with 8 patients found to have an inherited or acquired thrombophilia.

### **Conclusion:**

This study demonstrates the clinical heterogeneity of patients with newly diagnosed PVT. Almost all patients had a significant identifiable risk factor. Anticoagulant strategies varied widely, with evidence of successful recanalisation within 6 months in 63% of those assessed. Conversely 27% of the overall population died within 3 months of diagnosis. This pilot data will inform future studies of optimal treatment of PVT.

## **Paraneoplastic leukaemoid reaction in metastatic melanoma**

**Jessie Zhao**<sup>1</sup>, Song Chen<sup>1</sup>, Craig Underhill<sup>2</sup>, Mark Levin<sup>1</sup>

<sup>1</sup>Dorevitch Pathology, Heidelberg, Australia, <sup>2</sup>Border Medical Oncology, Albury, Australia

### **Background**

Leukaemoid reactions, usually defined as a persistent leucocytosis greater than  $50 \times 10^9/L$ , have been described in association with various solid malignancies. Thought to be driven by paraneoplastic secretion of granulocyte-colony stimulating factor, they often portend a poor prognosis[1]. We present a case of a paraneoplastic leukaemoid reaction in metastatic melanoma, an extremely rare phenomenon[2].

### **Case Report**

A 54-year-old woman with metastatic melanoma treated with checkpoint inhibitors presented with a persistent neutrophilic leucocytosis exceeding  $80 \times 10^9/L$ . The leucocytosis was not thought to be attributable to concurrent infection or offending medications. Peripheral blood smear showed primarily mature neutrophils, with no basophilia or blasts. Bone marrow biopsy showed a markedly hypercellular marrow with marked granulocytic hyperplasia and no excess of blasts; there was no evidence of tumour infiltration. Molecular testing for BCR-ABL1 and JAK2 V617F were negative. A presumptive diagnosis of paraneoplastic leukaemoid reaction was made.

### **Discussion**

Whilst paraneoplastic leukaemoid reactions are rare in malignant melanoma, they should be considered in patients with persistent marked leucocytosis.

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## **Haematologists' opinion on antimicrobial prophylaxis in patients with AML on supportive care**

**Roya Arabi<sup>1,2</sup>**, Alhossain Khalafallah<sup>2</sup>, Muhajir Bawa Mohamed<sup>2</sup>

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**Aim:** Patients with acute myeloid leukaemia receive supportive care when they are not fit to tolerate intensive chemotherapy or in relapsed-refractory AML after failing specific treatment options. We aimed to study the prescribing pattern of anti-infective measures by haematologists in Australia and New Zealand in patients with Acute Myeloid Leukaemia (AML) who are only receiving supportive care.

**Method:** A link for an anonymous online survey was distributed to Haematologists via the Australasian Leukaemia and Lymphoma Group (ALLG).

**Results:** Seventy-five haematologists participated in our survey. In situations where patients with AML only receive supportive care, the majority of haematologists do not consider prophylaxis for *Pneumocystis jirovecii* pneumonia (82%) and 71% do not prescribe antibiotic to prevent bacterial infection.

Antiviral medication to prevent reactivation of Herpes Simplex or Varicella Zoster viruses was considered by nearly half of the haematologists (51.5%) for this group of patients with AML. In this setting, while 28% of haematologists usually prescribe anti-fungal agents, 6% never prescribe it; 66% of participants prescribe it occasionally.

**Conclusion:** For patients with AML who receive supportive care only, the pattern of prophylactic antimicrobial prescription is widely varying among haematologists and much lower than in AML intensive chemotherapy group of patients. Clinical trials are required to show whether antimicrobials will help to reduce infection related morbidity and mortality in patients with AML who are not fit to receive intensive chemotherapy.

## **Use of Liposomal Amphotericin B in haematological patients with invasive fungal infection**

Briony Shaw<sup>1</sup>, **Luke Cardamone**<sup>1</sup>, Kylie Horne<sup>1</sup>, Claire Dendle<sup>1</sup>, Stephen Opat<sup>1</sup>, Benjamin Rogers<sup>1</sup>  
<sup>1</sup>*Monash Health, Clayton, Australia*

### **Aim**

Timely identification and treatment of invasive fungal infections (IFIs) in immunosuppressed patients with haematological malignancies is associated with improved survival outcomes, but often involves empirical use of costly, potent antifungal agents without proven disease. We assess benefits of Liposomal Amphotericin-B (LAmB) use and identify parameters to predict improved outcomes from its use in our large metropolitan Victorian catchment.

### **Methods**

Through retrospective analysis of pharmacy dispensation records across 2013 to 2016, 24 patients were identified. Following collection of haematological history including neoplastic diagnosis, lines of therapy and immunosuppressive complications, the progress of admissions in which LAmB was utilised was examined. Particular comparison was made to the use and clinical efficacy of the azole class, focusing on acute morbidity and mortality.

### **Results**

21 patients were included in the final analysis. 9 patients died acutely during this index admission to hospital. IFI was proven in only 3 of these cases, but clinically probable in 17. Likelihood of fungal infection was derived from characteristic bronchoscopic, tissue or radiological findings and divided into proven, probable and possible IFI. Three patients had been on azole prophylaxis prior to the admission. Six cases had documented indications for LAmB as 'suspected progression or resistance to an azole', where azole therapy had proven ineffective.

### **Conclusions**

In our small population, there was a high rate of mortality during admissions where LAmB was utilised, especially in cases where fungal infections progressed beyond Azole class treatments. Clear difficulties in the accurate diagnosis and effective treatment of the immunosuppressed patient were demonstrated. Invasive and non-specific investigations in combination with rapidly progressing critical illness resulted in broad, aggressive antimicrobial use. This pilot study indicates the need for more detailed analyses of the incidence and risk factors associated with suspected IFIs in haematological malignancy.

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## **Educational booklets for Aboriginal and Torres Strait Islander haematology patients.**

**Simone Champion**<sup>1</sup>

<sup>1</sup>*Queensland Health Primary Health Care Team, Longreach, Australia*

**Aim:** This poster presentation showcases educational booklets aimed to meet the comprehension needs of patients, in particular those whom identify as Aboriginal or Torres strait Islanders, undergoing diagnosis and treatments for haematological malignancies.

**Method:** This study was a qualitative study based on patient and carers stories as well as feedback from haematology staff, which identified a significant need for pictorial educational resources to combat vast language diversities within patient groups in the Northern Territory.

**Results:** Significant language diversity exists within Australian Indigenous languages as well as the wider multi - cultural population within the Northern Territory. Low literacy and in particular health literacy within mainstream society, is also an additional barrier identified when delivering health care. Transcending this diversity was met by developing pictorial booklets outlining diagnostics testings; scans and processes as well as treatments and the management of toxicities and side effects. Additional booklets include illustrations on auto and allograft stem cell transplants.

**Conclusion:** The booklets are in early stages of circulation within patient cohorts, thus this study has not been able to formally evaluate their impact. However earlier draft versions have meet favourably with both patients/carers and health care providers. They have shown to likely reduce fear of the unknown and promote patient engagement and rapport with staff. This study hopes to gain support to develop these tools further into digital applications for mobile phones; Ipads and other devices with relevant audio languages as voice overs. Further evaluations of these educational resources is planned for the future.

H193

## **Suitability of current staining quality across Western Australia for Cellavision DM9600 blood film review**

**Drew Craig**<sup>1</sup>, Aaron Osborn<sup>1</sup>, John Ivey<sup>1</sup>, Darryn Harris<sup>1</sup>, Jason Boothman<sup>1</sup>, Fauzan Al-Hamid<sup>1</sup>, Even Leow<sup>1</sup>, Matthew Wright<sup>1</sup>

<sup>1</sup>*Pathwest LMWA, Perth, Australia*

### **Aim:**

The Cellavision™ DM9600 was trialled at PathWest Fiona Stanley Hospital (FSH) in March 2019 to determine the benefit to the organisation in review of blood films referred to reference sites from regional laboratories. The aim was to gather information in a number of areas including the stain quality across the organisation and the feasibility of utilising a digital solution to eliminate the need to transport physical slides back to reference sites, resulting in improved turn-around for patient results.

### **Method:**

All 27 sites submitted 2 x stained blood films that had been made at FSH and sent unstained to each site. One film was fixed in methanol and one unfixed prior to staining. Each site outside FSH, QEII and RPH use a Siemens Hematek™ flat-bed staining machine while the three large sites have a Sysmex SP-10™ staining machine as part of a track. All submitted blood films were run on the Cellavision™ DM9600 SmearChecker program to determine the quality of the stain intensity and stain colour. The Cellavision™ DM9600 requires all blood films to meet a minimum smear and stain quality to be acceptable for digital analysis.

### **Result:**

Stained blood films returned from all 27 sites checked on the Cellavision™ DM9600 SmearChecker program show acceptable stain colour and stain intensity for digital analysis. Statistical analysis of Cellavision™ DM9600 SmearChecker results from blood films from all sites shows that the variation in smear colour and intensity had no statistical effect on the white cell differential count.

### **Conclusion:**

Stained blood films returned from all 27 PathWest sites were acceptable for analysis on the Cellavision™ DM9600. Current Haematology staining methods used across the organisation are of adequate standard to support the introduction of a Cellavision™ DM9600 without the need for changes in methodology.

**Post-marketing safety study to evaluate the occurrence of aseptic meningitis syndrome (AMS) in an adult population ( $\geq 18$  years) treated with doses of  $\geq 1$ g/kg INTRAGAM10®**

**Philip Crispin**<sup>1</sup>, Lynette Kiers<sup>2</sup>, Stephen Reddel<sup>3</sup>, Arman Sabet<sup>4</sup>, Ami Patel<sup>5</sup>, John-Philip Lawo<sup>6</sup>, Annmarie Pendleton<sup>7</sup>, Ellen Bonagua<sup>5</sup>, Paul Manwaring<sup>8</sup>

<sup>1</sup>Canberra Hospital, Canberra, Australia, <sup>2</sup>Royal Melbourne Hospital, Parkville, Australia, <sup>3</sup>Concord Hospital, Concord, Australia, <sup>4</sup>Gold Coast University Hospital, Southport, Australia, <sup>5</sup>CSL Behring, King of Prussia, USA, <sup>6</sup>CSL Behring, Marburg, Germany, <sup>7</sup>CSL Behring, Broadmeadows, Australia, <sup>8</sup>CSL Limited, Parkville, Australia

On 01Mar2017 INTRAGAM10 (10%IVIg) replaced INTRAGAM P (6%IVIg) in Australia. As part of a post-marketing regulatory commitment, CSL-Behring conducted a study to determine incidence of AMS, migraine and severe headache with INTRAGAM10.

The prospective cohort study was conducted in adult patients treated with INTRAGAM10 at  $\geq 1$ g/kg dose. Patients were required to report occurrence of any adverse event (AE) during and within 7 days of infusion.

From March2017 to July2018 39 patients were enrolled and 38 patients completed the study. One patient withdrew due to the occurrence of a rash. Clinical indications for INTRAGAM10 use were primarily neurologic and haematologic. Most patients (30/39; 76.9%) had not previously received intravenous immunoglobulin (IVIg). Median reported dose was 2g/kg with a median maximum infusion rate of 4mL/min.

Twenty-four patients (61.5%) experienced AEs within the 7-day period; 79.1% were mild/moderate, headache was the most common AE (11 patients (28.2%)). Three patients (7.7%) experienced severe headache related to the infusion that resolved 7hrs, 3 days and 12 days following onset. Confounding factors were present in two of the three patients: pre-existing headache associated with a lumbar puncture undertaken prior to initiation of INTRAGAM10 and in the second patient a history of migraine. Per investigator assessments no confirmed, or probable cases of AMS were reported.

The present study complements existing registration studies and post authorisation safety data and adds to the body of data about AMS with IVIg products. INTRAGAM10 was typically well-tolerated and has a safety profile consistent with IVIg class effects.

## **Iron deficiency anaemia and iron deficiency in pregnancy in women with severe mental illness**

**Rachel Currie**<sup>1</sup>, Thinh Nguyen<sup>1</sup>, Nathaniel Khoo<sup>1</sup>, Jacqueline Frayne<sup>1,2</sup>

<sup>1</sup>University of Western Australia, Crawley, Australia, <sup>2</sup>King Edward Memorial Hospital, Subiaco, Australia

### **Aim**

Iron deficiency anaemia (IDA) affects around 25% of pregnant women in Australia and has been associated with increased rates of postnatal depression. The prevalence of IDA in pregnant women with severe mental illness (SMI) is unknown. We aimed to determine prevalence rates and risk factors for anaemia and iron deficiency (ID) in women with SMI and report on treatment issues in this population.

### **Method**

Retrospective analysis of 397 live singleton births from women with SMI who attended the Childbirth and Mental Illness Antenatal Clinic at King Edward Memorial Hospital in Western Australia, between 2008 and 2016 were analysed. WHO anaemia criteria were used.

### **Result**

Anaemia prevalence in this cohort was 43.1% overall; 33% antenatally and 22.6% immediately postpartum. ID prevalence was 69.3%. Predictors for anaemia using logistic regression were parity  $\geq 3$  aOR 2.43 (95%CI 1.19 - 4.27) and schizophrenia diagnosis aOR 2.26 (95%CI 1.2 - 4.92). Predictors of ID were schizophrenia OR 1.92 (95%CI 1.0 - 3.80), low socioeconomic status OR 3.53 (95%CI 1.22 - 10.16) and age  $\geq 25$  OR 2.25 (95%CI 1.06 - 4.79). Postpartum haemorrhage (PPH) in this cohort was significantly higher than the Western Australian population (23.9% and 18.9%;  $p=0.010$ ). Oral iron replacement resulted in only 24.8% corrected antenatally.

### **Conclusion**

There is an increased prevalence of anaemia, ID and PPH in pregnant women with SMI. Antenatal correction of anaemia may improve with early identification and iron infusion if oral iron replacement is deemed inadequate.

## **Opportunity for improved palliative care practice in haematology units**

**Hannah George**<sup>1</sup>, Elango Subramonia Pillai<sup>1</sup>, Cameron Curley<sup>1</sup>, Kirk Morris<sup>1</sup>, Nicholas Weber<sup>1</sup>, Waqas Bokhari<sup>1</sup>, Jason Butler<sup>1</sup>, Glen Kennedy<sup>1</sup>

<sup>1</sup>Royal Brisbane and Women's Hospital, Herston, Australia

### **Aim**

We aimed to determine the outcome of patients with haematological malignancies admitted to our unit who underwent multiple medical emergency resuscitation team (MERT) calls to ascertain the number of patients with advanced malignancy potentially experiencing unnecessary medical intervention.

### **Methods**

We retrospectively reviewed the medical records of all haematology and bone marrow transplant patients admitted at RBWH between January 2016 to March 2019 who had two or more MERT calls in any 24-hour period. Patient demographics, disease diagnosis, pre-existing acute resuscitation plan (ARP) and post-MERT outcome data were collected and analysed descriptively.

### **Results**

In total, 81 individual patients had had multiple MERT calls during the time frame under review. Median age was 62yrs (range 20 – 90yrs), with 53% male. Primary underlying disease included AML in 38%, NHL in 26%, ALL in 4%, other lymphoproliferative disorders in 15%, MPN in 5%, MDS in 6%, and other diagnoses in 6%. Furthermore, 15 patients (18%) were being treated for post-transplant relapsed disease. Of the entire cohort, only 28% had a documented ARP and 5% previously referred to palliative care prior to initial MERT calls. Post MERT calls, a further 12% of patients (n=10) were subsequently referred to palliative care within 72hrs, including n=7 patients (9%) within 24hrs of initial MERT. Overall 48% of patients (n=39) were admitted to ICU post-MERT, with 33% of ICU-admitted patients subsequently not surviving hospitalization post ICU admission.

### **Conclusion:**

Our experience suggests that a significant proportion of patients with haematological malignancies admitted to hospital potentially undertake unnecessary medical interventions, with some actively palliated patients undertaking acute resuscitation, and 12% of patients rapidly palliated after an initial MERT. Overall only a minority of patients had a documented ARP prior to their hospital admission.

## Understanding the financial impact of cancer among Australian patients: Expanding what's in a COST

**Tracy King**<sup>4</sup>, Kate White<sup>1,2</sup>, Richard De Abreu Lourenco<sup>3</sup>, Patsy Kenny<sup>3</sup>, Lucy Lehane<sup>1</sup>

<sup>1</sup>Cancer Nursing Research Unit, The University of Sydney, Australia, <sup>2</sup>Sydney Local Health District, Australia,

<sup>3</sup>Centre for Health Economics Research and Evaluation, University of Technology Sydney, Australia,

<sup>4</sup>Institute of Haematology, Royal Prince Alfred Hospital, Sydney, Australia

**Aim:** 1) To examine cancer patients' experience of the financial impact of cancer, influences on decision making and strategies used to meet costs. 2) To examine the appropriateness of the COST instrument for Australia.

**Method:** In-depth interviews were conducted with 24 participants, 15 with haematological malignancy. Participants completed the COST questionnaire and commented on its relevance to their experience. Interview data were analysed thematically.

**Results:** Four themes were identified from the data: 1) *a ripple effect* on many aspects of daily life, extending to family income, work, and social life; 2) *influences on decision making* regarding cancer treatment, finances and family; 3) *shifting financial capability* as treatment periods extended and resources were depleted, often made worse by the challenges of negotiating income support through agencies not geared towards the long-term treatment effects of cancer; and, 4) *attitudes and expectation* where discussion of financial impacts was difficult for some, and none of the participants expected to be fully supported for all costs.

The majority of participants found the COST instrument easy to complete and relevant to their experience. Based on feedback, four items were added to the questionnaire: 1) I worry about my family's financial stability; 2) I am worried about the financial impact of my cancer and cancer treatment on my family's lifestyle; 3) I am aware of the financial assistance services available for people receiving cancer treatment; 4) I know how to access income support (e.g. income insurance, government benefits) if I need it.

**Conclusion:** The lives of patients and families were affected as a consequence of the financial impacts of cancer and treatment. The COST instrument, with the addition of 4 items, is potentially appropriate for use in the Australian context. Phase 2 of this project validating the extended instrument for use in Australia is underway.

**Post marketing safety data for Intragam 10 (10% intravenous immunoglobulin) following 2 years of clinical use in Australia**

**Nadia La Greca**<sup>1</sup>, Michael Araco<sup>2</sup>, Jyothirmayi Koppella<sup>3</sup>, Ellen Bonagua<sup>3</sup>, Brenda Cruz<sup>2</sup>, Giulio Barrese<sup>1</sup>, Sourabh Malandkar<sup>2</sup>

<sup>1</sup>CSL Behring Docklands, Melbourne, Australia, <sup>2</sup>CSL Limited, Parkville, Australia, <sup>3</sup>CSL Limited, King of Prussia, USA

Intragam 10, 10% intravenous immunoglobulin (IVIg) was introduced for clinical use in Australia in March 2017 to replace the predecessor product Intragam P (6% IVIg, available in Australia for 18 years). Previously we reported the adverse event (AE) rate for Intragam 10 following the first twelve months of distribution; 27.07 cases /10,000 infusions and 15.46 cases /10,000 infusions, during the first and fourth quarter respectively. This spontaneous AE rate was higher than observed with Intragam P (8.55-13.09 cases /10,000 infusions in the 12 months preceding Intragam 10 launch). Heightened vigilance is expected with newly marketed products and is typically associated with increased reporting. To assess if the AE rate for Intragam 10 had changed we conducted further analysis 2 years following launch.

A review was conducted of spontaneous AE reports following treatment with Intragam 10, recorded in the CSL Behring Global Safety Database. The analysis compared AE reports in the second year period since launch with previous 12 month data. The AE reporting rate was calculated over a 12 month period per 10,000 infusions using an estimated standard dose of 30g IVIg in a 75kg patient (0.4g/kg body weight).

In the first and second year, approximately 3 million grams and 3.2 million grams of Intragam 10 were distributed, respectively. The overall AE reporting rate for Intragam 10 had declined to 11.69 cases /10,000 infusions in the second year, which is comparable to that seen with Intragam P in the 12 months preceding Intragam 10 launch. Commonly reported AEs for Intragam 10 (Chills, Headache, Pyrexia, Dyspnoea, Rash) and Intragam P (Hypersensitivity, Rash, Headache, Pyrexia, Pruritus) were reflective of the known class effects of IVIGs.

Based on pharmacovigilance data, after a period of expected heightened vigilance, the AE reporting rate of Intragam 10 decreased to a rate comparable with Intragam P.

## **Safety from bag to vein: infusion management in a tertiary cancer centre**

**Jeanie Misko**<sup>1</sup>, Breigh Ridley<sup>1</sup>, Amy Finch<sup>2</sup>

<sup>1</sup>Fiona Stanley Hospital, Murdoch, Australia, <sup>2</sup>Becton Dickinson, Herdsman, Australia

### **Aim**

Errors involving chemotherapy and vascular access management (VAM) may cause serious patient harm. Dose error reduction software (DERS) safety limits are installed on all intravenous infusion devices, however average DERS compliance within the haematology/oncology profile was 8.5% lower than other adult areas within the hospital. To improve DERS and VAM compliance, a clinical review was undertaken.

### **Method**

A multidisciplinary working group of pharmacists, nurses and doctors with vendor representation was established to review medication entries in the DERS and coordinate an electronic survey assessing clinicians' satisfaction with the current profiles. SurveyMonkey was used to collect responses and tabulate data. DERS compliance was measured using vendor supplied Continuous Quality Improvement Software. A prospective observational audit was conducted to review VAM and compliance of running infusions with the corresponding prescription and organisational guidelines.

### **Result**

The working group made changes to 71 drugs, predominantly to realign with updated practice recommendations and reduce nuisance alerts. The group reviewed 150 patients with 59 infusions running via 57 infusion pumps during the audit. Most pumps (56, 98.2%) were in the correct profile with 44 of 46 DERS infusions (95.7%) reflecting the hanging bag. One hundred vascular access devices were observed with use of the preferred insertion site exceeding national benchmarking data, however 83% did not comply with local labelling requirements. Over the audit period, average compliance with DERS increased from 77.9% to 89.1%,  $p=0.17$ . Fifty eight staff responded across both surveys with the very satisfied rating increasing from 13.3% to 57.1%,  $p<0.005$ .

### **Conclusion**

A review group to improve the haematology/oncology DERS profile was successful in improving compliance. There was good compliance for vascular access insertion sites; however improvement in site and line labelling is required. Infusions running outside of DERS have been addressed by amendment of the DERS profile and feedback to clinical areas.

## **Providing flexible online education to improve the outcomes in haematological cancers**

Kyleigh Smith<sup>1</sup>, Andrew Roberts<sup>1,2,3,7</sup>, Michelle Barrett<sup>1</sup>, Yvonne Panek-Hudson<sup>2,3</sup>, Meredith Layton<sup>1</sup>, Hannah Cross<sup>1</sup>, Mary Stewart<sup>1</sup>, Andrew Grigg<sup>4</sup>, Chun Fong<sup>4</sup>, Eliza Hawkes<sup>4</sup>, Joel Wight<sup>4</sup>, Hang Quach<sup>5</sup>, Trisha Soosay Raj<sup>6</sup>

<sup>1</sup>Victorian Comprehensive Cancer Centre, Melbourne, Australia, <sup>2</sup>The Royal Melbourne Hospital, Melbourne, Australia, <sup>3</sup>Peter MacCallum Cancer Centre, Melbourne, Australia, <sup>4</sup>Austin Hospital, Melbourne, Australia, <sup>5</sup>St Vincent's Hospital, Melbourne, Australia, <sup>6</sup>Royal Children's Hospital, Melbourne, Australia, <sup>7</sup>Walter and Eliza Hall Institute, Melbourne, Australia

**Background:** A needs analysis of the haematology landscape was conducted across the ten clinical, education and research institutes of the Victorian Comprehensive Cancer Centre (VCCC)<sup>1</sup> in 2016. This provided the evidence base for the development of strategic activities in cancer research and education and training. A key educational need identified was for the collaborative development of online educational resources, especially for joining clinicians in a service role.

**Aim:** To develop a high quality, online sustainable resource to support the haematology training program now and into the future. This would also facilitate accessibility for the haematological oncology workforce and efficiencies for clinical educators. The program includes the production of a suite of online haematology case-based discussions in Lymphoma, Myeloma, Leukaemia and Chronic Lymphocytic Leukaemia.

**Method:** The VCCC identified existing high-quality clinical education programs, in order to record and share them across the alliance. During this consultative stage we not only identified pre-existing programming but also new and emergent educational ideas that would best support the haematological workforce.

**Result:** A first phase consultation was conducted across the VCCC haematology divisions to understand the state of play and elucidate key needs. This needs-based approach provided the evidence base for the development of strategic activities in cancer research, education and training in the subsequent phases of the program. An audit was completed in 2018 of haematology education and training programming across the VCCC partners. It was identified that the Austin Hospital Haematology Department was undergoing a tutorial series which would form the pilot for the development of the online educational program. These results will be reported.

**Conclusion:** The VCCC have utilised pre-existing educational programming to develop an online, flexible and sustainable online learning program. This will enable clinical educators to facilitate a deeper understanding amongst their junior clinicians. The presentation will explore the educational need, process for information gathering and product developed.

## **Establishing a Biobank in a private hospital setting: successes and lessons learnt**

**Costas Yannakou**<sup>1,2,3</sup>, Miles Prince<sup>1,2,3</sup>, Nicole Brooks<sup>1</sup>, Hayley Johnston<sup>1</sup>, Caroline Le<sup>1</sup>, Lucy Fox<sup>4,5</sup>

<sup>1</sup>Department of Molecular Oncology and Cancer Immunology (MOCI), Epworth HealthCare, Richmond, Australia, <sup>2</sup>Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Australia, <sup>3</sup>Department of Haematology, Peter MacCallum Cancer Centre, Melbourne, Australia, <sup>4</sup>Peter MacCallum Cancer Centre, Melbourne, Australia, <sup>5</sup>Epworth HealthCare, Richmond, Australia

**Aim:** Biobanks have a central role in unravelling the biology that drives malignant disease. In October 2018 we established the Molecular Oncology and Cancer Immunology (MOCI) Biobank Study at Epworth HealthCare. The purpose of this study is to create and maintain a repository for the storage of biospecimens and clinical information from patients with a variety of cancer types. This resource will drive investigator-initiated research focused on the prognostication, treatment and monitoring of cancer in the pursuit of increasingly personalised medicine.

**Method:** This is a single site, multi-centre study to be opened across Epworth HealthCare's 11 Victorian campuses. Ethics approval and governance authorisation was attained after the development of a governance framework and a quality management system. These encompassed standard operating procedures, policies governing both laboratory and hospital activities, funding arrangements, physical and digital security and material release and transfer agreements. The first phase of implementation involved two Epworth sites and focused on optimising study enrolment and logistical procedures.

**Results:** Ninety-two potential participants were approached within the first 8 months of the study. Of these, 9 (10%) declined to participate. Average accrual has been ~10 patients per month. The MOCI Biobank study currently holds over 1,000 frozen aliquots stored at -80°C from across 9 cancer types, primarily haematological malignancies (Fig 1 and 2). Biospecimen types collected thus far include whole blood, plasma, serum, bone marrow and tumour tissue.

**Conclusion:** Establishing a Biobank in the private hospital setting requires substantial infrastructural support from all units visited by the participant. Appropriate management of human resources and interdepartmental communication have proven to be vital to the success of the MOCI Biobank. Of note, the initial stages of implementation involved education of the research team, doctor's consulting room staff, hospital wards and service providers (radiology, operating theatre, pathology). An independent study team to coordinate Biobank participant visits is highly recommended.

O110

## **Simulation for transfusion medicine education**

**Katerina Pavenski**<sup>1</sup>

<sup>1</sup>*St Michael's Hospital, Toronto, Canada*

Transfusion knowledge is frequently assessed as sub-optimal in medical trainees. This could be a result of insufficient or ineffective transfusion teaching. Most of transfusion education is still imparted through lectures; however, digital platforms such as webcasts are also gaining in popularity. On the other hand, interactive digital content is still a rarity within transfusion education. For other areas of healthcare, simulations have become widely used as an enhanced training modality to augment traditional educational methods. This technique replicates real-world experiences in a fully interactive manner to achieve an educational goal. Simulations allow trainees to learn content, as well as technical and non-technical skills, in a risk-free environment. Within transfusion medicine, simulations may be used for focused task-training for procedural skills, multi-disciplinary team training using high-fidelity manikins, and communication training utilizing standardized patients. It is uniquely suited to teach about high-stress, high stakes and uncommon scenarios, such as massive hemorrhage. However, for successful implementation, simulations require investment of money, time, resources and appropriate training. An alternative approach may be to utilize immersive digital technologies, such as serious gaming and virtual reality. These digital tools can be portable and adaptable to different learning needs and may be of special value to trainees who are remote or in low resource settings. As emerging technologies become more accessible, they will transform the future of medical training.

O111

**Safety and efficacy of iron therapy in treating anaemia in critically ill adults and effect on RBC transfusion**

**Ed Litton**<sup>1</sup>

*<sup>1</sup>The University of Western Australia, Perth, Australia*

Evidence is accumulating that intravenous iron is biologically active in critical illness, in spite of the effects of acute inflammation. Although there has been a focus on reduction in red blood cell transfusion, other benefits, including decreasing the occurrence and severity of anaemia may also be beneficial in improving functional recovery after admission to the intensive care unit. These benefits need to be balanced against the potential risk of infection and oxidative stress in a vulnerable patient population.

O115

## **Transfusion associated necrotizing enterocolitis in neonates**

**Sanjay Patole**<sup>1</sup>

<sup>1</sup>*Neonatal Directorate, Kem Hospital for Women, Perth, Australia*

Survival of extremely preterm infants (Gestation <28 weeks) has improved following advances in neonatal intensive care. Nearly 90% of such infants receive red blood cell transfusions (RBCT) for anemia of prematurity. Necrotising enterocolitis (NEC  $\geq$  Stage II) is a potentially disastrous illness with significant mortality (25%) and morbidity including long-term neurodevelopmental impairment, in preterm infants. The outcomes (mortality 45% to 100%) are worse especially in extremely preterm infants with full thickness necrosis of the gut due to NEC.

First reported in late 1980s, NEC associated with transfusion for anemia of prematurity (TANEC: Development of NEC  $\geq$  Stage II within 48-72 hr after RBCT) has become a research priority given the mortality and morbidity associated with the condition and frequency of RBCT in high-risk preterm infants. Developing evidence based guidelines for RBCT for anemia of prematurity (Hb threshold) is difficult as there are no reliable early markers for tissue hypoxia. Controversies continue regarding not only the pathogenesis and management of TANEC, but also about the very existence of such an entity.

Current understanding of the pathogenesis, strategies for prevention and treatment of TANEC in preterm infants, and opportunities for research in this field are discussed.

O116

**Fetal neonatal alloimmune thrombocytopenia: Evidence-based care in 2019**

**Katerina Pavenski**<sup>1</sup>

*<sup>1</sup>St Michael's Hospital, Toronto, Canada*

Fetal neonatal alloimmune thrombocytopenia (FNAIT) results from maternal IgG alloantibodies to human platelet antigens crossing the placenta and clearing fetal platelets. FNAIT complicates 1 in 1000 births and may lead to serious bleeding complications including intracranial haemorrhage. Using a case-based approach, I will review the recently published international evidence-based recommendations on antenatal and postnatal management of FNAIT. I will also critically appraise these recommendations and briefly discuss future research priorities.

O117

## **Blood Service Plasma Strategy**

### **Stuart Chesneau<sup>1</sup>**

<sup>1</sup>*Australian Red Cross Blood Service*

Australian demand for intravenous immunoglobulin (IVIg) has increased on average by 10% or more per annum for the last decade. The international demand for IVIg has not been as pronounced but has been material (+6-7%) and is projected to continue in practically all regions. China has the potential to really impact market conditions and has increased its consumption of immunoglobulin products by 12% in each of the last two years.

This broad-scale growth is constraining the international market and leads to a number of questions around product availability, product costs and appropriate product usage.

Commercial companies are expanding rapidly to attempt to meet the growing need but many national services are also looking to transform their supply chains to increase the volume of locally sourced plasma at a price that presents a viable option to their respective governments to meet the clinical demand whilst also balancing risk and budgets.

The Red Cross Blood Service has similarly reviewed its end-to-end operations with a view to increasing domestic plasma supply and is on a journey of transformative change from front-end digital enablement to back-end automation.

O118

## **Intravenous immunoglobulin criteria version 3**

**Philip Crispin**<sup>1</sup>

<sup>1</sup>*Canberra Hospital, Canberra, Australia*

Intravenous immunoglobulin (IVIg) is widely used as immune replacement and immune modulating therapy. Increasing demand has stretched capacity well beyond the supply available from Australian plasma collections and continues to grow, with an ever-increasing reliance on internationally sourced plasma. Increasing use of B cell suppressing therapy is likely to see this trend continue in haematology. The Criteria for IVIg use in Australia are intended to be evidence-based, but the level of evidence for many indications is poor. They aim to encourage best practice, but are not guidelines for managing clinical conditions. The National Blood Authority has released Version 3 of the Criteria for immunoglobulin use aiming to optimise benefit from a scarce product with increasing clinical demands.

This presentation will review the Criteria and their development process. Key changes, including, formalisation of specific response assessments for ongoing supply in a number of conditions will be discussed. The evidence-base for haematological conditions will be reviewed with particular reference to common conditions and those for which substantial changes have been made and Australian IVIg availability will be placed in an international context.

O119

## **Immunoglobulin research: Trials and registries**

### **Erica Wood**

More than 20% of immunoglobulins (Ig) issued in Australia are directed towards prevention or treatment of infections in patients with acquired hypogammaglobulinaemia secondary to haematologic malignancies. However, the research on which current Ig policy and practice is based was mostly conducted 30-40 years ago, and many aspects of disease-specific treatment and supportive care for these conditions have changed dramatically in recent years. Up-to-date evidence to guide policy and practice is required. Moreover, there is substantial known variation in practice – between hospitals, between individual clinicians, and between jurisdictions.

This presentation will provide an update on several current research studies underway in Australia/NZ, focussing on use of Ig in blood cancers.

RATIONAL (Role of Antibiotic Therapy or Immunoglobulin On iNfections in hAematoLogy) is a randomised controlled feasibility trial comparing the efficacy of prophylactic Ig with prophylactic antibiotics in patients with acquired hypogammaglobulinemia secondary to haematological malignancies. Adult participants with blood cancers such as myeloma, non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukaemia (CLL) eligible for Ig have been randomised to receive either Ig or oral antibiotics. The hypothesis is that Ig replacement and oral antibiotics are similarly effective in preventing clinically significant infections. The study completed recruitment in early 2019 and follow-up is underway.

Concurrently, we are also conducting two prospective observational registry-based studies of Ig use in patients with haematologic malignancies. These are IMPROVE (Immunoglobulins in Myeloma Patients: Research into Outcomes, Variation in practice, and Epidemiology) and ICAN (Immunoglobulin use and outcomes in Chronic lymphocytic leukaemia And Non-Hodgkin lymphoma). This research leverages the infrastructure and networks of the Myeloma and Related Diseases Registry (MRDR) and the Lymphoma and Related Diseases Registry (LaRDR, which includes CLL), to efficiently (faster and at lower cost) capture additional data on Ig use, other interventions (such as use of prophylactic antimicrobials, vaccinations etc) and infectious outcomes in registry participants. Serial blood samples for novel immune profiling studies are being collected in subsets of participants for infectious risk stratification purposes.

These studies, all funded by the National Blood Authority, will provide essential up-to-date local clinical and laboratory data on the use of Ig and other therapies in these patients. The results will inform national and international policy and clinical practice; assist with planning and delivery of care; provide important new information to help monitor practice, costs, and outcomes; and establish a clinically annotated biobank resource for future research.

O120

**Clinical perspective on ABO incompatible renal transplants and the importance of ABO antibody titres**

**Robert Carroll**

The Royal College of Pathologists of Australasia is presenting an inaugural Transfusion Symposium on the importance of ABO titres in ABO incompatible renal transplants. The invited speakers are Jenny White, Scheme Director, Blood Transfusion Laboratory Practice at the United Kingdom National External Quality Assessment Service (UK NEQAS) and Professor Robert Carroll, Transplant Nephrologist at the Royal Adelaide Hospital. Jenny will be presenting on the ABO Titration UK NEQAS project and Professor Carroll on the clinical perspective on ABO mismatched renal transplants and the importance of ABO antibody titres. At the end of the presentations, there will be an expert panel discussion with the presenters and the audience.

O123

**UK NEQAS ABO Titration Scheme - supporting ABO incompatible renal transplant**

**Jenny White**

The Royal College of Pathologists of Australasia is presenting an inaugural Transfusion Symposium on the importance of ABO titres in ABO incompatible renal transplants. The invited speakers are Jenny White, Scheme Director, Blood Transfusion Laboratory Practice at the United Kingdom National External Quality Assessment Service (UK NEQAS) and Professor Robert Carroll, Transplant Nephrologist at the Royal Adelaide Hospital. Jenny will be presenting on the ABO Titration UK NEQAS project and Professor Carroll on the clinical perspective on ABO mismatched renal transplants and the importance of ABO antibody titres. At the end of the presentations, there will be an expert panel discussion with the presenters and the audience.

O125

## **Haemovigilance - the kiwi experience**

**Deepak Sandani**<sup>1</sup>

<sup>1</sup>*Waikato District Health Board, Hamilton, New Zealand*

First established in 2005, the New Zealand Haemovigilance Programme has just published its Fourteenth Annual Report for New Zealand.

The National Haemovigilance Office based in Wellington is managed primarily through the dedicated efforts of a single Technical Officer, who is an experienced Scientist. The reports, which are sent, by Blood Bank Scientists and Transfusion Nurse Specialists from across the country are received on a standardised form. This form includes a severity scale, an imputability scale, and definitions of transfusion-related adverse events (TRAE) based upon those agreed by the International Haemovigilance Network (ISBT/IHN).

Once submitted, after initial scrutiny the reports are reviewed by two Transfusion Medicine Specialists, who meet on a regular basis, to decide on the classification of the adverse event, imputability and severity score. Any missing information is sought either at the time of submission or review before allocating a case to a specific category.

The data collected over a year is then entered into a secure database without the clinician and patient names. Once the Annual Haemovigilance report is published, all paper records are destroyed and the unique patient identifier is then deleted from the database.

The Annual Haemovigilance report contains data and information from the previous calendar year. It contains information related to: Component usage, Analysis of reported adverse reactions and events, adverse events associated with the transfusion of fractionated products, bacterial monitoring of platelet concentrates, donor infectious disease testing, adverse events associated with blood donation and NZBS Blood Bank request form and sample labelling errors.

The presentation will highlight salient features from reports over the years, including key findings in the use of various blood components. Outcomes of the various preventive measures that New Zealand Blood Service have introduced to reduce the adverse events associated with the use of blood and blood components will be highlighted.

O127

## **Lessons on dissemination – can we do audit and feedback or guidelines better?**

**Simon Stanworth**<sup>1</sup>

<sup>1</sup>*John Radcliffe Hospital, Oxford, United Kingdom*

How do we stop clinicians giving transfusions to patients when the evidence indicates limited or no benefit? Put another way, how do we address the gaps between actual and recommended evidence-based practice. There are many approaches to implementation of practice change, including clinical guidelines, education, audit and feedback, and computerised decision support, many if not all, commonly applied in transfusion practice. As for any type of intervention, these types of interventions can be subjected to research scrutiny to help understand their effectiveness. Equally important, in the hospital environment in which costs are limited, clinicians and managers need information on the relative or comparative (including cost-) effectiveness of different interventions. Arguably, given the increasing numbers of completed randomised trials evaluating use of red cells in transfusion, clinical studies addressing implementation are now an equally, if not more, pressing requirement.

Audit and Feedback (A&F) is one of the most frequently used quality improvement strategies, aimed to improve patient care and outcomes. The impact of A&F has been subjected to research scrutiny; systematic reviews document only modest and variable effects, despite the likely high costs of A&F programmes, such as those undertaken nationally in UK. To understand and enhance A&F, a programme of research termed AFFINITIE (“Development & Evaluation of Audit and Feedback INTERventions to Increase evidence-based Transfusion practice”) has been completed in UK. AFFINITIE adopted a multidisciplinary approach that applied behavioural theory and evidence to optimise the design and delivery of feedback on transfusion practice. These interventions were then tested by embedding them in the context of transfusion national audits in two national randomized cluster trials. The audit topics were pre-operative surgery management and use of blood in patients with haematological malignancies. The emerging findings raise questions about the impact of current A&F on changing transfusion practice. There continues to be a need for robust studies to better establish a clearer role and methodology for effective A&F, and how studies can be designed to evaluate other interventions such as clinical guidelines.

## No association between storage time of transfused red blood cells and in-hospital mortality in massively transfused patients: results from the Australian and New Zealand massive transfusion registry

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### Background

Clinical trials comparing transfusion of fresher vs. older red blood cells (RBCs) have not focused on patients experiencing massive transfusion (MT). The clinical impact of storage lesions may be accentuated in this patient group.

### Methods

2007-2018 data from 25 participating hospitals in the Australian and New Zealand Massive Transfusion Registry were analysed to determine the association between in-hospital mortality and RBC storage time (ST) in MT cases ( $\geq 5$  RBCs within 4 hours, any bleeding context). Logistic regression was used with in-hospital mortality as the outcome, number of transfused RBCs as a co-variate, and mean storage time quartiles of transfused RBCs as the predictor, along with an interaction term. Two sensitivity analyses were run using (1) maximum storage time of the transfused RBCs and (2) proportion of RBCs  $\geq 30$  days old as predictors.

### Results

Mean storage times for the database's 7,890 MT episodes were (by quartile)  $ST_{\text{mean\_Q1}} = 13.0$  days;  $ST_{\text{mean\_Q2}} = 18.9$  days;  $ST_{\text{mean\_Q3}} = 23.5$  days;  $ST_{\text{mean\_Q4}} = 30.6$  days. Using the first quartile (freshest blood) as a control, the second quartile had a higher in-hospital mortality (OR = 1.30 [95% CI: 1.03 to 1.64;  $p = 0.02$ ]). Difference in mortality for other quartiles compared to the first were not statistically significant, nor was the interaction term for mean storage time and number of RBCs. Sensitivity analyses showed no difference in mortality between quartiles based on maximum storage time or proportion of longer-stored ( $\geq 30$  days) RBCs.

### Conclusions

No systematic correlation between in-hospital mortality and storage time of transfused RBCs was observed. The one statistically significant result (mortality of storage-time<sub>Q2</sub> vs. storage-time<sub>Q1</sub>) was not detected in either sensitivity analysis. These results are consistent with those of large multi-centre trials on the subject<sup>1-4</sup>. We find no previous study addressing this research question in a large cohort of MT patients.

### References

1. Lacroix J, Hébert PC, Fergusson DA, et al. Age of transfused blood in critically ill adults. *N Engl J Med.* 2015;372(15):1410-1418.
2. Steiner ME, Ness PM, Assmann SF, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. *N Engl J Med.* 2015;372(15):1419-1429.
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4. Cooper DJ, McQuilten ZK, Nichol A, et al. Age of Red Cells for Transfusion and Outcomes in Critically Ill Adults. *N Engl J Med.* 2017;377(19):1858-1867.

O129A

## **Iron deficiency and appropriate red cell transfusions in the emergency department – potentials for practice improvement.**

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**Aim:** Patients presenting to the emergency department with anaemia are frequently inappropriately transfused red blood cells.<sup>1</sup> Furthermore, appropriate investigations to determine the underlying cause of anaemia are often not instigated. The aim of this study was to review the appropriateness of red cell transfusions in the emergency department of a large adult tertiary public hospital, and to determine whether iron deficiency was appropriately considered and investigated as a potential cause of anaemia.

**Method:** A retrospective review of medical records was performed on non-trauma patients who received a red blood cell transfusion in the emergency department over a three-month period. Transfusion appropriateness was determined based on the presence of symptoms, expected tolerability of anaemia, severity of anaemia and the number of units transfused prior to reassessment. The need for iron studies was determined based on the mean cell volume (MCV) and clinical symptoms of bleeding.

**Results:** Over the study period, 77 patients received a red cell transfusion in the emergency department. The median age was 69 years (range 22 to 96 years). Forty-three patients (56%) were male. Thirty-five patients (45%) received an inappropriate transfusion; ten patients (13%) did not require a red cell transfusion (median haemoglobin 83g/L, range 66 to 127 g/L) and 25 patients (32%) received excessive units of red cells prior to reassessment (median haemoglobin 66g/L, range 26 to 83g/L).

Possible iron deficiency was identified in forty-three patients (56%) with microcytic anaemia or bleeding symptoms. Only twenty-four of these (56%) had appropriate iron studies performed, of which 18 patients were iron deficient.

**Conclusion:** Patients with anaemia presenting to the emergency department are being over transfused. Iron deficiency is a common cause of anaemia, though is often not suspected or investigated. Plans involving the hospital transfusion team and the emergency department are underway to improve clinical practice according to current patient blood management guidelines.<sup>2</sup> Focus is on avoiding unnecessary transfusions, adopting a single unit transfusion policy and treating underlying iron deficiency.

1. Spradbrow J, Lin Y, Shelton D, et al. Iron deficiency anemia in the emergency department: over-utilization of red blood cell transfusion and infrequent use of iron supplementation. *CJEM* 2017;19:167-74

2. National Blood Authority. Patient blood management guidelines: Module 3 Medical. Australia, 2012.

O129B

## **Management of iron deficiency in the emergency department – potentials for practice improvement.**

**Jeremy Ong**<sup>1</sup>, Christine Akers<sup>1</sup>, Leanna Pickles<sup>1</sup>, Susan Morgan<sup>1</sup>

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**Aim:** Patients with iron deficiency anaemia presenting to the emergency department are often inappropriately transfused, and their deficiency state may be unrecognised or not adequately treated with iron supplementation.<sup>1,2</sup> The aim of this study was to review the management of iron deficiency in a single emergency department, focusing on the rates of iron replacement and red blood cell transfusions.

**Method:** A retrospective review of medical records was performed on iron deficient patients (serum ferritin  $\leq 30$ mcg/L) who presented to the emergency department of a tertiary hospital over a three-month period.

**Results:** Over the study period, 78 emergency department patients were identified as iron deficient, of which 35 patients were discharged directly from the department. The median age was 37 years (range 4 to 95yrs). Twenty-six patients (74%) were female. Fifteen patients were anaemic (median haemoglobin 125g/L, range 56 to 152g/L). Four patients (11%) received parenteral iron, four patients (11%) received oral iron and a further four patients (11%) were already taking oral iron supplements. Three patients (9%) were referred for outpatient parenteral iron but did not receive the intended infusion. Follow-up with a GP or specialist clinic was arranged for iron deficiency in six patients (17%), but with no immediate iron replacement prescribed. Fourteen patients (40%) received no iron replacement or follow-up.

Three patients (9%) received red blood cell transfusions. One transfusion was appropriate: a symptomatic patient with haemoglobin 56g/L. One transfusion was inappropriate: an asymptomatic patient with no risk factors and haemoglobin 66g/L. One patient received excessive transfusions: two red cell units for symptomatic anaemia with haemoglobin 75g/L.

**Conclusion:** Iron supplementation is underutilised in the emergency department, whilst red cell transfusions may be given unnecessarily. Current plans involving the hospital transfusion team and the emergency department are underway to improve management of patients presenting with iron deficiency. A repeat audit is planned after the intervention strategy.

1. Spradbrow J, Lin Y, Shelton D, et al. Iron deficiency anemia in the emergency department: over-utilization of red blood cell transfusion and infrequent use of iron supplementation. *CJEM* 2017;19:167-74

2. Rohrig G, Klossok W, Becker I, et al. Prevalence of anemia among elderly patients in an emergency room setting. *European Geriatric Medicine* 2014;5:3-7

## High red blood cell (RBC) and platelet transfusion burden in patients with myelodysplastic syndromes (MDS)

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**Aim:** Despite transfusion being a cornerstone of MDS management, the evidence base to inform guidelines remains weak, and real-world data on outpatient transfusion practice are lacking. We aimed to describe current practice regarding transfusion of RBCs and platelets, including frequency, transfusion triggers, adjunctive medications and transfusion-related outcomes.

**Method:** Retrospective cohort study of all patients with MDS/CMML admitted at Monash Health from August 2016 to July 2018, using hospital medical record data.

**Results:** 180 MDS/CMML patients (61% male, median age 78y) were identified with a total of 809 admissions, including 513 day-admissions, of which 414 (81%) involved RBC/platelet transfusion. Transfused patients were more likely to be receiving azacitidine (32% vs 12%,  $p=0.002$ ).

**Table 1: Outpatient transfusions**

	Interval (days) between transfusions (median, IQR)	No. of bags of products transfused per episode (median, IQR)	Pre-transfusion count (median, IQR)	Post-transfusion increment (median, IQR)	No. of days post-transfusion increment taken (median, IQR)
<b>RBC transfusion</b>	14 (7–21)	2 RBC units (1–2)	Hb 80g/L (74–86)	+5g/L (-1–+13)	6 days (IQR4–8)
<b>Platelet transfusion</b>	7 (4–7)	1 bag of platelets (1-1)	11X10 <sup>9</sup> /L (9–15)	+1X10 <sup>9</sup> /L (-1–+13)	4 days (IQR2-7)

102 patients (56%) received 707 RBC units during 386 outpatient episodes. Table 1 shows transfusion interval, pre-transfusion counts and post-transfusion increments. Erythropoiesis-stimulating agents [ESAs] were prescribed in <10% of transfused patients (table 2). The RBC-transfused group had higher rates of fluid overload/acute cardiac failure (19% vs 6%,  $p=0.017$ ) despite similar baseline cardiac failure history. There was no difference in cardiac ischaemia. No further transfusion reactions were documented.

**Table 2: Adjunctive medication usage**

	Transfused n (%)	Non transfused n (%)	p-value
<b>RBC transfusions</b>			
ESAs	9/102 (8.8%)	2/78 (2.5%)	0.082
<b>Platelet transfusions</b>			
TXA	12/35 (34.3%)	4/145 (2.8%)	<b><math>p&lt;0.001</math></b>

**Table 3: Bleeding episodes**

	Admission with bleeding N=16	Admission without bleeding N=793	p-value
Admission platelet count (X10 <sup>9</sup> /L): median (IQR)	46 (26-142)	80 (45-138)	0.163
TXA use prior to admission: n (%)	2/16 (12.5%)	41/793= (5.2%)	0.196
Previous history of platelet transfusion: n (%)	2/16 (12.5%)	149/793 = 18.8%	0.523

35 patients (19%) received 107 bags of platelets in 88 outpatient transfusions (Table 1).

Approximately one third of patients receiving outpatient platelet transfusions were also receiving tranexamic acid (table 2). 16 bleeding episodes occurred (11 gastrointestinal, 1 intracranial and 4 other), which were not predicted by admission platelet counts or history of TXA use/ platelet transfusions (table 3). **Conclusion:** In a cohort of 180 MDS/CMML patients, we found a high transfusion burden, with 81% of admissions involving transfusion. Despite a restrictive RBC transfusion strategy, fluid overload/cardiac failure was common. Platelet increments post-transfusion were minimal, and although bleeding rates were low, one intracranial haemorrhage was reported. Prospective trials are required to investigate optimal transfusion practice and patient outcomes, including quality-of-life.

## Analysis of the Recent Mass Shooting Event in Christchurch, New Zealand from a Transfusion Medicine Viewpoint

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<sup>1</sup>New Zealand Blood Service, Christchurch, New Zealand

**AIM:** Examine demographics, injury severity score (ISS), tissue hypoxia, clotting, transfusion requirements, mortality, and their inter-relationships amongst the 45 patients involved in the March 2019 Christchurch mass shooting. **METHODS:** Christchurch Hospital and New Zealand Blood Service data. **RESULTS:** Injuries were mostly due to close-range, high-velocity, hollow-point, bullets. Six patients had minor injuries/complaints. Summary data are shown below (n=45 patients unless stated differently; laboratory values: first-available on the day; transfusion values: 1400–2400 h on the day).

Characteristic (n,patients)	Range/Ratio	Median/Mean	%
Age,y	2-69	46.5	
≥40			37
<b>Males</b>			96
ISS (38)	0-75	13/18	
≥15			45
<b>Base excess, BE (23)</b>	-16 to 3	-4/-4	
≤-6			35
<b>Lactate,mmol/L (21)</b>	1.3-13.3	4/5.1	
≥4			52
<b>Hb,g/L (37)</b>	91-170	142/140	
≤99			5
<b>Platelets,10e9/L (36)</b>	61-430	270/270	
≤99			6
<b>INR (33)</b>	0.8-1.4	1.0/1.1	
≥1.6			0
<b>APTT,sec (33)</b>	19-117	26/30	
≥42			6
<b>Fibrinogen,g/L (32)</b>	1.5-4.8	2.7/2.7	
≤1.5			3
<b>ABO group (A:B:AB:O:unknown)</b>	14:6:4:8:13		
<b>RhD group (pos:neg:unknown)</b>	29:3:13		
<b>RBC tx,u</b>	0-176	2/7.6	
0			55
≥10			4
<b>Platelet tx,AD</b>	0-16	0/0.6	
0			82
<b>FFP tx,u</b>	0-154	0/5.4	
0			80
<b>Cryoprecipitate tx,u</b>	0 to 63	0/5.4	
0			87
<b>FFP:Platelets:RBC</b>	0.7: 0.08:1		
<b>Mortality, 3m</b>			4.4

Correlation coefficients,  $r$ , between *explanatory* and outcome variables that are significant ( $\leq -0.5$ , or  $\geq 0.5$ ) are as follows. *ISS* and *BE*, lactate, *APTT*: 0.7, 0.6, 0.6 respectively; *Hb* and *INR*, *RBC*, platelet tx: -0.5 in each case; *BE* and *APTT*, *RBC*, platelet, *FFP* tx: -0.5, -0.7, -0.6, -0.8 respectively; *Lactate* and *INR*, platelet, *FFP*, cryoprecipitate tx: 0.5, 0.5, 0.5, 0.6 respectively; and *fibrinogen* and *RBC*, platelet: -0.5 in each case. **CONCLUSIONS:** Initial *Hb*, platelets, and clotting were mostly normal but initial *BE* and lactate were significantly abnormal in 35% and 52%. The roles of initial *Hb*, *BE*, lactate, and fibrinogen for predicting transfusion requirements in trauma needs examination.

O131B

## **Christchurch Mass Shooting - Critical Components**

**Susan Mercer**<sup>1</sup>

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### Introduction

New Zealand now has its own story of gun violence and racial hatred. Images of terror, armed police, grief, and innocent people taken before their time, once again remind us of an unforgettable event to befall the city of Christchurch.

On March 15, 2019, Christchurch Hospital Emergency Department (ED) triaged 46 patients. Staff initially considered warnings to expect multiple mass-shooting casualties with disbelief until ambulances and private cars arrived with the injured. Activation of the Massive Incident Plan alerted the only tertiary hospital in the region to prepare “for something”.

Amidst the eerie disquiet in ED, focused Health Professionals visually distinguishable by colour coded vests, formed teams to greet the wounded. The Transfusion Nurse Specialist occupied a central point with emergency red cells. Paramedic handovers conveying “multiple gunshot wounds, no exit” reflected the trauma of hollow-pointed ammunition that had immobilised many with critical internal injuries. Only imaging and surgery could reveal the true extent of tissue damage.

It is a story of collegial organisation and teamwork, where many people worked beyond their scope, despite the uncertainty of the situation. All but one patient survived. A courier and Lime scooter rider initially navigated the city lockdown with blood supplies. Patient “Bravo”, arrived pulseless requiring the first Massive Transfusion Protocol (MTP) activation. Seven of eight MTPs were activated within the first four hours, inevitably overlapping one another. Demand on blood was relentless as 54% of all patients required transfusion, one receiving 199 units by midnight. Behind the emergent scenario, someone ensured a supply of chest drains and antibiotics ahead of the weekend, Social Workers began identifying patients and consoling anxious family, and documentation reconciliation loomed in the aftermath.

### Conclusion

We never imagined this would happen in New Zealand. By sharing the story, we can reflect, learn and share ideas in readiness of another ‘never’ event.

O131C

## Christchurch mass shooting incident - The Blood Bank experience

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**Aim:** The mass shooting event of 15 March 2019 presented Christchurch Blood Bank with an unprecedented demand on our services. This describes the experience of the Blood Bank during this event.

**Method:** Information was collected from first-hand staff accounts, stock reports, and patient transfusion records.

**Results:** Notification of up to fifty patients with gun-shot wounds expected in the Emergency Department (ED) was received. The New Zealand Blood Service (NZBS) Emergency Management plan was activated. Demand for emergency blood was immediate, with an emergency blood station set up in ED to meet this. Eight Massive Transfusion Protocols were activated over the next 12 hours, as patients were taken to theatre.

Pre transfusion samples were labelled using various forms of identification, including disaster numbers. Many did not meet the minimum labelling requirements, and a group O bank was utilised. All components were labelled to a mock emergency patient, as demand did not allow issue to individual patients. All patients were switched to O RhD Positive blood and group A plasma. A large water bath was set up to thaw huge amounts of plasma and cryoprecipitate. Theatre staff queued outside the Blood Bank for product. Table 1 documents the number of units issued.

Stock was replenished from the Christchurch Donor Centre, with couriers having to navigate cordons to deliver product. The NZBS National Emergency Response team tracked issues and responded with supplies from Auckland, Hamilton and Wellington.

Reconciliation of units transfused occurred in the days following by inspection of patient records and other documentation.

**Discussion:** Learnings were taken from the 2011 earthquakes, but no two events are alike. Patient identification and sample labelling were again problematic and a group O bank essential. Issue of components to mock patients ensured quick release, but resulted in a large reconciliation effort, including inspection of patient records.

**Table 1. Summary of Issues from Christchurch Blood Bank 15<sup>th</sup> -18<sup>th</sup> March 2019**

Component	Friday 15th	Saturday 16th	Sunday 17th	Monday 18th	Total
Platelets	17	10	2	3	32
Red Cells	179	33	26	38	276
Cryoprecipitate	46	10	-	3	59
FFP	113	28	7	7	155

O132

## Targeting safer transfusions - Clinical incident review 2015-2019

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**AIM:** To identify trends by reviewing blood and blood product related clinical incidents at a major quaternary hospital group from 2015 to 2019.

**METHOD:** Since opening, the new hospital has recorded 28,000 clinical incidents. Data was extracted from the hospitals' Clinical Incident Management System (CIMS) for the period of January 2015- April 2019, for blood and blood products. The clinical incidents were sorted into five categories based on the 2018 Australian and New Zealand Society of Blood Transfusion (ANZSBT) Guidelines for the Administration of Blood and Blood Products.

**RESULTS:** 188 clinical incidents were logged under the Blood/plasma product category. On review, 7 clinical incidents were deemed not relevant, 181 clinical incidents were reviewed and categorised.

9. Consent for Blood Products n=3 (1%)
1. Prescription of Blood Products n=9 (5%)
2. Request for Blood Products and Pre-Transfusion Sampling n=60 (33%)
3. Storage, Collection and Transportation n=30 (17%)
4. Administration of Blood Products n=79 (44%)

Issues associated with administration of the blood product accounted for 44% (n=79) of clinical incidents reported. The most common incident was delay in administering the product (n=18 23%). Blood Product requests and pre-transfusion sampling incidents accounted for 33% (n=60) of CIMS. Severity of incidents reported: 1% (n=2) severe harm, 7% (n=12) moderate harm, 92% (n=167) minimal or no harm/near miss.

**CONCLUSION:** Staff have a culture of reporting clinical incidents to improve patient safety. The low number of serious transfusion incidents demonstrated good transfusion practice across sites. Review of the Clinical Incidents related to blood transfusion highlighted areas for improvement, and allowed targeted education to specific wards.

**Clinical simulation to embed improvements in critical bleeding management**

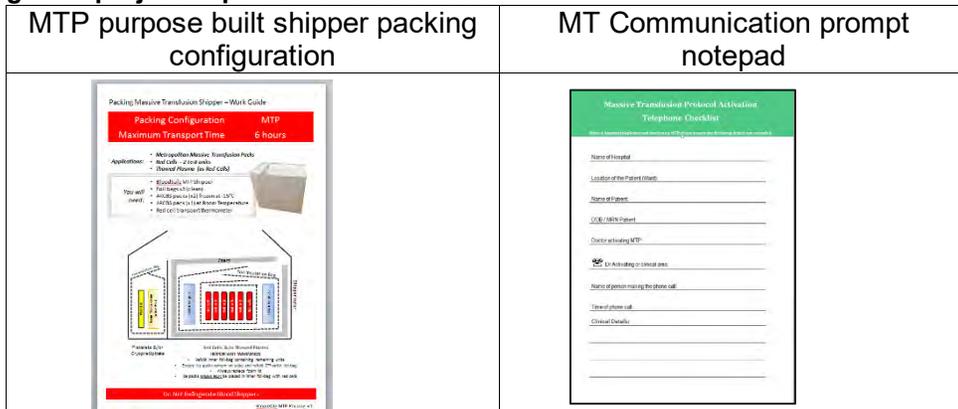
Alison Sarles<sup>1</sup>, **Duncan Bamford**<sup>1</sup>, Trish Roberts<sup>1,2</sup>, Sharon Blaney<sup>1</sup>, Tina Donaldson<sup>1</sup>  
<sup>1</sup>St Andrew's Hospital Inc, Adelaide, Australia, <sup>2</sup>Australian Red Cross Blood Service, Adelaide, Australia

**Aim:** To ensure reliable, efficient and sustainable processes and resources are utilised to improve the management of a patient experiencing a critical bleed in a Private Hospital without an onsite transfusion service provider.

**Method:** The hospital has a process to review all Massive Transfusion (MT) episodes. Gaps were identified with communication, product supply and traceability. A critical bleed working group formed, and using Clinical Practise Improvement methodology, the following areas were prioritised:

- 10. Development of purpose built shipper used to deliver products
  - Method for documenting the fate of all issued blood products, and
  - Communication between the clinical area and the laboratory.

**Figure 1-project improvement resources**



MTs occur infrequently in this private hospital and while there was widespread education to support new resources and processes, staff have limited experience in looking after a critically bleeding patient. To assist staff feel comfortable and confident in an unfamiliar situation, the use of simulation training has been employed. The hospital secured project funding for a filmed simulated activated MTP, showcasing the new resources – which is now embedded into the hospital eLearning system

**Figure 2 screen shots from MTP simulation**



**Results:** Cumbersome steps have been removed which previously took clinical staff away from the bleeding patient. Staff satisfaction with the use of the purpose built shippers is high - 100% indicated that the shippers made it easier to manage blood products in an emergency. Use of the MTP simulation film has resulted in increased staff awareness and knowledge regarding the care of the critically bleeding patient

**Conclusion:** The management of the bleeding patient in this private hospital has been improved, and with the use of a simulation, the practise improvement initiatives have been embedded into clinical practise.

## Itchy and scratchy – seriously!

**Christine Akers**<sup>1</sup>, Bridget Glazebrook<sup>1</sup>, Linley Bielby<sup>1</sup>, Kaylene Bastin<sup>1</sup>, Peter Beard<sup>1</sup>, Erica Wood<sup>2</sup>, Kobie Von Williegh<sup>3</sup>, James Daly<sup>4</sup>

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**Background:** Allergic reactions to blood products are well recognised adverse events. The management of these is the same as for any allergen/s. The serious transfusion incident reporting (STIR) system focuses on serious reactions rather than minor reactions.

**Aim:** To report on the clinical management/investigations of allergic reactions to blood products.

**Method:** STIR receives acute event notifications via an online form; triggering a reaction-specific detailed investigation form sent for completion. Severity, treatment at time of reaction and subsequent investigations were analysed against recommendations.

**Results:** From July 2012 – June 2018, STIR received 149 reports of allergic/anaphylactic reactions; 46% of all acute reactions. Reaction-severity was validated by expert review and determined to be mild (27%), moderate/severe (56%), or anaphylactic/anaphylactoid (17%).

Reactions related to platelets (69, 46%), FFP (51, 34%), RBC (29, 19%), other (9, 6%).

### Treatment reported

	Mild (n=40)	Moderate/severe (n=84)	Anaphylaxis (n=25)
Antihistamine	30 (75%)	58 (67%)	12 (48%)
Steroid	22 (55%)	57 (69%)	18 (72%)
Oxygen	2 (5%)	33 (39%)	9 (36%)
Fluids	2 (5%)	20 (24%)	12 (48%)
Inotropes	1 (2%)	44 (52%)	23 (92%)

There was inconsistency in approach. UK-Serious Hazard of Transfusion recommend giving antihistamine as first line; adrenaline if anaphylaxis is suspected. Steroid effect is delayed and should only be used to prevent late recurrence.

### Investigations reported

	Mild (n=40)	Moderate/severe (n=84)	Anaphylaxis (n=25)
Tryptase	2 (5%)	19 (23%)	12 (48%)
IgA levels	3 (7%)	21 (25%)	6 (24%)
Anti-IgA	2 (5%)	6 (7%)	7 (28%)

Allergy is a clinical diagnosis; however some investigations will assist in determining likelihood or cause. Although IgA testing is recommended in severe/anaphylactic reactions only 24% were tested.

**Conclusion:** Allergic reactions, contingent on the plasma content of blood products are a frequent source of reportable adverse events. Adherence to recommended management and investigation is inconsistent and highlights opportunities to improve knowledge for clinicians.

O135

## **Positive impact of small group face to face blood bank teaching on transfusion practice**

**Soyoung Choi-maxwell**<sup>1</sup>

<sup>1</sup>*NZ Blood Service, Auckland, New Zealand*

### Background

Auckland is the largest district health board in New Zealand, responsible for a population of nearly half a million, and New Zealand's biggest consumer of blood components and products. ADHB has been a relatively low reporter of transfusion-related adverse events. However it holds one of the lowest labelling error rates nationally, and Wrong Blood In Tube (WBIT) incidents are also lower than national average.

With recent expansion of ADHB Blood Bank in 2018 the transfusion nurse specialist now has a room equipped for running small-group face-to-face teaching. This started from late February 2019.

### Aim

To see if small group teaching was having an impact on adverse event reporting and sample labelling error rates.

### Method

We looked at adverse event reporting and labelling error rates delivered over six months for the same period in the year, before and after small group blood bank teaching.

### Results

Data comparing the first three months of 2018 vs 2019 has not shown a difference (0.26% adverse event reports per unit transfused and 1.7% sample labelling errors in each case). Labelling errors in two specialty areas identified with higher than average errors rates (women's health and children's health) went from 1.0% to 1.4% in women's health and 2.8 to 1.7% in children's health.

### Conclusion

The data at time of abstract submission does not show any significant increase in adverse event reporting nor decrease in sample error numbers. A small decrease in the number of labelling errors was shown in 2019 in children's hospital. However it is early to draw conclusions about the impact of this new initiative. Further data will be presented at the conference. It is possible that transfusion practitioners should concentrate on system changes rather than delivering individual teaching.

## **Assessing transfusion practice in elective surgical patients: a baseline audit to identify opportunities for improvement**

**Alana Delaforce**<sup>1,2</sup>, Jed Duff<sup>1</sup>, Judy Munday<sup>3</sup>, Janet Hardy<sup>2</sup>, Diana Moore<sup>2</sup>

<sup>1</sup>University of Newcastle, Newcastle, Australia, <sup>2</sup>Mater Health Services, South Brisbane, Australia,

<sup>3</sup>Queensland University of Technology, Kelvin Grove, Australia

**Background:** Externally generated hospital benchmarking data indicated that the blood transfusion rate within elective surgical orthopaedic and gastrointestinal patients at a metropolitan, tertiary healthcare facility was higher than comparable Australian hospitals.

**Aim:** To investigate factors contributing to the higher incidence of blood transfusion and identify areas for improvement.

**Methods:** A retrospective chart audit was completed of every major, elective, surgical orthopaedic and gastrointestinal patient who received a blood transfusion between July-December 2017 (both public and private patients). The audit assessed: i) if patients were screened and treated for preoperative anaemia and ii) if transfusions were according to the Perioperative Patient Blood Management (PBM) practice points. The key recommendations in the practice points include screening for anaemia preoperatively; the utilisation of restrictive transfusion thresholds (in conjunction with clinical assessment), and the administration of a single unit followed by clinical reassessment.

**Results:** Forty-five patients had 72 transfusion episodes (public 25, private 47), 40% (n = 29) of episodes were considered inappropriate. Of these, 76% (n = 22) did not have evidence of decompensation and of the remaining that did (24%, n = 7), there was no evidence of clinical reassessment after transfusion. 42% (n = 19) of patients were anaemic preoperatively (6 public, 13 private), and of the patients that were anaemic, only 21% (n = 4) had iron studies, and only 5% (n = 1) received intravenous iron preoperatively.

**Conclusion:** Opportunities exist to improve the preoperative anaemia screening processes and clinical decision making in transfusion practice. Work is being undertaken at the facility to improve preoperative anaemia screening and treatment, in addition to building awareness of best practice and generating new ways of communicating audit results.

O137

## **The WA Antibody Register – past, present and future**

**Brian Fisher**<sup>1</sup>

<sup>1</sup>*Australian Red Cross Blood Service, Perth, Australia*

Databases of patients with irregular red cell antibodies exist in various formats in Australian hospitals and the Blood Service Red Cell Reference Laboratory (RCRL) in each State. The Western Australian (WA) Antibody Register (AR) is unique in that:

11. It is a complete list of all persons in the State known to have irregular red cell antibodies
  - It is readily accessible by all transfusion laboratories in the State.
  - Pre-transfusion consultation has been incorporated into routine practice by WA laboratories as an initiative to improve transfusion safety.

As a joint initiative between the Blood Service and State transfusion laboratories the WA RCRL has since 1970 maintained a register of all persons in WA known to have irregular red cell antibodies in their plasma. From its inception the AR was made available to all public and private cross-matching laboratories in WA, initially by use of a typewriter/paper system with monthly update sheets posted to local laboratories. This was upgraded in the late 1970s to a mainframe computer which allowed generation of microfiche copies of the AR. In the 1980s this was replaced by the current system where a regularly updated electronic copy of the AR is transferred to a secure server at the WA Blood Service. This server is linked by optical cable to the WA Health Department's computer system and password-accessible in real time by public laboratories throughout WA. Private laboratories, unable to access the WA Health Department system, are regularly sent a password-protected copy of the AR via secure email.

The use of the AR is now integrated in WA transfusion laboratory practice where it is routinely consulted prior to issue of red cells for transfusion. Whilst not replacing serological testing its role is to alert the laboratory at an early stage to the presence of an antibody allowing appropriately phenotyped units to be organised with minimal delay, and also to identify those patients where the antibody may have fallen below a detectable level.

The WA AR is based on old technology and increasingly difficult to maintain. In 2020 the Blood Service would like to introduce a national web-based AR. An overview of the new national AR conceptual design will be included in the presentation.

## "Next Gen" sequencing in resolving difficult cases

**Eliza Schoeman**<sup>1</sup>

<sup>1</sup>*Australian Red Cross Blood Service, Kelvin Grove, Australia*

Difficult cases are one of the complexities of life for immunohaematologists but often a source new discoveries when resolved. Since the discovery of the first blood groups a range of tools have been developed to resolve difficult cases each with advantages and disadvantages. International sharing made panels of RBC with rare and unusual phenotypes, for investigation and identification of difficult antibodies, available in national reference laboratories. Tools to modify the RBC surface and thus presentation of antigens have also provided insights into the specificity of antibodies to RBC antigens. For RBC displaying unexpected typing, international sharing of collections of rare antisera have also provided tools for these investigations. PCR, Sanger sequencing and later SNP arrays have been applied to considerable effect. Since the development of massively parallel/next gen sequencing a new range of tools have become available and genomic analysis is useful in both research and reference settings. Indeed, the faster, cheaper generation of genomic data is driving the integration of genomics into all healthcare specialties. With appropriate sequencing and data analysis strategies, comprehensive cover for all 39 blood group systems is available in a single test. The limitations for NGS include the differences between reference sequences, the curation of tables listing blood group variants and significance of other variants in these genes, listed in public reference databases. When large scale application is proposed there is an additional requirement for reliable high throughput DNA extraction. I will present several cases illustrating the unique problem solving capacity of NGS as well as looking at genetic variations that require complex data analysis on this platform. For DAT-positive patients, multi-transfused patients and monoclonal antibody-treated patients genetic-based typing provides a basis for matching. Identification of donors with rare or unusual genotypes is an additional benefit. As for earlier methodologies, analysis of NGS data relies on international co-operation including free access to databases and tools for analysis of large sets of complex data.

## Extended life plasma - blood wastage and opportunities

**Monique Menzies Wojtowicz<sup>1</sup>**, Tony Greenfield<sup>1</sup>, Penelope Motum<sup>1</sup>

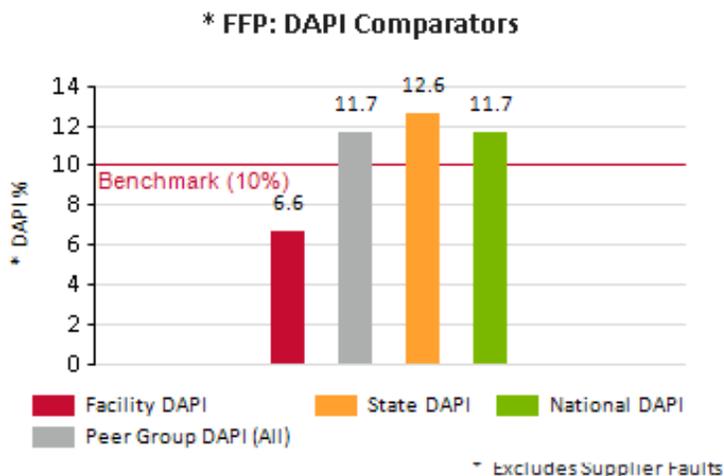
<sup>1</sup>Liverpool Hospital, Sydney, Australia

**Aim:** Extended life plasma (ELP) is Fresh Frozen Plasma (FFP) that has been thawed and intended for extended storage at 2-6 degrees Celsius beyond 24 hours and up to 5 days (120 hours). This extended shelf life provides an opportunity to reduce wastage, given that there is more time to utilise the product before expiry; as well as provide the product promptly for patients in emergency or retrieval settings, with the potential to develop trauma induced coagulopathy or coagulopathy from haemorrhage to improve survival.

**Method:** ELP was introduced as a pilot at Liverpool hospital in January 2018. We created a new standard operating procedure and provided ELP by default (with the exception of patients with haemophilia A, congenital factor V deficiency and neonates). ELP was updated on the laboratory information system as a product modification, thawed in a waterbath and relabelled to reflect the new ELP product name and new expiry date. ELP not used by the new 5 day expiry date was discarded.

**Result:** We were able to demonstrate a substantial improvement in our wastage of products via NBA DAPI rates (Discards As Percentage of Issues) as compared to Australian state and national figures. Specifically, we have halved our wastage from 9.6% in the 2017/2018 financial year to 6.6% for the 2018/2019 financial year (figure 1). This wastage reduction also led to a significant cost saving. Having ELP available allowed us to provide plasma for patients prior to hospital arrival (via our retrieval eskies) and more quickly within the hospital - in particular for massive transfusion patients and trauma patients.

Figure 1: FFP DAPI for 2018/2019 financial year



**Conclusion:** We have successfully implemented ELP at our institution and demonstrated a sustained wastage reduction, cost saving and the provision of blood products rapidly to trauma and massively bleeding patients. We plan to commence the use of ELP at two other sites in our health district and would also anticipate a further improvement in wastage.

**Use of nanoparticle tracking analysis to characterise microvesicles in red cell and platelet units: Effects of storage on microvesicle size and concentration**

**Rebecca Wellburn**<sup>1</sup>, Fergal Temple<sup>1,2,3</sup>, Gabriela Simonova<sup>1,2,3</sup>, John-Paul Tung<sup>1,2,3,4</sup>

<sup>1</sup>Australian Red Cross Blood Service, Brisbane, Australia, <sup>2</sup>Critical Care Research Group, Brisbane, Australia, <sup>3</sup>Faculty of Medicine, University of Queensland, Brisbane, Australia, <sup>4</sup>Faculty of Health, Queensland University of Technology, Brisbane, Australia

**Introduction:** Microvesicles (MVs) are small submicron (50 – 1,000 nm diameter) membrane-enclosed vesicles shed from cells upon activation and/or apoptosis. MVs are released from cells in blood components during routine storage and may impact transfusion outcomes in patients. MVs are commonly analysed using flow cytometry; however, this only reliably detects MVs larger than 400 – 500nm. Alternative techniques including nanoparticle tracking analysis are required to detect MVs smaller than 400 – 500nm.

**Aims:** To determine the size and concentration of small MVs present in red cell and platelet units during storage.

**Methods:** Standard leucoreduced red cells (PRBC) (n=4) and platelet concentrates (PC) (n=4) were stored routinely. Throughout storage, samples were collected aseptically, processed (dual centrifugation at 3,000 g for 15 minutes) and stored at -80°C. Processed samples were thawed, and then analysed using the Nanosight NS300 nanoparticle tracking analysis system (Malvern Instruments). Data were analysed by one-way ANOVA with Bonferonni's multiple comparisons test.

**Results:** The concentration of MVs in PRBCs increased steadily throughout storage (P=0.0276). Both the mean (P<0.0001) and mode (P<0.0001) size of the PRBC MVs increased during storage; however, this size increase primarily occurred in the first week of storage (d2 vs. d7: P<0.0001 for both mean and mode). A modest increase was seen in PC MV concentration (P<0.0001) and mean size (P<0.0001) however there was no significant difference in the mode size.

**Conclusions:** Nanoparticle tracking analysis demonstrated the presence of MVs smaller than 400nm in RBC and PC units. Both the concentration and size of MVs present in PRBC and PC units increased during routine storage, however the increases seen in PC units were much smaller. The concentration of these MVs was approximately 100-fold higher in PRBC than we had previously detected using flow cytometry indicating the advantages of more sensitive techniques in characterisation of MVs.

## What you didn't expect when you are expecting

**Jenny Morrison**<sup>1</sup>, Naomi Roots<sup>1</sup>, Robyn Turner<sup>1</sup>, Yew-Wah Liew<sup>1</sup>

<sup>1</sup>*Australian Red Cross Blood Service, Brisbane, Australia*

Non-Invasive Pre-Natal Assessment (NIPA) for fetal RHD status is primarily for RhD negative women, who are isoimmunised with anti-D and at high risk of HDFN. Occasionally, testing reveals unexpected outcomes that triggers further investigation. This study reports 3 cases of maternal RHD variants.

**Methods:** Fetal DNA is extracted from maternal plasma using the QIAamp MinElute Virus spin kit. The ffDNA is then tested using a qPCR real-time assay with the simultaneous amplification and detection of exons 4, 5 and 10 of the RHD gene, SRY gene and the CCR5 gene, on the QIAGEN RotorGene Q. The presence of ffDNA is confirmed using a qPCR assay for the hypermethylated RASSF1A gene. Genotyping was performed on the maternal samples using the Immucor BioArray RHD BeadChip Kit.

**Results:** Positive signals were detected in RHD exons 4, 5 and 10 in all three cases. The presence of a maternal RHD variant was suspected when the signals crossed the threshold before the DPOS/M control. This occurred in Exon 10 for case 1 and 2 and for case 3, all signals for Exons 4, 5 and 10 crossed the threshold before the DPOS/M control. Results from the RHD BeadChip genotyping of maternal genomic DNA is shown in Table 1.

**Table 1: Genotyping results**

Case	NIPA assay signals crossing threshold before DPOS/M control	RHD BeadChip Variant detected
1	Exon 10	RHD-CE(3-9)-D
2	Exon 10	DIIIa-CE(4-7)-D
3	Exons 4,5 and 10	IVS3+1G>A (Del)

**Conclusion:** Due to the co-amplification of fetal and maternal DNA, it is important to review the raw data for each of the exons individually to ensure a maternal variant is not missed. In all 3 cases, there were indications of maternal variants due to the signals for some or all of the exons crossing the threshold before the DPOS/M control. These samples were confirmed to be maternal variants by BeadChip genotyping, and therefore we were unable to predict the fetal RHD genotype.

## **An ovine model of severe haemorrhagic shock to assess novel fluid resuscitation strategies as alternatives to red blood cell transfusion**

**Wayne Dyer**<sup>1</sup>, John-Paul Tung<sup>2</sup>, Gianluigi li Bassi<sup>3</sup>, Karin Wildi<sup>3</sup>, Sacha Rozenchwajg<sup>3</sup>, Carmen Ainola<sup>3</sup>, Samantha Livingstone<sup>3</sup>, Gabriela Simonova<sup>2</sup>, Sara Chiaretti<sup>2</sup>, Fergal Temple<sup>2</sup>, Rebecca Wellburn<sup>2</sup>, Tristan Shuker<sup>3</sup>, Mahe Bouquet<sup>3</sup>, Lara Oller<sup>4</sup>, Aryeh Shander<sup>5</sup>, Jacky Suen<sup>3</sup>, David Irving<sup>1</sup>, John Fraser<sup>3</sup>

<sup>1</sup>Australian Red Cross Blood Service, Alexandria, Australia, <sup>2</sup>Australian Red Cross Blood Service, Kelvin Grove, Australia, <sup>3</sup>Critical Care Research Group, The Prince Charles Hospital, Chermside, Australia, <sup>4</sup>Hospital La Luz, Madrid, Spain, <sup>5</sup>Englewood Hospital and Medical Center, Englewood, USA

**Aim:** In severe haemorrhagic shock, attempts to restore perfusion and oxygen delivery by aggressively transfusing fluids and blood products may actually worsen microcirculatory dysfunction and reduce the delivery of oxygen to tissues. We established an ovine model of severe haemorrhagic shock to systematically measure the efficacy of a novel fluid (Oxsealife®) designed for enhanced microvascular perfusion and oxygen delivery.

**Methods:** In eight female Leicester-cross sheep, tissue-specific oxygenation and microvascular function was evaluated in brain, kidney, liver and skeletal muscle using invasive laser Doppler blood flow, oxygen partial pressure (PtO<sub>2</sub>), and micro-dialysis, benchmarked against continuous haemodynamic monitoring. Non-invasive regional oxygen saturation was assessed by near infra-red spectroscopy (NIRS), and sublingual capillary perfusion by incident dark-field imaging. Haemorrhagic shock was induced by withdrawal of 40% total blood volume (TBV) over 90min based on clinical tolerance including mean arterial pressure (MAP) >30mmHg. Shock was defined by central venous oxygen saturation <60% and arterial lactate >4mM. Sheep were randomised to Oxsealife®, allogenic packed red cells (PRBC), or PlasmaLyte®, dosed to the treatment target MAP >65mmHg.

**Results:** All shocked sheep demonstrated haemodynamic consequences of severe haemorrhage including critically reduced MAP (38.0±9.2mmHg) and cardiac output (36.0±8.8ml/kg/min). Evidence of tissue hypoxia was consistently achieved during shock-guided haemorrhage; NIRS demonstrated conserved cerebral oxygen delivery relative to muscle (16% vs. 76% decrease), while tissue perfusion and PtO<sub>2</sub> declined >50% and lactate increased 2-3 fold across all tissues. Volume replacement improved MAP (70.3±21.7mmHg) and cardiac output (84.7±13.2ml/kg/min) within 30min. Sustained recovery from shock, defined by increase to baseline tissue perfusion and oxygenation levels, and decrease in lactate: pyruvate ratios, was achieved independent of reduced haemoglobin after crystalloid treatment. All sheep survived the procedure.

**Conclusion:** A severe haemorrhagic shock model was established, and provided functional outcome measures suitable for pre-clinical efficacy assessment of novel resuscitation strategies compared to PRBC transfusion.

## Pretransfusion testing using laser incubation

**Heather Mcliesh**<sup>1</sup>, Clare Manderson<sup>1</sup>, Rodrigo Curvella<sup>1</sup>, Rico Tabor<sup>1</sup>, Gil Garnier<sup>1</sup>

<sup>1</sup>Monash University, Clayton, Australia

Safe blood transfusion requires pre-transfusion testing of both donor and recipient to prevent transfusion reactions. Red cell antibody screens for the detection of immunoglobulin G (IgG) antibodies requires incubation at 37 °C, often for up to 15 minutes. Current incubation technology predominantly relies on slow thermal-gradient dependent conduction, found in dry block incubators and air incubators. We have developed a rapid, optical heating method via laser, where targeted illumination of a blood-antibody sample in a diagnostic gel card is converted into heat, via photothermal absorption. Our laser-incubator is capable of heating the 75 µL blood-antibody sample to 37 °C in under 30 seconds, compared to over 2 minutes in a heating block. Anti-D FFMU (for further manufacturing use) with doubling dilutions is predominantly the antibody of choice for our investigation. K, Fy and Jk IgG antibodies have also been tested, resulting in similar outcomes. We show that laser incubation preferentially heats red blood cells, triggering rapid antigen-antibody binding. We detect no significant damage to the cells or antibodies for laser incubations of up to fifteen minutes. We demonstrate laser-incubated immunohaematology to be both faster and more sensitive than current best practice —with clearly enhanced positive results seen after just 40 seconds of laser incubation compared to regular methods.

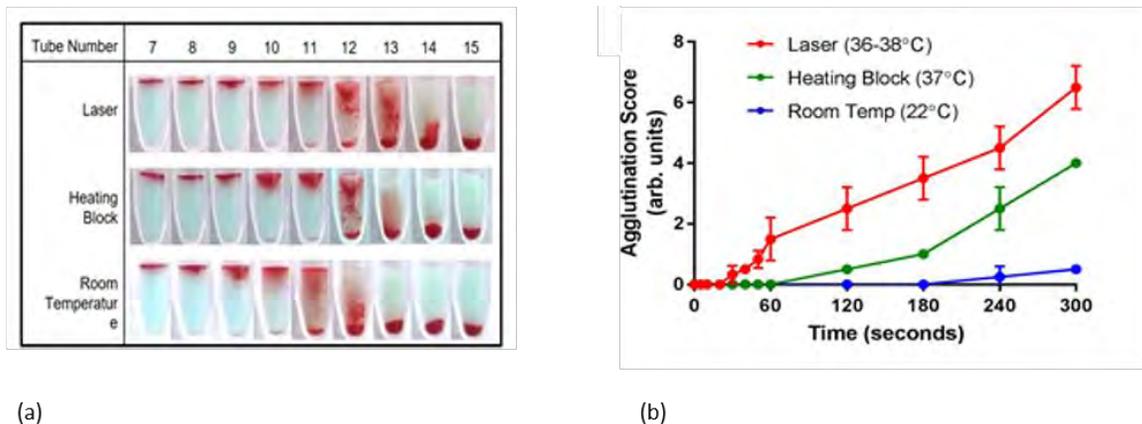


Figure. Comparison of incubation methods. Incubation at room temperature (22 – 24 °C) is compared to two methods of heating: heating block (37 °C) and laser illumination (36 – 38 °C).

(a) For a two-minute incubation time, subsequent dilutions of antibody show positive results (left) and negative results (right). Laser incubation gives clearer and more consistent positive results for weaker antibody solutions than the other two methods (giving a higher titre number).

(b) Sensitivity control check using 0.05 IU/mL anti-D antibody.

O145

## **The New Hospital Vending Machine - BloodTrack HaemoBank Remote Release**

Nicole Zacher<sup>1</sup>

<sup>1</sup>Capital Pathology, Deakin, Australia, <sup>2</sup>Haemonetics, Macquarie Park, Australia

Calvary Bruce Private Hospital is a new 118 bed hospital located in Canberra's North, the facility is serviced by Capital Pathology for the supply of blood products.

Calvary Bruce Private Hospital is 30 minutes travel from Capital Pathology's laboratory resulting in a blood delivery time exceeding one hour. This led to a need for Capital to go to market to investigate how existing systems could be improved and to avoid developing a laboratory for the hospital.

Capital Pathology's agreement with the hospital is to maintain an appropriate supply of blood products in a safe and timely manner. Capital Pathology's business requirements are to reduce blood product waste, increase staff efficiencies and reduce transport time and costs.

Haemonetics' BloodTrack system was installed to allow the storage of crossmatched, emergency and unallocated blood products at the point-of-care, where blood units are remotely assigned and dispensed from the BloodTrack HaemoBank located in the operating theatres.

The BloodTrack system has enabled Capital Pathology to move from a precautionary crossmatch system to a just-in-time (JIT) inventory management system, where blood units are crossmatched to the patient as they are required for transfusion. This has allowed Capital Pathology to store fewer units of blood at the hospital while maintaining high unit availability.

As a result of the BloodTrack implementation the following have been realised:

12. The crossmatch to transfusion ratio (C/T ratio) has reduced from a monthly average of 3.7 to 1.2
  - Increased staff time efficiencies
  - Reduced transport frequency

Manual blood register and manual processes have been eliminated

O147

## **Results from recent trials of platelet transfusions: Is less better?**

**Simon Stanworth**<sup>1</sup>

<sup>1</sup>*John Radcliffe Hospital, Oxford, United Kingdom*

Platelet transfusions are commonly administered to patients with thrombocytopenia, but understanding the exact nature of the relationship between benefit and harm has been challenging to define. There is a long history of conducting randomised trials of platelet transfusions in patients with haematological malignancies, one of the largest group of platelet recipients. Patients with haematological malignancies often develop severe thrombocytopenia, either as a consequence of their disease or its treatment, including chemotherapy and stem cell transplantation. In these patients, a general result across all platelet transfusion trials of dose and threshold, including the two largest studies, has been no difference in haemostatic outcomes between trial arms (i.e. no increased bleeding in the restrictive policy arms for transfusion by lower threshold or dose). More recently, randomised trials have been published in settings outside patients with haematological malignancies. The results of the recent 'PlaNet-2/MATISSE' study, a randomised trial of transfusion thresholds in preterm neonates, found evidence of harm with increased mortality and major bleeding when a liberal platelet count threshold ( $50 \times 10^9/L$ ) for platelet transfusion was compared to a more restrictive one ( $25 \times 10^9/L$ ). The PATCH trial investigated whether platelet transfusion in addition to standard care, compared with standard care alone, reduced death or dependence after intracerebral haemorrhage associated with antiplatelet therapy use, and reported a greater odds of death or dependence at 3 months in the platelet transfusion group. These findings question the safety of platelet transfusions in different clinical settings. Given that current policies for prophylactic platelet transfusions have only a limited role in reducing much of the bleeding seen in haematology patients undergoing intensive chemotherapy and/or stem cell transplantation, these findings also challenge haematology clinicians to apply cautious policies for platelet transfusions in patients with haematological malignancies and for researchers to identify alternative treatment strategies to minimise the burden of bleeding.

A002

## Evaluating five years of pre-transfusion patient and blood component identification observational audits: what have we learnt?

**Kaylene Bastin**<sup>1</sup>, Natalie Gaffy<sup>1</sup>

<sup>1</sup>Melbourne Health, Parkville, Australia

### Aim:

To determine the effectiveness of the pre-transfusion observational audit program at Melbourne Health (MH).

### Background:

Blood transfusions can be lifesaving; however a significant risk with each unit administered is the patient being given blood intended for someone else. MH transfuses > 1,000 red blood cells units each month, affording many opportunities for error. Pre-transfusion patient and product identification checks are essential to prevent erroneous administration. Yearly observational audits have been undertaken since 2013 by masters of nursing students (University of Melbourne) supervised by the transfusion nurse.

### Method:

Data collection tools, analysis, reporting methods and results were compared for consistency and improvement over time (2013-17).

### Results:

Yearly audits numbers varied from 37 to 97 (total = 361).

Each year the students changed, and questions were modified to improve data collection/useability.

Overtime the analysis and reporting methods have also varied, not allowing direct comparison.

The table shows an example of the changes and results over time:

Metric	2013 (N=45)	2014 (N=86)	2015 (N=95)	2016 (N=97)	2017 (N=40)
Patient wearing an ID band	98%	89%	97%	N/A	100%
Asked to state full name	44%	78% (combined)	79%	84% (combined)	73%
Asked to state DoB	64%		79%		75%
ID checked on wristband (x3 identifiers)	100%	80%	89%		100%
Patient asked to spell name	N/A	30%	38%	N/A	5%

### Conclusion:

While the methods used each year have not been directly comparable, the audits results have highlighted gaps that have been addressed and improved the quality of data collection and usability.

A003

## **How the blood champion role is contributing to patient safety in Victoria**

**Kaylene Bastin**<sup>1</sup>, Christine Akers<sup>1</sup>, Bridget Glazebrook<sup>1</sup>, Linley Bielby<sup>1</sup>, Peter Beard<sup>1</sup>, James Daly<sup>2</sup>  
<sup>1</sup>*Blood Matters, Department of Health and Human Services Victoria and Australian Red Cross Blood Service, Melbourne, Australia,* <sup>2</sup>*Australian Red Cross Blood Service, Brisbane, Australia*

### **Background**

Accreditation against the National Safety and Quality Health Service (NSQHS) Standards second edition commenced 2019. The focus of the Blood Management Standard (7) is to optimise the patient's own blood, reduce unnecessary transfusions and ensure that transfusion is appropriate and safe. Coordination of organisations response to the standard is often by Blood Management/Transfusion Nurse/Quality Officers, some are further supported by ward level blood champions (BC).

**Aims:** To understand:

- where and how the BC role is used in Victorian health services
- contributions BCs bring to patient safety.

### **Methods**

- Blood Matters surveyed 52 Victorian health services to identify attributes of the BC (March 2019).
- 4 Blood Management/Transfusion Nurses with BC portfolios shared experiences and provided further information through question/answer session at a Blood Matters Forum.

### **Results**

Thirty-one health services completed the survey (response rate 60%).

Fifteen (48%) reported active BC portfolio, 1-70 BCs per organisation; seven reported the BC role only in selected areas.

Levels of nursing staff in BC role ranged from nurse unit managers to Division 2 nurses.

Positive benefits reported:

- increased policy and procedure awareness, compliance and engagement
- reduced waste
- improved quality improvement activities participation.
- improved communication and awareness of best practice
- engagement to meet the NSQHS Standards.

Sixteen (52%) did not have BC role: three had previously implemented and abandoned, two never considered, two considered and decided not to implement, and nine with future implementation plans.

Drawbacks included time to educate and mentor, however outweighed by benefits.

### **Summary**

BCs are familiar and knowledgeable in their local area, making them an ideal conduits for information sharing and enablers of best practice. The BC role assists with meeting standards and provides professional growth for those involved. However, some health services reported difficulty with maintaining BC engagement, or are concerned about the time burden to support the role.

A005

## **Finding a match: the nationwide search to find indian-b antigen negative blood donors**

**Emily Black**<sup>1</sup>

<sup>1</sup>*Australian Red Cross Blood Service, Alexandria, Australia*

**Aim:** To conduct a nationwide search to identify Indian-B (In<sup>b</sup>) antigen negative blood donors for the Australian Red Cross Blood Service (ARCBS) inventory. In addition, to assist OneBlood and the American Rare Donor Program (ARDP) in search to find a compatible donor for a young patient with an aggressive form of neuroblastoma.

**Method:** A nationwide call out was conducted by the ARCBS National Contact Centre through various platforms. The call urged for donors who were group O or A, and exclusively Pakistani, Indian, or Iranian-descent to donate for the cause. Donors were asked to indicate that they were donating for the young patient at collection centres to alert staff of the importance. Each donation was then flagged and sent to ARCBS Red Cell Reference laboratories across Australia for In<sup>b</sup> typing to be performed.

**Results:** Whilst no new In(b-) donors were identified after testing over 200 donors, this process enabled recruitment of new donors which assists with increasing both inventory and the ethnic diversity of the donor pool. A previously known lapsed In(b-) donor from NSW, was made aware of the importance of the cause and successfully donated a whole blood donation that was compatible with the young patient.

**Conclusion:**

The ARCBS Red Cell Reference laboratories successfully found a compatible donor to assist OneBlood and ARDP for their young patient. In addition, numerous new donors were gained through the process which assists with low phenotyped inventories and the growing demand for donors from India, Pakistan and Iran as Australia's population diversifies. This case demonstrates the need to encourage and enable Australians from different ethnic backgrounds to donate blood. Stronger relationships were made with our international allies and the worldwide donor programs which strengthens the relationship between International Blood societies and corporations.

## Comparison of antibody titration methods across four platforms

**Hayley Brown**<sup>1</sup>, Annette Le Viellez<sup>1</sup>, Dianne Grey<sup>2</sup>, Elizabeth Fong<sup>2</sup>, Natalie Caldwell<sup>3</sup>

<sup>1</sup>Pathwest, Fiona Stanley Hospital, Murdoch, Australia, <sup>2</sup>Pathwest, QEII, Nedlands, Australia, <sup>3</sup>Immulab Australia, Perth, Australia

### Background:

ABO antibody titration may be useful in particular clinical conditions including solid organ and stem cell transplant and HDNB. The manual tube method (NICE) is the only method referred to in ANZSBT Guidelines however it is labour intensive and subject to poor reproducibility.

### Aim:

To evaluate the concordance of 4 methods for performing Anti-A/-B titrations.

### Method:

Patient samples and International Standards were used to assess anti-A and/or anti-B titrations (IgG and IgM) across 2 tertiary sites. NICE tube(T), BioRad CAT(B); automated Ortho CAT VisionMax(V), Immucor Capture Neo(N) were evaluated. The titre was the last reaction of 1+ (1-4+ grading). Concordance within target was considered median +/- 1 dilution.

### Results:

Total of 147 titrations were performed; 4 samples were run by 3 methods only. 85% of titre results were within target (n=125). The Nice tube technique was most frequently out of target range (13/22) particularly for IgM; 11 of 13 graded 2 dilutions higher. Other techniques out of range (9/22) graded mainly lower than the target.

	Group O		Group A		Group B	
	Within target	Outside range	Within target	Outside range	Within target	Outside range
Anti-A IgM	8/11	3 [T]			31/36	5/36 [4T,V]
Anti-A IgG	11/11	0			31/36	5/36 [T,B,V,2N]
Anti-B IgM	8/10	2 [T]	12/16	4 [2T, B,N]		
Anti-B IgG	11/11	0	13/16	3 [T,B,N]		

### Conclusion:

The range of methods showed concordant results for 85% of titrations performed. There was high consistency between automated methods. Laboratories should consider automation of titration studies to achieve consistency and efficiency.

## BloodSTAR Supporting a National Program

**Jo Cameron**<sup>1</sup>, Michael Stone<sup>1</sup>, Toby Keene<sup>1</sup>, Lyndsay Wall<sup>1</sup>, Tara Stevens<sup>1</sup>, Nicole Wicks<sup>1</sup>, Vesna Morosin<sup>1</sup>, Jennifer Roberts<sup>1</sup>, Karla Grant<sup>1</sup>

<sup>1</sup>National Blood Authority, Canberra, Australia

The National Immunoglobulin (Ig) Governance Program (the Program) is administered by the NBA on behalf of all Australian governments to ensure use and management of government funded Ig products reflects appropriate clinical practice and represents efficient, effective and ethical expenditure of government funds.

BloodSTAR is a world-first national online system developed to support those involved in the use and management of government funded Ig products in upholding their responsibilities as outlined in the *National Policy: Access to Government Funded Immunoglobulin Products in Australia*. The successful implementation of BloodSTAR in NSW with effect from 22 October 2018 completes the national rollout. BloodSTAR is now the sole channel for clinicians to seek authorisation for access to Ig products, in accordance with the *Criteria for the clinical use of intravenous immunoglobulin in Australia* (the Criteria).

The development and implementation of BloodSTAR including the incorporation of the Criteria involved two major cross-team projects spanning four years involving 251 training sessions in 83 sites with ongoing support encouraging feedback from over 13,000 users.

Implementation of the Program and BloodSTAR have facilitated better outcomes for patients, the NBA and Australian governments with:

- end to end usability from product supply to patient treatment plans and clinical outcomes;
- significantly-improved public health safety for patients through the appropriate allocation of Ig products;
- nationally consistent visibility and data collection; and
- a forecast 2018-19 \$25m savings to governments, with further \$34.5 to \$56.5 million savings expected over the next three years.

<b>BloodSTAR jurisdictional statistics</b>	
<b>All facilities in all states</b>	
Patients with active authorisations	13900
Active authorisations	13949
Registered number of users	13411

BloodSTAR captures data which is used to support Program activities such as quality assurance, education, compliance, supply management and planning, Criteria revisions, reporting and continuous performance improvement activities. The system is continuously undergoing improvements to ensure it is fit for purpose and continues to be a valuable tool in facilitating appropriate access to government-funded Ig and supporting the Program deliverables.

### **Version 3 of the Criteria for the Clinical Use of Immunoglobulin in Australia– 8 months on**

**Jo Cameron**<sup>1</sup>, Michael Stone<sup>1</sup>, Lyndsay Wall<sup>1</sup>, Vesna Morosin<sup>1</sup>, Nicole Wicks<sup>1</sup>, Tara Stevens<sup>1</sup>, Karla Grant<sup>1</sup>, Jennifer Roberts<sup>1</sup>

<sup>1</sup>*National Blood Authority, Canberra, Australia*

The *Criteria for the clinical use of Ig in Australia* (the Criteria) defines the eligibility for access to immunoglobulin (Ig) products funded by governments at no direct cost to the patient. The Criteria were developed in collaboration with expert specialist clinicians and identify the medical conditions and circumstances for which the use of Ig is considered to be clinically appropriate and where there are no safe, effective and cost-effective alternative treatments. The Criteria clearly articulate and standardise the qualifying and continuing Ig access requirements using a nationally consistent approach.

Originally published in hard copy in 2012 and 2014, Version 3 of the Criteria was released electronically in 2018 for use in the national ordering and outcomes system– BloodSTAR (Blood System for Tracking Authorisations and Reviews). The development and implementation of Version 3 Criteria in BloodSTAR was a major project spanning four years and involved wide public consultation to allow community consideration of proposed revisions.

Ongoing evolution of the Criteria is occurring following two formal process streams: Programmed Changes where substantial project and robust methodological approaches are required; and Progressive Changes which address clarifications, corrections and administrative improvements.

Following implementation, 7,680 patients have transitioned to Version 3 of the Criteria with an additional 7398 new authorisations approved. The NBA has received and responded to over 150 pieces of feedback from stakeholders relating to the strengthened access arrangements. Actions arising generally align with the Progressive changes stream and have been managed using a defined formal process of investigation and appropriate change approvals. Feedback related to BloodSTAR system functionality is managed using existing system improvement processes.

The Criteria will undergo incremental changes as required, based on feedback, issues or the emergence of new evidence. BloodSTAR and the NBA website is updated with any Criteria revisions in real time to ensure currency is maintained.

## Geographic Variation in Immunoglobulin Use in Australia

**Jo Cameron**<sup>1</sup>, Toby Keene<sup>1</sup>, Melissa Farrance<sup>1</sup>, Vesna Morosin<sup>1</sup>, Tara Stevens<sup>1</sup>, Nicole Wicks<sup>1</sup>  
<sup>1</sup>National Blood Authority, Canberra, Australia

Immunoglobulin (Ig) products offer significant therapeutic benefit to people with various chronic and acute conditions where immune replacement or modulation therapy is indicated. In Australia, the provision of Ig is managed and funded by the National Blood Authority (NBA) on behalf of all governments. Introduced in 2016, BloodSTAR (Blood System for Tracking Authorisations and Reviews) was developed by the NBA to manage access to government-funded Ig.

**Method:** Data from BloodSTAR was examined to determine the geographic distribution of Ig use. All Ig authorisations for the 2017-2018 financial year were included. Patient numbers were standardised per 1,000 population [1].

**Results:** 19,414 patients received 6,128,717 grams of government-funded Ig during 2017-18. Nationally, 0.8 patients per 1,000 population received Ig in 2017-18. There was geographic variation in use ranging from 0.5/1,000 to 1.0/1,000 between jurisdictions (see Figure 1). There is also variation in Ig use in grams per 1,000 population, ranging from 126.9 grams/1,000 to 324.2 grams/1,000. Comparing only the five largest Australian states, the variation in Ig use is 2.1 fold, ranging from 155.0 grams/1,000 to 324.2 grams/1,000.

**Discussion:** The reasons for this geographic variation are unknown but may represent differences in clinical practice, differing disease prevalence, variable access to alternative therapies, and/or access to specialist services across Australia. The prescription and dispensing of Ig products may vary between jurisdictions due to differences in local governance arrangements for Ig products.

**Conclusion:** There is considerable geographic variation across Australia in use and dosing of government-issued Ig when measured using BloodSTAR. Further investigation is required to understand the reasons.

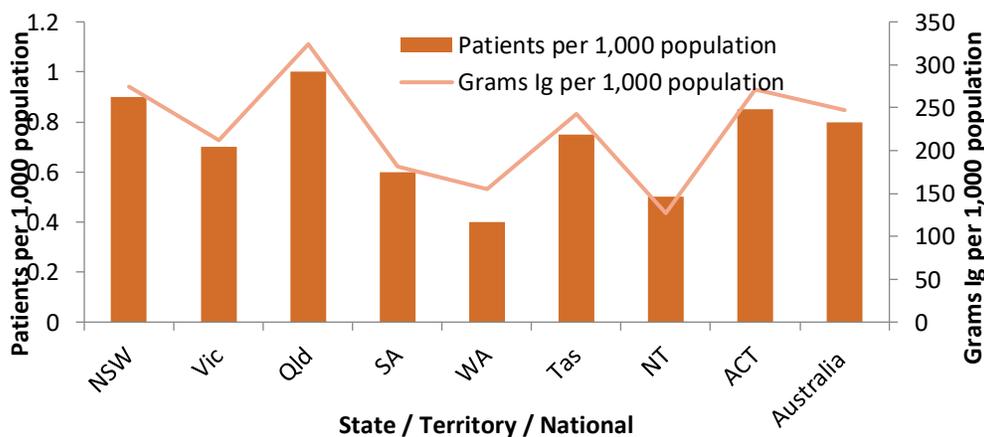


Figure 1. Patients and grams per 1,000 population by Australian state/territory compared to Australia nationally.

### References:

[1] Australian Bureau of Statistics Australian Demographic Statistics (cat. No 3101.0) Accessed at: <https://www.abs.gov.au/ausstats/abs@.nsf/mf/3101.0>

## The National Immunoglobulin Governance Program

**Jo Cameron<sup>1</sup>**, Tara Stevens<sup>1</sup>, Nicole Wicks<sup>1</sup>, Vesna Morosin<sup>1</sup>, Lyndsay Wall<sup>1</sup>, Michael Stone<sup>1</sup>  
<sup>1</sup>National Blood Authority, Canberra, Australia

The National Immunoglobulin (Ig) Governance Program (the Program) is an innovative initiative improving the use and management of government-funded Ig through nationally coordinated health sector governance arrangements. The Program brings together and improves a number of previously existing but disparate processes and these together with a number of new initiatives form the basis of the Program.

Since its inception in 2014, the Program has delivered major policy and process improvements and incorporates new and customised collaborative measures, some of which have not previously been implemented in the Australian health care system. Australia now has full traceability of Ig product from supply to patient administration, and capturing patients' responses to treatment provides valuable information to inform future work.

Over 19,000 patients access government-funded Ig in Australia each year at a cost of \$582.3 million. From 2008-9 to 2017-18 demand for Ig has been increasing at approximately 11% per annum, however trend analysis indicates that the rate of increase will reduce to 8% in 2018-19.

This reduction coincides with the implementation of Program initiatives designed to ensure Ig is directed to patients who are most likely to benefit based on current evidence and expert opinion. This includes the transition to Version 3 of the *Criteria for the Clinical Use of Ig in Australia* and the national implementation of the BloodSTAR system, a world-first national online ordering and outcomes database.

Moving forward, in addition to the continuation of established Program initiatives, the National Immunoglobulin Performance Improvement Strategy 2019-2022 (the Strategy) has been developed to continue the positive trend through the improvement of the prescription, use and management of government-funded Ig products. The strategy outlines the Program's intent to enhance various aspects of the Program through monitoring the governance arrangements within a continuous improvement cycle with a view to improving performance through focussed activities.

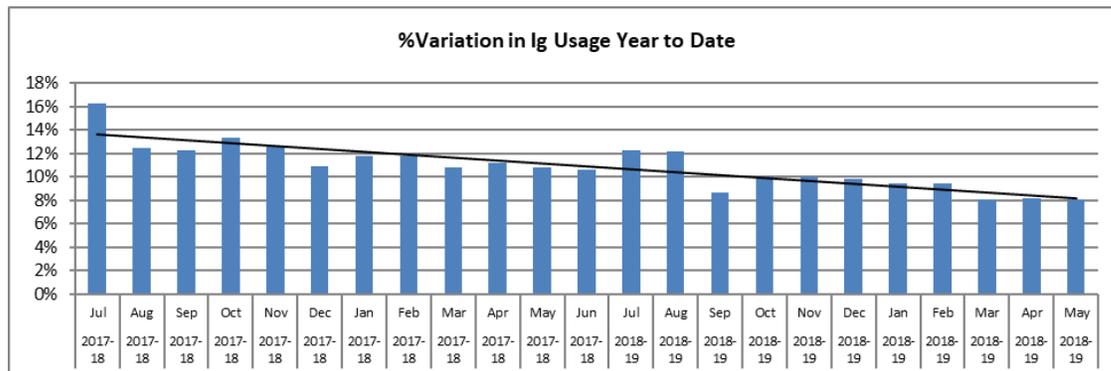


Figure 1: % Variation in Immunoglobulin Usage (Year to Date)

## Improving the Governance and Use of Immunoglobulin in Australia

**Jo Cameron**<sup>1</sup>, Vesna Morosin<sup>1</sup>, Toby Keene<sup>1</sup>, Lyndsay Wall<sup>1</sup>, Meliss Farrance<sup>1</sup>, Tara Stevens<sup>1</sup>, Nicole Wicks<sup>1</sup>, Michael Stone<sup>1</sup>

<sup>1</sup>National Blood Authority, Canberra, Australia

Immunoglobulin (Ig) products offer therapeutic benefit to people with chronic and acute conditions. In Australia, provision of Ig is managed and funded by the National Blood Authority (NBA) on behalf of all governments. Ig is a high cost blood product and the demand for use in Australia has been growing at an average 11% over the last five years [1]. In 2017-18, a total of 6.13 million grams of Ig was issued in Australia representing a cost of \$582.3 million (including plasma collection) [1].

The NBA is improving the effectiveness of the Ig governance program, assessing compliance with policy requirements, identifying areas for improvement, and implementing measures to drive improvement. The National Immunoglobulin Governance Performance Improvement Strategy 2019-2022 promotes a nationally consistent approach to monitoring effectiveness, identifying obstacles and challenges, and improving performance through a range of collaborative activities [2].

The Strategy identifies 5 key performance areas for measurement and improvement:

- Ig provision reflects appropriate clinical practice
  1. Uniform compliance with the National Policy
  2. Local Ig governance arrangements are robust and align with relevant requirements
  3. Service delivery is efficient and effective
  4. Data collection supports future work

These performance areas will drive performance improvement activities across 5 pathways as shown in Table 1.

Pathways to performance improvement	Examples of performance improvement activities
<b>Education and support</b>	Online education modules Patient information sheets
<b>Communications and relationships</b>	Supporting and strengthening governance committees and working groups Enhancing guidance on inventory management
<b>Program assurance and policy compliance</b>	Provision of data and reports to key stakeholders to support planning and management Support to prescribers on outcomes and effectiveness of Ig treatment
<b>Knowledge development Enhancing current policy and access arrangements</b>	Funding research to close knowledge gaps and improve outcomes Responding to feedback on our services Updating and improving access arrangements based on evidence

### References:

[1] National Blood Authority, Australia. *Annual Report 2017-2018*. [www.blood.gov.au/about-nba](http://www.blood.gov.au/about-nba)

[2] National Blood Authority, Australia. *National Immunoglobulin Performance Improvement Strategy 2019-2022*. [www.blood.gov.au](http://www.blood.gov.au)

A012

## Variable MSs typing indicates hybrid glycoporphins

**Tanya Cawthorne**<sup>1</sup>, Amy Tearle<sup>1</sup>, Yew-Wah Liew<sup>2</sup>, Brett Wilson<sup>2</sup>

<sup>1</sup>Australian Red Cross Blood Service, Perth, Australia, <sup>2</sup>Australian Red Cross Blood Service, Brisbane, Australia

Background: M/N antigens are carried on glycoporphin A (GPA) and S/s on glycoporphin B (GPB) and are encoded by *GYPA* and *GYPB* respectively. Variant glycoporphin molecules arise when *GYPA* and *GYPB* genes cross over forming GP(A-B) or GP(B-A) hybrids or where gene conversion events cause small sections of *GYPA* to insert into *GYPB* and vice versa forming complex GP(B-A-B) or GP(A-B-A) hybrids.

Aim: We investigated three samples giving variable results with different M, S or s blood group typing reagents.

Method: Samples were tested for M, S and s using at least two commercial blood grouping reagents as per the manufacturer's instructions. Additional phenotyping, genotyping and sequencing was performed where required.

Results:

Sample 1	Reagent	Clone	Result
Anti-M	1	11H2	Positive (weaker than control)
	2	BS57	Negative
	3	M2A1	Negative
Anti-S	4	MS-94	Negative (IS) 1+ (1 hr RT)
	5	P3S13JS123	Positive

- Immucor BioArray™ HEA Precise Beadchip: NTD
- Trusight™ One sequencing panel: *GYPA*\*02/02 *GYPB*\*04/\*06.02, predicted phenotype of M- N+ S+ s+ He+.

Sample 2 and 3	Reagent	Clone	Result
Anti-s	6	P3BER	Negative
	7	N/A	Positive

- Immucor BioArray™ HEA Precise Beadchip: predicted phenotype S+ s+
- Sample 2: Mia+ Vw- Mur+ MUT+, suggests GP.Mur
- Sample 3: Mia- Vw- Mur- Hil+ MINY+ MUT-, suggests GP.Hil

Conclusion: All samples had hybrid glycoporphins. The weaker/false M+ result in sample 1 was due to anti-M<sup>e</sup> activity in 11H2 clone which is known to react with M- He+ red cells. However this is the first S+ He+ sample we have seen that has given variable S typing. For samples 2 and 3, it has previously been reported that GP.Mur, GP.Hil and other hybrid glycoporphin s+ samples type as s- with reagents containing clone P3BER and s+ with polyclonal sources. All monoclonal antibodies target a specific area and may give variable or unexpected results with variant samples.

A013

## **Out-of-hospital red cell transfusions successfully implemented in Victoria with zero wastage – an audit of the first 4 years.**

**Edward Chew**<sup>1</sup>, Christopher Hogan<sup>1</sup>, Giles Kelsey<sup>1</sup>, Murray Barkmeyer<sup>2</sup>, Zoe McQuilten<sup>3</sup>, Michael Haeusler<sup>1</sup>

<sup>1</sup>Royal Melbourne Hospital, Parkville, Australia, <sup>2</sup>Air Ambulance Victoria, Essendon, Australia, <sup>3</sup>Department of Epidemiology and Preventive Medicine, Monash University, Clayton, Australia

### **Background**

Red cell concentrates (RCCs) have been supplied by the Royal Melbourne Hospital (RMH) Transfusion Laboratory for use by Air Ambulance Victoria (AAV) since 2011. Out-of-hospital RCC were administered as deemed clinically appropriate by the Trauma team.

### **Aims**

- To retrospectively audit the quality control of RCCs supplied to AAV.
1. To retrospectively audit the clinical RCC usage by AAV.

### **Methods**

RCCs supplied from April 2011 to December 2014 were assessed for “cold chain” integrity by reviewing the data logs of the dedicated controlled-temperature RCC storage box and refrigerators, and the temperature tags on the RCCs. The AAV notes were manually reviewed for clinical information and RCC usage.

### **Results**

RCCs supplied to AAV are blood group O Rh(D) negative and Kell negative. The “freshest” possible RCCs were supplied and if not used after 2 weeks, were returned to the RMH inventory. The RCC temperature tags showed no temperature excursions above 10°C. No RCC wastage was found.

During the 45 months audited, 87 patients (54 males, 33 females) had RCC transfusions. The median age was 36.5-years-old (range 13 to 82-years-old). Sixty-five patients (75%) were involved in motor vehicle accidents, of whom 2 were pregnant. The median number of RCCs transfused enroute was 2 (range 1 to 8 units) with 36 patients having 2 units of RCCs. Five patients died at the accident scene and 11 patients had an unrecordable blood pressure despite resuscitation.

### **Conclusion**

We have established a protocol for use of RCCs out-of-hospital by AAV. This audit showed integrity of the “cold chain” with no RCC wastage. The majority of patients (75%) transfused had blood loss due to motor vehicle accidents. Further research is underway to determine the long-term outcomes of patients who had out-of-hospital RCC transfusions. The impact of using tranexamic acid from 2015 will also be assessed.

## **Comparison of strength of haemagglutination scores and RhD molecular genotyping results for females of child-bearing potential: the Melbourne Pathology experience.**

**Michael Crennan**<sup>1</sup>, Ellen Maxwell<sup>1</sup>, Linda Saravanan<sup>1</sup>

<sup>1</sup>Melbourne Pathology, Collingwood, Australia

### **AIMS**

RhD genotyping distinguishes RhD variants capable of sensitisation to RhD from those variants without such potential ('Weak D' variants) but is only used in selected patients. The haemagglutination criterion for referral of a sample for RhD genotyping is  $\leq 2+$  (0-4+ scale)<sup>1</sup>. We reviewed haemagglutination scores in samples collected at Melbourne Pathology from women of child-bearing potential ( $\leq 50$  years) referred for RhD genotyping between November 2017–April 2019 with the aim of determining whether: 1. cut-off score  $\leq 2+$  is too high using our method; 2. haemagglutination scores using our method can be used to distinguish clinically important variants from Weak D variants.

### **METHOD**

Haemagglutination scores were derived from the BioRad IH-1000 reader software using BioRad Column Agglutination Technology (CAT), with manual adjustment of scores made where necessary according to documented procedures. RhD genotyping was performed at The Australian Red Cross Blood Service (Brisbane).

### **RESULTS**

159 samples met the criteria for genotyping referral. Genotyping confirmed 140 (88%) were Weak D Types 1, 2 or 3 and 19 (12%) were RhD Variants Capable of Sensitisation to RhD. Of the 140 Weak D variants, 100 (70%) had score 2+, 40 (29%) had score 1+ and 1 (1%) had score +/- . Of the 19 samples genotyped as a D Variant Capable of Sensitisation to RhD, 9 (47%) had score 2+, 4 (21%) had score 1+, 5 (26%) had score +/- and 5 (26%) had score 0.

### **CONCLUSION**

The data supports the current referral criterion ( $\leq 2+$ ) with our method. We could not distinguish clinically important variants from Weak D variants based on haemagglutination score, although score +/- was more frequent with clinically important D variants. In the absence of genotyping of all females of child-bearing potential, larger studies involving a variety of methods may be warranted to refine referral practices.

- Australia and New Zealand Society for Blood Transfusion (ANZSBT). *Guidelines For Transfusion and Immunohaematology Laboratory Practice*. ANZSBT 2016

A016

## **Impact of anaemia on muscle oxygen saturation during isometric exercise**

**Philip Crispin**<sup>1</sup>

<sup>1</sup>*Canberra Hospital, Canberra, Australia*

**Aim:** To determine whether changes in muscle oxygen saturation during a short isometric contraction with anaemia predict exercise performance

**Method:** Resting normal controls and haematology patients performed a 20s isometric handgrip contraction and then relaxed the forearm muscles. Measurement of muscle oxygen saturation in the forearm flexor muscles was undertaken by near infrared spectroscopy continuously prior to, during and after contraction for up two minutes, or until a plateau in oxygen saturation was seen. Participants also underwent a six minute walk test to determine functional capacity. Oxygen saturation parameters were determined on the control population, then examined in anaemic patients. Pearson's correlations with these parameters and haemoglobin and walk distance, as a measure of clinical impact of anaemia, were undertaken. Stepwise multivariate linear regression was performed to determine independent variables.

**Results:** From the graphed muscle oxygenation curves of controls (n=27), pre-test, exercise peak, nadir, end contraction and post-test peak saturations were identified parameters, as were the time to recovery to baseline saturations and the time to reach a plateau level of oxygen saturation. A total of 94 tests were performed, including 17 where tests were repeated with a change in haemoglobin concentration, mostly due to transfusion. Muscle oxygen saturation prior to the exercise (p=0.01), at nadir (p=0.01), peak (p<0.01) and at the end of contraction (p<0.05) were significantly correlated with haemoglobin concentration, with the latter losing significance on multivariate regression. Pre-test (p=0.02), nadir (p<0.01), peak (p=0.01) and end test saturations (p=0.01) were associated with the distance walked in 6 minutes, as were the recovery (p<0.01) and post-test peak (p<0.02) times, with recovery time and peak saturation predictive in linear regression.

**Conclusion:** Muscle oxygenation during isometric forearm contraction is impaired in anaemia and is associated with impaired function as measured by the 6 minute walk test distance.

A017

## **Blood products to improve coagulation in thrombocytopenia: an ex vivo study.**

**Philip Crispin**<sup>1</sup>, Lucy Coupland<sup>2</sup>, Elizabeth Gardiner<sup>2</sup>

<sup>1</sup>Haematology Department Canberra Hospital, Garran, Australia, <sup>2</sup>John Curtin School of Medical Research, Australian National University, Acton, Australia

**Aim:** To compare the ability of haemostatic blood products to improve ROTEM parameters in thrombocytopenia.

**Methods:** Whole blood from eight consenting haematological malignancy patients with platelet counts  $<20 \times 10^9/L$  were tested using the ROTEM assay, ExTEM. Blood was mixed with platelet concentrates and cryopreserved platelets (CPP) in ratios equivalent to one transfused unit per 70kg person. Fibrinogen concentrate (FibConc) was mixed equivalent to 100mg/kg and cryoprecipitate to match this, based on published specifications. Plasma derived FVIII/VWF concentrate and FXIII concentrate ratios were calculated equivalent to cryoprecipitate. CPP were prepared from group O pooled platelets and stored at  $-80^\circ C$  in 5% DMSO. ExTEM parameters were compared with paired T tests, with  $p < 0.05$  considered significant.

**Results:** Only cryoprecipitate improved all ExTEM parameters. Clotting time (CT) was reduced by cryoprecipitate and CPP, but not platelets, FVIII, FXIII or FibConc. Clot formation time (CFT) was improved by the addition of platelets and all fibrinogen containing products. The alpha angle was increased by cryoprecipitate and CPP. Platelets and cryoprecipitate were most effective at improving clot amplitudes at 20 min (A20) with FibConc alone, or with added FVIII, being significantly less effective. Subsequent analysis of the cryoprecipitate used revealed a higher fibrinogen concentration than expected, which may have contributed to the improved cryoprecipitate A20 over FibConc. Improvement in A20 was seen with FibConc despite normal to elevated patient baseline fibrinogen concentrations. CPP did not have a significant effect on amplitude values. Neither FVIII/VWF concentrates nor FXIII improved any ExTEM parameters.

**Conclusions:** Ex-vivo, platelets or cryoprecipitate seem similarly effective at improving clot amplitudes and CFT in thrombocytopenia, with cryoprecipitate also improving CT. The pro-coagulant effect of CPP is seen with improved CT, but not A20. Cryoprecipitate may be an alternative approach to improve coagulation if platelets are not available.

A018

## **Clinical consequences of extremely rare anti-PP1Pk (formerly anti-Tja) isoantibodies in pregnancy**

**Pietro Di Ciaccio**<sup>1</sup>, Jennifer Curnow<sup>1</sup>, Peta M Dennington<sup>2</sup>, Thushari Indika Alahakoon<sup>3</sup>, Sue Heath<sup>3</sup>

<sup>1</sup>Department Of Haematology, Westmead Hospital, Westmead, Sydney, Australia, <sup>2</sup>Australian Red Cross Blood Service, Alexandria, Sydney, Australia, <sup>3</sup>Westmead Institute for Maternal Fetal Medicine, Westmead Hospital, Westmead, Sydney, Australia

**BACKGROUND:** The P and Pk red cell antigens are of almost universal incidence. Their absence, together with absence of P1, is known as the extremely rare “p-null” phenotype. European prevalence of this phenotype is approximately 5.8 per million.

Such individuals spontaneously form anti-PP1Pk antibodies which are potent haemolysins associated with severe haemolytic transfusion reactions. The literature is limited to several case reports of association with spontaneous abortion and haemolytic disease of fetus and newborn (HDFN).

**CASE:** A 22 year old woman had anti-PP1Pk antibodies detected on routine antenatal screening during her first pregnancy, with no history of miscarriage or transfusion. No compatible donors were registered in Australia or discovered by family screening. An international search only yielded two potential p-null donors in Japan. Maternal haematinics were optimised. Autologous collection was unavailable in pregnancy.

Periodic fetal ultrasonography showed normal growth parameters. Middle cerebral artery peak systolic velocities, a surrogate of fetal anaemia, were normal to borderline in third trimester. Anti-PP1Pk titres fluctuated between 1:2 and 1:16. Insertion of the cord at the placental margin was considered a potential risk for post-partum bleeding.

Our patient entered spontaneous labour at term. After failing to progress, she underwent an uncomplicated caesarian section. Though not anaemic, the baby was moderately jaundiced with a positive direct antiglobulin test, consistent with HDFN, requiring treatment with phototherapy and IVIg infusion. Cord blood eluate showed panagglutination consistent with anti-PP1Pk. Mother and baby were discharged six days postpartum. Autologous blood collection and storage for future use will occur when breastfeeding is completed.

**CONCLUSION:** We report an extremely rare case of maternal anti-PP1Pk antibodies with uncomplicated delivery of a healthy baby with HDFN requiring therapy but not transfusion. Blood compatible for ABO group and p-null phenotype could not be sourced. Early referral to a high-risk fetomaternal unit is essential.

A019

**Validation process of the Pneumatic Tube System for blood product transport at The Queen Elizabeth Hospital, South Australia.**

**Adam Dichiera**<sup>1</sup>, Joanne Goodwin<sup>1</sup>

<sup>1</sup>*Sa-Pathology, Woodville South, Australia*

**Aim:**

The aim was to become the first hospital in SA to have a completely validated PTS system that would reduce time delays to treatment and provide a more efficient service delivery for patients. The Pneumatic Tube System (PTS) at TQEH underwent an upgrade with the additional intention to utilise the PTS for transportation of blood products to the majority of clinical areas. It was postulated that direct delivery would significantly reduce the need for foot transportation and therefore improve the time from when clinical staff request blood products, to the time they receive the blood for transfusion.

**Method:**

Prior to the PTS upgrade work commencing, decisions specific to the transportation of blood products were compiled. Once all required elements were in place, a validation process was planned and undertaken to assess the system for potential transportation of red cells, platelets and plasma between the blood bank and all clinical areas of TQEH. Validation method entailed sending red cells, platelets and FFP separately to each PTS outlet. Each journey and product was assessed for transport time, product integrity, temperature of the canister and product, g-force, audible and visual alarms, cold chain and chain of custody.

**Result:**

The validation of TQEH PTS confirmed that blood products remain at a safe and steady temperature during the journey from the blood bank to the clinical area. Nil effects to the product integrity, maximum 5 min travel time including pre-launch time. No problems with the integrity of the blood bags were noted during the audit.

Nurses in some clinical areas are able to request, receive, check and commence the blood within 15 minutes.

**Conclusion:**

PTS was assessed to be a reliable and efficient method of requesting and receiving blood products in the clinical area.

## **From then to now: a decade of fresh blood product use in Western Australia**

**Amanda Esson**<sup>1</sup>, Debbie Pinchon<sup>1</sup>, Sharon Nowrojee<sup>1</sup>

<sup>1</sup>*Department of Health (WA), Perth, Australia*

**Aim:** Following changes in transfusion practice and product management in Western Australia (WA), we examine state-wide issuance and discard trends and fresh blood component utilisation in WA metropolitan public hospitals (MHPs) over the past decade

**Method:** State-wide issuance and discard data were examined for trend over time, WA MPH transfusion data were analysed by admission type, major diagnostic category (MDC) and diagnostic related group.

**Result:** Over the past decade, WA's issuance per 1,000 population has seen a reduction in red cells and fresh frozen plasma (FFP), remained stable overall for platelets and increased for cryoprecipitate. MPHs received the majority of fresh blood product issued.

State-wide red cell discards decreased from 5.2% to 4.2% between 2015 and 2018.

In WA MPHs in 2018, most red cells were transfused in haematological (18%), neoplastic (15%) and digestive system disorders (14%), with platelets largely used in neoplastic (37%) and haematological (20%) discharges. Non-elective discharges used most red cell (66%), FFP (75%), and cryoprecipitate (71%) product, while platelets use was similar between admission types (51% non-elective). Non-surgical discharges used the majority of red cells (61%) and platelets (67%), while cryoprecipitate was largely used in surgical cases and FFP use was similar for surgical and non-surgical discharges. Between 2009 and 2019, mean red cell units transfused per discharge decreased in all MDCs, with the exception of 'Ear, Nose, Mouth And Throat' (0.6% of red cells).

**Conclusion:** From 2009-2018, issuance and transfusion increased in red cells and FFP and decreased in cryoprecipitate. Reduced WA MPH platelet transfusion was not reflected in WA issuance data. Sustained changes in blood use may be attributable to changing transfusion practice in both medical and surgical areas, potentially including uptake of technologies such as ROTEM, critical bleeding protocols and the proactive treatment of iron deficiency anaemia with oral and intravenous iron.

## **Modelling the Risk of Transfusion Transmitted Chagas Disease in Australia**

**Robert Flower**, Elvina Viennet, Helen Faddy

<sup>1</sup>*Australian Red Cross Blood Service, Kelvin Grove, Australia*

### **Aim**

The aim of this study was to estimate the risk of transfusion transmission of Chagas disease in Australia. There is an increased risk of spread outside South America as a result of migration of asymptomatic parasitemic individuals and the WHO has an initiative to measure risk in non-endemic countries.

In non-endemic countries Chagas disease (a zoonotic tick-transmitted parasitic disease endemic in South America) is transmitted congenitally or via blood transfusion.

### **Method**

Census data (2017) on immigration to Australia from South America and prevalence in source countries were used to estimate risk of parasitemia in immigrants from South America. The risk of a parasitemic donation was estimated on the basis of reported data from Canada.

### **Result**

Following published methodology it was estimated that 3.37% of South American immigrants were potentially parasitemic, representing 5,971 individuals in Australia. Based on published data from the Canadian Blood Service, it was estimated that 199 exposed potentially parasitemic individuals are likely to present to donate blood each year, with a risk of 3.6 antibody-positive donations. Amongst the immigrants it is estimated that there were 2,023 females of childbearing age and 90 births annually with 4.5 exposed, potentially parasitemic newborns, representing a negligible risk of a parasitemic donation from congenital transmission, when reaching adulthood.

### **Conclusion**

In Australia, the risk of a Chagas-disease positive donation is very low, in addition there is universal leukodepletion of the blood supply and published data suggests that a filtration step removes trypanosomes with the result that estimated risk is zero.

While in Australia two Chagas disease cases in immigrants from South America have been reported and diagnosis in immigrants from endemic regions of South America is an emerging challenge for general practitioners; the risk of transfusion transmission in Australia is essentially zero.

## **Integrated Bioinformatics Software to Provide a Complete Blood Group Genotype**

**Robert Flower**<sup>1</sup>, Sudhir Jadhao<sup>2</sup>, Elizna Schoeman<sup>1</sup>, Eileen Roulis<sup>1</sup>, Catherine Hyland<sup>1</sup>, Shivashankar Nagaraj<sup>2</sup>

<sup>1</sup>*Australian Red Cross Blood Service, Kelvin Grove, Australia*, <sup>2</sup>*Institute of Health and Biomedical Innovation, QUT, Brisbane, Australia*

### **Aim**

The objective of this study was to develop and validate an automated bioinformatics system for online application to genotype and predict phenotype for both known and novel variants for all 39 blood group systems from next generation/massively parallel sequence (NGS/MPS) data.

There is increasing availability of DNA sequence data from patients and donors however a built for purpose informatics system with rapid data processing to extract a full extended blood group profile with the potential to predict extended transfusion matching requirements is not yet available.

### **Method**

Development of a system for blood group (BG) profiling was divided into three steps: 1) Extract single nucleotide variants (SNVs) and copy number variation (CNVs) from NGS data; 2) Develop an algorithm to associate these with the known SNVs and CNVs that define blood groups (including those resulting from conversion, crossover and other recombination events); 3) Identify variants in blood group genes that many encode novel or rare antigens. Finally, integrate these elements into user-friendly software and validate the package by blinded analysis of sequences from individuals with extensive known serologically characterised blood group profiles.

### **Results**

The fully automated identification of genetic variants and prediction of BG phenotype was 100% accurate for 20 NGS sequences for which serological data was available. An additional file of potential novel variants was included in the output.

### **Conclusion**

The bioinformatics platform developed accurately and reproducibly extracted BG profiles and has real world advantages over current sequence analysis tools including a specific focus on blood group genes only, rapid data processing and scalability.

We are currently utilising this software to assist in rapid analysis of sequences from various population groups, including those with distinctive and complex BG profiles such as Sub-Saharan Africans, Indigenous Australians and the complex populations in the ethnic tapestry that is India.

## **In Silico Modeling of Glycophorin MNS System Blood Group Antigens**

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### **Aim**

To develop molecular models of the extracellular structures of Glycophorin A (GYPA) and Glycophorin B (GYPB) to understand the structural basis of antigenic variation resulting from missense mutations in these small molecules (71 and 40 residues defining 49 antigens). A further aim is to use these models as a basis for rational design of targets to evaluate novel blood typing reagents.

### **Method**

As there are no existing X-Ray crystallographic models of GYPA due to its high level of glycosylation (Chang et al., 2007; Lee, Fusco, & Sapphire, 2009). A set of six possible initial structural models were generated using a combination of ab initio structure prediction methods. The stability of these models was tested by performing Molecular Dynamics (MD) simulations in explicit water.

All MD simulations were performed using the GPU version of GROMACS 2019.1 on the Wiener HPC cluster at the University of Queensland, with the GROMOS 54A7 force field for modelling protein structures. Stability was analysed using Root Mean Square Deviation (RMSD) on backbone atoms, and clustering of the relevant combined MD simulation trajectories in which each 200 ns trajectory contained 10,000 frames.

### **Results**

The results indicate that GYPA is apparently an intrinsically disordered protein possibly stabilised by interactions with other surface molecules. However, the structure of the Exon 3-4 junction converges to a common structure across all models. This junction (amino acids 64 to 85), appears as a beta hairpin-like structure with externally facing side chains defining 9 blood group antigens arising from single amino acid replacement missense mutations (MNS12 Vr, MNS38 Osa, MNS16 Ria, MNS 14 Mta, MNS 37 ERIC, MNS 47 SARA, MNS 45 ENEV, MNS43 MARS, and MNS 39/41 HAG)

### **Conclusion**

The models from this study have been developed as a foundation for future work including the design of constrained and cyclic peptides to mimic the modelled form of the Exon 3-4 region of GYPA for use in development of typing reagents.

A027

**Anti-Sc2 identified through an incompatible crossmatch in a multi-transfused allo-immunised patient.**

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**Background:** A 41-year-old A Rh (D) Positive C+ D+ E- c- e+ multi-transfused male presented to a tertiary hospital with respiratory sepsis. The patient had a history of anti-c (2017) and anti-S (2015) which were undetectable. Anti-E was present and his direct antiglobulin test (DAT) was 1+ IgG and negative C3d. A sample was referred to the Red Cell Reference (RCR) laboratory as one of eight R1R1 S- red cell segments was 3+ incompatible by gel indirect antiglobulin test (IAT).

**Aim:** To investigate the cause of the incompatible crossmatch and determine if there was an additional antibody present.

**Method:** Standard serological procedures were used to perform phenotyping and determine antibody specificities in the patient's sample. A DAT was performed on both the patient and the incompatible donor. The patient's plasma was tested against the donor's cells following papain and dithiothreitol (DTT) treatment. Genotyping was performed using the Immucor BioArray™ HEA Precise BeadChip™ (HEA).

**Results:** The RCR laboratory confirmed the presence of Anti-E and suspected an antibody directed against a low incidence antigen as the incompatible donor segment was DAT negative. Reactivity with cells from the donor segment following papain and DTT treatment provided a clue to the implicated blood group system. The phenotype of the donor segment was Kp(a-) K:-17; Wr(a-); Co(b-); Sc:2. Additional testing confirmed the presence of anti-Sc2. An acid glycine eluate prepared from the patient's cells was non-reactive against a panel of cells including the Sc:2 donor. The patient and donor gave predicted phenotypes of Sc:1,-2 and Sc:1,2, respectively by HEA.

**Conclusion:** An unexpected single unit incompatible crossmatch may suggest an antibody to a low frequency antigen. Identification of these antibodies can be difficult and resolution is dependent on the availability of rare cells and antisera. Anti-Sc2 has been implicated in cases of haemolytic disease of the fetus and newborn but only rarely in haemolytic transfusion reactions.

## Antibody screen comparison between two analysers: AutoVue and Neo

**Dianne Grey**<sup>1</sup>, Elizabeth Fong, Annette Le Vielez, Natalie Caldwell

<sup>1</sup>Pathwest, Nedlands, Australia

**Aim:** To compare 3-cell antibody screen results between Ortho AutoVue and Immucor Neo analysers.

**Method:** Routine antibody screen samples, tested on our AutoVue analyser (Ortho), were selected for comparison on the Neo Immucor analyser (Immulab) (n=471). The Neo, based on solid phase technology (SPRCA) detects IgG antibodies, whilst the AutoVue is glass bead column agglutination (CAT) and captures both IgG and IgM. Immucor screening cells were used on the Neo and Immulab for the AutoVue.

**Result:** Results of the antibody screens are shown in Table 1; 75% of samples tested were positive by AutoVue; 49% by Neo. Table 2 shows the antibody specificities for samples positive by AutoVue but negative by Neo: anti-M, Lea/Leb and P1 accounted for 66% (91 of 138); only 14% (20 of 138) were considered clinically significant alloantibodies. 15 samples were negative by AutoVue but positive by Neo; 12 were known to be rhesus associated. We were not able to exclude the antigen expression on the screening cells as a factor in detection rates.

Table 1. Number of negative and positive antibody screen results using Neo and AutoVue

Antibody Screen Results	Neo	AutoVue
Negative	242 (51%)	119 (25%)
Positive	229 (49%)	352 (75%)
Total	471	471

Table 2. Antibody specificity for positive antibody screen by AutoVue but negative by Neo (n=138)

Antibody	Numbers
M	44
Lea &/or Leb	38
P1	9
RhDIg	4
Daraumumab	1
Isatuximab	1
Rh (-C, -E)	3
K	11
Fya	3
Fyb	2
S	1
Panreactive	4
Autoantibody	3
Weak non-specific	14

**Conclusion:** Distinct differences between antibody positivity by AutoVue (glass bead CAT) and Neo (SPRCA) were observed of which 86% would not be considered clinically significant. It is not known whether those clinically significant alloantibodies detected by only one analyser would translate into a haemolytic episode, as this was not evaluated.

A029

### **Multimodal platelet function testing during cardiopulmonary bypass - a pilot study**

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**Background:** Cardiopulmonary bypass (CPB) is associated with complex activation of hemostasis including platelets. In previous study we detected partial and selective preservation of platelet aggregation after CPB with using platelet-rich plasma (PRP) sequestration. Now we have tested a broad spectrum of platelet functions in this setting.

**Methods:** Adult patients scheduled for complex surgery with CPB were monitored by light transmission aggregometry (ristocetin, ADP, epinephrin and collagen), TEG-platelet mapping (kaolin, reptilase, arachidonic acid and ADP), flow cytometry of platelet receptors CD41 FITC, CD61 PE, CD42a PerCP, CD42b APC, CD36 FITC, CFDA, CD142 BV 421 and platelet microparticles. In a group of patients with initial hematocrit >0,35 we applied PRP sequestration using perioperative cell salvage of whole blood and PRP retransfusion at the end of surgery. Blood samples were collected 1/ after induction 2/ from sequestered PRP 3/ after PRP retransfusion 4/ at the end of surgery. Patients of control group were similar by demography and Euroscore (4,39 vs 4,88)

**Results:** We completed data of 10 patients. No difference (PRP vs control) in platelet count (214/151 vs 207/125) and reduction of RBC (2vs4) and FFP (0vs2) transfusion were recorded. No platelet transfusion was necessary in both group. The trend for preservation of ristocetin (99 to 97%) and ADP (95 to 75%) mediated aggregation were detected in PRP but not in control group. No difference in TEG-platelet mapping parameters and platelet receptor expression (except of higher microparticle CD expression in PRP group) were recorded.

**Conclusion:** We detected partial protection of platelet function with using PRP sequestration. The combination of methods is necessary to explore effect of PRP sequestration as a potentially useful method of platelet protection.

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## Linking blood use with clinical outcomes in haematologic malignancies: Pilot data from the national transfusion dataset project

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**Aim:** Patients with haematologic malignancies are major recipients of blood products; however comprehensive Australian data about clinical outcomes of transfusion are limited. As part of a feasibility study to establish a national comprehensive dataset of all transfusions and their outcomes, we analysed transfusion data for adult haematology/oncology patients from the first pilot site.

**Method:** Hospital electronic data on adult patients receiving any blood product ( $\geq 1$  RBC, platelet, FFP, cryoprecipitate, or plasma derivative) during 2017 were imported, linked and analysed using the expanded platform of the Australian and New Zealand Massive Transfusion Registry. Data included laboratory (for transfusion and blood tests) and hospital information systems records (for patient demographics, co-morbidities, admission and clinical outcome data). Haematology/oncology patients were identified by ICD-10-AM diagnostic codes. Analyses were performed using Stata software.

**Results:** Of 5859 transfused admitted patients, 767 (13%) were haematology/oncology patients. Of these 38% were acute leukaemias, 25% myeloma, 15% NHL, 7% chronic leukaemias, and 15% MDS and other haematopoietic neoplasms. Patient median age was 66.7y, [IQR, 57, 74], and 58% were male.

Haematology/oncology patients were 30% (3365/11201) of all admissions where a transfusion was performed; of which 56% were day-admissions. 61% of patients were admitted only once; 34% had 2-10 admissions and 5% had 11-100 admissions. They accounted for 33% RBCs, 69% platelets, 20% cryoprecipitate, 5% FFP and 13% IVIg (in grams) transfused. For outpatients receiving platelet transfusions, median [IQR] platelet count was  $17 \times 10^9/L$  [10, 51].

**Conclusion:** Haematology/oncology patients represented 13% of all transfused patients, but required significant proportions of the transfusion product inventory, including 69% of all platelets, consistent with published data. The ability to link and analyse readily available electronic hospital information as a single, comprehensive dataset is valuable for understanding blood use, monitoring alignment with practice guidelines, and providing risk-adjusted clinical outcomes.

<b>Haematology-Oncology Cohort (n=767 patients)</b>	<b>Value</b>
Total admissions, n	3365
Day-admissions, n (% of total admissions)	1895 (56%)
Length of stay for in-hospital admissions (n=1470)	
1-7 days, n (%)	532 (36%)
8-14 days, n (%)	245 (17%)
15-28 days, n (%)	391 (27%)
>29 days, n (%)	302 (20%)
First Haemoglobin level (g/L), median [IQR]	
In-hospital admissions	86 [77, 98]
Day admissions	78 [73, 81]
First Platelet count ( $\times 10^9/L$ ), median [IQR]	
In-hospital admissions	47 [21, 150]
Day admissions	11 [8, 17]
RBC units transfused, n (% of all RBC, n=24,766)	8,295 (33%)
PLT units transfused, n (% of all PLT, n=9,365)	6,457 (69%)
FFP units transfused, n (% of all FFP, n=7,701)	422 (5%)
Cryo units transfused, n (% of all Cryo, n=4,422)	880 (20%)
IVIg transfused, grams (% of all IVIg, 52,251 grams)	6861 (13%)

A031

## **A national transfusion dataset for Australia: linking blood use with clinical outcomes**

**Helen Haysom**<sup>1</sup>, Rosemary Sparrow<sup>1</sup>, Cameron Wellard<sup>1</sup>, Neil Waters<sup>1</sup>, Peter Cameron<sup>1,2</sup>, Zoe McQuilten<sup>1,3</sup>, Erica Wood<sup>1,3</sup>

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### **Aim:**

To determine the feasibility of an electronic dataset comprising hospital laboratory data, transfusion data (any fresh or manufactured product) and clinical outcomes in Australian hospitals. To provide a “missing link” in monitoring alignment of practice with, and impact of, Australian national patient blood management (PBM) policies and guidelines.

### **Method:**

Using the platform of the Australian and New Zealand Massive Transfusion Registry, all data from adult patients transfused any blood product at participating sites for 2017, including laboratory (for transfusion and other laboratory records) and hospital information systems data (for patient demographics, co-morbidities, admission and clinical outcome data) were extracted. Data were securely sent, imported into the database and data linkage algorithms applied. Analyses were performed using Stata software.

### **Results:**

Selected results from data analyses of the first pilot site are presented. During 2017, 5,859 patients received at least one transfusion product during a total of 11,201 separate admissions; of these, 3,407 (30%) were day-admissions. Length-of-stay (LoS) was  $\geq 10$  days for 51% of admissions. 21% of hospital stays included ICU admission, of which 25% (577/2307 ICU admissions) were  $>10$  days LoS in ICU. In-hospital mortality was 9.6% (565 deaths/5,859 patients), of which 28 deaths (5% of 565 deaths) were LoS  $<1$ -day Emergency admissions. Transfused blood products included 24,766 RBC, 9,365 PLT, 7,701 FFP, 4,422 Cryo, 52,251 grams IVIg and 6,301 vials of Prothrombinex.

### **Conclusion:**

This study demonstrates feasibility of a potential national dataset linking comprehensive information from readily available electronic hospital data sources on all patients transfused any type of blood product, including immunoglobulins and coagulation factor concentrates, with clinical outcomes data adjusted for demographics and co-morbidities. These data will be valuable for monitoring alignment with PBM policies and guidelines, and for understanding the impact of transfusion on patient outcomes and costs. The pilot is ongoing at additional sites.

A032

## **Blood administration in the digital age**

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In 2018, Metro South Hospital and Health Service (MSHHS) became Australia's first digital health service with all five hospitals and a community health service now digitalised. Digital Hospitals have an integrated electronic Medical Record (ieMR), integrated digital systems and a paper-light environment, enabling faster diagnosis, more accurate monitoring, complete patient information visible to clinicians at the bedside (and remotely) and improved accuracy in clinical decision-making and prescribing.

For blood management, this has transformed how patients are cared for by providing a legible prescription and administration record, a checklist for all blood components, mandatory fields for consistency and a standardised practice for documentation and audit requirements. This provides support for patient blood management guidelines of single and appropriate use of red blood cells to meet national benchmarking for the National Safety and Quality Health Service (NSQHS) Standard 7 Blood Management.

An incidental benefit of digital transparency has been realised with the early recognition by Pathology staff at point of testing from wrong blood in tube (WBiT). This is not an indication that WBiTs have increased with the digital system, rather the ability to recognise early and prevent near miss incidents.

The program has realised several patient safety and quality benefits and the potential for secondary benefits through business intelligence capability, using data to gain insights and make decisions. A collaborative proof of concept at PAH developed business-as-usual intelligence dashboards for each of the NSQHS Standards as well as numerous Operational Decision-Making Dashboards. Data from the ieMR is displayed in real time and able to be used for clinical decision making. A benefit for blood management is tracking patient outcomes in real time and assisting with real time auditing.

The ieMR has enabled real-time monitoring and reporting developing a closed loop within a double loop system.

## RCPAQAP ABO Titration Pilot Survey Project

**Tara Kahlyar**<sup>1</sup>, Associate Professor David Roxby<sup>2</sup>, Junho Kim<sup>3</sup>

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### Aim

ABO titration is performed in various clinical settings such as ABO mismatched renal transplant, haemopoietic stem cell transplant and determination of isoagglutinin levels to identify blood donors with low levels of anti-A and or anti-B. During April 2019, the first pilot survey was sent to the participating laboratories to perform ABO titrations using their own routine methods. The purpose of the pilot study was to investigate the diversity of techniques, test platforms and reagents that are currently in use in the various laboratories with the aim to develop an external quality assurance program (EQA).

### Method

The pilot survey included a patient's plasma sample as well as donor A<sub>1</sub>, A<sub>2</sub> and B cells. Participants were asked to perform ABO titration against all three donor cells using their own laboratory methods and test platforms and to submit their results. In addition, participants were required to specify and report the clinical settings for performing ABO titration, testing platforms, methods (direct, indirect or both methods and/or the use of DTT treated plasma), diluents, incubation temperature and end-point used.

### Results

Results were received from twenty-four participants from six countries. Some participants submitted multiple results as they performed ABO titrations using multiple platforms and methods. A summary of method platforms used by participants is displayed in table 1.

**Table 1:** Summary of method platforms

Method Platform	Number of participants
Tube	20
Ortho	9
Bio-Rad	13
Grifols	5

### Conclusion

There was a wide variation of titration results between and within different technologies which supports the need for an ABO Titration EQA. Development of a standard technique and participation in an EQA program should, over time, reduce variation and enable transferrable results across testing centres which will assist in consistent clinical interpretation.

A035

### **Fibrinogen concentrate in a post partum haemorrhage in a rural facility**

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There is little evidence available to demonstrate use of fibrinogen concentrate in the absence of viscoelastic haemostatic assays.

A 38 yo lady presented to a rural facility in early preterm labour. She had a bicornuate uterus. Obstetric history revealed that this was her 6<sup>th</sup> pregnancy, the last 3 deliveries caesarean sections and she had gestational diabetes. She was booked for a caesarean section at a regional facility the next week. Baby was suspected to have intrauterine growth retardation. Her membranes ruptured, and she was contracting 3-4 contractions in 10 minutes. A caesarean section was performed immediately, due to concern for a rupture of the scar as she was complaining of pain in that area and it would take several hours for retrieval to occur.

Intraoperatively, immediately post-delivery, the mother experienced heavy bleeding from the posterior wall of the uterus. She was given syntocinon, tranexamic acid and an obstetrician at the regional hospital was phoned for advice. Further steps included syntocinon infusions, misoprostol, sutures and a Bakri balloon. Ongoing wound ooze was evident. Measured blood loss was 3.1 Litres.

During the procedure, she received a total of 3 units of O negative 'Medivac' blood. Fibrinogen Concentrate 4G was administered to help with coagulation, as per Qld Clinical Guidelines- Primary postpartum haemorrhage. Surgeons noted immediate slowing of bleeding. Haemoglobin was 126 g/L 2 weeks prior and ferritin was 12ug/L. i-STAT performed immediately post operatively showed an estimated haemoglobin of 126g/L.

The mother was retrieved to the regional hospital, where her haemoglobin was 128g/L. A ROTEM was collected and revealed a FIBTEM A5 of 19mm. This revealed an ample level of functional fibrinogen. Her coagulation panel was within normal parameters. There was no further bleeding and she was discharged 4 days later.

Fibrinogen concentrate may be considered as an adjunct therapy in management of postpartum haemorrhage in rural facilities.

## **Transfusion Reaction Investigation EQA, a six-year review**

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### **Introduction**

In 2014, the RCPAQAP introduced an additional Transfusion Reaction Investigation (TRI) challenge to their General Compatibility Module.

We sought to review how well participants recognised transfusion reactions and if they had appropriate measure in place to carry out the relevant follow-up investigations.

### **Materials and Methods**

A review of RCPAQAP survey returns for TRI over a 6-year period was undertaken. The surveys included a pre-transfusion sample, a post-transfusion sample and two donor unit samples. Participants were asked to perform routine blood grouping and antibody screening on the pre-transfusion sample and to crossmatch the two donor units against the pre-transfusion sample. In addition, participants were provided with a clinical scenario on the patient's post-transfusion outcome (e.g. haematuria) and asked to perform their own TRI using the samples provided. The returned results were analysed and reviewed by the RCPAQAP Transfusion team and Transfusion Advisory Committee prior to release. The survey target values are not defined from the statistical analysis, but are based on the clinical scenarios selected by the program's advisory committee.

### **Results**

Over the 6-year period, we noted improved performance in evaluating transfusion reactions; however, there are areas requiring improvement. These included the need for elution studies to be routinely performed in every blood bank; recognising this may be limited due to resource or technical issues.

In addition, some participants continue to dismiss patient sample haemolysis as unimportant or a sample collection issue, but it is critical to recognise that haemolysis is part of the clinical manifestation in transfusion reactions.

### **Conclusion**

In this retrospective study, we determined that while most laboratories performed thorough TRI, we recommend more vigilance on the clinical significance of haemolysis and elution protocols.

Recognising such anomalies will potentially translate to better patient outcome.

This program clearly shows the value of an EQA which challenges how laboratories manage TRI's

## **Irradiated and seronegative blood products - Audit of current transfusion practice and complications in an Australian Tertiary Hospital.**

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**Introduction:** Provision of irradiated and Cytomegalovirus (CMV) seronegative blood products to at-risk patients is recommended as a method of preventing transfusion-associated graft versus host disease (TA-GVHD) and CMV disease respectively.

**Aim:** To retrospectively review current transfusion practices in a major tertiary hospital.

**Method:** Transfusion records (red cells and platelets) of patients under haematology care at Nepean Hospital, Western Sydney between April 2018 to April 2019 were retrieved from the blood bank. Patient clinical information was collected from medical records, including haematological diagnosis, location of diagnosis, treatment received, and occurrence of TA-GVHD and CMV disease. These records were assessed against the Australian and New Zealand Society of Blood Transfusion recommendations. Data was analysed using descriptive statistics.

**Results:** There were 1456 transfusions products provided to 157 patients. Most common diagnoses were acute leukaemia (21.67%), multiple myeloma (18.47%), and Non-Hodgkin Lymphoma (NHL, 15.93%). Diagnoses were made in outpatient clinic (43.95%), inpatient service (34.03%), and other hospitals followed by interhospital transfer (8.28%). Most common definite indications for irradiated blood products were autologous stem cell transplant (9.55% of all patients), followed by allogeneic transplant, purine analogue chemotherapy and treatment for Hodgkin's lymphoma (1.91% each). Of these, 79.62% received irradiated products. Patients with poorly defined indications (including NHL and acute leukaemias), 57.98% received irradiated blood products. 25.65% of patients with no apparent indications received irradiated blood products. Of 553 CMV seronegative blood products (37.98% of all blood products) were given, three had a definite indication (pregnancy). There were no definite cases of GVHD. Three patients had possible CMV disease.

**Conclusion:** Deviation from guidelines remain in the provision of irradiated and CMV seronegative blood products with high variability in patients with poorly defined indications. Regular audits and implementation of protocols promoting evidence-guided practices should be considered in routine hospital transfusion services.

## What! There is no blood? Blood management in antenatal patients with antibodies to high frequency antigens

**Chantal Mathews<sup>1</sup>**, Kobie Von Wielligh

<sup>1</sup>Red Cross Blood Service, Melbourne, Australia

**Aim:** To review the blood management of antenatal patients with antibodies to high frequency antigens who presented at the Red Cell Reference Laboratory (RCR) -Victoria

**Method:** 16 Antenatal samples referred to the RCR from January 2017- June 2019 had antibodies to high frequency antigens. Some of these antibodies have been implicated in haemolytic transfusion reactions (HTR) and haemolytic disease of the fetus and newborn (HDFN). The RCR laboratory assisted the hospital laboratories to identify the antibody, exclude other underlying alloantibodies and perform titres. Transfusion Medicine Specialists (TMS) at the Blood Service liaised with the hospital clinical teams to provide advice in developing a perinatal blood management plan.

**Result:** Limited supplies of fresh or frozen blood was available for 11 of the 16 patients.

Antibody	Patient #	Phenotyping/Genotype/Sequencing	Suitable blood available in Australia
Anti-Ge2	1	GE: -2,3,4	No
Anti-Ge2	2	GE:-2,-3,4	Yes
Anti-Ge2	3	GE:-2,3,4	Yes
Anti-H	4	H-	Yes
Anti-PP1Pk	5	p	Yes
	6	p	No
Anti-Lub	7	Lu(a+b-)	Yes
	8	Lu(a+b-)	Yes
Anti-Coa	9	Co(a-b+)	No
Anti-Jk3	10	Jk(a-b-)	Yes
Anti-U	11	U-	No
Anti-Inb	12	In(b-)	Yes
	13	In(b-)	Yes
Anti-Yta	14	Yt(a-)	Yes
	15	Yt(a-)	Yes
Anti-Cra	16	Cr(a-)	No

All 16 patients had uneventful deliveries with no blood for transfusion required.

**Conclusion:** Managing antenatal patients with antibodies to high frequency antigens requires a multidisciplinary approach with close liaison between TMS, RCR, the hospital laboratory and the hospital clinical teams. Limited supply of fresh or frozen red blood cells makes blood provision for these pregnancies challenging. Optimal patient blood management (risk assessment, haemoglobin optimisation, minimising blood loss, timely access to specialist blood product support, intra-partum optimisation (cell-salvage, point of care testing) is recommended for good outcomes.

## When less is more: red cell use at Perth Children's Hospital

**Victoria McDougall<sup>1</sup>**

<sup>1</sup>Perth Children's Hospital, Nedlands, Australia

**Aim:** To improve the quality of care provided to neonatal and paediatric patients ( $\leq 17$  years of age) by ensuring the appropriate use of red blood cell (RBC) and patient blood management practices (PBM).

**Method:** A retrospective standards based audit was undertaken at Perth Children's Hospital (PCH) measuring the appropriateness of RBC transfusions against PBM Guidelines: Module 6 Neonatal and Paediatrics for February 2019. All patients aged 0-17 years who received a RBC transfusion, excluding benign haematology, were included in the sample totalling 65 transfusion episodes.

### Result

Clinical area / Patient specialty	Number	%	Pretransfusion Hb (g/L) average (range)	Pretransfusion Hb (g/L) median	Age (years) average (range)
Oncology	49	75.38%	59 (23-91)	62	6 (0-17)
Cardiothoracic	9	13.85%	146 (111-187)	161	2 (0-7)
Neonatal	6	9.23%	85 (77-104)	80	0
Plastics	1	1.54%	80	80	1
Total	65	100.00%	74 (23-187)	63	5 (0-17)

- 96% (n=47) of the transfusion episodes in oncology had a pretransfusion Hb of  $<70$ g/L.
- 89% (n=8) of cardiothoracic surgeries used only one unit of RBC for priming the cardiopulmonary bypass and in 56% of cases autologous blood was returned.
- All neonatal transfusions were in accordance with the guidelines.
- The plastics case was for critical intraoperative blood loss and ROTEM was used.

Single unit transfusion		
Specialty	Number of Transfusion Episodes	Percentage
Oncology	45/49	92%
Cardiothoracic	8/9	89%
Neonatal	6/6	100%
Plastics	0/1	0%
Total	59/65	91%

91% of the transfusion episodes were single unit. In patients not actively bleeding one unit of RBC was prescribed followed by reassessment.

**Conclusion:** All reported transfusion episodes align with the current evidence based practice guidelines. The audit indicates that PBM guidelines are firmly embedded in practice and a restrictive transfusion strategy is employed at PCH.

## **Blood groups in the Northern Territory**

Antonia Mclean<sup>1</sup>, **Ferenc Szabo**<sup>1,3</sup>, Zhiqiang Wang<sup>2</sup>

<sup>1</sup>Royal Darwin Hospital, Darwin, Australia, <sup>2</sup>Menzies School of Health Research, Darwin, Australia, <sup>3</sup>Flinders University, Darwin, Australia

**Aim:** To establish the frequencies of the ABO and Rhesus (RhD) blood groups in the Aboriginal and non-Aboriginal population of the Northern Territory (NT), and to use findings to improve management of red cell and anti-D immunoglobulin inventory and administration.

**Method:** Retrospective data was collected from all patients who had a blood group sample processed by the NT public hospital laboratories from 01/01/2012 to 31/12/2012. We collected the blood groups for a total of 4343 individuals, of whom 1686 identified as Aboriginal and 2657 as non-Aboriginal. We used Chi-square test or Fisher's exact test as appropriate.

**Result:** The Aboriginal and non-Aboriginal populations had significantly different ABO and RhD distributions ( $p < 0.001$ ). For Aboriginal individuals 56% (938/1686) were O RhD positive and 39% (651/1686) were A RhD positive. In non-Aboriginal individuals 37% (991/2657) were O RhD positive and 31% (820/2657) were A RhD positive. We found that 98% (1646/1686) of Aboriginal individuals were RhD positive, compared with 84% (2225/2657) of non-Aboriginal individuals. Only 4% (62/1686) of Aboriginal individuals were group B or AB, compared with 18% (470/2657) of non-Aboriginal individuals. We found that O (67%) was more common than A (32%) in Aboriginal individuals in the Northern part of the NT, whereas there was similar distribution of O (45%) and A (54%) in Central Australia.

**Conclusion:** We found a significant difference between the ABO and RhD blood groups of Aboriginal and non-Aboriginal individuals ( $p < 0.001$ ). Additionally, we found a difference in ABO grouping between the Northern and Central Australian Aboriginal populations. These findings will aid inventory management and clinical practice throughout the Northern Territory, especially as a large part of our service is to Aboriginal communities.

A041

## **Double independent check vs double simultaneous check – assessing the risks**

**Rebecca McLean**<sup>1</sup>, Annette Le Viellez, Shane Gangatharan

<sup>1</sup>*Fiona Stanley Hospital, Murdoch, Australia*

**AIM:** To determine if introducing the Double Independent Checking Process (DICP) will decrease the incidence of transfusion errors at a metro quaternary hospital.

**METHOD:** The Australian and New Zealand Society of Blood Transfusion (ANZSBT) 'Guideline for the Administration of Blood Products' (2018) recommends 'double-independent checking' prior to administration of blood products. A literature review was performed to gather evidence for this change from current Double Simultaneous Check Process (DSCP). On site, clinical incidents are reported via the Clinical Incident Management System (CIMS). Data for "checking" related blood incidents was extracted between January 2015 and April 2019 and a risk assessment performed.

**RESULTS:** There is minimal literature supporting DICP, but the consensus was that if two people are checking, they should do so independently. However there is a likely increase in workload, risk in delay to transfusion with possible increase in blood waste.

Review of the CIMS reports identified four incidents related to checking process. One product (25%) was for Anti-D, where a patient received another patient's dose. The other three CIMS (75%) were for 'fresh products'. In the case of fresh products, patient compatibility labels were incorrect or absent. These errors were identified by DSCP prior to transfusion and blood products were returned to Transfusion Medicine for review.

The risk review identified that there needs to be robust systems in place to positively identify patients prior to blood administration, and current DSCP found minor errors in all but one product administration.

**CONCLUSION:** There is minimal literature to support DICP or the risks associated with change. Our data did not demonstrate DSCP to be associated with blood administration error, yet implementation of a new blood checking procedure may increase error and delay transfusion. Careful review of current site risk should be considered before implementing change.

## The Utilisation of HLA Compatible Platelets in Western Australian Haematology and Oncology Patients

**Anne McNae**<sup>1</sup>, Julianne Taylor<sup>1</sup>, Anastazia Keegan<sup>1</sup>

<sup>1</sup>*Australian Red Cross Blood Service, Perth, Australia*

International literature suggests the incidence of platelet refractoriness in haematology and oncology patients ranges between 15-25%<sup>(1-3)</sup>. However, the incidence of platelet refractoriness in Western Australian (WA) haematology and oncology patients is unknown.

**Aim:** To describe the utilisation of Human Leucocyte Antigen (HLA) compatible platelets by haematology and oncology patients with platelet refractoriness in WA.

**Method:** A retrospective analysis of the Australian Red Cross Blood Service's (Blood Service) HLA Compatible Platelet Database was undertaken from January 2015 to June 2019. All requests for HLA compatible platelets for haematology and oncology patients in WA were included for analysis.

**Results:** There were 85 requests for HLA compatible platelets to support a range of malignant conditions. 47 individual patients were supported over the 54 month study period. The vast majority of patients had high-grade myeloid malignancies with 45% presenting with Acute Myeloid Leukaemia and 17% presenting with a Myelodysplastic Syndrome. The mean age of these patients with platelet refractoriness was 54 years and there was a marked female predominance (83%). There was an equal distribution of blood group O and A patients (both 45%) of which 85% were RhD positive.

HLA compatible platelets were required to support this cohort of patients from one to 267 days with the median duration of support 23 days. 656 individual blood donors from the Blood Service's national Platelet Panel Database (PPD) were identified to donate 1,001 HLA compatible platelets of which 69% were transfused.

**Conclusion:** Platelet refractoriness can present significant challenges for clinicians, transfusion medicine laboratories and the Blood Service. This is the first time the WA utilisation of HLA compatible platelets has been examined, and has provided the foundation for future research plans to determine the incidence of platelet refractoriness in haematology and oncology patients in WA.

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## Fresh frozen plasma to red cell unit ratio in recipients of massive transfusion: results from the ANZ Massive Transfusion Registry

Zoe McQuilten<sup>1</sup>, Cameron Wellard<sup>1</sup>, Rosemary Sparrow<sup>1</sup>, Helen Haysom<sup>1</sup>, Erica Wood<sup>1</sup>

<sup>1</sup>Monash University, Melbourne, Australia

### Aim

To evaluate the association between FFP:RBC ratio and in-hospital mortality in patients receiving a massive transfusion (MT) for critical bleeding due to any cause.

### Method

Observational study of MT recipients at 28 hospitals from 2010-2018 using data from ANZ-MTR. Association between FFP:RBC ratio and in-hospital mortality was modelled by multiple logistic regression.

### Results

8,366 recipients of MT were included, with median age 61y and 63% male. Primary cause of bleeding was cardiac surgery 21%, vascular surgery 10%, gastrointestinal haemorrhage 17%, other surgery 18%, trauma 20%, obstetric 5%, and other 9%.

Median FFP:RBC ratio for the cohort was 0.53 (IQR 0.29-0.80). Patients who received lower FFP:RBC ratio were older, had lower median haemoglobin, APTT and higher platelet count and fibrinogen. After adjusting for age, total number of RBC units, APTT, fibrinogen, pH and Charlson co-morbidity index, higher FFP:RBC ratio remained significantly associated with higher in-hospital mortality (OR 1.48, 95% CI 1.26-1.73,  $p < 0.001$ ). To investigate a possible non-monotonic relationship between FFP:RBC and in-hospital mortality, and to identify an optimal ratio, we divided FFP:RBC into deciles and re-fitted both the unadjusted and adjusted logistic models described above. In both cases, the highest FFP:RBC ratio categories were associated with increased mortality, and no evidence of an optimal value (see figure 1).

Finally, we repeated the model stratified by bleeding category, which gave a positive association after adjustment between high FFP:RBC and in-hospital mortality for gastrointestinal haemorrhage, trauma and other surgery, but not the other categories.

### Conclusion

In MT recipients, we found no evidence of reduced mortality with higher FFP:RBC ratios after adjusting for potential confounders. These data support our current national guidelines for MT management which include FFP:RBC ratio of 1:2 rather than a higher ratio of 1:1.

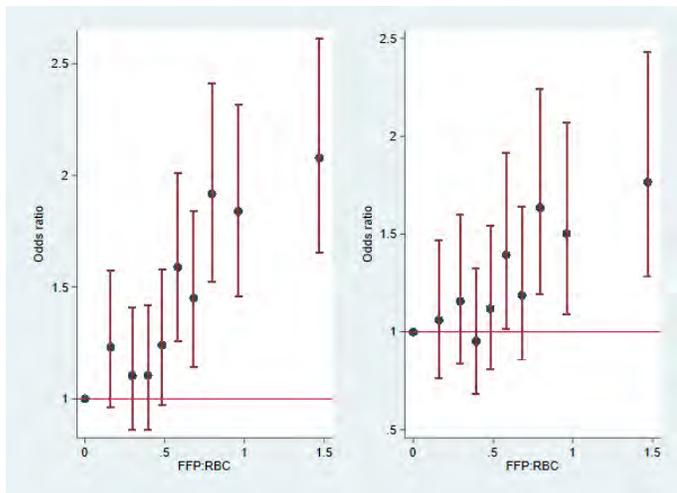


Figure 1: Unadjusted (left panel) and adjusted (right panel) odds ratios for in-hospital mortality according to decile category of FFP:RBC.

## **Understanding the clinical practice for selecting phenotyped red blood cell units and performing patient genotyping**

Rena Hirani<sup>1</sup>, Shaba Tarafdar<sup>1</sup>, **Phillip Mondy**<sup>1</sup>, Vanessa Milosz<sup>2</sup>, Tanya Powley<sup>3</sup>, James Daly<sup>3</sup>  
*<sup>1</sup>Australian Red Cross Blood Service, Sydney, Australia, <sup>2</sup>Australian Red Cross Blood Service, Melbourne, Australia, <sup>3</sup>Australian Red Cross Blood Service, Brisbane, Australia*

**Background/Aim:** Supply of phenotyped red blood cell (RBC) units is an ongoing challenge for the Australian Red Cross Blood Service (Blood Service) with increased demand for phenotyped RBC units despite the overall reduction in RBC usage. There is also increased demand to perform genotyping on patient samples. A number of patient requirements may be contributing to these requests. This survey was conducted to understand the current guidelines and practice for selecting phenotyped RBC units and which patient types require genotyping.

**Methods:** An electronic Qualtrics survey form was sent to 296 individual customers for completion. Survey questions were designed to understand which patients required phenotyped RBC units, under what circumstances was extended phenotyping or genotyping requested and which antigens are generally desired.

**Results:** 53 (18%) transfusion laboratories responded to this survey. Chronically transfused, sickle cell anaemia, thalassemia, myelodysplasia and monoclonal antibody therapy (MAB) patients usually require extended phenotyping and/or genotyping. Genotyping was requested to confirm the phenotype of recently transfused patients, analyse patients with multiple antibodies, prior to MAB therapy or for pregnancy-related transfusions. For patients without antibodies, sites indicated they electronically cross-match and issue the least incompatible RBC unit. For patients with current or historical antibodies, RBC units were matched as closely as possible including the required negative antigen. For all clinical indications, sites would prefer to have extended Rh and Kell RBC units available.

**Conclusions:** The Blood Service continues to increase the number of phenotyped RBC units and aims to type all RBC units for Rh and Kell so that resourcing can be provided to support more complex patient cases.

## Newsflash - Indian b is missing!

**Jenny Morrison**<sup>1</sup>, Maria Lizarazu<sup>1</sup>, Glenda Millard<sup>1</sup>, Brett Wilson<sup>1</sup>, Yew-Wah Liew<sup>1</sup>

<sup>1</sup>*Australian Red Cross Blood Service, Brisbane, Australia*

The Indian blood group system has made headlines recently due to a worldwide search for compatible blood for a child in USA. She has the rare Indian b (In<sup>b</sup>) negative blood type found mainly in Indians, Iranians and Arabs. Only a handful of donors with compatible In<sup>b</sup> negative blood were identified internationally. We report a complex antibody investigation resulting in the discovery of a lady with In<sup>b</sup> negative blood who has made anti-In<sup>b</sup> in the presence of an underlying HTLA type antibody.

**Clinical presentation:** A 29 year old lady, who has recently delivered her baby, was referred to Red Cell Reference Laboratory to confirm the presence of a HTLA antibody and possibly an anti-Le<sup>a</sup>. The antibody screen was pan-reactive with weak variable reactions.

**Method:** The patient's plasma was tested by saline tube technique at room temperature as well as indirect antiglobulin test (IAT) with untreated and papain treated red cell panel. Phenotyping was performed by standard serological procedures and genotyping was performed using Immucor BioArray HEA BeadChip. DNA sequencing was performed using the Illumina TruSight One Sequencing panel (TSO).

**Result:** Pan-reactivity was observed in IAT with untreated red cells and reactivity was abolished in 2 of the 11 cells in the papain treated red cell panel. The plasma was nonreactive in IAT with 2 examples of In(b-) red cells which were also Kn(a-) and McC(a-). The patient phenotyped as D+C+E+c+e+, K-, Fy(a+b-), Jk(a+b-), M+N+S+s-, Jr(a+), In(b-), Kn(a-), McC(a-). Sequencing confirmed homozygosity for the 137G>C nucleotide substitution which predicts the In(a+b-) phenotype. However, sequence analysis predicts a Kn(a+) and McC(a+) phenotype in this patient.

**Conclusion:** The presence of an underlying HTLA type antibody made it difficult to resolve the antibody investigation. The results indicate that the patient is In<sup>b</sup>- with anti-In<sup>b</sup>. The specificity of the HTLA antibody remains unconfirmed. Anti-In<sup>b</sup> may cause haemolytic transfusion reactions but has not been reported to cause HDFN.

## Discoveries and developments of systematic nomenclature for blood group variants since the 1980s.

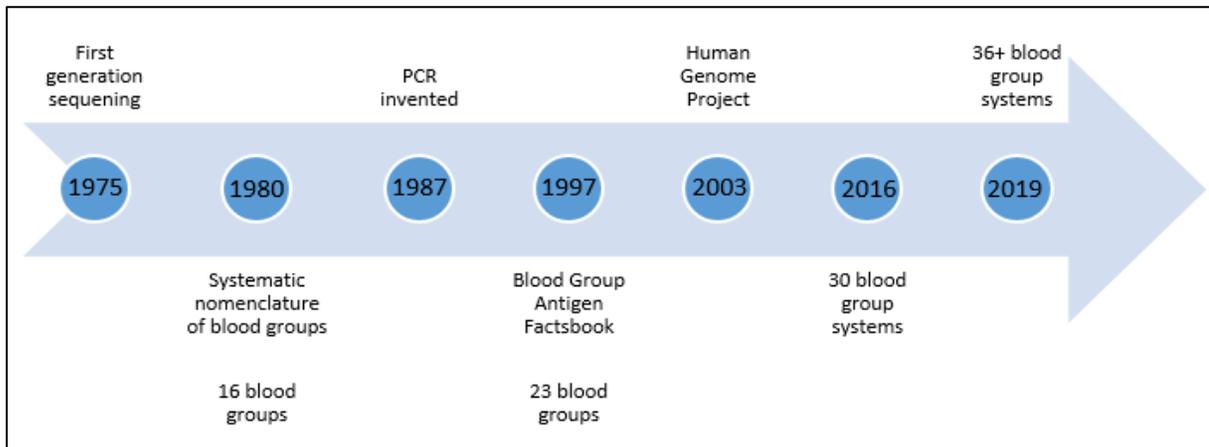
**Aoibhe Mulcahy**<sup>1</sup>, Robert Flower<sup>1</sup>, Catherine Hyland<sup>1</sup>

<sup>1</sup>Australian Red Cross Blood Service, Brisbane, Australia

**Aim:** To chart the discoveries and development in systematic nomenclature for blood group variants.

**Method:** A review of textbooks, the International Society of Blood Transfusion (ISBT) databases and scientific literature.

**Result:** At the first ISBT meeting in Montreal in the 1980s the currently used methodical nomenclature of blood groups and antigens was developed. Initially, discoveries were based on serological findings with tools such as chromosomal banding defining the location of blood group genes. Since then, there have been many advances, Figure 1.



*The Blood Group Antigen Factsbook*, was the first published reference assembly for all blood groups known at the time which included 23 systems with 38 unallocated high prevalence antigens in the 900 series database and 13 unallocated low incidence antigens in the 700 series database.

In 2003, the Human Genome Project was completed and the technology for Next Generation Sequencing (NGS) continued to emerge. This provided tools to assemble human reference genome sequences, required for NGS sequencing. Seven new blood group systems were discovered by 2013 with 30 systems recognised. In 2016, application of genetic technology enabled identification of six more systems, many moved from the 700 and 900 series. For instance, the 900 series high prevalence antigen Ata, discovered in 1967, was recognised by the ISBT as part of 36<sup>th</sup> blood group system Augustine (AUG). By 2018, 38 serologically defined antigens remained unassigned, a vast improvement to the 64 unassigned antigens remaining in the 700 and 900 series in 1985.

### Conclusion:

Significant progress in the identification of systematic nomenclature for blood group variants has been due to technological advances. Discoveries continue using serology and genomics. Remaining challenges include the application of systematic genetic terminology and lodging all the known variants in databases with precise co-ordinates.

## **Blood Drops WA- Leading a collaborative state-wide approach to enhanced stewardship of blood and blood products**

**Deborah Pinchon<sup>1</sup>**, Sharon Nowrojee<sup>1</sup>, Amanda Esson<sup>1</sup>, Bradley Webster<sup>1</sup>, Carly Olsen<sup>1</sup>

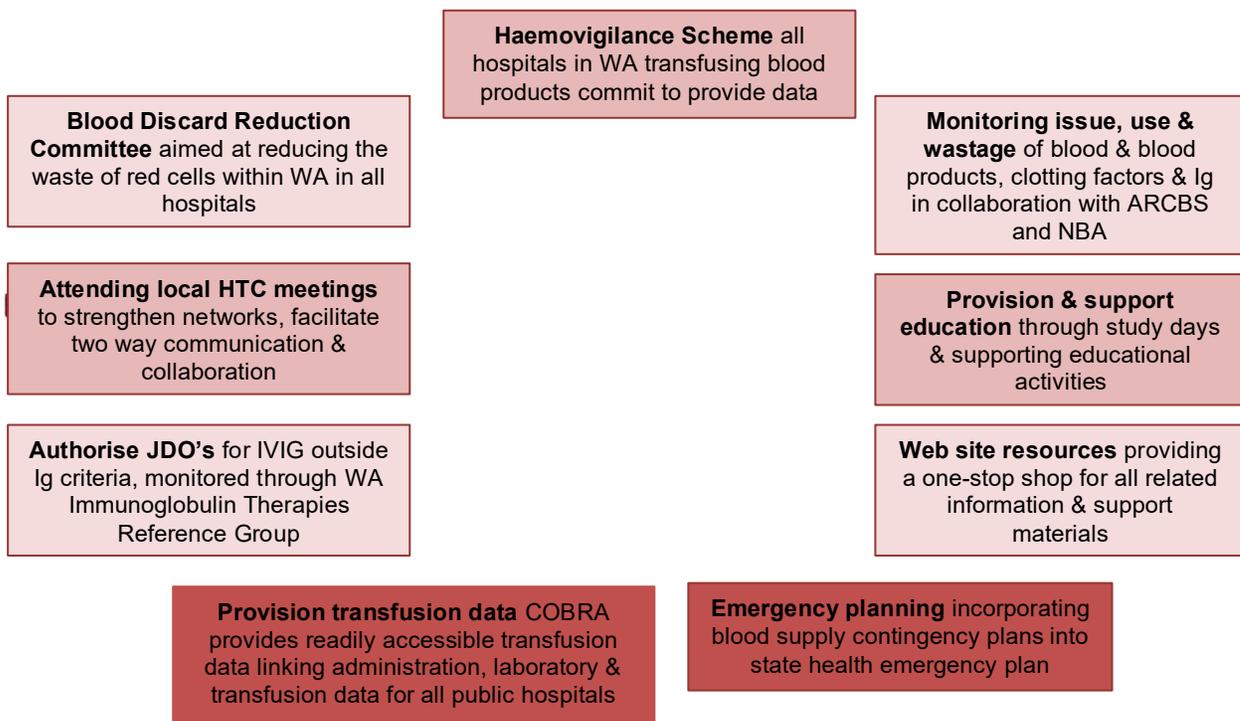
<sup>1</sup>Office of the Chief Medical Officer, Perth, Australia

The Office of the Chief Medical Officer within the Department of Health has responsibility for:

- overseeing policy, supply and support for blood and blood products, to ensure the State has sufficient blood products to meet demand
- ensuring that blood and blood product use in WA is consistent with national criteria and standards
- contributing to the development and implementation of national blood policy

Our team's philosophy is based on Blood Drops WA (dynamic, responsive, objective and professional system manager). Our aim is to provide expert medical and clinical advice to the WA health system in relation to enhanced stewardship and patient blood management. The team is made up of a Medical Advisor, Senior Policy Officer, Policy Officer and a Project Officer.

Our role is intrinsically linked to NSQHS standard 7 and we lead and facilitate the following initiatives:



Looking ahead we are working with the Office of Emergency Management to ensure contingency planning for blood shortages is incorporated into our State Health Emergency Plan.

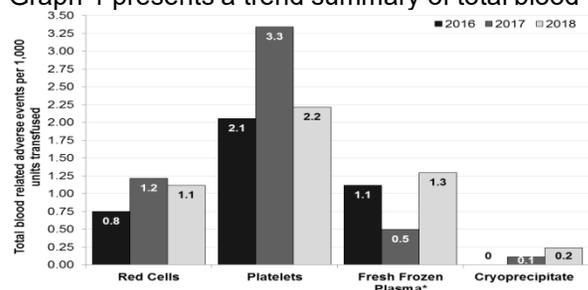
### Haemovigilance in WA – what does 3 years of state - wide reporting tell us?

**Deborah Pinchon**<sup>1,2</sup>, Sharon Nowrojee<sup>1,2</sup>, Amanda Esson<sup>1</sup>, Bradley Webster<sup>1</sup>, Carly Olsen<sup>1</sup>

<sup>1</sup>Office of the Chief Medical Officer, Perth, Australia, <sup>2</sup>WA State Haemovigilance Committee, Perth, Australia

The WA Haemovigilance Program commenced in 2015 and all WA hospitals which administer blood and blood products have committed to the collection and submission of haemovigilance data as part of our program. Reporting activities focus on blood products and includes reinfusion of blood from intraoperative/postoperative reinfusion devices.

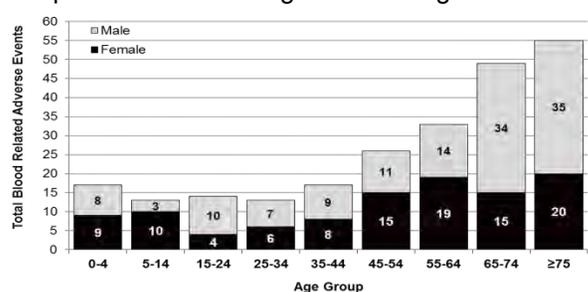
Graph 1 presents a trend summary of total blood related events per 1,000 units transfused.



	2016	2017	2018	Total
No. imputability ≤2	20	22	38	80
No. imputability >2	42	67	38	147
No. excluded/NA	2	2	5	9
Others	0	0	1	1

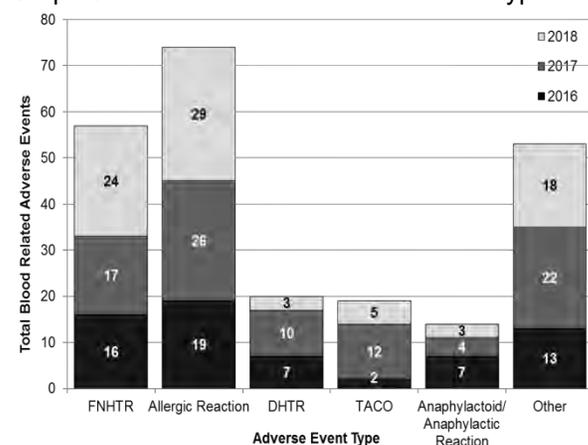
Overall 1/3 of reported events were deemed unlikely to be attributable to the transfusion

Graph 2 demonstrates gender and age trends in analysis of the data cumulatively from 2016 -18.



Time of A/E	M	T	W	T	F	S	S
Unknown	2	0	1	0	0	0	0
Night: 1900-0659	1	8	1	1	1	6	5
Day: 0700-1859	2	1	2	3	3	1	1
Total	3	2	4	4	4	2	2
	7	6	1	8	1	3	1

Graph 3 demonstrates the adverse event type from 2016 – 18.



	2016	2017	2018	Total
TTI	2	4	7	13
TTI (Bacterial)	2	5	0	7
DSTR	1	4	4	9
AHTR	3	1	2	6
TAD	0	2	1	3
IBCT	1	1	1	3
HTR (Hypotensive)	2	0	0	2
ABO incompatibility	1	1	0	2
TRALI	0	0	1	1
Unclassifiable	1	4	2	7
Total	64	91	82	237

Looking ahead within our Haemovigilance Program we are keen to examine data relating to near miss events in transfusion, to use as an opportunity to prevent adverse events of the future. The data is currently not required for the purpose of WA haemovigilance reporting. We are looking at methods to address the inclusion of near miss events in the WA haemovigilance reporting process in the future.

We would like to acknowledge all the centres who have submitted data to the program to date.

**Assessing anaemia screening and treatment in major elective colorectal surgical patients: a clinical audit.**

Edgar Poon<sup>1</sup>, David Pache<sup>1,2,3</sup>, **Alana Delaforce<sup>2,4</sup>**, Treasure McGuire<sup>1,2,3</sup>

<sup>1</sup>The University of Queensland, Brisbane, Australia, <sup>2</sup>Mater Health, Brisbane, Australia, <sup>3</sup>Bond University, Gold Coast, Australia, <sup>4</sup>University of Newcastle, Newcastle, Australia

**Background:** Preoperative anaemia is associated with poor surgical outcomes, including increased transfusion rate. The National Blood Authority of Australia developed guidelines through Patient Blood Management (PBM) to redress this issue. There is increasing use of iron infusion in the surgical setting, with associated adverse drug events including permanent skin discolouration and hypophosphataemia.

**Aim:** This project assessed: appropriateness of anaemia screening, use of iron, and impact on outcomes in major surgery associated with bleeding risk.

**Methods:** A pharmacist-led multi-disciplinary team retrospectively reviewed 586 patients admitted for elective major colorectal surgery (DRG: G02A/B/C) in a metropolitan tertiary hospital, January 2016 to December 2018. An electronic audit tool was designed to collect: patient demographics (age, gender, private/public status), any anaemia screening within six weeks of surgery (haemoglobin and iron studies), pre/post-operative use of iron (oral or intravenous) and postoperative outcomes (transfusion and hospital length of stay).

**Results:** Four hundred (68.3%) of 586 patients were preoperatively assessed for anaemia. Of these, 152 (38%) were classified as anaemic; and 38 (23.7%) of this anaemic group received preoperative iron. However, quality of preoperative anaemia assessment was poor, with only 34 (8.5%) of tested patients having PBM recommended iron studies, including ferritin, performed. Most anaemia assessments (43%) were conducted 0 to 1 day prior to surgery. This is insufficient for anaemia to be corrected. Two iron infusions were used in patients without anaemia. The perioperative transfusion rate was significantly higher in the anaemic group compared to the non-anaemic group (Chi-square: 19.7% vs 2.8%,  $p < 0.0001$ ).

**Conclusion:** This audit demonstrated that preoperative anaemia is poorly assessed and managed in colorectal surgical patients, potentially increasing surgical risk and health expenditure. Feedback to surgeons on the clinical impact of audit findings has improved their awareness of PBM guidelines. Pharmacists play a key role in improving surgical quality use of medicines.

A051

## **Validation of the Lamson pneumatic tube system for the Transportation of Blood Components to Intensive Care and Ambulatory Care**

**Joseph Rigano**<sup>1</sup>, Emma Dowell<sup>1</sup>, Diana Kolar<sup>1</sup>, Chris Hogan<sup>1</sup>

<sup>1</sup>*Austin Health, Heidelberg, Australia*

### **Aim:**

The Lamson pneumatic tube system (PTS) utilises pressure and vacuum suction to transport carriers through a network of pipes from one location to another. The air-flow within the system is generated by blowers which control the speed of the carriers through the pipes. This validation focused on the suitability for the safe and timely transportation of blood components by the PTS from Blood Bank to the Intensive Care Unit (ICU) and Ambulatory Care Centre (ACC). Validation of a PTS is a *National Pathology Accreditation Advisory Council (NPACC)* requirement.

### **Method:**

Blood components routinely prepared and issued by the Blood Bank were tested. These included packed red blood cells (PRBC), fresh frozen plasma (FFP), extended life plasma (ELP), cryoprecipitate and platelets. The effect of the inherent nature of the PTS on blood components was evaluated as well as appropriate transit time and intended destination. Blood components were subjected to physical and laboratory testing pre and post PTS transportation.

### **Result:**

Post transportation, the PTS had no effect on blood components when visually inspected. Transit times and temperatures of the carriers and all blood components were within acceptable ranges. All carriers arrived at their intended destination. There was no significant change in the platelet count or platelet function and the degree of haemolysis in PRBC was below the TGA requirement.

### **Conclusion:**

This validation has determined that the Lamson PTS is suitable for the safe and timely transportation of blood components from Blood Bank to ICU and ACC.

A052

**Product usage between a fixed and a Viscoelastic Haemostatic Assay(VHA) guided Massive Transfusion Protocol (MTP) – four case reviews with unanticipated massive intra operative bleeding.**

**Shaun Roberts**<sup>1</sup>, Rae Duffy<sup>1</sup>, Danielle Volling-Geoghegan<sup>1</sup>

<sup>1</sup>*Princess Alexandra Hospital, Woolloongabba, Australia*

**Introduction**

The Princess Alexandra Hospital is a 688 bed, major tertiary surgical referral hospital with expertise in trauma, renal and liver transplantation. The PA hospital has both VHA systems. In April 2018 a revised MTP was released with a VHA arm and a fixed product transfusion arm. A subsequent pilot study evaluating the use of the TEG 6s and ROTEM Sigma VHA in the management of intra operative bleeding patients was conducted to evaluate the degree of correlation between the two systems.

**Aims**

To observe the impact of VHA systems on actual product requirement in intraoperatively bleeding patients recruited to the TEG 6s vs ROTEM Sigma pilot study.

**Method**

After machine validation, 30 bleeding patients were randomly recruited by anaesthetic staff from May to December 2018. VHA assessments were done to determine intraoperative, product requirement. Citrated viscoelastic haemostatic assays were run on the same citrated blood samples. Data for time to test, time to transfuse, product transfusion, emergency and ICU admission data, anaesthetic management and qualitative anaesthetic feedback on relevance and actual use of VHA was collected.

**Results**

4 cases of non-trauma related intraoperative activation of MTPs are presented to highlight the contrast between fixed MTP product usage and the actual VHA results and real life product transfusions used. In 3 of 4 of these cases there was agreement between the VHA results in both systems and the subsequent product recommendation of the respective VHA algorithms employed at PA. There is a notable difference in the increased quantity of fibrinogen replacement used in the VHA guided MTP contrasted to the fixed transfusion arm.

**Conclusions**

VHA systems contribute to our intra operative assessment of bleeding and subsequent product transfusion. The data collected in this pilot study suggests that surgical induced and gastro intestinal bleeding has a different profile to trauma induced coagulopathy and bleeding. Further investigation with a larger, bleeding, patient cohort is recommended to enhance data acquisition and explore VHA transfusion concurrence.

**Ethics Approval** HREC/18/QPAH/131 – SSA/18/QPAH/132 Queensland Health Metro South Research Governance

## When something historical reveals something new. – A case of Anti-LW

**Naomi Roots**<sup>1</sup>, Brett Wilson<sup>1</sup>, Jenny Morrison<sup>1</sup>, Robyn Turner<sup>1</sup>, Kelli McGrath<sup>1</sup>, Glenda Millard<sup>1</sup>, Dianne Grey<sup>3</sup>, Elizabeth Fong<sup>3</sup>, Tanya Cawthorne<sup>2</sup>, Yew-Wah Liew<sup>1</sup>

<sup>1</sup>Australian Red Cross Blood Service, Brisbane, Australia, <sup>2</sup>Australian Red Cross Blood Service, Perth, Australia, <sup>3</sup>PathWest, Nedlands, Australia

**Introduction:** Blood group gene *ICAM-4* encodes the antigens of the LW blood group system; LW<sup>a</sup>, LW<sup>ab</sup> and LW<sup>b</sup>. It is phenotypically related to the Rh antigen, and anti-LW can often be easily mistaken for anti-D. Although anti-LW is not uncommon, the transient nature of this antibody means that it is often difficult to identify if it is an auto or alloantibody. We report a case with historical anti-LW that is not anti-LW<sup>a</sup>.

**Case presentation:** A specimen from a 66 year old female, of Indigenous Australian background was referred to the Red Cell Reference Laboratory for genotyping to confirm the LW status. Patient has a history of an autoantibody and an anti-LW since 1983.

**Methods:** Standard haemagglutination techniques were used for phenotyping. Antibody investigation was performed using a panel of phenotyped RBC and cord blood cells. DNA from the patient was isolated and genotyped using Immucor BioArray HEA BeadChip and sequenced using the Illumina TruSight One sequencing panel (TSO).

**Results:** Genotyping predicted a phenotype of LW(a+b-) in concordance with serology and phenotyped as LW(ab+). LW (*ICAM4*) gene sequencing detected a homozygous c.309C>A novel mutation. An antibody with LW specificity was detected in the IAHG tests. Results of testing with adult and cord blood (D+ and D-) were consistent with anti-LW. Rhnull and LW(a-b-) cells were compatible. Investigations of family members indicated that all 3 siblings have the novel mutation, with one having the same homozygosity as the proband.

**Conclusion:** An antibody recognizing an epitope on the LW glycoprotein was identified. This new antibody has specificity as LW but is not anti-LW<sup>a</sup> nor anti-LW<sup>ab</sup>. Further investigation and family studies will be required to characterize this novel LW mutation. Anti-LW has not been reported as causing transfusion reaction or HDFN and most patients can be successfully transfused with cross-matched incompatible D- red cells.

A054

## **New Zealand Blood Service, Southern Region, Donation Accreditation Laboratory, Process Improvement Project**

**Ghobrial Roufail**<sup>1</sup>, Grace Agustin<sup>1</sup>, Kaye Mayo<sup>1</sup>, Ricardo Van Wyk<sup>1</sup>, Jessie Tracy<sup>1</sup>, Rebecca Kruger<sup>1</sup>

<sup>1</sup>*New Zealand Blood Service, Christchurch, New Zealand*

The New Zealand Blood Service (NZBS) conducts process improvement projects throughout its departments as part of its continuous improvement strategy. NZBS utilises the DMAIC (Define, Measure and Analyse, Innovative Improvements, and Control and Continue) methodology in these projects, as outlined below for the Southern Region Donation Accreditation Laboratory process improvement project.

**Define:** The capacity, optimal physical layout and workflow required in the Christchurch Donation Accreditation (DA) department was unknown.

**Measure and Analyse:** Video analysis of both sample and operator processes were conducted. Each process step was classified as an action, and the proportion of each action was calculated. Walking maps were also drawn to investigate the efficiency of the laboratory layout.

Analyser capacity and utilisation rates were measured to identify the laboratory's testing capacity.

Data on sample throughput and their delivery times were also collated to measure daily workload.

Suggestions for improvement were collected from the laboratory's team members.

The measure and analyse phase identified the peaks and troughs in workload and the laboratory layout as opportunities for improvement.

**Innovative Improvements:** Five pilots were created following the findings of the measure and analyse phase. Two pilots focussed on streamlining sample processing and retrieval, while minimising non-value add tasks such as transport and paperwork.

Two pilots addressed the peaks and troughs in the workload. The level loading pilot increased the rate of day 1 testing without severely affecting release time of blood products. This was carried out by reducing the laboratory's testing cut-off times. The new work pilot involved staff collating ideas on testing that can be conducted Inhouse to increase the workload.

The final pilot focussed on the laboratory's layout. The layout was reconfigured to allow for a more optimal workflow.

**Continue and Control:** Day 1 testing implementation is being trialled for 3 months, and result release data is being analysed to measure effect on end product release. Finally, the new laboratory layout and streamlined processes have been shared with the Auckland Donation Accreditation Laboratory prior to its redevelopment within the next year.

## **Maternal anti-Do(a) and Unexplained Fetal Anaemia**

**Kylie Rushford**<sup>1</sup>, Kerman Buhariwala<sup>2</sup>, Erica Wood<sup>1</sup>

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**Introduction** – Patients with clinically significant unusual antibodies can cause challenges in the Blood Bank Laboratory in their identification. The problems are further complicated in the pregnant patient when the fetus requires an intrauterine transfusion (IUT).

Case Report – A 34-year-old woman (G3P2) with no atypical red cell antibodies at booking presented for a routine ultrasound at 20 weeks gestation. A significant fetal pericardial effusion and a thickened nuchal fold were noted.

The fetus developed significant hydrops by 24/40. The MCA-PSV measurements by Doppler predicted fetal anaemia and a sample was collected for routine pre-transfusion testing for a planned IUT. Atypical red cell antibodies were detected by IAT, but specificity could not be resolved by the routine hospital laboratory. The Blood Service identified the antibody as anti-Dombrock<sup>a</sup>, which would not explain the significant fetal anaemia.

Logistical difficulties were encountered when sourcing suitable blood for the IUT, because of the unavailability of commercial antisera. Most panels do not have Do(a) typing stated on their antigrams, which made testing problematic.

Close interaction between the treating team and Blood Service sourced suitable red cells and the fetus was transfused from 21g/L to 128g/L. Extensive investigations including a TORCH screen, Kleihauer test, FISH test and chromosomal microarray failed to elucidate the cause of the hydrops. However, the fetus was also noted to have skeletal abnormalities with short long bones.

The fetus was closely monitored but no further IUTs were required. At birth the baby had a positive DAT and jaundice that resolved with phototherapy.

**Conclusion** – Anti-Do<sup>a</sup> is rarely encountered as a single specificity, and has not been reported to cause significant haemolytic disease of the fetus and newborn. We report a case of unexplained fetal anaemia in the presence of anti-Do<sup>a</sup>, which required close co-ordination between the hospital obstetric team, transfusion laboratory and clinical haematology teams and the Australian Red Cross Blood Service to manage testing and IUT requirements.

A056

## **An Analysis of the Transfusion reactions with increased respiratory rate: A Hemovigilance window**

**Lakhvinder Singh**<sup>1</sup>, Ashish Jain<sup>1</sup>, Ratti Ram Sharma<sup>1</sup>, Neelam Marwaha<sup>1</sup>

<sup>1</sup>*Post Graduate Institute of Medical Education and Research, Chandigarh, India, Chandigarh, India*

### **Aims**

To analyze the transfusion reactions presenting with increase in the respiratory rate along with other defined signs and symptoms to give an insight to the spectrum of PTR's.

### **Materials and Methods**

This was a prospective study conducted over a period of 7 months. All the transfusion reactions with post transfusion increase in respiratory rate were included in the study. Clinical parameters of the patient were compared with type of transfusion reaction and its association with the respiratory symptoms.

### **Results**

Over the period of 7 months, 117 transfusion reactions were reported. Amongst these, the most common transfusion reaction was FNHTR (70.94%) followed by allergic reaction (22.22%). A total of 12 reactions were due to PTR's. It was found that increase in respiratory rate is significantly associated with the febrile reactions. And 75% of the PTR's also had febrile response in the patients. Out of all the reactions, 54 cases were associated with increase in the respiratory rate. The mean rise in the respiratory rate in patient with FHNTR only and FNHTR with TAD was 7 and 12 respectively (p value = .013). However there was lot of overlap between the minimum and the maximum values. We also observed an increasing trend in the respiratory rate as the severity of FNHTR increase from simple chills and rigors to rise in temp more than 2 degrees Celsius.

### **Conclusion**

Increase in the respiratory rate can occur as a part of the spectrum of FNHTR. Patient with FNHTR with Increased respiratory rate should be categorized as having PTR only if some other objective sign of pulmonary involvement is present.

A057

## **An analysis of the blood components ratio (PRBC:FFP: Platelet) used during massive transfusion in a tertiary care centre**

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### **Aim**

To compare the ratio of usage of blood products and their role in outcome of massive transfusion cases.

### **Method**

This observational study was performed over a period of 12 months, where cases with massive hemorrhage requiring and fulfilling the criteria of massive transfusion were registered from the clinical areas and followed up based on clinical and investigational parameters till death or discharge in our institute.

### **Result**

A total of 71 patients were included in the study who were transfused with 1894 blood components. 35.2 % of the total components transfused were red cell components. The percentage of FFP, platelets components and cryoprecipitate transfused were 32.8%, 25%, 7% respectively. Major indication for massive transfusion included trauma 34%, Obstetric haemorrhages (28%) and others which included vascular and cardiac injuries. Out of 71 patients, 48 (67.6%) required intubation and 58 (81.7%) were started on inotropic support. There was no fixed ratio of PRBC to other components for patients with massive haemorrhage. The average ratio of PRBC:FFP:PC was 1:0.9:0.6. The minimum and maximum PRBC : FFP ratio used were 1 : 3 and 9 : 0 respectively. The minimum and maximum PRBC : PC ratio used were 1 : 1.9 and 9 : 0 respectively. We found that blood component therapy with PRBC: FFP ratio between 0.5 to 1.5 was associated with significantly decreased bleeding ( $p=0.02$ ) and a significant rise in post acute phase hemoglobin. We could not find any significant association with red cell to platelet transfusion ratio. Major complications noticed in the massively transfused patients were acute renal failure requiring dialysis (14.1%), Disseminated Intravascular Coagulation (8.4%), positive antibody screen (4.2%) and one transfusion reaction.

### **Conclusion**

Appropriate blood component therapy during the acute bleeding phase in massively transfused patients can further decrease the transfusion demand and transfusion related complications. Hence, there is a need to establish the massive transfusion protocol for the clinical areas requiring massive transfusion.

## Evaluation of a novel hypoxic storage system for red blood cells in different additive solutions

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<sup>3</sup>Hemanext, Lexington, USA

### Background

Hypoxic storage of red blood cells (RBCs), achieved by depletion of oxygen (O<sub>2</sub>) and carbon dioxide, is reported to influence erythrocyte metabolism and maintain 2,3-DPG. Processing methods and RBC additive solutions can impact erythrocyte metabolism during storage. This study assessed the impact of hypoxic and conventional storage using three RBC additive solutions; SAG-M, AS-3 and PAGGSM.

### Method

RBCs were prepared from whole blood held overnight (<18 hours) and resuspended in SAG-M, AS-3 or PAGGSM. Pairs of RBCs in each additive solution were pooled-and-split and then processed with either the Hemanext® storage system (HRBC) or conventionally (CRBC). RBCs in each study arm (n=8) were tested on storage days 2, 7, 14, 21, 28, 35 and 42. Data were analysed by two-way repeated measures ANOVA.

### Result

The sO<sub>2</sub> of HRBCs was <20%, with pO<sub>2</sub> maintained at <20 mmHg throughout storage in all additives. In contrast, sO<sub>2</sub> of CRBCs increased from 40-60% to over 90% at end of storage, significantly increasing cumulative exposure of stored CRBCs to oxygen. HRBCs in PAGGSM consumed significantly more glucose (p=0.0032) and HRBCs in all additives produced more lactate (p<0.0001). HRBCs in all additive solutions maintained significantly higher 2,3-DPG concentrations than CRBCs (p<0.0001); 2,3-DPG was over 10-fold higher on day 7, 14 and 21 in HRBCs stored in SAG-M and PAGGSM. Hemolysis was slightly higher in HRBCs although not statistically significant. HRBCs in SAG-M had significantly higher potassium release (p< 0.0001). Supernatants from HRBCs and CRBCs did not activate human umbilical vein endothelial cells, with no differences in secretion of IL-8, IL-6, RANTES or sCD62P, or expression of endothelial activation markers E-selectin and V-CAM.

### Conclusion

Hypoxic storage of RBCs better maintains 2,3-DPG compared to conventional storage and present *in vitro* data suggest hypoxic storage is suitable for use with AS-3 and PAGGSM, but not with SAG-M.

## **HPA Compatible Platelets Support for Suspected FNAIT Cases in Western Australia**

**Julianne Taylor**<sup>1</sup>, Anne McNae<sup>1</sup>, Anastazia Keegan<sup>1</sup>

<sup>1</sup>*Australian Red Cross Blood Service, Perth, Australia*

**Background:** International literature suggests the incidence of Foetal and Neonatal Alloimmune Thrombocytopenia (FNAIT) ranges between 0.5-1.5 per 1000 live births. However, the incidence of FNAIT in Western Australian (WA) is unknown.

**Aim:** To describe the utilisation of Human Platelet Antigen (HPA) compatible platelets in cases of suspected FNAIT in WA.

**Method:** A retrospective analysis of the Australian Red Cross Blood Service's (Blood Service) HPA Compatible Platelet Database was undertaken from January 2015 to June 2019. All requests for HPA compatible platelet support for suspected FNAIT cases in WA were included for analysis.

**Results:** There were twelve requests for HPA compatible platelet support for suspected FNAIT cases during the 54 month study period. 83% of requests occurred during the antenatal period following the detection of HPA antibodies in the maternal serum. 75% of mothers in this cohort had antibodies to HPA-1aa and 25% had antibodies to HPA-5bb. Ten mothers received antenatal intravenous immunoglobulin (IVIg) with four babies receiving IVIg after birth.

HPA compatible platelets were arranged to support nine babies, but only three babies required platelet transfusions. Seven babies were born with platelet counts  $<100 \times 10^9/L$  but only three had platelet counts  $<30 \times 10^9/L$  at birth. Twenty-two blood donors were identified from the Blood Service's national Platelet Panel Database (PPD) to provide HPA compatible platelets to support FNAIT babies in WA during the study period.

**Conclusion:** This is the first time the WA utilisation of HPA compatible platelets for suspected FNAIT cases has been examined, and forms the basis of future plans to report the utilisation of HPA compatible platelets to support suspect FNAIT cases across Australia.

## **Clinical practices and outcomes of RhD immunoglobulin prophylaxis following large-volume fetomaternal haemorrhage in Queensland, Australia**

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<sup>3</sup>School of Clinical Medicine, University of Queensland, St Lucia, Australia

### **Background**

Guidelines for laboratory assessment of fetomaternal haemorrhage (FMH) was published by the Australia and New Zealand Blood Transfusion Society (ANZSBT) in 2002. However, data on adherence by practitioners and clinical outcomes are lacking.

### **Objectives**

The primary objective of this audit is to retrospectively examine the follow-up testing and provision of additional RhD immunoglobulin in RhD negative women who experienced large volume FMH (> 6ml of foetal red cells) within the state of Queensland, Australia. The secondary objectives are to examine the rate of RhD alloimmunisation and its associated risk factors in these women.

### **Methods**

RhD negative women who required additional dose(s) of RhD immunoglobulin for FMH from February 2007 to February 2018 were identified through the supply tracking analysis reporting system at the Australian Red Cross Blood Service (Blood Service). For each patient, the volume of FMH, methods and timing of FMH quantitation, dose of RhD immunoglobulin received, maternal and foetal blood groups, and results of antibody screen and identification were retrieved and analysed.

### **Results**

There is a wide variation in follow-up testing and provision of additional RhD immunoglobulin after administration of supplemental RhD immunoglobulin based on the initial FMH quantitation, with only 11.5% adhering to current ANZSBT guidelines. Despite the provision of single supplemental RhD immunoglobulin at a ratio of 100IU RhD immunoglobulin to 1ml foetal red cells, the rate of RhD alloimmunisation in RhD negative women with RhD positive foetus or foetus of unknown RhD status following FMH > 6 ml is at least 8%.

### **Conclusion**

Poor compliance with guidelines for the follow-up and management of large FMH may be contributing to increased risk of RhD alloimmunisation. Further analysis of national data is warranted.

A062

**Is it a match made in heaven? Improving patient identification processes in the day infusion centre.**

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**Aim:** Incorrect patient identification and mismatching to clinical interventions have led to adverse events and poorer patient outcomes. Ambulatory care settings such as day infusion centres are at particular risk for matching errors owing to a high turnover of patients and a high number of clinical interventions, including administration of blood and blood products. Anecdotal evidence from our Local Health District Infusion Units indicate that there is poor compliance with international, NSW Health and Local Health District (LHD) policies and procedures identification and procedure matching. This pilot investigates current patient identification and matching practices in these settings, and to improve compliance with a small scale intervention.

**Method:** 4 Infusion Units across three hospitals in a Sydney LHD were identified. An observational implementation project using Joanna Briggs Institute Practical Application of Clinical Evidence System (PACES) and Getting Research into Practice (GRIP) audit and feedback tool was used to identify current patient identification and matching practices. A baseline audit was completed, and from the audit results patient identification bands were introduced. An interim audit was then undertaken followed by implementation of additional support strategies and a final audit is planned for July 2019.

**Result:** In the baseline audit, 39 patient procedures were observed involving 14 staff, and 41 patients were interviewed. The units varied in practices and compliance levels. Factors affecting implementation of the guidelines were identified, such as personal beliefs and activity level of the unit. After the interim audit there was resistance from some staff regarding the introduction of patient identification bands. This presentation will focus on the experiences and factors that affected implementation at all stages of the project with recommendations given for future similar projects.

**Conclusion:** Through education and intervention, correct patient identification and procedure matching processes have improved when patients are receiving procedures in the Infusion Units.

**Donor anti-HNA-3a antibodies induce monocyte-mediated HLMVEC damage in a two insult in vitro model**

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**Aim:** Transfusion-related acute lung injury (TRALI) is a leading cause of blood transfusion associated mortality. One cause of TRALI is the transfusion of blood components containing antibodies against human leucocyte antigens (HLA class I and II) and/or human neutrophil antigens (HNA). Anti-HNA-3a antibodies have been implicated in severe cases of TRALI even though the mechanism is unclear. A pathway involving endothelial cells, complement and monocytes has been described for monoclonal antibody MHC class I-mediated TRALI in mice. We investigated whether HNA-3a antibodies may mediate TRALI in humans through the same pathway.

**Methods:** Human lung microvascular endothelial cells (HLMVECs) were cultured  $\pm$  lipopolysaccharide (LPS; 6 hours). Isolated monocytes were then added (30 minutes). Sera (10% final) from either a control donor (sera C), or donors with either antibodies against HLA class I, HLA class II and HNA-3a (sera A) or an antibody against HNA-3a only (sera B)  $\pm$  plasma (as a complement source; 3% final) were then added (30 minutes). After trypan blue staining, 3-5 fields per condition were acquired via microscopy and viable HLMVECs were identified by ImageJ analysis. Data presented as mean  $\pm$  SEM. P-values by one-way ANOVA.

**Results:** Control-treated (sera C) HLMVEC showed a viability of  $89 \pm 2.3\%$ . Sera A or sera B caused HLMVEC damage only in the presence of LPS, monocytes and complement (cell viability decreased to  $65\% \pm 6.4$  ( $p=0.0028$ ) and  $63 \pm 5.5\%$  ( $p=0.0097$ ). Blocking the complement pathway (using an anti-C5a antibody) partially restored cell viability to  $88.8 \pm 2.8\%$  and  $88.3 \pm 2.9\%$  respectively.

**Conclusion:** These results suggest that anti-HNA-3a antibodies may mediate TRALI through a pathway involving endothelial cells, monocytes and complement.

## Western Australian Blood Discard Reduction Project

### **Bradley Webster**<sup>1</sup>

<sup>1</sup>Department of Health (WA), Perth, Australia

**Aim:** WA's 2017/18 red cell discards as a percentage of issuance (DAPI) was 4.9%, well above the national DAPI of 2.2%. This represents 2,388 discarded units with an associated cost of \$985,442. The Department of Health (WA) initiated the WA Blood Discard Reduction Project in June 2018 to determine root causes of WA red cell discards and develop mitigating strategies.

**Method:** Extensive collaboration with public and private sector approved health providers (AHP's), National Blood Authority (NBA) and Australian Red Cross Blood Service. This included establishment of the Blood Discard Reduction Advisory Committee (BDRAC), interviews with stakeholders (39) and selected jurisdictions (3) and a stakeholder questionnaire to assess accessibility of available blood discard reports.

### **Results:**

**Table 1: Causes and recommendations**

<b>Cause</b>	<b>Recommendation</b>
<b>System oversight</b> Limited Department of Health (WA) knowledge of existing practices.	<ul style="list-style-type: none"> <li>• Department of Health (WA) improve knowledge through BDRAC and stakeholder meetings.</li> </ul>
<b>Data issues</b> <ul style="list-style-type: none"> <li>• Lack of bidirectional interface between NBA and PathWest systems leading to incomplete NBA data for public AHP's impacting transfer, DAPI and discard reason data.</li> <li>• Challenges using existing NBA discard reports.</li> </ul>	<ul style="list-style-type: none"> <li>• Improved completeness of transfer data.</li> <li>• Improved incorporation of PathWest discard reasons data in NBA reports.</li> <li>• Improved entry of discard reasons data by AHP's.</li> <li>• Adaption of NBA discard reports.</li> </ul>
<b>Stock rotation</b> Challenges for AHP's to utilize rotated stock.	<ul style="list-style-type: none"> <li>• AHP's review stock rotation practices.</li> </ul>
<b>Geographical issues</b> Higher DAPI in rural areas associated with higher inventories and stock rotation challenges.	<ul style="list-style-type: none"> <li>• Targeted education program.</li> <li>• Review of inventory levels.</li> </ul>
<b>Executive engagement</b> Need for improved executive engagement.	<ul style="list-style-type: none"> <li>• Development of quarterly reports for hospital Executives.</li> <li>• Ongoing engagement with PathWest Executives.</li> </ul>

**Conclusion:** WA's red cell DAPI was 3.5% in April 2019, with reductions in both public and private sectors. Projected cost saving for 2018/19 from the reduction in discarded red cell units is \$228,754. The WA Blood Discard Reduction Project is ongoing.

A066

## **NEO and improved method for screening rare donors**

**Nadya Jivani**<sup>1</sup>, Kristina Wheal<sup>1</sup>

<sup>1</sup>*New Zealand Blood Service, Auckland, New Zealand*

### **Introduction**

The New Zealand Blood Service (NZBS) is a national organisation that aims to supply safe and appropriate blood and tissue products to meet the transfusion needs of patients nationwide, regardless of the complexity of their red cell serology.

In January 2018 a rare antibody to a high incidence antigen belonging to the Lutheran blood group system, anti-Lu<sup>b</sup>, was identified in a pre-transfusion sample from a 14 year old male with  $\beta$ -thalassaemia.

Providing compatible blood to patients with rare antibodies such as anti-Lu<sup>b</sup> is difficult because of the rarity of antigen negative donors in the New Zealand population. This patient's haematological disorder made it vital we identify more Lu<sup>b</sup> negative donors in order to meet regular transfusion requirements.

### **Method**

NZBS Red Cell Reference Laboratory initially screened random donors using patient plasma containing anti-Lu<sup>b</sup>. Any donor sample with a compatible serological crossmatch was then confirmed using a commercial anti-Lu<sup>b</sup> antisera.

From September 2018 NZBS Donation Accreditation Laboratory (DA) in Auckland began daily screening of group O donors using the Galileo Neo blood group analyser cross-matching protocol. As with the manual method, any compatible crossmatches were sent to the Red Cell Reference Laboratory to be confirmed.

### **Results**

13,828 donors were screened using the Galileo Neo in the space of 4 months resulting in 13 new Lu<sup>b</sup> negative donors. At the end of April 2019 screening began at Christchurch DA, and only 8 weeks post implementation the results look promising with 14 new Lu<sup>b</sup> negative donors confirmed.

### **Conclusion**

Identifying new Lu<sup>b</sup> negative donors using automation has enabled us to supply our patient with two fresh or frozen red cell units monthly. By informing each new donor that their donations are rare and vital, we hope they are encouraged to donate regularly.

O148

## **Haemostatic and non-haemostatic roles of plasminogen activation**

**Robert Medcalf**

The fibrinolytic system is renowned for its role the removal of blood clots and fibrin deposits via the generation of the potent enzyme, plasmin, from its precursor plasminogen. Two main plasminogen activating enzymes are responsible for this process: tissue type plasminogen activator (t-PA) and urokinase (u-PA). The targeted removal of fibrin via t-PA and u-PA initiated their clinical development for use in patients with thromboembolic conditions. However, over the past two decades it has become apparent that the plasminogen activating system plays fundamental roles in various aspects of normal physiology and pathophysiology. Initial reports linked this system with wound healing, development and metastatic spread. Cell surface receptors for t-PA, u-PA and plasminogen have been discovered that not only facilitated localised plasmin generation, but also provided a means to transmit intracellular signals that can modulate gene expression and cell metabolism. Indeed, at least 12 separate plasminogen receptors have now been identified on numerous cells. These plasminogen receptors are notably found on key innate immune cells. Plasmin generation on the surface of dendritic cells, for example, provides a potent immunosuppressive stimulus that has now been associated with infection risk. In addition to these roles, essentially all components of the fibrinolytic system have been linked with numerous aspects of brain function, including synaptic plasticity, NMDA receptor activation, memory, learning and blood-brain barrier permeability. This presentation will overview these emerging non-haemostatic roles of the fibrinolytic system and how this evolving research has a bearing on the clinical use of thrombolytic and anti-fibrinolytic agents.

O150

**What is the mature, functional coagulation protein?**

**Philip Hogg**

Proteins are responsible for all of life's processes and are the most sophisticated molecules made in nature. The covalent structure of proteins is defined by peptide bonds that link the amino acid residues and disulphide bonds that link pairs of cysteine amino acids. Our current understanding is that the disulphide bonds are fully formed in the mature, functional protein. Thousands of protein crystal structures, where the disulphide bonds are almost invariably intact, support this concept of the mature protein. We have recently shown that this is not the case for coagulation proteins in human blood. The results indicate that the proteins exist in hundreds, perhaps thousands, of different disulphide-bonded states in the human circulation. These findings change our concept of the mature, functional protein. They have significant implications for how coagulation proteins function generally, how we target them in experiments and for development of drugs.

**The ribosomal biogenesis inhibitor CX5461 is an anti-cancer therapeutic that increases platelet count in mice and in humans**

**Amandeep Kaur**<sup>1</sup>, Samina Nazir<sup>1</sup>, Samantha Montague<sup>1</sup>, Si Ming Man<sup>1</sup>, Kylee Maclachlan<sup>2</sup>, Poortinga Gretchen<sup>2</sup>, Simon Harrison<sup>2</sup>, Ross Hannan<sup>1</sup>, Kate Hannan<sup>1</sup>, Elizabeth Gardiner<sup>1</sup>

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**Aim:** Ribosomal biogenesis inhibitor CX5461 is a candidate anti-cancer therapeutic, which increases platelet count in diseased mice. We investigated mechanisms that may contribute to increased platelet count following CX5461 treatment in disease-free mice and evaluated blood data from patients with haematological malignancies treated with CX5461.

**Method:** We evaluated blood cell numbers, bone marrow megakaryocytes, platelet receptors, immature platelets, platelet function, thrombopoietin (TPO) and inflammatory cytokine levels in disease-free C57BL/6 KaLwRij mice treated with 35 mg/kg CX5461 or vehicle (n=15). We evaluated temporal platelet count, and platelet activation marker (sGPVI) in patient plasma samples who received single dose of 25-250 mg/m<sup>2</sup> CX5461 (n=16) with 1-way ANOVA.

**Result:** Mice (disease-free) treated for up to 14 days (6 x 35 mg/kg doses) with CX5461 showed ~60% increase in platelet count; notably white and red cells were depleted in this timeframe consistent with Hein et al, 2017 Blood. The CX5461-mediated platelet increase at d7 (p<0.0005) was reversible within 1 week. At d14 (p<0.01, 1.7-fold increase in platelet count) a significant increase in megakaryocytes (p<0.05) and immature platelets (p<0.01) was observed. CX5461 treatment had no effect on plasma TPO, platelet lifespan or platelet glycoprotein (GP)VI or GPIIb $\alpha$  levels. Integrin  $\alpha$ IIb was significantly elevated. Inflammatory cytokines interleukin (IL)-6 (p<0.05) and TNF $\alpha$  (p<0.01) increased at d7 in plasma. In 8/16 patients receiving CX5461, increases of up to 34% in platelet counts were measured at day 15 of CX5461 treatment, but no change in sGPVI.

**Conclusion:** CX5461 treatment in mice increased platelet count, megakaryocyte number and immature platelet fraction after two weeks. A role for TNF $\alpha$  and IL-6 in enhancing megakaryopoiesis is proposed. CX5461 treatment in malignancy patients resulted in small increases in platelet count but no effect on platelet activation. Future work will explore the link between CX5461 treatment and megakaryopoiesis and thrombopoiesis.

## The effect of the combined deletion of PECAM-1 and Ceacam1 on thrombus formation

**Fahd Kuriri**<sup>1</sup>

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### Background:

Knockout mice models have been invaluable for determining the role of ITAM and ITIM bearing receptors in the context of platelet haemostasis and thrombosis. PECAM-1 KO and Ceacam1 KO each have a hyper-responsive platelet:collagen phenotype indicating they are not redundant, and collectively these Ig-ITIM bearing receptors play an important role in regulating platelet-collagen interactions *in vivo*.

### Aims:

To develop a double ITIM receptor knockout mouse to study whether the deletion of two receptors has a synergistic effect on thrombus formation using *in vitro* and *in vivo* models.

### Methods:

Haematological parameters were analysed from murine whole blood by using Cell-DYN Emerald analyser.

Intravital microscopy was used to determine thrombus formation and stability in wild-type, Ceacam1<sup>-/-</sup> and double-knockout *in vitro* using micro-slides or following ferric chloride (FeCl<sub>3</sub>) induced vascular injury of mesenteric arterioles. Z-stack digital AxioCam mRm camera and Axiovision software was used to capture images. Three dimensional (3D) deconvolved reconstructions of thrombi formed were analysed for surface coverage of platelet aggregates ( $\mu\text{m}^2$ ), thrombus height ( $\mu\text{m}$ ) and thrombus volume ( $\mu\text{m}^3$ ).

### Results:

All haematological parameters including platelet count were normal in DKO, Ceacam1<sup>-/-</sup> compared to wild-type mice.

DKO model revealed a significant increase in thrombus formation compared to the hyper-responsive single Cc1<sup>-/-</sup> phenotype versus the WT phenotype.

### Conclusions:

Double PECAM-1<sup>-/-</sup>.Ceacam1<sup>-/-</sup> had a synergistic effect on platelet activation and *in vitro* and *in vivo* thrombus formation.

O154

## **Platelet deficiency of ERp5 is compensated for by increased levels of ERp57, ERp72 and PDI**

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### **Background/Aim**

Endoplasmic reticulum 5 (ERp5) is a member of the vascular thiol isomerase family, which also includes protein disulphide isomerase (PDI), ERp57 and ERp72. Thiol isomerases are released from activated platelets and bind to platelet integrin  $\alpha\text{IIb}\beta\text{3}$ . Platelets deficient in PDI, ERp57 or ERp72 have decreased aggregation and thrombus formation *in vivo*. We have recently demonstrated that ERp5 enables fibrinogen release from  $\alpha\text{IIb}\beta\text{3}$  by cleaving the disulphide bond 177-184 in the  $\beta\text{3}$  subunit of  $\alpha\text{IIb}\beta\text{3}$ . The aim of this study is to further characterize ERp5 function in platelets using a platelet-specific knockout mouse.

### **Methods**

Conditional ERp5 knockout mice (PF4Cre+ Pdia6 fl/fl) (CKO) were generated by CRISPR-Cas9 technology. Mice carrying the floxed ERp5 gene without PF4Cre (PF4Cre- Pdia6 fl/fl) were used as controls. Thrombin activation of integrin  $\alpha\text{IIb}\beta\text{3}$  was measured from binding of JON/A antibody. Hemostasis was measured by tail bleeding time and APTT. Platelet adhesion to fibrinogen under flow was measured in a microfluidics device.

### **Results**

ERp5 protein levels in CKO mouse platelets were <2% of control platelets. CKO mice had a 10% reduction in platelet count compared with WT. Depletion of ERp5 resulted in increased levels of ERp57 (3-fold), ERp72 (2-fold) and PDI (2-fold) protein. ERp5 CKO mice had normal expression of platelet surface integrin  $\alpha\text{IIb}\beta\text{3}$ , normal hemostasis and similar levels of JON/A binding to  $\alpha\text{IIb}\beta\text{3}$  following thrombin stimulation. Adhesion of the CKO platelets to fibrinogen compared with WT showed no statistical difference at shear rate of 100 s<sup>-1</sup> and 500s<sup>-1</sup>.

### **Conclusion**

Our data support a compensatory mechanism by which ablation of ERp5 increases the levels of platelet isomerases ERp57, ERp72 and PDI resulting in normal platelet adhesion to fibrinogen. This finding implies that a hemostatic threshold of thiol isomerases is critical to maintain normal adhesion of platelets to fibrinogen.

## **Experimental measurement of clotted blood particle cohesion**

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### **Aim**

In the development of thromboembolic-induced occlusions, little is known about whether particles may aggregate and deposit on the vessel wall – increasing the occlusion likelihood, promoting myocardial infarction or stroke. The mechanical interactions between colliding thromboembolic particles are poorly understood – experimental outcomes are a requirement for improved computational tracking of embolic particle fate in the arterial tree.

### **Method**

A micromechanical force apparatus was applied to study clotted blood particle cohesion, utilising a four-step pull-off technique – an application of Hooke's Law. This study introduces distributed inter-particle separation force properties between clotted blood particles, giving insight to the mechanism(s) of cohesion; pre-load (contact) force, contact time, and bulk-phase chemical modification. Clotted blood particles were loaded onto the tips of carbon fibre cantilevers, secured in place by micro-manipulators (Eppendorf Patchman NP2), and suspended in modified bulk phases; DI water, modified blood (porcine serum, porcine albumin) and pharmaceutical (alteplase, aspirin, tranexamic acid).

### **Results**

The sensitivity of the measurement on introduction of surface-active species was assessed, after a chemically repeatable baseline measurement was established ( $0.79 \pm 0.06$  [mN/m]). This served as reference with an understanding of the pre-load force and contact time dependence. The measurement reduced with increasing additive mass fraction – we hypothesize this to be a direct result of surfactant adsorption (between  $1E-6$  –  $1E-1$  wt%) to the clot-fluid interface. Alteplase offered the highest performance in force reduction from the baseline.

### **Conclusion**

The results provide direction to better understand thromboembolic cohesion mechanisms in the arterial tree – results of which can be directly applied to computational models to study aggregation and improve upon simplified numerical solutions of particle fate. The measurement is dependent on contact time on the order of  $>1$  minute, which may have implications for particles collecting & colliding in stagnant or recirculation zones. The technique may be utilised to assess surfactant adsorption to the clot-fluid interface.

O156

### **Pancreatic cancer-derived exosomes effect on endothelial cell function**

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**Aim:** Pancreatic cancer (PaCa) patients are at high risk of developing thrombosis. Cancer-derived microparticles expressing tissue factor have been found in the circulation of cancer patients which correlated with increased thrombotic events. The integrity of endothelial cell lining of blood vessels plays a role in preventing thrombosis and endothelial dysfunction is commonly observed in cancer patients. Thus we aim to investigate the effect of pancreatic cancer-derived exosomes on endothelial cell integrity and function and hypothesise that PaCa-derived exosomes promote endothelial dysfunction.

**Method:** Exosomes were isolated from pancreatic cancer cells and exposed to primary endothelial cells for functional assays including permeability, activation and signal transduction.

**Result:** Isolated exosomes were characterised using western blot and scanning electron microscopy. PaCa-derived exosomes increased endothelial monolayer permeability and activation through upregulation of adhesion molecule receptors.

**Conclusion:** PaCa-derived exosomes contribute to endothelial dysfunction that is commonly observed in cancer patients, through processes such as disruption of endothelial integrity, and upregulation of adhesion molecule receptors which may promote attachment and activation of immune cells thus facilitating in the development of thrombosis.

O157

## **Ticagrelor; an antiplatelet agent, potentiates the anticancer activity of gemcitabine in pancreatic cancer in vitro and in vivo**

**Omar Elaskalani**<sup>1</sup>, Norbaini Binti Abdol Razak<sup>1</sup>, Alice Domenichini<sup>1</sup>, Marco Falasca<sup>1</sup>, Pat Metharom<sup>1</sup>

<sup>1</sup>*School of Pharmacy and Biomedical Sciences, Curtin University, Perth, Australia*

### **Aim**

Pancreatic cancer is associated with a high risk of thromboembolic complications <sup>1</sup>. Platelets are small anucleate blood cells that are central to primary haemostasis and thrombosis. Our previous work demonstrated that pancreatic cancer cells could activate platelets directly and indirectly, and in turn, platelets can promote proliferation, migration and chemotherapy resistance in pancreatic cancer cells in vitro <sup>2-4</sup>. This study explored the therapeutic potential of combining the antiplatelet agent ticagrelor, with the chemotherapeutic drug gemcitabine in pancreatic cancer.

### **Methods**

Ticagrelor is an inhibitor of ADP-P2Y<sub>12</sub> signalling axis in platelets. Therefore, this study first examined, *in vitro*, the expression and signalling of P2Y<sub>12</sub> in pancreatic cancer cells using different pharmacological and siRNA inhibitors. The antitumour effect of ticagrelor as a single agent or in combination with various chemotherapeutic agents (gemcitabine, paclitaxel and cisplatin) was investigated using proliferation, apoptosis and immunoblot assays. The therapeutic potential of ticagrelor in combination with gemcitabine was assessed *in vivo* using a xenograft mouse model of human pancreatic cancer BxPC-3 cells and NOD/SCID mice.

### **Results**

Pancreatic cancer cells expressed a functional P2Y<sub>12</sub> receptor which contributed to cancer growth. Ticagrelor displayed an antiproliferative and proapoptotic effect on pancreatic cancer cells *in vitro* mainly through the inhibition of AKT-mediated survival signalling. Ticagrelor exhibited synergism with gemcitabine, paclitaxel and cisplatin *in vitro*. Ticagrelor in combination with gemcitabine significantly reduced tumour growth *in vivo*, whereas ticagrelor or gemcitabine as single agents had minimal effects.

### **Conclusion**

Ticagrelor, a clinically available antiplatelet agent, and potent inhibitor of AKT survival signalling in pancreatic cancer cells could be a novel option in the treatment of pancreatic cancer patients with a high risk of thrombosis.

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O160

## **Why direct-acting oral anticoagulants (DOACs) fail in patients with mechanical heart valves**

**John Eikelboom**

Valvular heart disease (VHD) affects 2.5% of the population and is a major cause of morbidity and mortality. The definitive treatment of severe VHD is prosthetic valve replacement. Mechanical valves are preferred over biological valves in younger patients because they are more durable, but require lifelong anticoagulation because they are prothrombotic. Vitamin K antagonists (VKAs) are effective for prevention of valve thrombosis and related embolic complications but have important limitations that have prompted the search for effective, safe and more convenient alternatives.

Direct acting oral anticoagulants (DOACs) that target thrombin or Factor Xa are replacing warfarin for most indications and it was hoped that they would also provide an alternative to VKAs in patients with mechanical heart valves. Animal studies supported the potential for dabigatran to prevent thromboembolic complications related to mechanical valve prostheses but the phase-II RE-ALIGN trial demonstrated that despite aggressive dosing, dabigatran was less effective than warfarin for prevention of thromboembolic complications while increasing bleeding. The lack of efficacy of dabigatran in patients with mechanical heart valves may be explained by the downstream inhibition of thrombin activity which is overwhelmed when the contact pathway is activated in response to exposure of blood to an artificial surface.

Based on the results of the RE-ALIGN trial there is reluctance among the manufacturers of DOACs that target coagulation Factor X to evaluate their use in patients with mechanical heart valves, despite the attractive results of animal studies with rivaroxaban and apixaban. Future drug development involving agents that target the contact pathway (e.g., factor XIa inhibitors) appear to offer greater potential to replace warfarin in patients with mechanical valves, and are currently entering phase 2 evaluation.

O161

**Can we use DOACS in APS?**

**Eileen Merriman**

Antiphospholipid syndrome is a systemic autoimmune disease characterised by thrombotic (arterial, venous, microvascular) or obstetric events occurring in patients with persistent antiphospholipid antibodies. Until recently, most patients with APLS and thrombotic events have been managed with warfarin. However the direct oral anticoagulants are now the preferred treatment for most patients with VTE. In this session, we will review the evidence for the efficacy and safety of DOACs in APLS.

**O165**

**Arterial thrombosis - role for direct-acting oral anticoagulants (DOACs)**

**John Eikelboom**

Clinicians have historically distinguished platelet-rich “white” thrombi that form in the arterial circulation and that appear to be the most responsive to antiplatelet therapy, from fibrin-rich “red” thrombi that form in the venous circulation and that appear to be most responsive to anticoagulant therapy. However, evidence from randomized controlled trials (RCTs) indicates that warfarin given alone or in combination with aspirin is also effective for prevention of recurrent cardiovascular (CV) events in patients with arterial thrombosis, although at the cost of a high risk of bleeding.

Initial trials of direct acting oral anticoagulants (DOACs) in patients with a recent acute coronary syndrome (ACS) produced mixed results, possibly reflecting drug targets as well as suboptimal DOAC dosing. However, the ATLAS ACS2 TIMI 51 and COMPASS trials demonstrated that rivaroxaban 2.5 or 5 mg twice daily on a background of antiplatelet therapy reduced major adverse CV events and mortality in patients with arterial vascular disease, with an acceptable risk of bleeding. Collectively these results highlight the potential for DOACs in patients with arterial thrombosis and are likely to result in the widespread use of the combination of rivaroxaban and aspirin for long term secondary prevention. Additional trials testing the combination of rivaroxaban 2.5mg twice-daily and antiplatelet therapy have recently been completed in patients with heart failure (COMMANDER HF) or are soon to be reported in patients with PAD and recent revascularization (VOYAGER PAD).

## **Acute bilirubin ditaurate exposure attenuates ex vivo platelet reactive oxygen species production, granule exocytosis and activation.**

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### **Aim**

Bilirubin, a by-product of haem catabolism, possesses potent endogenous antioxidant and platelet inhibitory properties. These properties may be useful in inhibiting inappropriate platelet activation and ROS production; for example, during storage for transfusion. Given the hydrophobicity of unconjugated bilirubin (UCB), we investigated the acute platelet inhibitory and ROS scavenging ability of a water-soluble bilirubin analogue, bilirubin ditaurate (BRT) on ex vivo platelet function to ascertain its potential suitability for inclusion during platelet storage. This study determined the impact of acute exposure on platelet function and ROS production, to assess potential suitability for inclusion during platelet storage.

### **Method**

The inhibitory potential of BRT (10–100  $\mu$ M) was assessed using agonist induced platelet aggregation, dense granule exocytosis and flow cytometric analysis of P-selectin and GPIIb/IIIa expression. ROS production was investigated by analysis of H2DCFDA fluorescence following agonist stimulation while mitochondrial ROS production investigated using MitoSOX™ Red. Platelet mitochondrial membrane potential and viability was assessed using TMRE and Zombie Green™ respectively.

### **Results**

Our data shows  $\leq 35$   $\mu$ M BRT significantly inhibits both dense and alpha granule exocytosis as measured by ATP release and P-selectin surface expression, respectively. Significant inhibition of GPIIb/IIIa expression was also reported upon  $\leq 35$   $\mu$ M BRT exposure. Furthermore, platelet exposure to  $\leq 10$   $\mu$ M BRT significantly reduces platelet mitochondrial ROS production. Despite the inhibitory effect of BRT, platelet viability, mitochondrial membrane potential and agonist induced aggregation were not perturbed.

### **Conclusions**

These data indicate, for the first time, that BRT, a water-soluble bilirubin analogue, inhibits platelet activation and reduces platelet ROS production ex vivo and may, therefore, may be of use in preserving platelet function during storage.

## **Remote ischemic preconditioning reduces infarct size, procoagulant platelet formation and protects against platelet mitochondrial membrane loss**

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Remote ischemic preconditioning (RIPC), consisting of brief cycles of non-harmful ischemia to a peripheral limb, protects the myocardium during acute myocardial infarction (MI). The mechanism remains unclear. We hypothesize that RIPC attenuates procoagulant platelet formation via protection against platelet mitochondrial membrane depolarisation.

**Aim:** To investigate the effect of RIPC on procoagulant platelet formation in human stable coronary artery disease (CAD) and a rat model of MI.

**Method:** Human subjects with angiogram-proven stable CAD were exposed to RIPC (3x5min cycles, 200mmHg using sphygmomanometer on arm). Rats were subjected to RIPC (3x5min limb ischaemia) or no RIPC followed by MI induction by ligation of their left coronary artery. Blood was collected from all subjects pre- and post-RIPC, and from rats 24h post-infarct. Procoagulant platelets were measured by combined uptake of GSAO/CD62P, and platelet mitochondrial membrane potential ( $\Delta\Psi_m$ ) was measured using the [TMRE flow cytometry assay](#). MI area was measured by histology.

**Results:** Human CAD patients had increased procoagulant platelet formation ( $p < 0.05$ ) and increased loss of TMRE+ platelets ( $p < 0.01$ ) in response to agonist stimulation compared with healthy controls. RIPC was associated with a reduction in procoagulant platelets and a corresponding reduction of TMRE loss ( $p < 0.01$ ) in these patients. RIPC prior to MI in rats significantly reduced infarct size in the animals ( $p < 0.0001$ ) and resulted in protection against procoagulant platelet formation ( $p < 0.05$ ). 90% of animals without RIPC demonstrated a reduction in TMRE+ platelets with agonist stimulation post-MI. With RIPC, ~60% of rats demonstrated an increase in TMRE+ platelets post-MI (chi-squared  $p < 0.05$ ).

**Conclusion:** MI and CAD are associated with increased procoagulant platelet formation. RIPC protects against this phenomena if given prior to MI in a rat model, or given during steady state in human subjects with stable CAD. The platelet effect suggest a mechanistic link to the protective effect of RIPC in cardiovascular diseases.

## Anti- $\alpha$ IIb $\beta$ III autoantibodies induce platelet desialylation in immune thrombocytopenia

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### Aim

Immune thrombocytopenia (ITP) is a bleeding disorder caused by anti-platelet and anti-megakaryocyte antibodies. Anti-GPIbIX antibodies have been reported to induce platelet desialylation but not anti- $\alpha$ IIb $\beta$ III antibodies<sup>1</sup>. We aim to establish if auto anti- $\alpha$ IIb $\beta$ III antibodies from ITP patients can cause platelet desialylation and study the effect of desialylation inhibition in a murine model of ITP.

### Method

The study was approved by the institutional Human and Animal Ethics Committees. Sera were collected with informed consent from 5 ITP patients with sole anti- $\alpha$ IIb $\beta$ III antibodies confirmed on MAIPA and from 20 healthy controls. Washed platelets were treated with patients' or controls' plasma followed by incubation with fluorescent-labelled anti-Neu1 antibody and RCA-1. Samples underwent flow cytometry analysis. Furthermore, a non-obese diabetic/severe combined immunodeficient murine model of ITP was established to examine the therapeutic effect of oseltamivir in platelet preservation from auto anti- $\alpha$ IIb $\beta$ III antibody mediated platelet clearance.

### Result

Plasma from ITP patients with anti- $\alpha$ IIb $\beta$ III antibodies caused significant platelet desialylation ( $p < 0.01$  and  $p < 0.0001$ , for RCA-1 and NEU-1 respectively; Mann-Whitney test). *In vivo* experiments demonstrated that the neuraminidase inhibitor oseltamivir protected human platelets from auto anti- $\alpha$ IIb $\beta$ III antibody induced clearance ( $p < 0.05$  Mann Whitney test).

### Conclusion

Platelet neuraminidase expression and desialylation is not exclusively induced by anti-GPIbIX antibodies in ITP. Anti- $\alpha$ IIb $\beta$ III autoantibodies are capable of causing platelet desialylation and platelet destruction. Neuraminidase inhibition is likely to protect platelets from hepatic removal in patients with auto- $\alpha$ IIb $\beta$ III antibodies. A collaborative clinical trial is warranted.

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## First report of rituximab dependent anti-platelet antibodies as cause of acute thrombocytopenia

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**Background:** Rituximab induced acute thrombocytopenia (RIAT) is a rare side effect characterised by severe thrombocytopenia within hours of first episode drug exposure. The mechanism remains unclear. We hypothesise that RIAT is immune-mediated secondary to drug-dependent auto-anti-platelet antibodies.

**Aims:** To clarify the mechanism of rituximab induced acute thrombocytopenia.

**Method:** Serum was analysed from three patients with severe first dose rituximab infusion reaction who developed thrombocytopenia within two to 24 hours post infusion. Serum samples taken post rituximab exposure or control serum(1:25) were incubated with washed donor platelets in the absence and in the presence of 600µg/ml of rituximab and analysed for anti-platelet antibody binding by flow cytometry using anti-human IgG-AF647. Control serum was pre-exposure serum when available or normal serum.

**Results:** All patients had marginal zone lymphoma with bone marrow infiltration and splenomegaly. One patient also received bendamustine prior to the documented thrombocytopenia. Thrombocytopenia nadir ranged from 5-60 x 10<sup>9</sup>/L. Rituximab-dependent antibody binding on platelets was not seen with control serum. In the post-rituximab exposure serum samples, antibody binding was detected only in the presence of added rituximab (Figure 1).

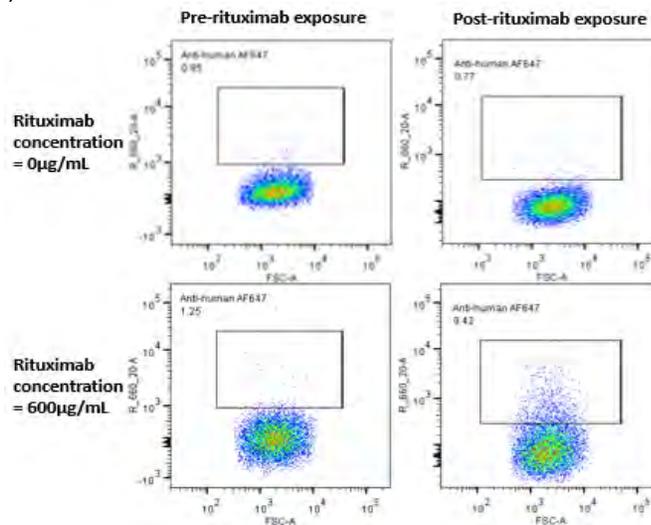


Figure 1. Representative flow cytometry results from patient 1: serum samples were incubated with normal donor platelets in the absence and presence of rituximab. There was increased antibody binding to platelets detected in post-rituximab exposure serum samples in patients who developed thrombocytopenia.

**Conclusion:** Rituximab-dependent anti-platelet antibodies were identified in three patients with acute thrombocytopenia following first dose of rituximab. The rapidity of onset suggests peripheral destruction and the testing is consistent with immune mediated platelet clearance due to drug-dependent recognition of platelet antigen. To our knowledge, this is the first demonstration of rituximab dependent anti-platelet antibodies and suggests that the cause of the rapid thrombocytopenia in these cases was immune mediated.

**A Multicentre single-arm open label study evaluating the efficacy and safety of Eltrombopag among patients with severe persistent immune thrombocytopenia (ITP) within six months of diagnosis**

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**Aim:** To evaluate the efficacy and safety of eltrombopag in patients with severe persistent ITP within 6 months of diagnosis.

**Method:** A multicentre, single arm open label study involving patients with severe ITP (a) with platelet count of  $<30 \times 10^9/L$  despite a daily dose of prednisolone of 1mg/kg for  $\geq 2$  weeks from diagnosis OR (b) requiring prednisolone  $\geq 10$ mg daily and/or recurrent doses of IvIg to maintain a platelet of  $\geq 30 \times 10^9/L$  within 6 months of diagnosis. Patients were initiated on eltrombopag 50mg daily and doses was increased by 25mg every 2 weeks to a maximum of 150mg daily if the platelet count remains  $<30 \times 10^9/L$  or bleeding. The steroid was progressively weaned to zero over 6 weeks.

The primary endpoint was overall response rate (ORR) at week 12, defined as the proportion of patients achieving complete response (CR; platelet  $>100 \times 10^9/L$ ), partial response (PR; platelet  $>50 \times 10^9/L$ ) or minor response (MR; platelet  $\geq 30 \times 10^9/L$  with  $\geq 50\%$  reduction in the dose intensity of concomitant ITP therapy compared with screening). The protocol specified a 1-sided 5% level binomial test of the null hypothesis that  $ORR \text{ at week } 12 \leq 30\%$  and reporting of a 90% two-sided confidence interval (CI).

**Result:** Of the 39 patients enrolled, the median age (Q1 Q3), time since ITP diagnosis, and screening platelet count was 53 (38, 68) years, 2.3 (1.1, 5.4) months, and  $21(13, 34) \times 10^9/L$  respectively. Prior treatments included steroids (95%), IVIG (54%), and immunosuppression (26%). The median dose eltrombopag at week 12 was 50 (50, 100) mg daily.

At week 12, the ORR was 69% ( $p < 0.001$ ; 90% CI: 57–81%); the median platelet count among responders was  $168 (89, 252) \times 10^9/L$ . At week 26, the ORR was 44% (90% CI 28–59). 23 of 34 patients (68%) have a duration of PR greater than 24 months.

Two patients had serious adverse events with two episodes of venous thromboembolism.

**Conclusion:** When administered to patients with ITP diagnosed for  $\leq 6$  months, eltrombopag was generally well tolerated and the majority had a favourable overall response.

O171

## **Direct-acting oral anticoagulants in cancer-related thrombosis**

**John Eikelboom**

Patients with cancer or receiving chemotherapy are at high risk of thromboembolism and present challenging problems for prevention and treatment.

Short-term anticoagulation is routinely used for the prevention of thromboembolism in hospitalized patients, including in those with cancer. In addition, however, recent trials have evaluated the use of long-term direct-acting oral anticoagulant (DOAC) therapy in patients with cancer deemed to be at high risk of thromboembolism. The results of the AVERT and CASSINI trials demonstrated that long-term DOAC compared with placebo reduced the incidence of thromboembolism, particularly in the on-treatment analysis, but did not reduce mortality and increased bleeding. Based on these results it seems that the uptake of long-term DOAC therapy for primary prevention will be limited to selected cancer patients deemed to be at extreme risk of thromboembolism.

Observations in patients with cancer-related thrombosis of a high risk of breakthrough thrombotic events despite therapeutic warfarin prompted the evaluation of long-term low-molecular-weight heparin (LMWH) therapy as an alternative to warfarin. Based on the results of multiple randomized trials controlled trials demonstrating their superior efficacy, LMWH subsequently became the standard of care for cancer-related thrombosis.

More recently, the advent of DOACs has prompted their evaluation as alternatives to LMWH for the management of cancer-related thrombosis. The Hokusai-VTE Cancer Study compared an initial 5 days of dalteparin followed by edoxaban with dalteparin, and SELECT-D study compared rivaroxaban with dalteparin, in patients with cancer related thrombosis. Both trials demonstrated non-inferiority of DOAC compared with LMWH for the composite outcome of recurrent venous thromboembolism or major bleeding. In both trials, there was an excess of gastrointestinal (GI) bleeding with DOACs in the subgroup of patients with GI cancer. An additional trial with apixaban is ongoing.

Based on these results, DOACs are likely to replace LMWH as the standard of care for cancer-related thrombosis, with the possible exception of patients with GI cancer.

O172

**An overview of the role of platelets in cancer**

**Pat Metharom**

The link between platelets and cancer has long been recognised. Accumulating evidence has established that cancer cells are capable of activating platelets, leading to the release of hundreds of bioactive factors that influence the tumour microenvironment, impede the host immune response, and promote tumour survival and metastasis. However, we are just beginning to unravel the complex molecular mechanisms underpinning the role of platelets in cancer. This presentation will highlight crucial signalling pathways that mediate the crosstalk between platelets and tumour cells, the diagnostic and prognostic value of platelets, and the potential benefit of targeting platelets in cancer treatment.

## Evaluation of Global Coagulation Assays in Patients with Chronic Kidney Disease

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### Aim

Chronic kidney disease (CKD) confers increased thrombotic risks in addition to traditional cardiovascular disease (CVD) risk factors. However, current coagulation assays are limited in their capacity to predict thrombotic outcomes. We aim to evaluate the use of global coagulation assays (GCA) in CKD.

### Methods

In this prospective observational study, subjects with CVD risk factors were recruited into two groups: eGFR<30 ml/min/1.73m<sup>2</sup> and (n=75) and eGFR≥30 ml/min/1.73m<sup>2</sup> (n=221). The results were compared to healthy controls (n=138). In addition to baseline investigations, GCA were performed: whole blood thromboelastography (TEG), platelet-poor calibrated automated thrombogram (CAT) and overall haemostatic potential (OHP).

### Results

Compared to controls (mean age 41.8 years, 67% female), CKD subjects (mean age 65.8 years, 39% female) had increased von Willebrand factor (VWF) antigen (178 vs 102%, p<0.001), factor VIII (183 vs 108%, p<0.001) and prothrombotic TEG parameters with increased maximal amplitude (MA) (69.3 vs 60.3mm, p<0.001) and decreased clot lysis (0.0 vs 0.5%, p<0.001). While thrombin generation was not significantly different, fibrin generation parameters were increased (OHP 39.0 vs 27.3, p<0.001) with impaired fibrinolytic potential (OFP) (40.8 vs 51.9%, p<0.001). The differences remained with multivariate analysis modelling for age and sex. Elevated urea did not predict hypocoagulability. When comparing CKD to CVD risk factor population (mean age 63.6 years, 49% female), MA remained increased (p=0.010) with increased OHP (p<0.001) and decreased OFP (p<0.001). D-Dimer (930 vs 430, p<0.001) was increased in CKD although it did not correlate with OHP parameters. Comparisons of pre-dialysis (n=19), haemodialysis (n=46) and peritoneal-dialysis (n=10) subpopulations did not identify significant differences between groups for most GCA parameters.

### Conclusion

CKD appears to confer a prothrombotic state as described above, contrary to previous reported association to increased bleeding risk. The clinical significance of these results and the use of GCA to stratify thrombosis risk warrant further investigation.

## **A retrospective case series analysis of the inpatient management of isolated distal deep vein thrombosis at the Alfred Hospital**

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Controversy remains regarding the optimal management of isolated distal deep vein thrombosis (IDDVTs). We aimed to establish the inpatient management of IDDVTs at the Alfred Hospital. We performed a retrospective case series analysis of consecutive patients diagnosed with IDDVT whilst an inpatient at The Alfred over a 4-year period, from October 2014 to October 2018. Choice of anticoagulant, duration of anticoagulation, utilisation of serial imaging, bleeding complications, thrombus progression and IVC filter utilisation were recorded.

Of 152 cases identified, 69 (46%) were treated with therapeutic anticoagulation, while 81 (53%) were not. Therapy could not be determined in 2 (1%) cases. The most frequently used anticoagulant was rivaroxaban (36%), and direct oral anticoagulants accounted for 46% of treated cases. An increase in DOAC prescription was noted over time (27% of cases in the first 12 months of data, compared to 70% in the most recent 12 months). No major bleeding complication or thrombus extension was identified in patients receiving DOACs. Most patients (60%) were treated for the recommended duration of 6 weeks to 3 months, while a significant number of patients (32%) received longer durations due to a variety of reasons, including concomitant atrial fibrillation, stroke, and presence of an IVC filter. Of the patients who did not receive anticoagulation, a significant proportion (33%) did not undergo serial ultrasound monitoring for thrombus progression. Finally, a small number (12) of IVC filters were placed in patients thought to be at high risk of thrombus progression and were usually (80%) employed in combination with anticoagulation.

The results of our study describe increasing utilisation of DOACS for IDDVT diagnosed as inpatients. These agents appear safe and effective, even in this high-risk population. Our results highlight the difficulties of arranging serial ultrasounds in patients not treated with anticoagulation, even in hospital inpatients. Finally, our study reveals a proclivity for the use of IVC filters in combination with anticoagulation in a minority of patients with IDDVT. There is little evidence to support this practice.

## Evidence of impaired dabigatran absorption following Roux-en-Y gastric bypass surgery: the Auckland regional experience (2011-2018)

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**Aim:** Dabigatran is a direct-acting oral anticoagulant (DOAC), licensed for use in atrial fibrillation and venous thromboembolism (VTE). Absorption is thought to occur in the lower stomach and duodenum [1]. Roux-en-Y gastric bypass (RYGB) is the second most commonly performed bariatric procedure globally [2] and results in the greatest post-operative weight loss [3]. It involves diversion of the distal stomach and duodenum, leading to reduced absorptive area and altered luminal pH. Previous case reports suggest dabigatran absorption may be impaired post-RYGB [4, 5]. While there is no established therapeutic range, phase 2 trial data based on 150mg bd dosage showed a mean peak of 180ng/mL and mean trough of 90ng/mL [6].

**Method:** A retrospective audit was conducted of all patients who underwent RYGB at Auckland City, Middlemore and North Shore Hospitals between July 1, 2011 and December 31, 2018. Dispensing records were reviewed to identify those prescribed dabigatran. These patients were then contacted and underwent measurement of serum peak and/or trough levels and serum creatinine at their local community laboratory.

**Result:** Nine patients were identified as eligible and consented to measurement of serum levels. Median age was 57 years (range 48-85 years). Five had AF, three VTE and one seronegative antiphospholipid syndrome. Eight were prescribed 150mg bd and one 110mg bd. Median peak level was 27.0ng/ml (range 10-64 ng/ml). Two patients had additional trough measurements of 17 and 28 ng/ml. All patients had normal serum creatinine (median 68 umol/L, range 50-81 umol/L).

**Conclusion:** This is the largest published case series of serum dabigatran levels post-RYGB and demonstrates markedly and consistently reduced levels relative to phase 2 trial data. This suggests impaired absorption and raises significant concern regarding risk of future thromboembolic events. We therefore advocate patients on dabigatran planned for RYGB undergo conversion to an appropriate alternative anticoagulant prior to surgery.

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## Two-centre review of real-life idarucizumab use

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**Background:** Idarucizumab has been approved since 2016 for rapid dabigatran reversal to facilitate emergency surgery and treat life-threatening bleeding. In the Sydney Local Health District, idarucizumab has been available since May 2016 and administration is under Haematology supervision according to local hospital policies. To date, there are few reports of real-life experience with dabigatran reversal.

**Aims:** To evaluate the indication for usage, laboratory monitoring and clinical outcomes of patients who had idarucizumab dispensed from Concord and Royal Prince Alfred Hospitals.

**Methods:** Retrospective review of medical records and pathology results was conducted of all patients who received idarucizumab between May 2016 to May 2019.

**Results:** Twenty-six patients received idarucizumab a total of 28 times during the study period. Indications for idarucizumab use were: intracranial haemorrhage in ten patients (38%), gastrointestinal bleeding in nine patients (35%) of which two required idarucizumab on two separate occasions, and urgent procedure in seven patients (27%). The majority of cases (86%) had thrombin time (TT) or dabigatran level measured prior to idarucizumab administration. The median dabigatran level was 159ng/ml. Nineteen (68%) cases had coagulation profile testing 1 to 17 hours following idarucizumab administration and all had an undetectable drug level or TT indicating undetectable dabigatran effect. Thirteen (46%) cases had a repeat drug level at 24 hours or greater, of which one demonstrated a detectable dabigatran level. Adverse patient outcomes were noted in five patients including gastrointestinal bleeding and haemorrhagic transformation of ischaemic stroke. Four patients recommenced anticoagulation on discharge. No ischaemic events were noted in patients following idarucizumab administration.

**Conclusion:** Idarucizumab use appears appropriate in this small population. A potential area of improvement include repeating coagulation profiles at 24 hours after administration. Ongoing involvement of supervising haematologists in the approval of idarucizumab use is recommended in order to ensure its appropriate use and monitoring.

O178

## **Viper venom and algorithms: Lupus Anticoagulant Diagnosis in the days of the DOAC.**

**Anneke Vanderham**<sup>1</sup>, Robyn Coleman<sup>1</sup>

<sup>1</sup>*Sullivan Nicolides Pathology, Bowen Hills, Australia*

### **Aim:**

In an effort to provide a better quality of lupus diagnosis to our patients, a review was performed of Lupus patient results, clinical history and DOAC (Direct Oral Anti-Coagulant) usage to investigate the possibility of creating a more straightforward diagnostic process in a general population where DOAC use is increasing at a rapid rate

### **Method:**

In our central laboratory, a retrospective review was done of 1388 patients tested over a 10 week period. This review PT, APTT and lupus screening assays on all patients, with Lupus confirmatory assays also reviewed on patients where an abnormality was detected in the initial screen (341 patients). Anti-Xa and TCT assays were performed to confirm DOAC presence where none was recorded. Also reviewed with these results were the lupus diagnosis reported and the patient's clinical notes and history (including drug history). These were then analysed to see the impact of DOAC use on the results and diagnosis.

### **Results:**

The analysis showed those 48 % were not on DOACs, 25% did not know or disclose if they were on DOACs, with 27% disclosing some form of OAC. Furthermore, it was determined that this undisclosed DOAC usage was contributing to significant, and sometimes insidious, difficulties with diagnosis, and the interpretation Lupus confirmatory tests were adversely impacted.

### **Conclusion:**

Based on the results, introduction of a combination of pre-testing with Anti-Xa and TCT assays, coupled with introduction of new reflex rules both on board our automated analysers, and within our LIS system allowed us to easily identify patients on DOAC regardless of available clinical history, and provide a clear method for handling these patients, allowing for easier interpretation of Lupus confirmatory tests.

O179

### **Long term changes in immune profile and platelet function in burn survivors**

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Burn injury initiates an acute thrombo-inflammatory response and susceptibility to thrombosis but little is known about long-term consequences of burn injury on haemostasis, inflammation and immunity. However, recent data suggests all burn survivors, including those with non-severe injuries, are at an increased life-long risk of cardiovascular outcomes and infection, suggesting enduring changes to the immune and haemostatic systems in burn survivors beyond the acute phase. Here we investigate whether non-severe burn injury is associated with long lasting changes in immune profile and blood platelet function.

We demonstrate increased platelet responsiveness to collagen receptor stimulation (as measured by CD62P expression) in a mouse model of 8% full thickness thermal contact burn vs sham control up to 28 days after burn injury. This finding was supported by preliminary data from human patients at 2 weeks after non-severe burn injury vs age/sex-matched controls (n=21). Circulating monocyte-platelet aggregates and platelet responsiveness to collagen receptor stimulation (as measured by PAC1 binding) was elevated. No difference in platelet response to other agonists was observed in either mice or humans.

Elevated multifunctional Th1-type cytokines IFN- $\gamma$ , IL-2, TNF $\alpha$  as well as pleiotropic IL-7 were seen in burn survivors 2+ years after injury in humans (n = 38). These patients also showed diminished pertussis, pertactin, and tetanus toxin specific IgG responses. Using a bespoke 39 parameter mass cytometry panel analysed by unsupervised FlowSOM cluster comparison we identified changes in memory and naive T cell subsets from paediatric patients who suffered a non-severe burn injury at least 3 years prior to sample collection vs age/sex matched barcoded controls (n=27 each) .

Therefore, using mouse and human data we show preliminary evidence of persistent platelet hyper-responsiveness and a altered immune response following a non-severe burn injury.

O180

## **New approach to thrombosis treatment**

### **Justin Hamilton**

Thrombin is the body's most potent activator of platelets and is a major contributor to platelet-dependent arterial thrombosis. Thrombin activates platelets via two protease-activated receptors (PARs), PAR1 and PAR4, and both receptors are targets for anti-platelet therapies. A PAR1 antagonist (vorapaxar) was recently approved for clinical use and PAR4 antagonists are in development.

We have pioneered the development of PAR4 antibodies as anti-platelet agents. Specifically, we have made the first fully-human, monoclonal, function-blocking antibodies against human PAR4. We have shown that these antibodies are highly specific and effective antagonists of the receptor. Lead candidates display strong affinity (sub-nanomolar  $K_D$  values) and selectivity (no detectable binding to any of PAR1, PAR2 or PAR3), and are capable of near-complete inhibition of thrombin cleavage and activation of PAR4 ( $IC_{50}$ s in the 2 – 5  $\mu$ g/ml range). Further, lead candidate antibodies significantly impair human thrombosis in an ex vivo whole blood thrombosis assay, with single agent treatment preventing thrombus growth by ~50%.

Finally, a commonly expressed SNP in PAR4 that results in a PAR4 sequence variant has recently been described that may impact the efficacy of PAR4 antagonists. The frequency of this SNP in PAR4 (rs773902) is remarkably high (19–82% of people, depending on the population) and renders the receptor hypo-responsive to antagonists. However, our antibodies act equivalently across PAR4 sequence variants and provide equal anti-thrombotic effects in individuals expressing the various PAR4 variants.

*Our studies reveal that antibody-mediated inhibition of PAR4 cleavage and activation provides robust antithrombotic activity, even when given alone, and that the efficacy of this approach is unaffected by the rs773902 PAR4 sequence variant. Our findings suggest clinical development of PAR4 inhibitory antibodies for anti-thrombotic therapy is warranted.*

O181

## **The role of next-generation sequencing in platelet disorders**

**David Rabbolini**

Inherited disorders of platelet function (IPFD) and/or number (IPND) are heterogeneous conditions that result in variable mucocutaneous bleeding symptoms as a result of deranged primary haemostasis caused by platelet dysfunction or thrombocytopenia.

In the last decade the application of high-throughput next generation sequencing (NGS) has progressed beyond the boundaries of research laboratories exploring platelet biogenesis and the mechanisms of disease, becoming an increasingly available diagnostic tool employed in the haematology clinic and endorsed by many professional societies into guidelines and diagnostic algorithms. An understanding on the role of NGS in platelet disorders is therefore important to scientists and practitioners in the field. This lecture will focus on the utility and relevance of NGS platforms from gene discovery to routine diagnostics and therapeutics in the setting of inherited platelet disorders.

## Use of Extracorporeal Membrane Oxygenators can amplify complement and trigger atypical Haemolytic Uraemic Syndrome - a Cautionary Tale

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**Case:** A 24-year-old woman with early stage unfavourable risk HL presented with dyspnoea and bulky mediastinal disease. She achieved complete metabolic response (CMR) to 2-cycles of escalated BEACOPP<sup>1</sup>, and was de-escalated to AVD<sup>2</sup> for a further 2-cycles followed by 30Gy mediastinal involved field radiotherapy, but had early biopsy-proven relapse within the radiation field. We administered BeGEV<sup>3</sup> salvage to CMR followed by GemBuMel<sup>4</sup> autologous stem cell transplant (ASCT). Post-transplant brentuximab maintenance<sup>5</sup> was recommended due to high risk of disease relapse.

Despite no respiratory symptoms prior to brentuximab, she developed sudden severe respiratory failure 12-days after the second dose and 3.5-months post ASCT. Repeat respiratory function tests were consistent with pneumonitis and she required intubation, then ECMO due to ongoing severe hypoxia. Three days later she developed anuric renal failure, then severe microangiopathic haemolysis requiring extensive transfusion support. Drug-induced haemolysis, thrombotic thrombocytopenic purpura and STEC-HUS were excluded and due to the clear temporal association with ECMO, Eculizumab was initiated to treat presumed ECMO-induced aHUS. Haemolysis gradually improved following multiple doses of Eculizumab and the patient was eventually weaned from ECMO and hemofiltration with full recovery of lung and renal function. No mutations in complement regulatory genes were identified.

**Discussion:** Pneumonitis was likely the inciting event causing complement activation, with exposure of blood to the synthetic ECMO circuit facilitating complement amplification and leading to aHUS. Brentuximab is the most likely cause of pneumonitis in our patient, but prior gemcitabine and radiation could also have contributed. More than ever, with the advent of novel therapeutics in HL, the primary goal should be long-term disease control while limiting toxicity of therapy and our case emphasises the potential for cumulative toxicities with current regimens. Although temporary complement activation with ECMO has been described,<sup>6,7</sup> we believe this to be the first reported case of ECMO-induced complement amplification triggering aHUS.

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## Do anti- $\beta$ 2GP1 antibodies increase shedding of platelet GPVI?

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### Aim

Anti-beta-2-glycoprotein-1 (anti- $\beta$ 2GP1) antibodies are associated with increased risk of thrombosis in patients with systemic lupus erythematosus (SLE). The effect(s) of anti- $\beta$ 2GP1 antibodies on platelets are unclear, as collagen-induced platelet aggregometry studies demonstrated conflicting results. Platelet activation in response to anti-platelet antibodies has been shown to induce shedding of the ectodomain of the platelet collagen receptor, glycoprotein VI (GPVI), releasing soluble GPVI (sGPVI). To evaluate the potential effect of anti- $\beta$ 2GP1 antibodies on platelets, we analysed the levels of sGPVI in plasma from SLE patients with anti- $\beta$ 2GP1 antibodies, as well as in platelet rich plasma (PRP) from healthy donors treated with either purified IgG fractions from patients with SLE, animal-derived anti- $\beta$ 2GP1 antibodies, or isotype controls.

### Method

A validated in-house enzyme-linked immunosorbent assay was used to determine levels of sGPVI in; 1) platelet poor plasma (PPP) of SLE patients, and 2) PRP from healthy donors spiked with 2  $\mu$ g/mL of SLE-derived IgG fractions, animal-derived anti- $\beta$ 2GP1 antibodies or isotype control antibodies, for 0, 1 and 2 hours.

### Result

The levels of sGPVI ( $103.52 \pm 12.32$  ng/mL) were found to be increased in the PPP of patients with SLE compared to healthy individuals. Spiked healthy PRP showed time dependent shedding of sGPVI, with the highest level demonstrated following 2 hours incubation. SLE-derived IgG fractions and animal-derived anti- $\beta$ 2GP1 antibodies had negligible effects on the shedding of sGPVI ( $\pm 2.00$   $\mu$ g/mL) compared to isotype control antibodies ( $P > .05$ ).

### Conclusion

Taken together with previous aggregometry studies, the current data suggests anti- $\beta$ 2GP1 antibodies do not affect collagen-mediated platelet aggregation. We speculate that anti- $\beta$ 2GP1 antibodies possibly have secondary effects on aggregation requiring pre-activation of platelets (*in vitro*) or following blood vessel injury (*in vivo*). Other weak agonists could be used in further studies as the secondary effects from antibodies can be masked by a strong collagen activation signal.

## **Platelet function in paroxysmal nocturnal haemoglobinuria**

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**Aim:** Paroxysmal nocturnal haemoglobinuria (PNH), a rare acquired clonal haematopoietic stem cell disorder, is characterised by haemolytic anaemia, thrombosis and bone marrow failure. As thrombosis is a leading cause for morbidity and mortality in PNH patients, platelet and clot formation were evaluated in PNH patients in an attempt to elucidate the underlying pro-thrombotic mechanisms.

**Method:** Whole blood was collected from five PNH patients and compared to same-day healthy donor controls. Platelet protein surface levels including activation markers (P-selectin, phosphatidylserine (PS) exposure) were assessed using flow cytometry. Plasma soluble GPVI (platelet activation marker) levels were measured by ELISA. Clot formation and elasticity were assessed by viscoelastic testing (ROTEM). Digital Holographic Microscopy (DHM) was used to characterise thrombus parameters following perfusion of whole blood.

**Results:** Clinical characteristics of PNH patients were variable: two patients had a history of thrombosis, three patients were on Eculizumab and four patients were thrombocytopenic ( $<150 \times 10^9/L$ ). GPIb,  $\alpha$ IIb $\beta$ 3, GPVI and ADAM10 platelet surface levels of patients were at lower end of normal range whereas P-selectin and PS levels under resting and activated conditions were equivalent to controls. There was a trend for lower soluble GPVI levels in PNH patients. ROTEM analysis showed no difference in fibrin and platelet contributions to clot formation, taking into account the reduced platelet numbers. Peak thrombus height and volumes analysed by DHM were within healthy ranges in patients at venous and arterial shear rates, however, both parameters were increased at arterial shear when adjusted for platelet count ( $p < 0.01$ ).

**Conclusion:** Analysis of these PNH patients with highly variable clinical characteristics did not identify a unifying platelet lesion. However, DHM analysis suggests enhanced thrombogenic potential in PNH patients. Mechanisms beyond platelet activation that contribute to increased thrombosis in these patients need to be explored further.

## 10 year experience of portal vein thrombosis at Northern Health, Melbourne

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**Aim:** Portal vein thrombosis (PVT) is associated with significant morbidity and mortality. The optimal duration of anticoagulation in these patients is unclear<sup>1</sup>. This review provides an overview of our management of PVT.

**Methods:** Retrospective evaluation of PVT presentations at Northern Health, Melbourne, from 1 January 2009 – 31 December 2018.

**Results:** 38 patients (median age 60.5, 63% male) presented with PVT. The most common reported symptom was abdominal pain (58%), although 16% were asymptomatic. Nineteen patients (50%) had cirrhosis and/or malignancy at the time of diagnosis; five had both. Of the remainder, ten had other intra-abdominal pathology. A thrombophilia screen was performed in 47%, with three patients found to have antiphospholipid syndrome (APLS). 68% received anticoagulation (median duration six months, range 2 days to lifelong). The reasons for not giving anticoagulation were mainly coagulopathy, active bleeding and comorbidities. Of six patients where no cause for PVT was found, four received long-term anticoagulation, while one developed recurrent PVT after ceasing anticoagulation. 34% required ICU admission, most commonly for management of concomitant sepsis. Fifteen patients developed decompensated liver disease; three had intestinal infarction. One patient developed a haemorrhagic stroke due to anticoagulation. Overall mortality was 42%, which was significantly higher in the malignancy and/or cirrhosis group (63% vs 21%,  $p=0.008$ ). The median time from diagnosis to death was 25 days. However, mortality was directly related to PVT in only five patients (four due to PVT itself and one due to bleeding).

**Conclusions:** Our review showed high mortality in patients with PVT, largely due to concomitant illness (cancer and cirrhosis) that predisposes to PVT. Idiopathic PVT is associated with APLS and the rate of recurrence (7%) was not insubstantial, with 1 in 2 patients with unprovoked events not receiving anticoagulation in the small cohort recurring. Careful risk assessment for long-term anticoagulation is suggested.

	Cancer (n=10)	Cirrhosis (n=14)	No cancer or cirrhosis (n=19)	Cancer and/or cirrhosis vs others
Median age	62	62	44	P=0.07
Male gender	7 (70%)	8 (57%)	14 (74%)	P=0.18
Provoking event (surgery, infection, pancreatitis)	6 (60%)	8 (57%)	10 (53%)	RR 1.4, p=0.18
Inherited thrombophilia screen done	0	3 (21%) 0 positive	15 (79%) 0 positive	<b>RR 0.2, p=0.0001</b>
Antiphospholipid screen done	0	4 (29%) 0 positive	13 (68%) 3 (16%) positive	RR 8.75, p=0.14
Myeloproliferative neoplasm screen done	2 (20%) 0 positive	4 (29%) 0 positive	11 (58%) 0 positive	
Anticoagulation given	6 (60%)	8 (57%)	15 (79%)	RR 0.74, p=0.16
Long-term anticoagulation	0	0	8 (42%)	
Mortality	8 (80%)	8 (57%)	4 (21%)	<b>RR 3, p=0.009</b>
PVT related mortality	2 (20%)	1 (7%)	2 (11%)	RR 1.5, p=0.63
Recurrent thrombosis	0	1 (7%)	1 (7%) 1 in 2 not on anticoagulation	
Significant bleeding	0	1 (7%)	0	

## Investigation of a prolonged APTT reveals a rare finding

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A 12 month old boy born to consanguineous parents from Pakistan was referred to our Haemophilia Treatment Centre with a possible diagnosis of haemophilia B. The boy had an incidental finding of prolonged activated partial thromboplastin time (APTT) on blood tests to investigate global developmental delay. The APTT of 78.6 seconds seemed disproportionately prolonged compared to his mildly reduced factor IX level of 33%. There was no personal or family history of bleeding. Immunisations and circumcision had not resulted in any bleeding.

Repeat testing on 2 subsequent occasions revealed persistently prolonged APTT that corrected with 50/50 mix. Factors VIII, IX, XI and XII returned normal levels, indicating the initial mildly reduced factor IX level was likely spurious. A contact pathway deficiency was therefore suspected. The boy had an undetectable prekallikrein level on an APTT based prekallikrein assay.

Prekallikrein (also known as Fletcher factor) is one of the contact factors. Its active form, kallikrein, is involved in initiation of the intrinsic pathway of the coagulation cascade, as well as having immunological functions. Deficiency of prekallikrein is a rare autosomal recessive disorder that is not associated with clinical bleeding. Prekallikrein deficiency should be considered in a patient with isolated prolonged APTT that corrects with mixing study, normal factor VIII, IX, XI and XII levels, and absent bleeding symptoms.

Table 1. Patient's coagulation blood results

Blood test	Initial	Repeat	HTC test	Reference range
APTT (seconds)	<b>78.6</b>	<b>101.2</b>	<b>99.2</b>	23-38
APTT 50/50 mix (seconds)	29.6		30.2	23-38
Prothrombin time (seconds)	10.3	10.1	10.2	10-14
Factor VIII (%)	101.3		111.3	50-200
Factor IX (%)	<b>33.1</b>	50.5	63.2	50-200
Factor XI (%)	100.3		113.7	50-200
Factor XII (%)	123.5		126.6	50-200
Prekallikrein (%)	Not done		<b>&lt;1</b>	60-150

## Extended half-life clotting factor use in Australia

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**Background:** Patients with haemophilia A and haemophilia B in Australia have been treated with standard half-life (SHL) recombinant factor VIII (FVIII) and factor IX (FIX) clotting factors. In 2018, the National Blood Authority made extended half-life (EHL) FVIII and FIX products available to selected patients under a limited interim supply arrangement.

**Aim:** To review the 'real-life' current practice of EHL usage in Australia.

**Method:** Data will be extracted from the Australian Bleeding Disorders Registry (ABDR) for all patients commenced on EHL products. Prescribing practice, factor usage, and clinical outcomes will be analysed. The uptake of "MyABDR", an app and web site for patients to self-record treatment and bleeds, will also be analysed. Data regarding the half-life characteristics of the differing products in this patient group will also be presented.

**Results:** Two hundred and seven patients are currently receiving EHL factors through the limited interim supply arrangements (Table1). There is significant variability in prescribing practice. Further results will be presented at Blood.

Table 1. Characteristics of patients receiving EHL products.

Bleeding disorder	Haemophilia A	Haemophilia B
<b>Total number on EHL</b>	138	69
<b>EHL product (N)</b>	Adynovate 92 Eloctate 46	Alprolix 69
<b>Patient age</b>		
1. Adult	59 (43%)	34 (49%)
2. Paediatric	79 (57%)	35 (51%)
<b>Severity</b>		
1. Mild	0	1 (1%)
2. Moderate	14 (10%)	11 (16%)
3. Severe	124 (90%)	57 (83%)

**Conclusion:** The limited interim supply arrangements have provided 207 patients with access to EHL factors for their regular prophylaxis, enabling significantly fewer injections.

T007

### **SMS bleed capture project**

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**Background:** Patients with moderate or severe haemophilia A and haemophilia B experience bleeds despite prophylactic therapy with regular clotting factor replacement. Patients and their families may not necessarily report bleeds to their treating team, whether it be through direct communication or self-reporting on the "MyABDR" app. Accurate bleeding history is critical for the delivery of optimal haemophilia care.

**Aim:** To improve the accuracy of recording patients' bleeding history using short message system (SMS).

**Method:** Participants receive an SMS every Sunday questioning whether they have had a bleed in the past week. If they answer 'Yes' to a bleed that has not been reported on the Hospital Information System or MyABDR, the patient is contacted by the haemophilia nurse. If a reply is not received by 48 hours, a second SMS is sent. Lack of response to the second SMS is also followed up by the haemophilia nurse.

**Results:** The study commenced in late May 2019 with 17 patients, with the plan to continue participant recruitment. Over the first few weeks, several bleeds were captured via the SMS project that had not otherwise been reported. The number and type of bleeds captured through the SMS project, rates of self-reporting on MyABDR, and patient participation from May to October 2019 will be presented at Blood.

**Conclusion:** The SMS bleed capture project is expected to improve the accuracy of the bleeding history for patients with haemophilia A and haemophilia B who are on regular prophylaxis.

## Management of isolated distal deep vein thrombosis: comparison of DOAC vs warfarin era

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**Aim:** There is no consensus in the management of patients with isolated distal deep vein thrombosis (IDDVT), with recommendations ranging from no treatment to 3 months. We aim to evaluate safety outcomes in patients anticoagulated for IDDVT using direct oral anticoagulants (DOAC) in our institution, in comparison to the historical warfarin era.

**Method:** Retrospective audit of patients with IDDVT commenced on therapeutic anticoagulation with DOAC at Northern Health, Melbourne between September 2013 and September 2016. This is compared to our historical warfarin-based database audited between July 2011 and December 2012. Patients with active malignancy were excluded.

**Results:** A total of 117 cases of IDDVT were identified in the DOAC era compared to 146 in the warfarin era. The most commonly used DOAC was Rivaroxaban (110/117; 90%). Patients treated during the warfarin era were slightly older (59 vs 55 years;  $p=0.020$ ) and more likely provoked (65.8% vs 43.6%,  $p<0.001$ ). Average duration of treatment was 4 months compared to 3 months in the DOAC era ( $p=0.036$ ). There were 4 episodes of clinically significant bleeding in the warfarin cohort (2.7%) including two spontaneous bleeds compared to one episode (0.9%) in the DOAC cohort, which was spontaneous. There was no significant difference in rate of progression and/or recurrent thrombosis between the cohorts with 3.4% ( $n=4$ ) in the DOAC cohort (including one in whom anticoagulation was temporarily withheld) and 0.7% ( $n=1$ ) in the warfarin group in the context of subtherapeutic INR. Subsequent malignancy was detected in 3 patients in the warfarin cohort (2.0%) and 1 in the DOAC cohort (0.9%).

**Conclusion:** Therapeutic anticoagulation with DOACs is safe with a low rate of bleeding complications (0.9%) in our study. Individualised patient risk assessment is required to assess the risk and benefit of treatment in the DOAC era where delivery of anticoagulation is both safe and effective.

	DOAC Era (n=117)	Warfarin Era (n=146)	p-value
Age (median years)	55	59	<b>0.020</b>
Male	46.2% (n=54)	56.2% (n=82)	0.107
Rivaroxaban Apixaban	94.0% (n=110) 6.0% (n=7)		
Provoked event	43.6% (n=51)	65.8% (n=96)	<b>&lt;0.001</b>
Duration of anticoagulation (median months)	3	4	0.036
Past history of VTE	19.7% (n=23)	18.5% (n=27)	0.810
Clinically significant bleeding	0.9% (n=1)	2.7% (n=4)	0.267
Progression/ recurrent thrombosis	3.4% (n=4)	0.7% (n=1)	0.107

## Dabigatran reversal with Idarucizumab prior to thrombolysis for ischaemic stroke: a case series

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**Aim:** Direct thrombin inhibitor, dabigatran is often prescribed for stroke prevention in non-valvular atrial fibrillation although the rate of stroke despite dabigatran is still 1.1-1.5% in the clinical trials. Dabigatran is unique among the direct oral anticoagulants (DOAC) as there is an available reversal agent, idarucizumab. There is strong evidence for thrombolysis in the treatment of acute ischaemic strokes, however the role for reversal of dabigatran to allow for thrombolysis is unclear. We aim to evaluate the outcomes of patients receiving idarucizumab for reversal of dabigatran prior to receiving thrombolysis for ischaemic strokes.

**Method:** We present a retrospective case series of patients receiving idarucizumab for dabigatran reversal prior to thrombolysis treatment at acute presentation with ischaemic stroke. Five cases were identified between October 2016 and May 2019 at Northern Health, Melbourne.

**Results:** All patients were male with median age 85 years (range 46-92) and median CHA<sub>2</sub>DS<sub>2</sub>-VASC score 3 (range 1-7). Two patients had previous history of ischaemic stroke while none had a history of significant bleeding. Four (80%) were on dabigatran 110mg BD including one patient not meeting criteria for reduced dosing. All patients had ischaemic strokes confirmed on imaging and received 5g of idarucizumab prior to thrombolysis with alteplase. One patient with complete occlusion of left middle cerebral artery (MCA) infarct (NIHSS score 34) died following haemorrhagic transformation post thrombolysis. One patient had contralateral MCA stroke 36 hours after initial thrombolysis while off anticoagulation. There were no other captured thrombotic complications at 30-days. The remaining three patients had stable modified Rankin score with no adverse outcomes.

**Conclusion:** In our small case series of high-risk patients, the use of idarucizumab for dabigatran reversal pre-thrombolysis was associated with bleeding and recurrent stroke risk (1/5 each). Further studies are required to investigate the safety of this practice.

Case	1	2	3	4	5	
Gender	Male	Male	Male	Male	Male	
Age	68	85	46	90	92	
CHA <sub>2</sub> DS <sub>2</sub> -VASC	3	3	1	6	7	
Dabigatran dose	150mg BD	110mg BD	110mg BD	110mg BD	110mg BD	
Pre thrombolysis	APTT seconds (25.0-38.0)	32.8	27.1	26.7	35.4	46.9
	Thrombin Time seconds (<21.0)	>60.0	>60.0	14.9	>60.0	NA
Post thrombolysis	APTT seconds (25.0-38.0)	26.6	NA	NA	NA	46.9
	Thrombin Time seconds (<21.0)	17.8	NA	NA	NA	NA
Pre thrombolysis Modified Rankin score	3	5	2	5	4	
Post thrombolysis Modified Rankin score at 30 days	1	6	5	5	4	
Clinically Significant Bleeding within 30 days	No	Yes	No	No	No	
Further stroke within 30 days	No	No	Yes – 36 hours post idarucizumab administration	No	No	
Anticoagulation at discharge	Dabigatran 150mg BD	Deceased due to haemorrhagic transformation	Dabigatran 150mg BD	Apixaban 2.5mg BD	Apixaban 5mg BD	

## The Impact of Emicizumab on the Societal Costs of Moderate and Severe Haemophilia A in Australia

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**Aim:** Patients with Haemophilia A (HA) experience frequent bleeds, substantial morbidity and reduced quality of life. New treatments like emicizumab offer innovative approaches for sustained protection from bleeds. Clinical trials show emicizumab reduces bleeding rates and improves HR-QOL in paediatric and adult populations with and without inhibitors, but studies have not examined its impact on the costs of HA. The aim is to estimate non-treatment direct and indirect costs of moderate and severe HA in Australia under current treatment practices and to model the likely impact of emicizumab prophylaxis on these costs

**Methods:** The number of Australian males with moderate or severe HA was estimated from Australian Bleeding Disorders Registry data. Adopting a cost-of-illness approach, publicly available secondary data and findings in the literature were used to estimate costs in 2018. The assumptions used in modelling the likely cost impact of emicizumab were derived from the published outcomes of the HAVEN studies. All patients with currently present inhibitors and not on ITI (26 patients aged  $\geq 12$  years; 12 aged  $< 12$  years) were assumed to switch to emicizumab prophylaxis. The assumed uptake rates for those without inhibitors are given in Table 1.

**TABLE 1** Modelled Uptake of Emicizumab for HA Patients Without Inhibitors

Age Group	Treatment	Moderate			Severe		
		Pop (No)	Uptake (%)	Uptake (No)	Pop (No)	Uptake (%)	Uptake (No)
Paediatric (<12 years)	on-demand	28	0	0	17	25	4
	prophylaxis	11	80	9	173	80	138
Adult ( $\geq 12$ years)	on-demand	139	0	0	91	25	23
	prophylaxis	47	60	28	391	60	235

**Results:** Non-treatment direct costs totalled AU\$12.3m, hospitalization for bleeds accounting for 20.0% and target joint surgery for 32.3% of these costs. Annual indirect costs totalled AU\$14.3m with 56.4% of indirect costs attributed to lost productivity due to patients' HA. In its first year of use, emicizumab was estimated to reduce non-treatment direct costs by 30.7% (AU\$3.8m) and indirect costs by 19.1% (AU\$2.7m). Reduced hospitalization was estimated to save AU\$1.9m, reductions in lost productivity including work absenteeism and presenteeism AU\$1.3m and reduced need for informal care over AU\$1.2m.

**Conclusion:** The clinical and HR-QoL benefits of emicizumab confer significant savings in the societal costs of HA, even within the first year of use.

T011

## **Severe post thrombotic syndrome improving with late endovascular recanalisation**

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A 42-year-old man initially presented with extensive deep vein thrombosis (DVT) from the level of the inferior vena cava (IVC) to the ankle. CT venogram confirmed chronic IVC occlusion below the level of renal veins with multiple collaterals, and recent thrombosis in bilateral common iliac veins (CIV). Therapeutic anticoagulation was commenced and decision was made against catheter-directed thrombolysis due to the chronicity and extent of occlusion. He also had persistently raised anti-cardiolipin IgG, meeting the criteria for the diagnosis of antiphospholipid syndrome.

Despite therapeutic anticoagulation, our patient continued to experience debilitating symptoms of PTS, including limited mobility to 50 metres and inability to drive due to frequent leg cramps, culminating in incapacity to work as a stone-mason and significant depression.

This case was discussed extensively by our vascular team with international experts and twenty-three months following initial presentation, our patient underwent bilateral endovascular deep venous reconstruction using self-expanding kissing stents in both CIV and along the path of IVC to the intrahepatic level. Post-intervention Duplex ultrasound showed patent stents with no thrombus in the IVC and CIV and chronic non-occlusive thrombus in the right femoral vein. The procedure resulted in remarkable symptomatic improvement for our patient who is now planning to gradually return to work.

In summary, our case describes a young man with life-changing severe PTS from previously undiagnosed chronic IVC obstruction with superimposed iliofemoral DVT who had remarkably good outcome following endovascular intervention almost two years after diagnosis of the DVT. While vascular intervention has traditionally been considered mostly in cases of acute iliofemoral DVT, late intervention for treatment of PTS in expert centres should be considered in carefully selected patients.

T012

## **Treatment failure resulting in primary or recurrent venous thromboembolism in patients on direct oral anticoagulants (DOACs)**

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**Aim:** Routine monitoring is not required for DOACs. Treatment failure has been demonstrated in 2-3% of patients, although there is lack of data describing these cases. We aim to assess and characterise DOAC treatment failures in our institution.

**Method:** Patients with primary or recurrent thrombotic events (new/recurrent venous thromboembolism (VTE) or radiologically-proven progression) while reportedly compliant on DOACs were identified. Non-compliant patients or those with DOAC withheld were excluded.

**Results:** Twenty-two patients (12 male; mean age 54 years (range: 28-81)) were identified. These events occurred on apixaban 2.5 mg BD (1/22), apixaban 5 mg BD (3/22), rivaroxaban 20 mg OD (14/22) and rivaroxaban 15 mg BD (4/22). Initial indication for DOAC included AF (4/22) and VTE (18/22). Median duration between DOAC initiation and failure was 225 days (7-2713 days). Failure events include progression of DVT (14/22, 64%) and new VTE (8/22, 36%). Most events were unprovoked (15/22, 68%). There were high rates of obesity (>100 kg) (8/22, 36%) and post thrombotic syndrome (6/18 DVT, 33%). Three patients (14%) had active malignancy and five (23%) had positive thrombophilia screen (including one antiphospholipid syndrome). No patients were on contraindicated medications. Five patients had anti-Xa levels at presentation – 3 had detectable random levels (apixaban anti-Xa 55, 107 ng/ml; rivaroxaban anti-Xa 133 ng/ml) and two males weighing 89kg and 90 kg respectively had undetectable trough rivaroxaban levels on 20 mg OD.

All patients were rotated to enoxaparin. Subsequently, 3 patients were bridged to warfarin, 2 patients commenced warfarin and then alternate DOAC, 6 commenced alternate DOAC, 5 eventually resumed initial DOAC, and 6 continued on LMWH.

**Conclusion:** A relatively high proportion of patients who failed DOAC therapy were obese (36%), with a significant quantity of unprovoked events (68%) and post thrombotic syndrome (33%). Optimal treatment in suspected cases of DOAC failure remains unclear and further studies are warranted.

## **Accuracy of Measuring Acute Venous Thromboembolism Occurrences in Hospitalised Medical Patients Using ICD-10-AM Codes in an Australian Public Hospital**

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**Aim:** To evaluate the accuracy and potential sources of error which may be introduced when using International Classification of Diseases (ICD-10) codes for identifying deep vein thrombosis (DVT) and/or pulmonary embolism (PE) occurrences in hospital administrative data.

**Method:** Medical records were retrieved for 40 patients admitted to Westmead Hospital in 2016 with a diagnosis of venous thromboembolism (VTE). Pregnant patients and those admitted under a surgical team were excluded. ICD-10 codes including I26.0, I26.8, I26.9, I80.1, I80.2, I80.3, I80.8, I80.9, I82.2, I82.8 and I82.9 were used to identify events. All VTEs were identified and confirmed from physicians' documented discharge diagnoses and diagnostic imaging reports. Coding discrepancies were quantified and categorised with a coder and clinician blinded to patient details. All events were reviewed and cross checked using existing 3M™ Codefinder software algorithms to identify whether discrepancies were due to misunderstanding, interpretation or algorithm error.

**Results:** Median age was 69 years (IQR: 46.3-80.0). There were 45 VTE ICD-10 codes with 17 (37.8%) errors identified. Of these, five (11.1%) were falsely positive due to coding of superficial thrombophlebitis as DVT or coding of historical VTE as acute events. Eight (17.8%) incorrectly classified DVT site, three (6.7%) coded isolated DVT as embolic and one (2.2%) failed to code a PE patient for cor pulmonale. Overall, six (35.29%) errors were due to Codefinder algorithms that lead coders to select an incorrect description while the remaining eleven (64.71%) were true errors due to misinterpretation by the coder.

**Conclusion:** Findings highlight limitations in administrative data to provide accurate measurement of VTE occurrences. Overestimation of this hospital acquired complication and system wide efforts to "price-prevent" leads to significant financial penalties for health services as a consequence. Improvements in Codefinder algorithms, coder education and attention to detail in clinician documentation is required to improve the accuracy of administrative data.

T014

## **A Case Report: A Severe Coagulopathy Caused by Brodifacoum Poisoning**

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Brodifacoum is a 4-hydroxycoumarin vitamin K antagonist anticoagulant poison, which has been widely used as pesticides, typically used as a rodenticide (brand name is Ratsak in Australia). It is characterised as a “superwarfarin” due to the high potency and a very long half-life (20-130 days).

Here we report a severe coagulopathy caused by Ratsak poisoning in a 7 year-old boy.

An autistic non-verbal boy presented with prolonged bleeding after he accidentally pulled out his tooth. He was taken to the theatre for suturing but bleeding was not controlled. A coagulation profile was performed showing aPTT >180 seconds and INR >10 with normal TCT and fibrinogen. Mixing study showed a complete correction indicating factor/factors deficiency. Factor studies demonstrated very low levels of factor II, VII, and X (XI not done). Ratsak poisoning was suspected as the cause of coagulopathy given the boy has a pica with no previous history of bleeding. He was treated with FFP followed by a high dose of Vitamin K for a prolonged duration. Bleeding was resolved with normalised aPTT and INR.

T015

## **Elective surgery in patients with inherited bleeding disorders: a retrospective analysis.**

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### **Aim:**

This study aims to evaluate the outcomes of adult patients with inherited bleeding disorders, who received factor replacement approved by the NSW/ACT Health Haemophilia Advisory Committee (HAC) for elective surgery. It also endeavours to assess adherence to relevant guidelines in terms of Haemophilia Treatment Centre (HTC) utilisation and appropriate factor replacement.

### **Method:**

A retrospective analysis of the Australian Red Cross Blood Service's Supply Tracking Analysis Reporting System (STARS) was performed between 2000 and 2018 to describe patient characteristics, surgical details, factor provision and outcomes. Univariate analysis (Chi square test and logistic regression) was used to determine variables associated with guideline adherence. Covariates with  $p < 0.1$  were included in the multivariate analysis.

### **Results:**

There were 1065 surgeries performed on 571 patients with inherited bleeding disorders. Diagnoses included Haemophilia A (43.5%), Haemophilia B (9.7%), von Willebrand disease (45.3%) and rare bleeding disorders (Factor X, XI deficiencies and dysfibrinogenaemia, 1.6%).

### **Outcomes**

Bleeding complications were reported in 14 surgeries and a further 19 patients received factor replacement beyond standard duration of post-surgical prophylaxis.

### **Guideline adherence**

Approximately 50% of all surgeries were performed in an HTC. Multivariate analysis demonstrated that non adherence to performing surgery within a HTC was associated with diagnosis ( $p=0.0013$ ), surgical category ( $p=0.0036$ ), sex ( $p<0.0001$ ) and year ( $p<0.0001$ ).

### **Factor replacement**

Factor replacement was as expected with the exception of Biostate usage in patients with von Willebrand disease undergoing major bleeding risk surgery who received less doses than expected. The only variable associated with this dosing deviation was the type of von Willebrand disease ( $p=0.0006$ ).

### **Conclusion:**

Low complication rates demonstrate that elective surgery in Australia is being safely performed in patients with inherited bleeding disorders however non-compliance with published guidelines exist. This study highlights areas of practice and policy discrepancies that warrant further exploration.

**An interesting case of spontaneous bleeding – don't forget vitamin C**

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A 51-year-old male presented with a one day history of abdominal bruising. Lower limb petechiae had been present for one week and he was otherwise asymptomatic. His past medical history included psychotic depression and chronic back pain. He had used alcohol to excess and intravenous drugs however had been abstinent for 13 years and 20 years respectively. Medications included mirtazapine, venlafaxine, risperidone, gabapentin, atorvastatin, meloxicam, buprenorphine and nitrazepam. There was no history of trauma, previous bleeding events or significant family history. On examination his weight was 67kg, with a BMI of 23. There were widespread petechiae and perifollicular haemorrhages affecting both lower limbs, large bruises on both flanks and thighs and firmness to palpation of the abdomen. An abdominal CT scan demonstrated an extensive haematoma involving the anterior abdominal wall and bilateral flanks. The coagulation studies and platelet count were normal and the haemoglobin was 79. Platelet function analysis was normal; factor VIII level was mildly reduced at 53% (normal 75-155%). Dietary history revealed minimal intake of fruit and vegetables. A provisional diagnosis of scurvy was made and vitamin C supplementation with 1g orally daily was commenced. There was rapid resolution of the petechiae, perifollicular haemorrhage and bruising over several days. A markedly reduced Vitamin C level of 0.2mg/L (normal range 4-14mg/L) confirmed the diagnosis. At clinic follow-up three weeks after discharge the haematoma was improving and vitamin C and factor VIII levels had normalised.

Vitamin C deficiency is an uncommon cause of spontaneous bleeding in developed countries. It should be considered routinely in the differential diagnosis of spontaneous, unexplained bleeding. A dietary history is crucial. Classic features include perifollicular haemorrhage and mucosal bleeding. The response to vitamin C supplementation is usually rapid.



## **Long-term efficacy and safety of recombinant factor IX fusion protein (rIX-FP) in previously treated patients with haemophilia B: Results from a phase 3b extension study**

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**Background:** rIX-FP, recombinant human coagulation factor IX (FIX) genetically fused to recombinant human albumin by a cleavable linker, has an extended half-life compared with standard-acting FIX concentrates. Two phase 3 studies demonstrated the efficacy and safety of rIX-FP in prophylaxis, with dosing intervals of 7, 10 and 14 days in previously treated patients (PTPs).

**Aim:** To evaluate the long-term efficacy and safety of rIX-FP prophylaxis in a phase 3b extension study over a range of dosing intervals.

**Methods:** PTPs with haemophilia B (FIX  $\leq 2\%$ ) received rIX-FP prophylaxis every 7 (35–50 IU/kg), 10 or 14 days (50–75 IU/kg). PTPs  $\geq 18$  years could switch to a 21-day regimen (100 IU/kg) if well controlled on a 14-day regimen. The primary outcome was the development of FIX inhibitors. Secondary outcomes included annualised spontaneous bleeding rate (AsBR).

**Results:** Eighty-three PTPs (59 adult/adolescent [13–63 years] and 24 paediatric [2–11 years]) participated in the study (mean duration: 36 months). Dosing intervals of 7, 10 and 14 days were maintained in 53 PTPs (64%) while 22 PTPs (27%) extended their dosing interval. Of the 11 PTPs switched to the 21-day regimen, two switched back to a 14-day regimen to reduce their bleeding frequency. At the end of the study, 29% of paediatric PTPs had a dosing interval of 10 (n=3) or 14 days (n=4). Four paediatric PTPs who started a dosing interval of 14 days switched back to shorter intervals. Low AsBRs were achieved with all regimens. Mean steady-state trough levels were  $>5\%$  across all regimens. Seventy-eight (94%) PTPs had  $\geq 100$  exposure days to rIX-FP. No PTPs developed inhibitors or antibodies to rIX-FP.

**Conclusion:** These results demonstrate the long-term efficacy and tolerability of rIX-FP prophylaxis. For selected patients, rIX-FP enables treatment intervals of 21 days in adults and 14 days in children.

## **Management to Optimise Heparin Infusion Therapy Out west: Results from the MOHITO study**

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**BACKGROUND:** Heparin is a high risk medicine, with infusion management requiring monitoring of activated partial thromboplastin time (APTT) and titration according to a protocol. In NSW heparin is in the top 10 medications involved in clinical incidents. Review of incidents in Western Sydney Local Health District (WSLHD) identified non-adherence to local protocol, inappropriate indications for use and variation in clinician knowledge of heparin guidelines and management.

**AIM:** 95% patients receiving intravenous (IV) heparin will receive appropriate care that complies with district guidelines for prescribing, monitoring and administration.

**METHODS:** Quality improvement methodology was utilised to map current processes, identify primary and secondary drivers, develop change ideas and test them with plan, do, study, act (PDSA) cycles. IV heparin management was audited against the district guideline, focussing on prescription, APTT monitoring and infusion adjustment. Clinician knowledge of heparin protocol and bleeding management was surveyed. A structured multi-disciplinary IV heparin education program was developed based on audit and survey findings and piloted with Cardiology nursing and medical clinicians, followed by repeat audit and survey.

**RESULTS:** Over 90% clinicians received education with correct IV heparin prescribing increasing by 15%. Performance and verification of baseline APTT increased by 15%, documentation of weight increased by 25%, selection of correct starting heparin rate increased by 35%, with a 40% reduction in time taken to act on APTT results and 30% decrease in time taken to achieve therapeutic range.

**CONCLUSION:** The multidisciplinary education program improved clinician knowledge and management of intravenous heparin with respect to prescription, monitoring and administration, reducing unwarranted clinical variation. Findings from this project have been incorporated into statewide initiatives to optimise intravenous heparin therapy.

## The current standard of practice with duration and type of anticoagulation in patients with newly diagnosed venous thromboembolism

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**Background:** Warfarin was previously the sole oral anticoagulant available, however, since the introduction of the direct-acting oral anticoagulants (DOACs) in Australia, the prescription and duration of anticoagulation for venous thromboembolism (VTE) has been evolving. To date, this change has not been described in an Australian cohort.

**Aim:** To describe the changes in management of patients with newly diagnosed VTE with regards to the type and duration of anticoagulation.

**Method:** Retrospective single-centre review of patients with newly diagnosed VTE from November 2016 to November 2017.

**Results:** 289 consecutive patients with VTE were identified. Baseline characteristics and types of VTE are displayed in **Table 1**. Low molecular weight heparin (LMWH) was the initial anticoagulant used for 189/289 (65.4%) patients. Maintenance anticoagulation for all 289 patients are shown in **Table 2**. The factor Xa inhibitors, rivaroxaban and apixaban, were the most common maintenance anticoagulants, used in 99/289 (34.3%) and 67/289 (23.2%) patients respectively. Warfarin was prescribed for 54/289 (18.7%) patients.

Follow-up occurred for 207/289 (71.6%) patients with a median duration of 6.7 months [range 0.9-31.8]. Of these, anticoagulation was ceased in 105/207 (50.7%) patients at a median duration of 3.6 months [range 0.2-18.8]. Extended anticoagulation was intended for 81/207 (39.1%) patients and of these, 36/81 (44.4%) were prescribed low-dose apixaban (2.5mg twice daily), followed by rivaroxaban (20mg once daily) in 17/81 (21.0%) and warfarin in 10/81 (12.3%).

Comparison of warfarin and DOACs revealed no statistically significant difference in rates of major bleeding (3.7% versus 1.8%,  $p=0.42$ ) or recurrent VTE (3.7% versus 3.0%,  $p=0.80$ ).

**Conclusion:** Our data demonstrates the change in prescribing practices since the introduction of DOACs, with a large portion of patients remaining on extended anticoagulation. This real-world dataset demonstrates that rates of both major bleeding and recurrent VTE have remained unchanged.

**Table 1: Demographics of patient cohort**

	n=289 (%)
<b>Age [range]</b>	62 [18-92]
<b>Weight [range]</b>	80 [40-180]
<b>Male gender</b>	160 (55.4)
<b>Type of VTE</b>	
<b>PE</b>	139 (48.1)
<b>Proximal DVT</b>	104 (36.0)
<b>Distal DVT</b>	82 (28.4)
<b>Other</b>	35 (12.1)

**Table 2: Maintenance anticoagulation**

	n=289 (%)
<b>Rivaroxaban</b>	99 (34.3)
<b>Apixaban</b>	67 (23.2)
<b>LMWH</b>	56 (19.4)
<b>Warfarin</b>	54 (18.7)
<b>No anticoagulation</b>	12 (4.2)

T021

## **Paraprotein-associated coagulopathy and bleeding diathesis: a case series**

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<sup>1</sup>*Fiona Stanley Hospital, Murdoch, Australia*

### **Aim:**

To present 5 cases of paraprotein-associated bleeding diathesis in patients known to the Western Australian state Haemophilia and Haemostasis service, with a focus on the laboratory investigational challenges in diagnosis and the related clinical management issues.

### **Method:**

Clinical and laboratory information from the WA state Haemophilia and Haemostasis service based in 2 major teaching hospitals was reviewed, including clinic letters, inpatient discharge summaries, and routine assays of coagulation.

### **Result:**

One male and four female patients of various ages over 50 at the time of diagnosis presented with bleeding complications associated with a prolonged APTT, either spontaneous/minimally traumatic, or post-operative. In terms of the mechanism of coagulopathy, three were found to have acquired von Willebrand's disease, one had an acquired factor XI inhibitor, and one had a heparin-like anticoagulant. All were found to have an associated paraproteinaemia, which had complicated laboratory assay investigations into the mechanism of coagulopathy. The underlying disorder was Monoclonal Gammopathy of Uncertain Significance in four, and in one case an indolent B-cell non-Hodgkin lymphoma. Treatments aimed at the paraproteins themselves were either unsuccessful at inducing sustained response in terms of bleeding phenotype or declined by the patient in one case. In all cases, determining the precise mechanism of anticoagulation was critical as this dictated the form of product replacement required for as-needed transient reversal of anticoagulation in acute bleeding episodes and for procedural prophylaxis.

### **Conclusion:**

Acquired bleeding disorders are a rare manifestation of paraprotein-secreting haematological disorders and present unique challenges in terms of both laboratory characterization and management. Our case series illustrates the typical natural history of these disorders, and underlines the importance of characterizing their precise mechanism in order to appropriately tailor management.

T022

## **The Incidence of Venous Thromboembolism after Abdominopelvic Surgery in Cancer Patients: Single Centre Review**

**Monique Ishak**<sup>1</sup>, Matthew Jakab<sup>1</sup>, Nicholas Bingham<sup>1</sup>, Huy Tran<sup>1</sup>, Natasha Curtin<sup>1</sup>, Trish Walker<sup>1</sup>, Kay Htun<sup>1</sup>

<sup>1</sup>*Peninsula Health, Frankston, Australia*

### Background

Venous thromboembolism (VTE) is one of the most common causes of preventable death. The overall incidence of VTE after different types of cancer surgery is reported at approximately 4%-40%. It depends on the type of cancer surgery, as well as patient-, cancer-, and treatment-associated factors. Current international guidelines recommend thromboprophylaxis up to 4 weeks in cancer patients undergoing abdominal and pelvic surgery.

### Study Aim

This study will determine the overall incidence of symptomatic VTE after abdominopelvic cancer surgery including laparoscopic surgery up to 3 months and describe the bleeding events associated with prophylactic anticoagulant therapy, recurrent thromboembolic events, and mortality associated with VTE.

### Study Outcomes:

The primary outcome is the incidence of symptomatic VTE in cancer patients who underwent major abdominal and pelvic surgery at Frankston Hospital.

### Secondary outcomes include:

1. Incidence of VTE associated with different types of surgery (colorectal, gynaecologic and urologic) and surgical approach (open versus laparoscopic)
2. Bleeding events in CRT patients as per ISTH criteria
3. Adherence to local hospital VTE guidelines for both in-hospital and extended pharmacological thromboprophylaxis
4. Death

### Data Analysis:

Demographic and clinical characteristics of patients and types of surgery will be summarized with frequency tables and descriptive statistics. Proportion of patients experiencing various study outcomes will be provided.

### Study Significance:

This study will provide data on the incidence symptomatic VTE in cancer patients who underwent different types of major abdominal and pelvic surgery. This will allow us to understand current hospital practice in different surgical units and adherence to local VTE guideline. This will further identify potential areas for improvement and ultimately improve patient care.

T023

## **Cephalosporin Induced Acquired Haemophilia A – An elderly, healthy patient presenting to a large regional hospital.**

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<sup>1</sup>*The Townsville Hospital, Douglas, Australia*

### **Objectives:**

Acquired haemophilia A (AHA) is a rare bleeding disorder caused by antibodies against factor VIII. Causes include autoimmune conditions, malignancy, pregnancy and certain medications. This case describes a patient who presented with AHA due to cephalosporin exposure.

### **Clinical Features:**

An 83-year-old female presents to hospital with worsening bruising and swelling in the left hip/sacrum. There was no trauma, no obvious alternative cause of bleeding and no fevers. Bloods suggest a new coagulopathy, due to prolonged APTT (83), a drop-in haemoglobin from 115 on 20<sup>th</sup> May, to 47 on the 25<sup>th</sup> June. Factor 8 inhibitor was detected (4.2 BU) and a diagnosis of Acquired Factor VIII deficiency was confirmed.

### **Interventions, case progress, and outcomes:**

Treatment for AHA is a two-step approach. To reduce bleeding, treatments included NovoSeven, PRBC transfusions and Desmopressin. To reduce factor 8 inhibitors treatments included Prednisolone daily and Rituximab weekly. Eleven days post admission, haemoglobin, factor 8 and APTT were within normal limits

There was no evidence of malignancy, pregnancy or autoimmune diseases. Certain medications such as penicillins, cephalosporins, chloramphenicol and anticonvulsant agents have a well-established association with causing onset of autoantibodies in the blood, leading to AHA. A few weeks earlier the patient was treated for kidney stones and prescribed IV ceftriaxone followed by oral cephalexin.

### **Conclusion:**

It is concluded that this patients' onset of AHA was due to the recent exposure of cephalosporins. The patient currently remains in hospital recovering well.

## **Bringing thrombin generation into the diagnostic setting: standardisation and establishment of normal reference intervals for a commercial thrombin generation system**

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<sup>1</sup>*NSW Health Pathology - Liverpool Hospital, Sydney, Australia*, <sup>2</sup>*Charles Sturt University, Wagga Wagga, Australia*

**Aim:** Abnormal thrombin generation plays a key role in the pathophysiology of abnormal bleeding and thrombosis. Global thrombin generation assays are promising tools, but the lack of standardisation in its methodology has hampered its translation into the diagnostic setting. To standardise pre-analytical and analytical processes using a commercially available thrombin generation assay (Calibrated Automated Thrombogram) and commercial reagents; evaluate the effects of pre-analytical variables on thrombin generation and establish reference intervals for the normal healthy population.

**Methods:** Seventy-four healthy adult individuals (31 males and 43 females) were used in this study. Participant informed consent and approval were obtained from SWSLHD ethics committee. Platelet pool plasma was prepared under two different centrifugation conditions and at different time points from collection. Thrombin generation was assessed using the Calibrated Automated Thrombogram. The effect of different pre-analytical variables on thrombin generation parameters in five normal donors were assessed using repeated measures one way ANOVA multiple t tests. Reference ranges for thrombin generation parameters (lag time, time to peak, peak height and endogenous thrombin potential) were calculated and differences between gender in this normal healthy population were assessed using unpaired t test and differences across age groups using one way ANOVA, multiple comparisons.

**Results:** No statistically significant differences were seen across the different centrifugation conditions and the different time points from collection to processing for thrombin generation in five normal donors. No significant differences were seen between different sex and age related reference intervals compared to all normal reference intervals.

**Conclusion:** Using standardised pre-analytical and analytical conditions, thrombin generation "local" reference intervals can be established taking into account gender and age related differences. Further collaboration and inter-laboratory harmonisation is required before thrombin generation can be employed in the diagnostic setting.

### **Funding information:**

Study funded by Haematology Research Trust fund, Liverpool Hospital, Sydney, Australia.

## Tissue-type plasminogen activator (t-PA)-mediated increase in blood brain barrier (BBB) permeability involves intracellular complement activation and can be inhibited by small molecule C5a receptor 1 (C5aR1) inhibitors but not eculizumab.

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**Background:** t-PA can increase BBB permeability, triggering the infiltration of immune cells into the brain. t-PA or plasmin can also activate various intracellular signaling pathways in brain endothelial cells (BECs) or astrocytes that in turn influence BBB permeability. Complement activation may occur concomitantly with immune cell infiltration and has been linked with BBB permeability. Since plasmin possesses C3 and C5 convertase activity, we hypothesised that plasmin-driven complement activation increases BBB permeability and inhibition of this pathway may offer a novel means to attenuate this process.

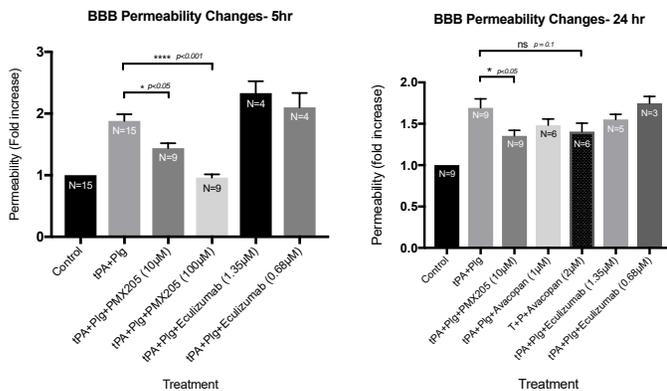
**Aim:** To evaluate the effect of C5 and C5aR1 inhibitors on t-PA- and plasminogen (plg)-mediated opening of the BBB.

**Methods:** Our *in vitro* model of the BBB included co-cultures of human BECs and astrocytes separated by a porous membrane assembled in transwell plates. The endothelial compartment was stimulated with t-PA+Plg in the presence of PMX205 (non-competitive C5aR1 inhibitor) or Avacopan (C5aR1 antagonist) or Eculizumab (humanised monoclonal human C5 inhibitor). BBB permeability was assessed at 5hr and 24hr by evaluating fluorescent tracer passage across the porous membrane. Immunofluorescence was used to detect changes in C5aR1 expression in cells.

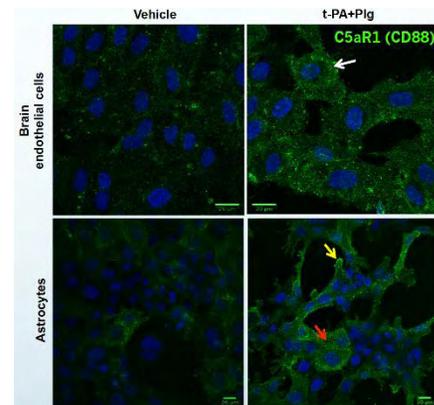
**Results:** PMX205 reduced t-PA and Plg-mediated increase in BBB permeability by 24% at 5hr (Fig 1A) and 20% at 24hr (Fig 1B). Avacopan showed a non-significant trend towards reduced permeability at 24hr. Interestingly, eculizumab was ineffective at either time point. Immunofluorescence analysis revealed increased C5aR1 expression following tPA+Plg treatment which was predominantly intracellular in distribution (Fig 2, arrows).

**Conclusion:** t-PA and plasmin-mediated increase in BBB permeability is partly driven by C5a receptor activation and involves upregulation of intracellular C5aR1. Small molecule inhibitors of C5aR1 may be effective at reducing BBB permeability and may have therapeutic implications in reducing the t-PA mediated compromise of the BBB. Eculizumab fails to inhibit this process most likely due to its inability to target the intracellular compartment.

**Figure 1**



**Figure 2 C5aR1 staining**



## **Cancer-associated venous thromboembolism: a 10-year retrospective cohort in a single centre in Hong Kong**

**Man Fai Law**<sup>1</sup>, Carmen Cheung<sup>1</sup>

<sup>1</sup>*Prince of Wales Hospital, Shatin, Hong Kong*

**Background:** Venous thromboembolism (VTE) is a common cause of morbidity and mortality in cancer patients. The incidence of cancer-associated thrombosis (CAT) in Hong Kong Chinese is increasing.

**Methods:** We conducted a single centre retrospective study in Hong Kong Chinese patients suffered from VTE and cancer. Clinical Data Analysis and Reporting System (CDARS) were used to identify cancer patients with ICD-9 codes of malignancy (140-149; 150-159; 160-165; 170-175; 176; 179-189; 190-199; 200-208; 230-234; 235-238 and 239). Among the identified cancer patients, those who suffered from phlebitis and thrombophlebitis (451), portal vein thrombosis (452), other venous embolism and thrombosis (453) and pulmonary embolism (PE) (415.1) were selected for detail analysis.

**Results:** Between year 2007 to 2016, 41,495 cancer patients were identified and 924 of them had VTE. The estimated incidence was 2.23%. Brain cancer, gynaecological cancer and pancreatic cancer were associated with highest incidence of VTE (7.4%, 5.35% and 4.28% respectively). 55.52% patients developed VTE within one year after cancer diagnosis. Presence or absence of symptoms did not correlate with the levels of PE (P=0.169). Of the 734 patients received treatment with anticoagulants, 32 had recurrent VTE within the first six months of treatment. LMWH and warfarin demonstrated similar incidence of recurrent thrombosis (P=0.288) and major bleeding (P=0.111).

**Conclusion:** The incidence of cancer-associated thrombosis in Hong Kong Chinese is comparable to Caucasian population. LMWH and warfarin showed similar efficacy and safety as treatment for patients suffered from CAT.

T027

## **Acquired Haemophilia A - a laboratory perspective**

**Dianne Lovelock**<sup>1</sup>

<sup>1</sup>*Sullivan Nicolaides Pathology, Bowen Hills, Australia*

### **Aim**

Acquired Haemophilia A is one of the most challenging problems encountered in the diagnostic coagulation laboratory. We will discuss some of the difficulties in identifying acquired haemophilia A and in interpretation of results, and share some of our experiences with these patients.

### **Method**

#### *Case Review*

Acquired Haemophilia A is a rare bleeding disorder which is characterised by autoantibodies directed against circulating factor VIII. Early identification of these inhibitors is key to optimising treatment and improving outcomes for patients. However, the presentation of these autoantibodies is heterogeneous, and detection and quantitation are often delayed. Interpretation of results can be difficult due to patient co-morbidities and conflicting laboratory results. We present three cases identified in our laboratory during a five-month period which highlight the diversity in clinical and laboratory presentation of patients with factor VIII autoantibodies. The first case is that of an 89-year-old male who presented with intracranial haemorrhage following a fall. The second case is an 84-year-old male who presented with a thigh haematoma. The final case is of a 69-year-old female with a history of chronic myelomonocytic leukaemia and historical lupus anticoagulant who presented with extensive bruising.

### **Conclusion**

The laboratory diagnosis of and quantitation of antibody levels in acquired haemophilia A can be challenging due to the comorbidities of the patients, and the limitations of the coagulation assays used to identify these autoantibodies. Our cases highlight the difficulties faced by diagnostic laboratories in managing these complex patients.

## **Superficial Venous Thrombosis – A Benign Entity?**

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### **Aim**

Superficial vein thrombosis (SVT) is considered benign and treatment recommendations are heterogeneous. We aim to provide an overview of the management of SVT and associated complications.

### **Methods**

Retrospective evaluation of SVT presentations from January 2017 to December 2018 at the Northern Hospital, Melbourne.

### **Results**

131 patients (median age 58 years; 59% female) were reviewed (mean follow-up 13 months). 53.4% SVTs (70/131) involved lower limbs, particularly involving the great saphenous vein (39/70). 39 patients (55.7%) had concurrent varicose veins and 22 (31.4%) were provoked, mainly pregnancy (n=9) or surgery (n=9). 72.8% received anticoagulation including 78% (40/51) with enoxaparin (65% prophylactic, 30% intermediate, 5% therapeutic) and the remaining with direct oral anticoagulants (DOAC), while 12.9% received aspirin, 7.1% antibiotics, and 7.2% managed conservatively. Nine patients developed clot progression (13%) including five provoked cases and three cases despite intermediate (n=2) and therapeutic (n=1) anticoagulation. Seven patients (10%) reported VTE recurrence including 3 deep vein thrombosis (2 provoked, 1 antiphospholipid syndrome) following anticoagulation cessation.

The main involved vein in upper limb SVTs was cephalic vein (64%) with the majority related to venepuncture or line insertion (84%). 45.9% (28/61) were treated with anticoagulation of varying doses. Three cases had clot progression – two despite prophylactic enoxaparin and one was managed with antibiotics. No line-related SVT progressed. Two patients developed pulmonary embolism (1 unprovoked, 1 malignancy-related) post anticoagulation cessation. Overall, there was 0.8% bleeding rate (1/131 – traumatic thigh haematoma).

### **Conclusion**

Upper limb SVT is distinctly different from lower limb SVT and is typically line-related with lower risk of progression. However, SVT is associated with 9.2% progression rate overall, some despite anticoagulation, and 6.9% first-year recurrence rate after anticoagulation cessation. This suggests that SVT can be associated with significant thrombotic complications and decision regarding anticoagulation should be individualised and reviewed especially in the new era of DOAC.

## **Increased inflammation and platelet activation: A role in increased thromboembolism post-splenectomy**

**Sarah Luu**<sup>1</sup>, Ian Woolley<sup>2</sup>, Zane Kaplan<sup>3</sup>, Ashwini Bennett<sup>3</sup>, Samantha Montague<sup>4</sup>, Elizabeth Gardiner<sup>4</sup>, Robert Andrews<sup>1</sup>

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**Background:** Splenectomised individuals have an elevated risk of thromboembolism post-operatively and in the long-term. However, as the underlying mechanisms are unclear, there are no specific treatments to prevent thromboembolism in this cohort. It has been shown previously that platelets behave differently following splenectomy. We aimed to evaluate whether an alteration to platelet parameters plays a role in thromboembolism, in order to characterise the underlying mechanism(s) for the increased thrombogenicity seen.

**Methods:** We prepared platelet-rich plasma (PRP) and platelet-poor plasma (PPP) from whole blood collected from long-term splenectomised adults (received their splenectomy at least 1 year prior to their visit) and healthy donors. We performed monochromatic flow cytometry on PRP to evaluate platelet surface protein expression and platelet activation. We also assessed proinflammatory markers in double-spun PPP using Luminex multiplexing.

**Results:** Splenectomised individuals (n=34) expressed more resting platelet P-selectin than healthy donors (n=25) (p=0.0065) and had levels of interleukin (IL)-6, IL-1b, monocyte chemoattractant protein-1, interferon- $\gamma$  and IL-17 within normal ranges but elevated plasma TNF $\alpha$  (n=30) compared to healthy donors (p=0.0002). Individuals splenectomised for trauma (n=22) expressed less platelet surface GPIIb/IIIa than those splenectomised for non-traumatic indications (p=0.0212). Interestingly, individuals with residual functional splenic tissue (FST) (n=6) expressed less platelet surface GPIIb/IIIa than healthy donors (p=0.0273) but no statistically significant difference was observed between those without FST. Individuals with FST had more plasma TNF $\alpha$  than those without FST (p=0.008). There was no significant difference in platelet P-selectin expression between individuals with and without FST.

**Conclusion:** The post-splenectomy state appears to be pro-inflammatory, where platelets appear to be "hyper-activated" long-term after splenectomy and aged in the presence of FST.

## Evaluation of global coagulation assays for assessment of clotting function and venous thromboembolism risk in pregnancy

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**Introduction:** Women are at higher risk of venous thromboembolism (VTE) in pregnancy and postpartum. Current routine coagulation tests cannot discern the physiological hypercoagulability of pregnancy. Global coagulation assays (GCA) including thromboelastography (TEG), thrombin generation using calibrated automated thrombography (CAT) and fibrin generation using the overall haemostatic potential assay (OHP) may be more representative of the coagulation process. We aim to evaluate the ability of GCA to detect the hypercoagulability of pregnancy and differentiate coagulability depending on VTE risk profile.

**Methods:** Women undergoing term elective Caesarean section at The Northern Hospital provided a single pre-operative blood sample for routine baseline blood tests and experimental testing with TEG, CAT and OHP. Citrated whole blood was used for TEG. Platelet-poor plasma for CAT and OHP was obtained from double-centrifuged citrated whole blood. Data from 47 healthy non-pregnant women aged 18-45 years were used as controls. Data was analysed with SPSS using the Shapiro-Wilk, independent t-test, Mann-Whitney U test and a generalised linear regression model.

**Results:** Sixty women with term singleton pregnancies were included. 41.7% (n=25) were obese ( $\geq 30\text{kg/m}^2$ ) at booking and 88.3% (n=53) were multiparous. All GCA parameters were significantly more hypercoagulable in pregnant women compared to normal controls, particularly with increased maximum amplitude (clot strength) (71.5 vs 60.6 mm,  $p < 0.001$ ), endogenous thrombin potential (1895.22 vs 1399.33 nM.min,  $p < 0.001$ ) and fibrin generation (79.01 vs 55.87 units,  $p < 0.001$ ). Pregnant women with booking BMI  $\geq 30\text{kg/m}^2$  had significantly higher maximum amplitude compared to pregnant women of normal BMI (18.5-25 $\text{kg/m}^2$ ) (73.2 vs 66.1 mm,  $p < 0.001$ ). Statistical significance was maintained after controlling for age, parity, smoking status and diabetes.

**Discussion:** GCA are able to detect the hypercoagulability of pregnancy and may potentially correlate with obesity in the pregnant population. GCA hold promise as adjuncts to risk factor-based criteria for VTE thromboprophylaxis during pregnancy and the puerperium.

Assay	Variable	Pregnant	Non-pregnant	p-value
TEG	R value	n=59	n=37	0.013
	K value			<0.001
	Alpha-angle			<0.001
	Maximum amplitude			<0.001
	Lysis 30	n=58		<0.001
CAT	Lag time	n=60	n=47	0.001
	Endogenous thrombin potential			<0.001
	Thrombin peak			<0.001
	Velocity index			0.001
OHP	Overall haemostatic potential	n=59	n=47	<0.001
	Overall coagulation potential			<0.001
	Overall fibrinolysis potential			0.022

T031

## **The impact of a formal laboratory reporting process for a first unexpected isolated prolonged activated partial thromboplastin time.**

**Jeremy Ong**<sup>1</sup>, Andrew Wallis<sup>1</sup>, Susan Morgan<sup>1</sup>

<sup>1</sup>*Alfred Health, Melbourne, Australia*

A prolonged activated partial thromboplastin time (APTT) may be due to causes that increase the risk of bleeding, or thrombosis, or have no impact on either. Clinical correlation and secondary laboratory investigations are often required to understand the underlying cause of an isolated prolonged APTT.

**Aim:** This study aimed to review and improve processes in a tertiary public hospital laboratory for investigating an unexpected isolated prolonged APTT.

**Method:** Patients with a first presentation of an isolated prolonged APTT have a 1:1 mixing study performed, as well as other tests to exclude anticoagulation therapy. In conjunction with the clinical history and previous tests, further investigations are ordered by the haematology laboratory registrar. Contact with treating clinicians is at the discretion of the registrar.

A retrospective audit of medical records was performed on patients who had a first isolated prolonged APTT during a five-month period to determine if further appropriate testing and follow-up was performed.

Following the audit, a formal coagulation report, available on the electronic medical record, was created for subsequent patients with a first unexpected isolated prolonged APTT. A repeat audit is nearing completion to assess whether the coagulation report improves laboratory and clinical practices.

**Results:** Seventy-five patients were reviewed for a first unexpected isolated prolonged APTT during the audit period. Thirty patients (40%) had a likely explanation for a prolonged APTT and no further tests were required. A repeat coagulation profile was recommended in 28 patients, though was only performed in nine patients. Five patients had intrinsic factor levels performed. Testing for a lupus anticoagulant was recommended in 12 patients, of which 11 patients had this completed, and was detected in nine patients.

**Conclusion:** Further investigations are commonly required to explain an isolated prolonged APTT. Without communication with the clinician, further tests are frequently not performed. The results of the follow-up audit will help inform whether a formal electronic coagulation report can improve adherence to recommended secondary investigations, and produce useful diagnostic information.

**Predicting predisposition to thrombosis in obese pregnant women using a D-dimer assay.**

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<sup>1</sup>The University of Melbourne, Parkville, Australia, <sup>2</sup>Western Health, Sunshine, Australia, <sup>3</sup>The Royal Women's Hospital, Parkville, Australia

**Aim:** To assess whether D-dimer is elevated in obese pregnant women compared to their non-obese counterparts.

**Method:** Antenatal patients from the Royal Women's Hospital and Sunshine Hospital, Melbourne were recruited and consent was obtained. Maternal and neonatal characteristics were documented. 9ml samples of blood were drawn via venepuncture into sodium citrate tubes. Samples were collected at 3 gestational time points: 26 – 28 weeks, 36 – 40 weeks and 6 – 12 weeks postpartum. Platelet poor plasma was analysed using a Thermofisher Human D-Dimer ELISA Kit to examine D-dimer concentrations present. Repeated measures-ANOVA statistical analysis was completed using the IBM Statistical Package for Social Science (SPSS) software at all time-points. Linear regression analysis was completed using SPSS for comparisons between logged mean D-dimer concentration and BMI. A  $p$  value of  $\leq 0.05$  was deemed statistically significant. Equal variance was assumed within each test group. Homogeneity of variance was tested between each group at each time-point.

**Result:** 200 pregnant women were recruited between February 2016 and December 2018. Group 1,  $n=80$  obese women, average BMI =  $43.06\text{kg/m}^2$ ; Group 2,  $n=77$  non-obese, average BMI =  $23.26\text{kg/m}^2$ ; and Group 3  $n=26$  overweight, average BMI =  $28.00\text{kg/m}^2$ . On preliminary analysis, at 26 – 28 weeks Group 1 had D-dimer levels on average of  $6.52 \pm 0.03\text{pg/ml}$  vs. Group 2  $6.53 \pm 0.02\text{pg/ml}$  ( $p \geq 0.05$ ). At 36 – 40 weeks, Group 1 had D-dimer levels of  $6.55 \pm 0.03\text{pg/ml}$  vs. Group 2  $6.43 \pm 0.04\text{pg/ml}$  ( $p \geq 0.05$ ). D-dimer postpartum for Group 1 was  $6.22 \pm 0.07\text{pg/ml}$  vs. Group 2  $6.49 \pm 0.05\text{pg/ml}$  ( $p = 0.003$ ). There were higher rates of postpartum haemorrhage (Group 1,  $533.51 \pm 349.40\text{ml}$ ; Group 2,  $449.51 \pm 377.35\text{ml}$ ;  $p \geq 0.05$ ) and higher birth weights of infants (Group 1  $3418.16 \pm 531.93\text{g}$ , Group 2  $3243.84 \pm 557.99\text{g}$ ,  $p \geq 0.05$ ) in the obese vs. non-obese group. Complete analysis including data for overweight women will be completed in July 2019.

**Conclusion:** No statistically significant correlation between BMI and mean D-dimer concentration was found across all gestational periods for both obese and non-obese women.

T033

## **Safety and Efficacy of Low Dose Apixaban for Extended Treatment of Venous Thromboembolism in a 'Real-Life' Cohort**

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<sup>1</sup>*Fiona Stanley Hospital, Murdoch, Australia*

### **Background**

Following completion of 6-12 months of standard anticoagulation for venous thromboembolism (VTE), patients may continue anticoagulation with low dose Apixaban (2.5mg bd) to prevent recurrence, based on data from the AMPLIFY-EXT trial. However, the population that might benefit from this strategy is not clearly defined, and outcomes may differ in real life cohorts on extended prophylaxis.

### **Aim**

To review the safety and efficacy of extended duration low dose apixaban in a real life patient cohort with a history of VTE.

### **Methods**

Patients taking low dose Apixaban for VTE were identified retrospectively from a database of electronic clinic letters from a tertiary centre thrombosis clinic from January 2015 to June 2019. Data was obtained from patients' electronic medical record, results system and from their general practitioner.

### **Results**

Eighty-four patients were identified, mean age 60 years (18-87). 34% had a history of a previous VTE. At the index presentation, 44% had DVT, 34% PE and 19% both. The VTE was associated with a major transient risk factor in 18%, a major ongoing risk factor in 18% and was unprovoked in 64%.

Mean follow-up of patients on prophylactic dose apixaban was 16.5 months; 86% of patients remained on treatment. There was one (1.2%) major bleeding event (variceal haemorrhage), and 2 minor. There was one (1.2%) recurrent thrombotic event. An additional patient had a PE after ceasing low dose apixaban post varicose vein stripping procedure.

### **Conclusion**

Our study findings suggest a low rate of bleeding and recurrent VTE in a real life cohort on extended duration low dose apixaban, comparable to published data from the AMPLIFY-EXT study. This is despite the significant heterogeneity in the treatment group regarding risk factors and recurrence risk.

## **Heterotopic Ossification - a rare complication in haemophilia**

**Kristen Piper**<sup>1</sup>, Robert Russo<sup>2</sup>, Stephen Matthews<sup>1</sup>, Jane Bleasel<sup>3</sup>, Liane Khoo Khoo<sup>1</sup>

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**Introduction:** Heterotopic ossification (HO) is the unexpected presence of bone in soft tissue. It is rare post-operative complication. We examined a case severe Haemophilia B patient, who required a right elbow replacement. His case was complicated by HO in the replaced joint. With only 6 cases of HO in the haemophiliac population previously reported, our study aimed to review the patient's haematological profile in conjunction with his changing orthopaedic function and monitor progress through treatment in order to elicit the best management strategies for HO amongst the haemophiliac population.

**Methods:** At regular intervals, haematological profile was assessed through the measurement of FIX levels and orthopaedic profile was assessed using X-ray and Head-US, as well as quality of life measures.

**Results:** During his elbow surgery and post operatively, he received prophylactic FIX (BeneFIX). His immediate post-operative X-ray demonstrated a successful procedure with good alignment and minimal swelling. Day 2 post surgery, he suffered severe blistering at the wound site and postoperative bleeding. His 1-month follow-up X-ray revealed soft tissue calcifications within and surrounding the elbow joint. Ultrasound of the elbow showed patchy calcification in several muscle groups, consistent with HO. His increased pain and incidence in bleeding lead to his previous on-demand treatment being changed to prophylactic treatment). Trough FIX levels were 4-5% on Alprolix. Range improved by the 3-6 month time-point; and a year post operatively his pain and range were back to baseline. There was also marked improvements in quality of life measures.

**Conclusions:** In this case, conservative management with adequate factor replacement was shown to be effective in the management of HO after a joint replacement. These factors combined highlight the importance of further research and investigation into prevention and optimal management of HO in patients with haemophilia.

**Successful Transition to Extended Half-Life (EHL) Therapies (Eloctate, Adynovate and Alprolix) as part of the National Blood Authority (NBA) limited agreement in Australia – a single centre real world experience.**

**Kristen Piper**<sup>1</sup>, Stephen Matthews<sup>1</sup>, Robert Russo<sup>2</sup>, Jane Bleasel<sup>1,3</sup>, Joshua Wakefield<sup>1</sup>, Liane Khoo<sup>1</sup>

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**Background:** Australian patients with Haemophilia A and B have funded access to standard half-life Factor VIII or Factor IX products. Since March 2018, EHL FVIII products (Eloctate and Adynovate) and FIX products (Alprolix) have approved and funded by the NBA in Australia as part of a limited interim agreement.

**Aims:** EHLs have been proven in clinical trials to be safe and efficacious. The aim of this study was to evaluate real world experience of EHLs in patients.

**Methods:** Outcome data collected included: factor consumption, bleed rate, haemophilia joint health score (HJHS), quality of life questionnaires, and Pharmacokinetic data pre- and post-transition.

**Results:** At our centre, 4 haemophilia A patients and 3 haemophilia B patients transitioned to EHLs. Data at the 3, 6 and 12-month time points demonstrated significant improvements in quality of life (QOL) as shown through participants' responses to HAQ-DI and Haem-A-QoL. Patients report greatest improvement in physical activities and ability to participate in sports and leisure. Aspects of self-care were also improved, as was the way patients perceived their future. Qualitative findings were matched a reduction in factor usage, a reduction in bleed rate, and improvements in individual pharmacokinetic profile. In addition, joint health scores remained stable or demonstrated improvement providing evidence that EHL products may provide additional benefit in the stabilisation of usually progressive haemophilic arthropathy.

**Conclusion:** Our data suggests that in conjunction with objective improvements, patients who transition to EHL have significantly improved QOL. Our study adds additional data demonstrating the real world effectiveness of EHL whereby significant improvements in patients' QOL are paralleled by their improved clinical state

## **Appropriateness of Thrombophilia Testing in a Regional Centre**

**Nirija Ranjit Anderson**, Hilda Mangos, Howard Mutsando, Joel Collins

### **Aim:**

Thrombophilia testing is problematic for numerous reasons including; inappropriate patient selection, incomplete testing, and a limited utility in altering patient management. Thrombophilia testing incurs a financial cost to the healthcare system, and also patient implications with diagnosis of low risk thrombophilias and anticoagulation management. We report a retrospective audit of thrombophilia testing at Toowoomba Base Hospital, a large regional hospital in Queensland. We assessed the appropriateness of thrombophilia testing over 12 months to identify areas for improvement.

### **Method:**

Retrospective data was collected through the hospital laboratory information system (AUSLAB). Patients were selected based on the following testing: inherited thrombophilias, antiphospholipid antibodies, PNH flow and/or JAK2 mutation testing between 1 January to 31 December 2018. Chart reviews were performed on a random selection of patients to assess the indication for thrombophilia testing, completeness of testing and impact of results on patient management.

### **Result:**

A total of 250 patients had thrombophilia testing; a chart review was performed on 150 patients. 29(19%) yielded a positive test result, and 18(12%) had their clinical management changed due to this. 57(38%) of patients did not have an appropriate indication matching current recommended guidelines for thrombophilia testing, and 93(62%) had incomplete testing performed. 8 out of the 29 positive results were in patients who did not have an appropriate indication for testing. Testing was most frequently requested by the General Medicine (37%), Obstetrics (20%), Stroke Unit (13%) and the Emergency Department (11%).

### **Conclusion:**

Indiscriminate thrombophilia testing is prevalent our centre despite published of clinical guidelines for appropriateness testing being widely available. Continued education for clinicians needs to be provided to ensure correct patient selection, completeness of testing and interpretation of results to improve patient care and optimise healthcare utilisation.

## Evaluation of DOAC-Stop® to Eliminate the Interference of Direct Oral Anticoagulants on Thrombophilia Assays

**Joseph Rigano**<sup>1</sup>

<sup>1</sup>Austin Health, Heidelberg, Australia

**Aim:** Direct oral anticoagulants (DOACs) are known to interfere with thrombophilia assays. The impact of DOACs on result interpretation can cause misdiagnosis and clinical consequence. Interruption of anticoagulation for the purpose of thrombophilia testing exposes patients to an increased risk of thrombosis. We aim to evaluate DOAC-Stop® (Haematex Research, Australia) to eliminate the interference of DOACs on thrombophilia assays.

**Method:** 48 DOAC treated patients (12 dabigatran, 23 rivaroxaban and 13 apixaban), 56 lupus anticoagulant (LA) positive patients, 42 LA positive patients spiked with DOACs and 33 normal controls were enrolled. Antithrombin (AT) activity (HemosIL® - Liquid Antithrombin), dRVVT screen and confirm (HemosIL® - dRVVT Screen and Confirm), APTT (HemosIL® - SynthASil) and plasma concentrations of DOACs (HemosIL® - Liquid Anti-Xa) were assayed on the ACL TOP CTS 500 analyser (Instrumentation Laboratory). Pre and post DOAC-Stop® procedure results were compared using a paired *t*-test.

**Result:** A significant decrease in dabigatran (251.4 to 2.6 ng/mL,  $p = 0.004$ ), rivaroxaban (223.9 to 4.1 ng/mL,  $p < 0.0001$ ) and apixaban (255.6 to 2.2 ng/mL,  $p < 0.0001$ ) plasma concentrations was observed in DOAC treated patients following DOAC-Stop®. Similar results were observed in LA positive patients spiked with dabigatran (350.1 to 1.3 ng/mL,  $p = 0.02$ ), rivaroxaban (395.4 to 3.5 ng/mL,  $p = 0.01$ ), apixaban (388.3 to 1.7 ng/mL,  $p = 0.02$ ) and edoxaban (361.9 to 3.1 ng/mL,  $p = 0.005$ ). Prior to DOAC-Stop®, all DOAC treated patients had false positive LA assay results and following DOAC-Stop® had negative LA assay results. Following DOAC-Stop®, LA positive patients spiked with DOACs remained positive for all LA assays. A significant overestimation of AT was observed in all direct Xa inhibitor treated and spiked patients following DOAC-Stop® (Table 1). No significant difference was observed in LA positive and normal control patients following DOAC-Stop®.

**Conclusion:** The DOAC-Stop® procedure is effective at eliminating DOAC interference on thrombophilia assays to allow accurate interpretation of results in patients receiving DOAC therapy.

Thrombophilia Assay	DOAC Treated LA Negative Patients (n = 48)						DOAC Spiked LA Positive Patients (n = 42)							
	Dabigatran (n = 12)		Rivaroxaban (n = 23)		Apixaban (n = 13)		Dabigatran (n = 7)		Rivaroxaban (n = 17)		Apixaban (n = 11)		Edoxaban (n = 7)	
	191 ng/mL (22-870)		205 ng/mL (50-454)		212 ng/mL (109-604)		75 ng/mL (45-141)		137 ng/mL (75-259)		222 ng/mL (143-355)		241 ng/mL (138-372)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
	DOAC-Stop®		DOAC-Stop®		DOAC-Stop®		DOAC-Stop®		DOAC-Stop®		DOAC-Stop®		DOAC-Stop®	
dRVVT Screen (ratio)	2.42	1.09	1.77	1.00	1.41	1.05	4.78	2.38	2.96	1.72	2.65	1.84	3.01	1.49
	$p = 0.001$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p = 0.005$		$p = 0.0008$	
dRVVT Confirm (ratio)	2.34	1.05	1.41	0.97	1.73	1.01	1.97	1.09	1.36	1.05	1.46	1.09	1.94	1.02
	$p = 0.001$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p = 0.0005$		$p = 0.0006$	
dRVVT Screen/Confirm (ratio)	1.04	1.03	1.26	1.03	0.83	0.97	2.42	2.18	2.17	1.65	1.80	1.68	1.56	1.46
	$p = 0.51$		$p = 0.0004$		$p = 0.0007$		$p = 0.01$		$p < 0.0001$		$p = 0.03$		$p = 0.02$	
APTT (seconds)	59	31	41	34	39	32	132	63	83	64	96	80	66	45
	$p = 0.0006$		$p < 0.0001$		$p = 0.0008$		$p = 0.0005$		$p = 0.003$		$p = 0.008$		$p = 0.002$	
Antithrombin (%)	107	106	127	107	128	110	111	108	127	113	122	98	121	106
	$p = 0.39$		$p < 0.0001$		$p < 0.0001$		$p = 0.33$		$p < 0.0001$		$p = 0.004$		$p = 0.0005$	

**Table 1.** Effect of the DOAC-Stop® procedure on thrombophilia assays

## The Prevalence of Antiphospholipid Syndrome Criteria and Non-criteria Antibodies in Patients with Unprovoked Venous Thromboembolism

**Joseph Rigano**<sup>1</sup>, Wai K Ho<sup>1</sup>

<sup>1</sup>Austin Health, Heidelberg, Australia

**Aim:** The antiphospholipid syndrome (APS) is defined by the laboratory detection of at least one of three antiphospholipid (aPL) autoantibodies (lupus anticoagulant (LA), anti-cardiolipin (aCL) or anti- $\beta_2$ -glycoprotein I antibodies (a $\beta_2$ Gpl)) and the clinical manifestation of either thrombosis or pregnancy morbidity in a patient. Recognising APS and administering appropriate therapy is important to reduce risk of recurrent venous and/or arterial thrombosis, and to prevent pregnancy morbidity. In some instances, patients having clinical manifestations highly suggestive of APS are persistently negative for these antibodies but instead have other aPL autoantibodies.

Antiprothrombin (aPT), antiphosphatidylserine/prothrombin (aPS/PT), anti-annexin A5 (aANXA5) and anti- $\beta_2$ -glycoprotein I Domain I (a $\beta_2$ Gpl DI) antibodies have been associated with increased risk of thrombosis in various studies. This has led to proposals for some of these antibodies to be considered another of the APS criteria antibodies. We aim to determine the prevalence of aPT, aPS/PT, aANXA5 and a $\beta_2$ Gpl DI among patients with unprovoked venous thrombosis.

**Method:** Sera from 155 patients who had undergone laboratory testing for the current APS criteria antibodies were enrolled in the study. IgG and IgM aPT (Demeditec Diagnostics), aPS/PT (Inova Diagnostics) and aANXA5 (Demeditec Diagnostics) antibody assays were performed manually by traditional ELISA method. IgG a $\beta_2$ Gpl DI (IL/Werfen) antibody assays were performed by chemiluminescent immunoassay method using the HemosIL<sup>®</sup> AcuStar.

**Result:** IgG aPT, aPS/PT, aANXA5 and a $\beta_2$ Gpl DI was detected in 13.6%, 10.3%, 6.5% and 5.2% of patients respectively. IgM aPT, aPS/PT and aANXA5 was detected in 4.5%, 7.7% and 1.3% of patients respectively. LA, IgG aCL and a $\beta_2$ Gpl was detected in 2.6%, 3.9% and 1.2% of patients respectively. In this cohort, the prevalence of APS non-criteria antibodies was higher than APS criteria antibodies (Table 1).

**Conclusion:** The detection of these APS non-criteria autoantibodies has potential therapeutic implications for patients with unprovoked venous thrombosis as long-term anticoagulation will be indicated.

Autoantibodies	Isotypes	APS Positive (n = 8)	APS Negative (n = 147)
aPT	IgG only	1	19
	IgM only	0	6
	IgG & IgM	2	3
aPS/PT	IgG only	0	11
	IgM only	1	10
	IgG & IgM	2	0
aANXA5	IgG only	0	10
	IgM only	0	2
	IgG & IgM	0	0
a $\beta_2$ Gpl DI	IgG only	2	4

**Table 1.** Distribution of non-criteria antibodies among patients with and without APS.

## **Evaluation of the Automated HemosIL® AcuStar HIT IgG Chemiluminescent Immunoassay for the Diagnosis of Heparin-induced Thrombocytopenia**

**Joseph Rigano**<sup>1</sup>, Chris Hogan<sup>1</sup>

<sup>1</sup>*Austin Health, Heidelberg, Australia*

### **Aim:**

Heparin-induced thrombocytopenia (HIT) is a severe complication of heparin therapy, due to IgG antibodies binding to platelet factor 4 (PF4) and heparin complexes. These complexes cause platelet activation and subsequent aggregation, contributing to venous and arterial thromboses. Diagnosis includes the 4T score, based on clinical presentation and laboratory findings. This study evaluated the HemosIL® AcuStar HIT IgG chemiluminescent immunoassay against the HPIA IgG ELISA and STic Expert® HIT methods.

### **Method:**

The HemosIL® AcuStar HIT IgG chemiluminescent immunoassay detects IgG antibodies directed against PF4 when complexed with heparin. Magnetic particles, coated with PF4 and complexed to polyvinyl sulfonate, capture PF4-Heparin (PF4-H) antibodies. Added isoluminal-labelled anti-human IgG antibody tracer subsequently binds to the PF4-H antibodies, and a luminescent reaction is initiated by the addition of a trigger reagent. Emitted light is measured optically as relative light units and is directly proportional to the PF4-H IgG antibody concentration. AcuStar HIT IgG was performed on thawed citrated platelet poor plasma stored at -80°C, from patients who had previously been tested for IgG PF4-H antibodies using HPIA IgG ELISA and STic Expert® HIT assays. Results obtained from the confirmatory 'gold standard' serotonin release functional assay (SRA) were also evaluated.

### **Result:**

44 patients were tested (26 positive and 18 negative by ELISA) using the AcuStar HIT IgG assay with a sensitivity and specificity of 92% and 100% respectively. Sensitivity is further improved by optimising the diagnostic cut-off provided by the manufacturer. The automated AcuStar produced a result in 40 minutes, compared to 4 hours using the manual ELISA technique.

### **Conclusion:**

The AcuStar HIT IgG assay is diagnostically comparable to the HPIA IgG ELISA method. However, the AcuStar assay has the advantage of a decreased cost per test with a reduction in workload and result turnaround time.

## Evaluation of the Nijmegen and CDC modifications to the Classical Bethesda Inhibitor Assay

**Joseph Rigano**<sup>1</sup>, Niki Lee<sup>2</sup>

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### **Aim:**

Inhibitors to factor VIII (FVIII) are common in inherited haemophilia A patients receiving factor replacement therapy. Acquired haemophilia A is a rare condition and inhibitors occur mostly in elderly and postpartum patients. Detecting and quantitating inhibitors in these patients is important for managing haemorrhage and monitoring inhibitor elimination. The Classical Bethesda Assay (CBA) was described as a uniform measurement of inhibitors to FVIII using pooled normal plasma (PNP) and imidazole buffer (Kasper *et al.*, 1975). In 1995 Verbruggen *et al.* showed that PNP buffered with imidazole at pH 7.4 and FVIII deficient plasma as a patient diluent improved FVIII stability by maintaining constant protein concentration and pH dependant loss of FVIII activity. In 2014 Miller *et al.* introduced a 56°C 30 minute pre incubation procedure to denature endogenous and exogenous FVIII increasing the inhibitor sensitivity. We aim to evaluate these modifications to the CBA.

### **Method:**

From 2017 to 2019, 47 samples that were requested for inhibitor assays were tested in parallel using the CBA and the CBA with the Nijmegen/CDC modifications. The CBA involves performing doubling dilutions of patient plasma with imidazole buffer. The patient dilutions are then mixed 1:1 with PNP and incubated at 37°C for 2 hours. Following incubation, FVIII activity is determined for each dilution. The dilution which generates a residual FVIII activity closest to 50% represents one Bethesda Unit/mL and is then multiplied by the dilution titre. The Nijmegen/CDC modifications mentioned previously were introduced to the CBA.

### **Results:**

Increased FVIII inhibitor levels were detected in all 47 samples (from 5.70 BU/mL to 8.78 BU/mL,  $p = 0.09$ ) using the CBA with the Nijmegen/CDC modifications. 9 samples that were negative using the CBA were positive using the CBA with the Nijmegen/CDC modifications.

### **Conclusion:**

The Nijmegen and CDC modifications to the CBA show increased sensitivity to FVIII inhibitor detection which is important in the management of haemorrhage in patients who develop inhibitors.

T041

## **TEG 6s vs ROTEM Sigma – A Comparison of Two Viscoelastic Haemostatic Assays in the Management of Major Haemorrhage**

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<sup>1</sup>*Princess Alexandra Hospital, Woolloongabba, Australia*

### **Introduction**

Princess Alexandra Hospital is a 688 bed, tertiary adult hospital in Brisbane specializing in trauma, liver and renal transplantation. The emergency department and Intensive Care Unit use Rotem Sigma VHA analysis in assessment of bleeding. The Anaesthetic Department and 26 Theatre Operating Complex use the TEG 6s Cartridge system.

### **Aims**

This pilot study compared equivalent VHA parameters using TEG 6s and Rotem Sigma in patients with major bleeding undergoing non-cardiac and non-transplant surgery.

### **Method**

In early 2018 VHA device validation was undertaken on 15 patients. 30 bleeding patients were randomly recruited by anaesthetic staff from May to December 2018. Citrated viscoelastic haemostatic assays were run on the same citrated blood samples. Data for time to test, time to transfuse, product transfusion, parameters for equivalent assays ie CFF - Fibtem, CRT - Extem, CK – Intem and anaesthetic team feedback was collected. R Coefficient for VHA parameters was derived as per R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.

### **Results**

Results showed a strong correlation for CFF and Fibtem A10 all results, CFF - Fibtem A10 with normal values and Maximum Amplitude and Clot Formation Time in CRT – Extem and CK – Intem. There was weaker correlation between abnormal CFF - Fibtem A10 results, as well as R time and Clotting Time in the CRT – Extem and CK – Intem assays across all values.

### **Conclusions**

Despite consistency, the different CFF-Fibtem results when abnormal triggered different fibrinogen dosing as per our TEG 6s and Rotem algorithms.

Further investigation with a larger, bleeding, patient cohort is recommended for data acquisition and investigation of potential savings in both product usage and cost.

### **Ethics Approval**

HREC/18/QPAH/131 – SSA/18/QPAH/132 Queensland Health Metro South Research Governance

T042

## **Using ADAMTS13 Levels to Predict Relapse in Thrombotic Thrombocytopenic Purpura and to Guide Pre-emptive Rituximab Treatment**

**Ross Salvaris**<sup>1</sup>, Simon He<sup>1</sup>

<sup>1</sup>*Austin Health, Heidelberg, Australia*

### **Aim:**

To present an interesting case to highlight the potential use of surveillance ADAMTS13 levels in predicting relapse of thrombotic thrombocytopenic purpura (TTP) and to guide pre-emptive use of rituximab to mitigate relapse.

### **Method:**

We reviewed a complex case of a 68 year old lady with multiply relapsed TTP who had routine ADAMTS13 levels taken regularly. She was initially diagnosed and treated for TTP in August 2013 on a background of psoriasis treated with adalimumab which was ceased due to concerns about a drug induced thrombotic microangiopathy. Despite successful initial treatment, the patient relapsed two months later again requiring plasma exchange, immunosuppression with prednisolone and treatment with rituximab. She then relapsed in 2015 and 2017 requiring treatment with plasma exchange and rituximab. In her third relapse in 2017, she had required prolonged hospitalisation and there was significant concern about her ongoing risk of relapse.

### **Result:**

Due to the high risk of recurrent TTP, regular, routine ADAMTS13 level monitoring was instigated. From October 2018 to February 2019, her ADAMTS13 level dropped from 58% to 24% (40-130%). Her platelet count remained normal during this time. However, due to the concern about recurrent TTP we instigated treatment with a single dose of intravenous rituximab at 375mg/m<sup>2</sup>.

One month after treatment, her ADAMTS13 level was retested and it had improved to 78.4%. She had no detectable B cells in her peripheral blood after therapy.

### **Conclusion:**

Thrombotic thrombocytopenic purpura is a potentially life-threatening disease with a significant risk of relapse. In our case, we successfully used surveillance ADAMTS13 levels to help mitigate a possible and likely TTP relapse.

T045

## Deletion of T type calcium channel causes reduction in thrombosis

**Hem Kumar Tamang**<sup>1</sup>, Chien-Chang Chen<sup>1</sup>

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### Background

Platelets play important role in hemostasis and wound healing. However, inappropriate aggregation of platelets during pathologic conditions may lead to myocardial infarction and stroke. Various calcium channels mediated increase in intracellular calcium concentration change during platelet activation is important for platelets activity. Role of low voltage activated T-type calcium channels ( $Ca_v3.1$ ,  $Ca_v3.2$  and  $Ca_v3.3$ ) have been studied in various excitatory and non-excitatory cells. However, there is no report about the role of T-type calcium channels in platelets.

### Objective

To study the role of T-type calcium channel in platelet function

Methods: We developed transgenic mice (global  $Ca_v3.2$  knockout and Platelet specific  $Ca_v3.2$  knockout) to study the role of T-type calcium channel  $Ca_v3.2$  in platelet activation and thrombosis. We used  $FeCl_3$  induced thrombosis assay to investigate thrombosis in our mouse model. Similarly, we used aggregometry to study platelet aggregation, bioluminescence assay to measure the platelet ATP release and ratiometric method for intracellular calcium measurement. Additionally, we used TTA-A2([2-(4-cyclopropylphenyl)-*N*-((1*R*)-1-{5-[(2,2,2-trifluoroethyl)oxo]pyridin-2-yl}ethyl), potent and selective T-type calcium channel blocker, to investigate its effect in platelet activity.

### Results

The blood flow results show that deletion of  $Ca_v3.2$  both globally and platelet specific leads to decreased  $FeCl_3$  injured carotid artery occlusive thrombus formation. However, tail bleeding results show that  $Ca_v3.2$  has no role in hemostasis. Interestingly,  $Ca_v3.2$  deficient platelets and TTA-A2 treated platelets show reduction in aggregation, ATP release and intracellular calcium concentration change when activated with collagen. Compared to controls, western blot results of both  $Ca_v3.2$  deficient platelets and TTA-A2 treated platelets show decreased phosphorylation of ERK and P38, indicating reduced calcium signaling.

### Conclusion

Deletion or inhibition of  $Ca_v3.2$  may lead to reduced intracellular calcium change during platelet activation leading to decreased degranulation, aggregation and thrombosis.

## Primary immune thrombocytopenia: A single centre experience comparing first-line dexamethasone and prednisolone therapy

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### Introduction

Corticosteroid therapy is standard of care in the up-front management of immune thrombocytopenia purpura (ITP). Despite initial responses with prednisolone of 50-60%, durability is low. Pulsed dexamethasone offers an alternative with potential reductions in total corticosteroid exposure and adverse events. Studies report initial and sustained responses to dexamethasone of 85% and 54% respectively. We examined our experience with these two approaches.

### Method

We performed a multicentre retrospective observational analysis of efficacy and safety of prednisolone (1mg/kg) or pulsed dexamethasone (40mg for 4days) in newly diagnosed ITP between January 2016 and March 2019.

### Results

Twenty-two patients received dexamethasone and 11 prednisolone. Initial response rates and median time to response were comparable. Sustained responses (>6 months) were greater with lower median cumulative corticosteroid exposure in the dexamethasone group. Steroid-sparing agent use was greater in the dexamethasone group. Corticosteroid side effects were greater in the prednisolone group; three patients experienced infective complications including one fatality. At follow up, one patient in the dexamethasone group and five in the prednisolone group remained on corticosteroid therapy.

Characteristics	Dexamethasone-treated patients (n=22)	Prednisolone-treated patients (n=11)	P-value
Age, median (range)	59 (18-78)	72 (54-96)	0.01
Overall response, n(%)	14 (64)	10 (91)	0.21
Median time to response, days (range)	3 (2-8)	5 (2-25)	0.16
Sustained response, n(%)	7 (32)	1 (9%)	0.22
Median initial inpatient duration, days (range)	3 (2-56)	6 (3-20)	0.02
Median steroid exposure, prednisolone-equivalent	2133mg (1067-7854)	2416mg (1645-8740)	0.86
Steroid side effects, n(%)	5 (23)	9 (82)	0.0023
Infection n(%)	0	3 (27%)	
Steroid-sparing therapy n(%)	11 (50)	2 (18)	0.13
Splenectomy, n(%)	2 (9)	0	

Table: Mann-Whitney U-test for continuous, Fishers exact test for categorical variables

### Conclusion

Dexamethasone provides an effective alternative for initial management of ITP. It offers fewer side effects and potentially lower cumulative steroid dose with comparable response rates, in our real-world data.

T047

## **Thrombosis in the Top End - Outcomes of Thrombophilia Screening**

**Rose Turner**<sup>1</sup>, Ferenc Szabo<sup>1</sup>

<sup>1</sup>*Royal Darwin Hospital, Darwin, Australia*

**Aim:** Despite the availability of local and international guidelines for the diagnosis and management of venous thromboembolism (VTE), wide variation in clinical practice exists. Recent recommendations have de-emphasised the need for thrombophilia screening based on limited utility in guiding management. We performed a clinical review of patients presenting to the haematology thrombosis clinic at the Royal Darwin Hospital over a 5 year period to assess for frequency of thrombophilia screening, indications, investigation results, and any resultant changes in patient management.

**Method:** A review of 200 patients presenting to the Royal Darwin Hospital Thrombosis Clinic between 2013 and 2017 was performed. Data including patient demographics, nature of the VTE, performance and results of thrombophilia screens, and whether these results altered patient management, was extracted from electronic medical records and analysed using simple statistical methods.

**Results:** Thrombophilia screens were performed in 47% of patients presenting with VTE, with a further 6% of patients having had screens performed historically. 40% of screens were performed in the setting of a provoked VTE, although a personal or family medical history of VTE was documented in a third of these patients. Screens returned positive in 31% of patients, with the most common finding being that of heterozygosity for Factor V Leiden, followed by anti-phospholipid syndrome. Positive findings were considered to have significantly changed patient management in 14% of patients who would not have been otherwise committed to lifelong anticoagulation in the setting of recurrent VTE.

**Conclusion:** Despite evidence that thrombophilia screening has limited utility in the setting of VTE management, testing continues to be performed, often when there is no clinical indication. Recurrent history of VTE remains the strongest factor guiding VTE management.

T048

## **Thrombosis in the Top End – incidence and outcomes of venous thromboembolism in the Northern Territory**

**Rose Turner<sup>1</sup>**, Ferenc Szabo<sup>1</sup>

<sup>1</sup>*Royal Darwin Hospital, Darwin, Australia*

**Aim:** Venous thromboembolism (VTE) remains a major health problem in Australia, with an estimated annual incidence of 83 per 100,000<sup>1</sup> Australians. Rates of VTE in Aboriginal and Torres Strait Islanders (ATSI) has not been well documented to date, but is estimated to fall well short of this national incidence<sup>2</sup>. In the current study we have reviewed the real-world VTE occurrence and recurrence rates, and clinical outcomes within both the ATSI and general population.

**Method:** A review of 200 patients presenting to the Royal Darwin Hospital Thrombosis Clinic between 2013 and 2017 was undertaken. Data, including patient demographics, nature of the VTE, means of diagnosis, management, and rates of recurrence and complications, was extracted from electronic medical records and analysed using simple statistical methods.

**Results:** Data analysis revealed that only 6% of patients referred to the thrombosis clinic were Aboriginal or Torres Strait Islander, despite a local ATSI population of almost 40% within the Northern territory. The majority of these patients were of young age (younger than 50 years), with 40% of VTEs considered to be provoked and 60% idiopathic in nature. Pre-existing risk factors in the form of personal or family medical history of VTE were found in 30% of patients. No patients experienced a recurrence of VTE following cessation of anticoagulation.

**Conclusion:** Real-world rates of VTE among the ATSI population of the Northern territory was found to be significantly lower than that of the general population. A tendency towards idiopathic VTE and a younger patient population was also identified. These findings may suggest an evolutionary advantage to low incidence of venous thromboembolism among the ATSI population.

## Non-specific reversal agents for factor Xa inhibitors

### **Stephanie Wallwork<sup>1</sup>**

<sup>1</sup>St Vincent's Hospital Melbourne, Australia

Directly acting oral anticoagulants (DOACs) are now in common clinical practice. In Australia, a specific reversal agent is currently not available for the factor Xa inhibitors (rivaroxaban and apixaban). For patients who have major bleeding or who require urgent invasive procedures, clinicians are choosing to administer non-specific plasma-derived products. Prothrombinex is a 3-factor prothrombin complex concentrate (3-PCC) which contains coagulation factors II, IX and X. Factor Eight Inhibitor Bypassing Agent (FEIBA) is an activated prothrombin complex concentrate containing factors II, IX, X and activated factor VII. These agents are becoming standard of care for reversal of factor Xa inhibitors despite a lack of evidence on their safety and efficacy.

### **Method**

We conducted a retrospective analysis of the use of Prothrombinex and FEIBA for the reversal of factor Xa inhibitors at St Vincent's Hospital Melbourne from 1/1/17 to 1/6/19. Thirty-five adult patients who had received these agents for DOAC reversal were identified using the transfusion laboratory database.

### **Results**

	<b>Prothrombinex</b>	<b>FEIBA</b>
Total number of patients	15	20
Average Age (years)	74.9	73.1
No. patients on apixaban	9	7
No. patients on rivaroxaban	6	13
CrCl < 30 mL/min	3 (20%)	6 (30%)
Indication: intracranial bleed	1 (6%)	9 (45%)
Indication: non-neurosurgical bleeding	10 (66%)	6 (30%)
Indication: pre-op for urgent intervention	4 (26%)	5 (25%)
Pre-reversal INR	1.60 (1 – 3.2)	2.15 (1 – 6.4)
Post-reversal INR	1.39 (1 – 2.2)	1.45 (1 – 4)
Recurrent bleeding within 72hr or operative bleeding complication	0	0
Thrombotic complication during admission	1 (Day 5 CVA)	1 (Day 9 CVA)

### **Conclusion**

Both Prothrombinex and FEIBA are effective agents for partial reversal of factor Xa inhibitors, as demonstrated by reduction in INR. In conjunction with a definitive procedure to control bleeding, adequate haemostasis can be achieved. However, the risk of thrombotic complications requires careful consideration for each individual patient.

## **Audit of acute Immune Thrombocytopenia (ITP) at a tertiary Children's Hospital in 2016/17.**

Vanessa Verissimo<sup>1</sup>, **Helen Wright<sup>1</sup>**, Tina Carter<sup>1</sup>, Meredith Borland<sup>1</sup>

<sup>1</sup>Perth Children's Hospital, Nedlands, Australia

**Background:** Immune Thrombocytopenia (ITP) in children is usually a self-limiting condition, which can be managed conservatively unless there is significant bleeding, or social indications for treatment.

**Aim:** An audit of ITP at the tertiary paediatric hospital in Western Australia (WA) in 2010 demonstrated elevated admission rates and use of intravenous immunoglobulins (IVIg) and steroids in low risk patients. Clinical practice guidelines (CPGs) based on international evidence and recommendations were developed to address this, with improvements shown in a 2013 re-audit.

The aim of this audit was to evaluate rates and reason for hospital admissions of ITP, and to re-audit the response after a change in the hospitals CPGs and ongoing education.

**Method:** A retrospective medical record review of children with acute ITP presenting to the state tertiary paediatric hospital in WA from November 2016 to October 2017 was performed. Inclusion criteria were patients under the age of 18 with ITP using search criteria 'immune thrombocytopenia' 'purpura' 'petechiae' and 'thrombotic thrombocytopenia'. Exclusion criteria were patients over 18 years of age; with chronic ITP (more than six months); or with other causes of purpura.

**Results:** There were 13 patients with acute ITP. Ages were: eight (62%) under two years; four (31%) between 2 and 10 years; one (7%) over ten. Six (46%) were discharged from the emergency department. Six of seven (54%) had documented reasons for admission. None received IVIg. Four (31%) were treated with steroids.

**Conclusion:** Adherence with the ITP CPG at the tertiary children's hospital was variable. The majority of patients admitted with ITP had clinical indications, however nearly a third of patients admitted were prescribed steroids with no documented indication. This study demonstrates the need for ongoing education about ITP and the CPG.

## The impact of treating specialty on the management and outcomes of idiopathic axillosubclavian vein thrombosis

**Hiu Lam Agnes Yuen**<sup>1</sup>, Noel Chan<sup>1</sup>, Sanjeev Chunilal<sup>1,2</sup>

<sup>1</sup>Monash Health, Clayton, Australia, <sup>2</sup>Monash University, Clayton, Australia

**Background:** Anticoagulation is the standard of care for the management of idiopathic axillosubclavian vein thrombosis (IASVT) but it is unclear how the uptake of ancillary modalities such as thrombolysis and decompressive surgery, and subsequent outcomes vary according to the initial treating speciality.

**Aim:** To determine the impact of the treating speciality on the management and outcomes of IASVT.

**Method:** Retrospective chart review of patients diagnosed with IASVT from January 2006 to April 2019 at Monash Health, Melbourne. The outcome measures were the effect of the initial treating speciality on anticoagulation duration, and the rates of additional interventions, residual vein thrombosis, VTE recurrence, and ISTH-defined bleeding.

**Result:** Patient characteristics, treatment and outcomes are shown in Table 1. Of 47 patients who presented acutely to the emergency department, 12 (26%) and 35 (74%) were initially referred to the vascular surgery (VS) and haematology service (HS), respectively, for further management. Both services were subsequently involved in 9 (75%) and 9 (26%), respectively. Compared with patients referred to HS, those referred to VS were more likely to undergo additional interventions (83% vs. 0%,  $p=0.0001$ ). Anticoagulation duration was similar between the two groups. The proportions of thrombus resolution (42%vs26%, RR1.27; 95%CI: 0.76-2.1) and VTE recurrence rates were similar in VS- and HS-referred patients. (0%vs3%, RR0.92; 95%CI: 0.04-21.3), but rates of clinically relevant bleeding (CRNMB and major bleeding) were numerically higher in the VS group (17%vs3%, RR13.8; 95%CI: 0.7-270). The one VTE recurrence (LLDVT and PE) occurred 3 months post IASVT whilst on anticoagulation, likely secondary to non-compliance.

**Conclusion:** Patients with IASVT who were referred to VS were more likely to undergo interventional management than those referred to HS. Despite this, anticoagulation duration and thrombus resolution rates were similar. Although both groups had low VTE recurrence rates, clinically relevant bleeding appeared higher in patients referred to VS.

Table 1. Patient characteristics, treatment and outcomes

(* = $p<0.05$ )	Haematology service	Vascular surgery
N (%)	35 (74%)	12 (26%)
Age (median, range, years)	40 (17 to 86)	42.5 (17 to 60)
Male, n (%)	17 (49%)	9 (69%)
Right-sided IASVT, n (%)*	17 (49%)	10 (83%)
Concomitant PE, n (%)	11 (31%)	1 (8%)
<b>Treatment</b>		
Anticoagulation alone, n (%)	35 (100%)	6 (50%)
Anticoagulation duration (median, range, months)	6 (3-32)	6.6 (4-15)
All additional/ancillary intervention, n (%)*		
Thrombolysis	0	3 (25%)
Angioplasty	0	2 (17%)
First rib resection	0	5 (42%)
<b>Treatment outcomes</b>		
Follow-up duration (median, range, months)	17 (0-121)	11 (0-85)
Thrombus resolution, n (%)	9 (26%)	5 (42%)
Recurrent VTE	1 (3%)	0
<b>Bleeding</b>		
CRNMB, n (%)	1 (3%)	0
Major bleeding, n (%)	0	2 (17%)

## Dynamic upper limb ultrasound in idiopathic upper extremity deep vein thrombosis

**Hiu Lam Agnes Yuen<sup>1</sup>**, Sanjeev Chunilal<sup>1,2</sup>

<sup>1</sup>Monash Health, Clayton, Australia, <sup>2</sup>Monash University, Clayton, Australia

**Background:** Dynamic upper limb ultrasound (DULUS) is often undertaken in the investigation of thoracic outlet syndrome (TOS) to assess compression of thoracic outlet structures, such as the subclavian vein (SCV) in venous TOS (VTOS), subclavian artery (SCA) in arterial TOS and brachial plexus in neurogenic TOS. DULUS measures peak systolic velocities (PSV) in the subclavian artery (SCA) at various degrees of abduction as well as assessing SCV compression. However, there is no data on expected values in subjects with antecedent idiopathic upper extremity deep vein thrombosis (IUEDVT).

**Aim:** To describe DULUS findings in upper limbs with and without antecedent IUEDVT.

**Method:** We reviewed all DULUS performed between January 2014 and May 2019 at Monash Health, Melbourne. At our institution, SCA PSV at neutral, 45°, 90° and 130° abduction, military brace (MB) and reverse stop (RS) positions are recorded. We expressed the PSV obtained at these positions over neutral as the PSV ratio. Other measures included assessment for SCV compression at 90° abduction.

**Result:** DULUS on 27 upper limbs were included (9 males, mean age 37 years [range 26-54]). Nine sides had antecedent IUEDVT and 18 had not. Age and gender were not different between the two groups. 10 patients had right-sided symptoms. We found SCA PSV ratios at 90° and 130° abduction were higher in the IUEDVT-affected sides compared to non-IUEDVT affected sides (Figure 1). Nearly all cases demonstrated some degree of SCV compression at 90° abduction.

**Conclusion:** On DULUS, upper limbs with antecedent IUEDVT had higher SCA PSV ratios at 90° and 130° abduction than non-IUEDVT sides but compression of the SCV was commonly observed at 90° in both groups. The clinical significance of these observations is uncertain and requires correlation with clinical outcomes to determine prognostic significance.

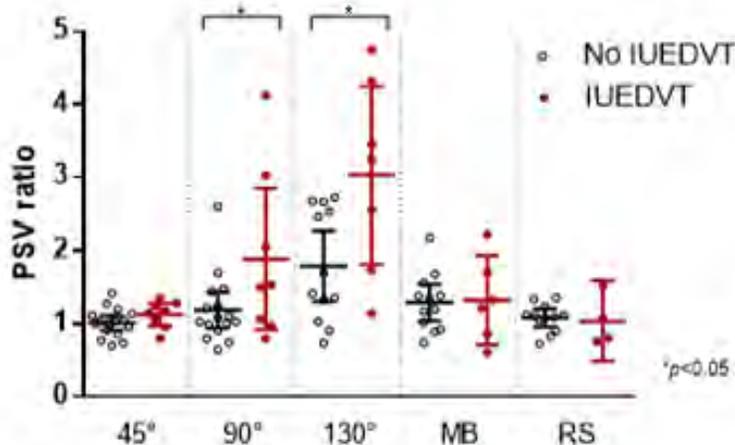


Figure 1. DULUS SCA PSV ratio at different positions

T053

## **D-dimer is useful in the assessment of suspected recurrent venous thromboembolism in patients on rivaroxaban or apixaban**

**Hiu Lam Agnes Yuen<sup>1</sup>**, Patrick Leung<sup>1</sup>, Erica Malan<sup>1</sup>, Joanne Clifford<sup>1</sup>, Sanjeev Chunilal<sup>1,2</sup>  
*<sup>1</sup>Monash Health, Clayton, Australia, <sup>2</sup>Monash University, Clayton, Australia*

### **Background:**

Rivaroxaban and apixaban are increasingly being used to treat venous thromboembolism (VTE). Whilst on these agents, the use of D-dimer in the prediction of recurrent VTE (rVTE) is yet to be established.

### **Aim:**

To assess the efficacy of D-dimer for predicting symptomatic rVTE in patients continuing to receive rivaroxaban or apixaban.

### **Method:**

We undertook a chart review of patients on rivaroxaban or apixaban who had suspected rVTE from March 2016 to May 2019 at Monash Health, Melbourne. Only patients who had a measured anti-Xa drug level (IL Test), concurrent D-dimer (IL Test D-dimer HS) and objective imaging were included. The primary outcome measure was sensitivity and specificity of D-dimer in predicting rVTE utilising our standard D-dimer threshold of 0.23mg/l.

### **Result:**

Of 40 patients included, 50% were male. The mean age was 54 years (range 24-85) with 40% on apixaban. All patients were on prophylactic or therapeutic anticoagulation for VTE. Suspected rVTE occurred at a median of 5.8 months post index VTE episode (range 0.03-100) with anti-Xa levels and D-dimer shown in Figure 1. The suspected rVTE comprised deep vein thrombosis, pulmonary embolism or both in 36%, 57% and 7% respectively. rVTE was radiologically confirmed in 10 cases. The sensitivity and specificity for D-dimer was 80% (95%CI 44 to 98%) and 78% (95%CI 60 to 91%) respectively. 8 cases with negative D-dimer and VTE imaging studies have not had 30-day follow-up.

### **Conclusion:**

Our data show that in patients with suspected rVTE who are taking rivaroxaban or apixaban, the IL Test D-dimer is not universally suppressed. In these patients, the routine laboratory threshold of 0.23mg/l may retain its utility in excluding rVTE despite concurrent use of an anti-Xa medication.

## D-dimer is useful in assessment of suspected venous thromboembolism in pregnancy

**Hiu Lam Agnes Yuen**<sup>1</sup>, Alvin So<sup>1</sup>, Ian Jong<sup>1</sup>, Dee Nandurkar<sup>1</sup>, Sanjeev Chunilal<sup>1,2</sup>

<sup>1</sup>Monash Health, Clayton, Australia, <sup>2</sup>Monash University, Clayton, Australia

**Background:** Pregnancy is known to increase the D-dimer test, leading to an increased false-positive rate. In the absence of pregnancy-specific reference ranges and prospectively validated clinical prediction rules, clinicians rely on objective imaging to confirm deep vein thrombosis (DVT) or pulmonary embolism (PE) with consequent radiation exposure to these young women.

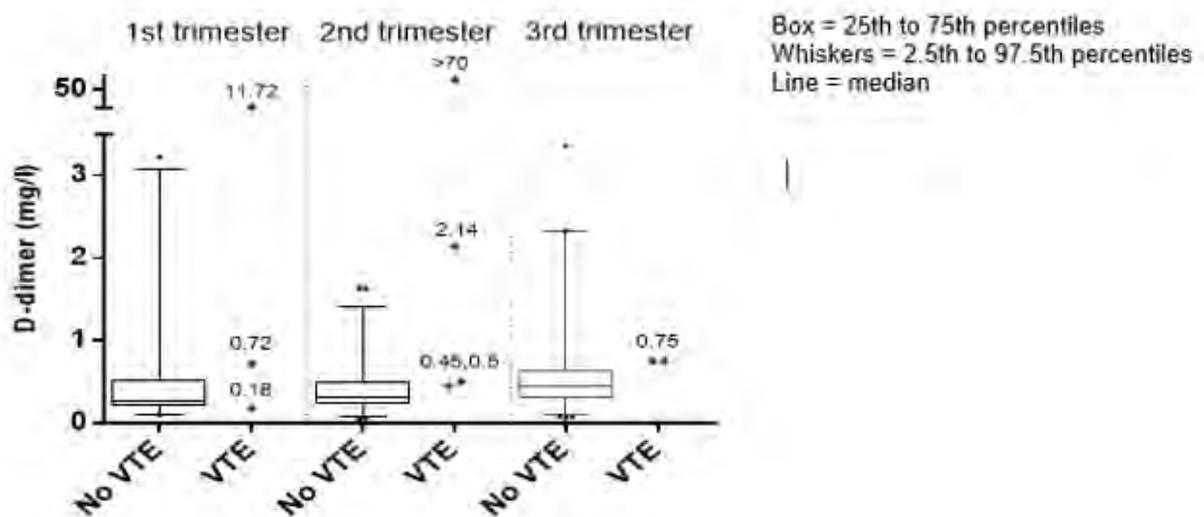
**Aim:** To assess the utility of D-dimer for predicting symptomatic venous thromboembolism (VTE) in pregnancy.

**Method:** We undertook a chart review of pregnant patients who had suspected VTE from January 2007 to June 2019 at Monash Health, Melbourne. Only patients who had concurrent D-dimer results (IL Test D-dimer HS) and objective imaging were included. The primary outcome measure was sensitivity and specificity of D-dimer in predicting VTE utilising our standard D-dimer threshold of 0.23mg/l and exploring a higher threshold which retained specificity equal to the non-pregnant population.

**Result:** 311 pregnant women had concurrent D-dimer results with VTE imaging which comprised 293 VQ scans (94%), 5 CTPA (2%) and 86 lower limb doppler ultrasounds (28%). Median age was 29 years (range, 19 to 46). Most cases were in the second (36%) or third (48%) trimester. There were 6 PE and 3 DVT. D-dimer levels according to VTE and trimester are shown in Figure 1. Using the standard D-dimer threshold yielded a sensitivity of 89% (95%CI 52-100) but specificity was poor at 16% (95%CI 12-21). At a D-dimer threshold of 0.4mg/l, sensitivity was retained whilst specificity increased to 53% (95%CI 47-59).

**Conclusion:** Our data show that a higher D-dimer threshold such as 0.4mg/l has increased specificity whilst retaining sensitivity in pregnancy.

Figure 1. D-dimer according to VTE and trimester



## Variability of management of upper extremity superficial vein thrombosis

**Hiu Lam Agnes Yuen**<sup>1</sup>, Wendy Fang<sup>2</sup>, Sanjeev Chunilal<sup>1,2</sup>

<sup>1</sup>Monash Health, Clayton, Australia, <sup>2</sup>Monash University, Clayton, Australia

**Background:** Despite peripheral catheter-related upper extremity superficial vein thrombosis (PCRUESVT) being relatively common, the optimal treatment strategy to avoid thrombus extension is not known.

**Aim:** To describe PCRUESVT risk factors, management strategies, complications and rates of radiologically confirmed extension.

**Method:** We reviewed all patients diagnosed with symptomatic, PCRUESVT from March 2015 to December 2017 at Monash Health, Melbourne. Patients with a central catheter or concurrent indication for anticoagulation were excluded. The primary outcomes were the effect of identified risk factors and PCRUESVT management on rates of ISTH-defined bleeding and radiologically confirmed thrombus resolution or extension.

**Result:** Of 93 patients included, 54 were male (51%), median age 57 years (range 20-91). PCRUESVT characteristics, management and outcomes are shown in Table 1. PCRUESVT risk factors identified included underlying cancer (25%) and infection (28%). 73% involved a single segment  $\geq 5$ cm and 63% were proximal to the cubital fossa. 69% were admitted at diagnosis and therefore continued on prophylactic anticoagulation. 28 cases (30%) had 1-3 repeat scans. Compared to group 1, all thrombus resolution occurred in group 2 (0vs25% RR1.44 95%CI: 0.2-10.7) and group 3 (0vs36% RR1.27 95%CI: 0.2-9.3) whilst only group 3 had radiologically confirmed extension (0vs8% RR1.67 95%CI: 0.2-12) and bleeding (0vs4% RR1.9 95%CI: 0.26-13.4). All cases of extension/bleeding had active malignancy and extension only occurred in thrombi  $\geq 5$ cm in length.

**Conclusion:** PCRUESVT management is variable and ranged from observation/symptomatic treatment to prophylactic and intermediate/therapeutic dose anticoagulation. The rates of superficial and deep extension were both low at 1% (95%CI: 0.2-5.9). Both thrombus extension and bleeding only occurred in patients with active cancer who received intermediate/therapeutic anticoagulation.

Table 1. PCRUESVT characteristics, management and outcomes

		Group 1 Observation or symptomatic relief	Group 2 Prophylactic dose anticoagulation	Group 3 Intermediate or therapeutic dose anticoagulation
Patient	N (%)	34(37)	35 (38)	24 (26)
	Cancer, n (%)	11 (48)	4 (17)	8 (35)
	Infection, n (%)	4 (15)	15 (58)	7 (27)
	No cancer or infection, n (%)	19 (43)	15 (34)	10 (23)
Thrombus	Single segment $\geq$ 5cm, n (%)	25 (27)	25 (69)	17 (77)
	Proximal to cubital fossa, n (%)	22 (64)	26 (72)	10 (42)
Treatment	Duration (weeks, median, range)	NA	1.07(0.1-25)	3 (0.6-31.9)
Treatment outcomes	Bleeding, n (%)	0	0	1 (4)
	Thrombus resolution, n (%)	0	2 (25)	5 (36)
	Extension, n (%)	0	0	2 (8)

T056

**Consumptive coagulopathy induced by Prothrombin Complex Concentrate (PCC) in chronic liver disease**

Peter Wood<sup>1</sup>, **Paul Zerafa**<sup>1</sup>, Matthew Harwood<sup>2</sup>

<sup>1</sup>Pathology Queensland, Brisbane, Australia, <sup>2</sup>Gold Coast University Hospital, Australia

Two patients with chronic liver disease presented to our hospital with presumed spontaneous bacterial peritonitis. Both patients were treated with antibiotics and paracentesis was planned. Patients were given prothrombin complex concentrate (PCC) to correct a coagulopathy in preparation for diagnostic paracentesis. Neither patient had clinical bleeding prior to PCC. Within 24 hours of PCC administration both patients developed symptomatic bleeding and a severe derangement of coagulation testing with features similar to disseminated intravascular coagulation. The coagulopathy slowly resolved over the next 24 hours. We will present the two clinical cases with laboratory testing results and discuss the haemostatic defects in chronic liver disease. We will also postulate how PCCs may disturb this delicate balance with significant clinical bleeding.

T057

### **Acquired Factor XIII inhibitor causing a significant bleeding phenotype**

Peter Wood<sup>1</sup>, **Paul Zerafa**<sup>1</sup>, Joanne Beggs<sup>1</sup>

<sup>1</sup>*Pathology Queensland, Brisbane, Australia*

A 35 year old Aghani refugee presented with an acute nephritis in May 2018. He proceeded to renal biopsy and developed a left perinephric haematoma post procedure. In July 2018 he developed a spontaneous right psoas and retroperitoneal bleeds of uncertain aetiology. No cause for the bleeding was identified. In August 2018 he developed a further right paracolic bleed and during investigation with CT scan was shown to have a large thrombus involving both iliac veins and extending to the inferior vena cava. As there was no active bleeding and despite the previous bleeding history he was anticoagulated with warfarin.

Further investigation for an underlying coagulopathy showed normal prothrombin and activated partial thromboplastin time. Fibrinogen was normal. An acquired factor VIII inhibitor was suspected but not found. Subsequent investigation revealed a factor XIII level of <0.01 U/L. The factor assay demonstrated non-linearity and a Bethesda assay demonstrated an inhibitor with an activity level of 2.9 Bethesda units.

There was no personal or family history of a prior bleeding disorder.

The patient was treated with prednisolone 1mg/kg and Rituximab 100mg for four weekly doses. The clinical bleeding resolved but the factor XIII level repeated on several subsequent occasions failed to increase. He was given prophylactic cryoprecipitate for several weeks with no further bleeding.

Six months after the initial event the patient has had no further clinical bleeding and the factor XIII level remains <1%.

The patient developed a right pleural effusion in August 2018 which had significantly progressed by March 2019 and pleural aspirate was considered. Recombinant FXIII was obtained to cover the procedure which was ultimately deferred because of bleeding concerns.

We will discuss the possibility of inherited versus acquired factor XIII deficiency particularly in this ethnic population and the use of recombinant factor XIII in treating this disorder.

O182

**Novel therapies in lymphoma; where are we and where are we heading?**

**Kat Lewis**<sup>1</sup>

<sup>1</sup>*WA Health, Perth, Australia*

Novel therapies have revolutionised treatment of haematological malignancy including lymphoma over the last decade.

Selecting appropriate targeted therapies can be a challenge, and evidence is continually emerging using different novel agents in different lymphoma subtypes and using combinations of novel agents. This session provides an overview of the different classes of novel agents currently utilised in treatment of lymphoma, and an insight into future developments in this rapidly evolving field.

O183

## **Research in nursing: Developing nurse led interventions through research**

**Sarah Liptrott**<sup>1</sup>

<sup>1</sup>*European Institute of Oncology, Milan, Italy*

The incidence of haematological cancers is increasing, however developments in treatment and survival rates mean that longer-term prognosis is improving. The impact of cancer and its treatments remains, often resulting in persisting unmet supportive care needs. This presentation will describe one such nurse-led intervention attempting to address patients unmet needs. It will highlight some of the pitfalls experienced where interventions are not evidence based, and show how application of the Medical Research Council Framework for the development of complex interventions (Craig et al., 2013), incorporating evidence from key stakeholders can facilitate the realisation of an intervention that is acceptable both for those receiving and those delivering the intervention.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., Petticrew, M. (2013). 'Developing and evaluating complex interventions: the new Medical Research Council guidance', *International Journal of Nursing Studies*, 50(5), pp.587-92.

## **Therapeutic Plasma Exchange in Tiger Snake Envenomation.**

**Danielle Hovey**<sup>1</sup>

<sup>1</sup>*University Hospital Geelong, Grovedale, Australia*

This case is of a 51-year-old professional snake catcher (DK) who developed a venom induced consumptive coagulopathy with thrombotic micro-angiopathic haemolytic anaemia (MAHA) and renal failure following a tiger snake bite, even with prompt presentation and treatment at a tertiary emergency centre.

DK was transferred to our Intensive Care Unit for initial management and observation. After showing initial signs of improvement in his coagulopathic state, his renal function continued to deteriorate and haemofiltration was commenced some 50 hours following initial presentation. Despite normalisation of his coagulation markers in the first 24 hours, as feared, signs and symptoms of MAHA were evident and continued to worsen.

Following a haematology consult observation and a daily haemolytic screen was recommended. A therapeutic plasma exchange (TPE) was considered but not initiated due to scant evidence to guide the use of TPE in the treatment and management of patients following envenomation<sup>1</sup>. Following continued deterioration and difficulty maintaining a haemodialysis circuit due to pro-thrombotic state, intermittent dialysis had to be replaced by continuous haemofiltration, where citrate is used in preference to heparin in anti-coagulating the extracorporeal (ECP) circuit. By day 6 of the admission, there was little improvement in DK's renal function and haemolysis, therefore the decision was made by the haematology team to introduce TPE into the treatment pathway.

In total 5 TPE's were performed over 5 consecutive days with a rapid improvement in haemolytic markers, smaller gains in renal function were achieved, although DK remained dialysis dependent on discharge.

He now continues handling snakes some 3 months' post discharge. DK's haemolysis and renal function has returned to normal and DK is no longer requiring dialysis. Although the outcome is multi-factorial this case study adds to existing reports available.

1.Schwartz, J. et al, Guidelines on the use of Therapeutic Apheresis in Clinical Practice- Evidence-Based Approach from the Writing Committee of the American Society for Apheresis. *Journal of Clinical Apheresis* 2016; 31:268-269

O185

## **Paediatric apheresis in Western Australia**

**Jesper Jensen**<sup>1</sup>

<sup>1</sup>*WA Health, Perth, Australia*

Apheresis on paediatric patients in Western Australia was first undertaken at Princess Margaret Hospital in 1983 with the purchase of a Baxter CS3000. The program was transferred to Perth Children's Hospital on its opening in June 2018 with the closure of Princess Margaret Hospital. During this time there has been over 750 apheresis episodes.

The tyranny of distance and a period of relatively low apheresis activity enabled the paediatric program in Western Australia to be set up independently of other programs around Australia and the world. The most striking difference to our approach is our utilisation of arterial access for our apheresis.

The development of the program and the involvement of the Haematology Laboratory, general and paediatric specific considerations, procedures undertaken at PMH/PCH and our results will be discussed.

O187

## **Are we on auto-pilot when administering blood?**

**Monique Craven**<sup>1</sup>

<sup>1</sup>*Royal Perth Bentley Group, Perth, Australia*

The aim of this oral presentation is to raise awareness in the area of transfusion safety and associated risk. All too often we don't realise how complacent we are until we have a near miss or an actual incident. Haematology nurses deal with transfusions on a daily basis, administering transfusions is extremely common in the haematology patient cohort and could be considered a repetitive task. The frequency of adverse events occurring is low compared to the volume of product administered, but the risk remains real and can have catastrophic outcomes for the patient in situations of ABO incompatibility or severe allergic reactions.

Complacency is a natural function of the brain; the brain is designed to automate repetitive behaviour. Complacency is not the result of apathy, carelessness, or a flaw in personality; it is the way our brain functions. Most of our day-to-day behaviour is at risk of being automated; it happens without conscious or deliberate thought. Where we are familiar with tasks such as administering a transfusion it can be very easy to slip into 'auto-pilot', because we know what we are doing. We develop confidence from our 'knowledge' and start believing that a shortcut won't matter or a check can be skipped without worry, or we even don't realise we have taken a 'short-cut'. We even sometimes allow ourselves to be fooled into thinking that taking the time to stop and consider the hazard is time wasted, especially when we are busy. Strategies for nurses and organisations to create a safety culture in their workplace and curb complacency will be discussed.

By raising awareness of transfusion associated risk and learning strategies, we can create a safety culture in our organisations, minimising risk through increased knowledge, skill and awareness.

O188

**Health care professionals are fallible: Improving transfusion safety using situation awareness strategies**

**Sue Darby**<sup>1</sup>

*<sup>1</sup>Sir Charles Gairdner Hospital, Nedlands, Australia*

The aim of this oral presentation is to raise awareness that to err is human and that healthcare professionals are not infallible in their clinical practice. However, implementing situation awareness strategies may assist in improving transfusion safety.

Situation awareness can be used as a strategy to improve patient safety in transfusion practice. Healthcare professionals need to be aware how human factors impact on patient safety. Healthcare professionals need education in situation awareness strategies to be able to learn how to risk assess their clinical area and scan the environment to determine if they more likely to make errors due to workload, staffing levels and team communication.

The task of pre transfusion phlebotomy and checking blood products at the patient's bedside are multistep processes. When these tasks are performed many times there could be a level of automaticity as well as 'cutting corners' because of poor working memory due to fatigue and stress. Multiple interruptions are common in a busy clinical environment. Critical tasks require protected time to complete them without interruption. If interruptions are inevitable, consciously, the clinician needs to take time to re-establish the task sequence to prevent errors. To reduce the risk of forgetting steps in the process due to poor short term memory or interruptions, checklists or pictorial prompts or flowcharts could be used to facilitate this.

O189

**What do I do if a patient appears refractory to platelet transfusion?**

**Rebecca Howman**<sup>1</sup>

<sup>1</sup>*Sir Charles Gairdner Hospital, Nedlands, Australia*

Prophylactic platelet transfusions are routinely given to patients with severe thrombocytopenia (platelet count  $<10 \times 10^9/L$ ). Platelet transfusion plays a vital role in preventing major bleeding complications and has been shown to reduce morbidity in patients with bone marrow failure. Unfortunately, some patients have an inadequate response to platelet transfusion. This can be due to many factors, one of which is alloimmunisation.

This presentation will discuss how to recognise platelet refractoriness; what are the common causes, what diagnostic approach should be followed and how to best manage these patients.

## **Therapeutic monoclonal antibodies: A challenge for transfusion**

**Annette Le Vielez**<sup>1</sup>

<sup>1</sup>*WA Health, Perth, Australia*

Therapeutic monoclonal antibodies are used to treat haematological malignancies. Recent antibodies have been introduced: Daratumumab, Isatuximab, for multiple myeloma and a trial of Hu5F9-G4 for acute myeloid leukaemia and myelodysplastic syndrome. These drugs target cell markers on cancer cell lines but red cells also express the markers and this affects routine transfusion testing for blood group and antibodies. Platelets express some markers and may also be affected. The challenge for transfusion laboratories is to provide compatible red cells and platelets when pre-transfusion tests are invalid due to interference. Transfusion laboratories have found strategies to work around this problem, but testing requires planning and takes time. The effect of therapy on transfusion support must be considered in overall care of the patient.

The delay to immediate provision of compatible blood creates risks to patients and causes delay in treatment areas. Strategies to manage timely transfusion support include:

13. Communication to Transfusion laboratory of patients prior to commencement of treatment – medical team, pharmacy
  - Transfusion plan including clear medical history of drug treatment on transfusion requests
  - Communication between health care providers for patients who may arrive at other institutions
  - Patient knowledge of issues – information cards
  - Emergency transfusion plan

Communication and collaboration is key to timely provision of blood and this can be achieved with a multi-discipline approach.

O191

## **HPC processing, what really happens in the cell processing laboratory**

**Paul Chiappini**<sup>1</sup>

<sup>1</sup>*BMTL Pathwest Fiona Stanley, Murdoch, Australia*

**Introduction:** This presentation will provide an overview of the processing steps a FACT accredited laboratory will undertake from the initial point of HPC receipt to the final infusion at the recipient's bedside. It will allow an insight into the steps required to ensure HPC product quality assurance is adhered to as various manipulations are applied to the HPC graft.

**Aim:** To detail the processes a transplant laboratory adheres to from receipt of the HPC graft, processing of the HPC graft, storage of the HPC graft and distribution of the final product into a recipient. To allow a greater understanding of the quality aspect of graft processing and the importance of the initial graft quality collected via the processes of apheresis.

**Results:** Adherence to standard operating procedures allows the Bone Marrow Transplant Laboratory (BMTL) guidelines in areas of receipt, processing, storage and distribution of collected HPC grafts from both allogeneic and autologous donors. This presentation will allow for a greater understanding of the analytical approach transplant scientists use to perform various manipulations and which allow for the safe transplant of an HPC graft. This presentation will also outline the importance of the initial quality of collected grafts during the apheresis process and how variables such as %CD34, peripheral CD34 counts, WCC and collect volume potentially limit the processing options of a transplant scientist.

**Conclusion:** A greater understanding of the processing steps performed by the transplant laboratory and having a greater understanding of the process limitations based on the initial apheresis product.

O192

**Case studies in MM transplant – it's never as easy as you think**

**Bradley Augustson**

*WA Health, Perth, Australia*

The talk will look at a few case studies where autologous stem cell transplant hasn't followed the norm. Looking at difficulties in transplanting the older adult, difficult transplant side effects, graft issues. This session aims to be interactive, inviting questions and sharing experiences around Australia.

O193

**Quality of life during mobilisation**

**Sarah Liptrott**<sup>1</sup>

*<sup>1</sup>European Institute of Oncology, Milan, Italy*

With increasing numbers of stem cell transplants being performed, understanding quality of life aids understanding of- and support for- the physical, psychological and social aspects of donation. This presentation will look at the issues faced by healthy donors and patients in relation to stem cell mobilisation and collection. Findings in relation to quality of life during mobilization will be discussed along with strengths and weaknesses of different methodological approaches. Further suggestions for future research in this area will also be considered.

O194

**eviQ and eviQ education – haematology and BMT updates**

**Tejnei Vaishnav**

eviQ is an Australian Government, freely available online resource of cancer treatment protocols and information developed by multidisciplinary teams of cancer specialists. With a goal to improve patient outcomes and reduce treatment variation, eviQ provides evidence-based information to support health professionals in the delivery of cancer treatments at the point of care

eviQ Education provides free, evidence-based cancer eLearning resources for health professionals.

This presentation will provide an update of what's new in these two programs and relevant to a nursing and Haematology BMT audience, particularly the Intro to Haem and BMT online modules that are currently being developed in collaboration with ACI BMT Network.

O195

### **Rainy Day Care Project pilot**

**Elise Button**<sup>1</sup>, Natasha Roberts<sup>1</sup>, Sarah Northfield<sup>1</sup>, Avalon Kelly-Austin<sup>1</sup>, Nicole Gavin<sup>1</sup>, David Wyld<sup>1</sup>, Raymond Chan<sup>3</sup>, Shelley Kulperger<sup>2</sup>, Glen Kennedy<sup>1</sup>, Patsy Yates<sup>4</sup>

<sup>1</sup>Royal Brisbane And Women's Hospital, Underwood, Australia, <sup>2</sup>Metro North Hospital and Health Services, Herston, Australia, <sup>3</sup>Department of Cancer Services, Princess Alexandra Hospital, Woolloongabba, Australia, <sup>4</sup>Queensland University of Technology, Kelvin Grove, Australia

**Aim:** Identifying risk of deteriorating and dying can help improve the provision of anticipatory care planning for people with progressive incurable illness and facilitate 'rainy day thinking' where patients are encouraged to 'hope for the best... and prepare for the rest'. This project aimed to develop and test a practical, bundle approach to 'identify, assess and plan' for people who may be in their final six months of life.

**Methods:** The Rainy Day Care bundle was developed using academic literature and pre-existing palliative care resources. Implementation was facilitated by nurses with specialist knowledge of palliative care who adapted the bundle to various clinical areas and focused on marketing and language of the conceptual approach. The bundle was piloted in Cancer Care Services of the Royal Brisbane Hospital in Cancer Care. The iPARIHS (Promoting Action on Research Implementation) framework was used to guide implementation and evaluation. Qualitative and quantitative data was collected on Rainy Day Care provided and staff acceptance of the bundle.

**Results:** Nursing and medical staff identified 67 patients who were at risk of dying from January-June 2019. Of these, 52.2% were deceased at the time of the project finishing. The average time from enrolment to death was 51.26 days (IQR 15-87). Nursing and medical staff were enthusiastic and embraced the Rainy Day conceptual approach. However, even with education and support, staff lacked the confidence, skills and time to identify people at risk of dying and initiate, engage and document assessments of palliative care needs, advance care planning, greater focus on holistic needs, and referrals and collaboration with specialist palliative care services.

**Conclusion:** The bundle is feasible however, staff need significant support to identify patients at risk of dying and provide Rainy Day Care due to contextual and cultural issues present in the hospital environment.

## **The unique patient education opportunities for haematology nursing in Australia's Northern Territory**

**Hayley Williams**<sup>1</sup>, Simone Champion<sup>1,2</sup>

<sup>1</sup>*The Royal Darwin Hospital, Darwin, Australia*, <sup>2</sup>*Queensland Health, Longreach, Australia*

**Aim:** This study's aim is to examine the unique educational opportunities faced in delivering haematology services to multiple, culturally diverse people groups, across vastly remote areas of Australia's Northern Territory. Including a review of how current practices and interventions are used to successfully meet the comprehension needs of patients and carers, as well as highlighting recommendations for developing future, teaching resources to support care planning and care provision.

**Method:** This study undertook a qualitative review of the educational needs of two patient case studies. Both cases were adult patients, which were treated at The Royal Darwin Hospital. One a young Indigenous Australian father aged 20 years, with FLT-3+Acute Undifferentiated Leukaemia, whom lives in a remote Arnhem Land community. The second a young Caucasian women, with Hodgkin's Lymphoma, living with her same sex partner in a remote Northern Territory township.

**Results:** Both case studies' were useful in identifying an array of significant patient and carer's comprehension needs which provided a focus for haematology nurses, working within the Northern Territory. The key findings highlighted that continued opportunities existed for nurses, to further meet the comprehension and literacy needs of diverse and remotely located people groups, within their care.

**Conclusion:** The review was able to highlight areas where current educational practices were addressing some patient and carer's comprehension needs and was advantageous in prioritising and focusing where to channel future work and resources.

## **The physical, psychosocial and spiritual wellbeing of patients with a haematological malignancy who are near the end of life**

**Elise Button**<sup>1</sup>, Brigid Scanlon<sup>1</sup>, Nicole Gavin<sup>1</sup>, Jason Butler<sup>1</sup>, Shirley Chamber<sup>2</sup>, Raymond Chan<sup>3</sup>, Gillian Nasato<sup>1</sup>, Patsy Yates<sup>2</sup>

<sup>1</sup>Royal Brisbane And Women's Hospital, Underwood, Australia, <sup>2</sup>Queensland University of Technology, Kelvin Grove, Australia, <sup>3</sup>Department of Cancer Services, Princess Alexandra Hospital, Woolloongabba, Australia

### **Aim**

To explore the physical, psychosocial and spiritual wellbeing of people with a haematological malignancy who are near the end of their life.

### **Method**

People with any type of haematological malignancy who had refractory, relapsed or persistent disease and/or treatment limitations were recruited from the Royal Brisbane and Women's Hospital in- and out-patient areas. Validated questionnaires were delivered including the Hospital Anxiety and Depression Score, Edmonton Symptom Assessment Scale, Functional Assessment of Cancer Therapy – General, and Functional Assessment of Chronic Illness Therapy - Spiritual Wellbeing. The clinical condition of patients was assessed using the Palliative Care Outcomes Collaboration Phase Assessments. Participants were followed for up to six months.

### **Result**

Between February – October 2018, eighty people were recruited. The mean age was 63 (min 38, max 89) and 65% were male (n=52). At baseline, most participants were in the unstable phase (67.5%, n=54) or deteriorating phase (22.5%, n=18). The worst physical symptoms (range 0 best possible/10 worst possible) were tiredness (mean 5.4, SD 2.9), poor feelings of wellbeing (mean 4.4, SD 2.76), and low appetite (mean 4.29, SD 3.26). Although 47.5% (n=38) of patients reported feeling slowed down all the time, they also reported they enjoyed things just as much as they use to (38.8%, n=31) and could laugh and see the funny side of things as much as they ever did (72.5%, n=58). In terms of spiritual well-being, (range 0 – not at all/4 – very much), 58.8%, (n=47) of participants reported they had a reason for living very much, and 43.8% (n=35) reported they were able to reach deep down into themselves for comfort very much.

### **Conclusion**

Despite being clinically unstable and experiencing physical symptoms, participants still reported positive psychosocial and spiritual wellbeing in some domains.

## **Implementation of Venetoclax dose escalation in the public setting – a single site experience**

**Ashley Whitechurch**<sup>1</sup>

<sup>1</sup>*Peter Mac, Melbourne, Australia*

Venetoclax, a BCL2 inhibitor gained PBS approval for relapsed/ refractory Chronic Lymphocytic Leukaemia (CLL) in March 2019. Venetoclax is a highly effective drug with overall response rates of 79% in patients with relapsed or refractory CLL<sup>1</sup>. Due to its effectiveness it carries a high risk of Tumour Lysis Syndrome (TLS)<sup>2</sup>. This paper describes the process of implementing the outpatient Nurse-Led dose escalation program and the realistic barriers of implementation in the public system from a Melbourne based hospital experience.

Patients are stratified as low, medium or high risk TLS<sup>3</sup>. Patients with low or medium risk TLS are dose escalated in the outpatient setting until they reach optimum dosage.

Implementation of the outpatient dose escalation program consists of the following; weekly-baseline phone assessment, baseline pathology including TLS, early morning dosing of drug, 6-8 hr post TLS pathology and 24hr post TLS pathology. The nurse consultant is responsible for patient phone assessment, timely review of pathology results, and facilitating implementation of interventions of TLS as required.

This program was structured from the AIM study<sup>4</sup>, as the VCCC was and continues to be the hub for Venetoclax trials. A total of 5 patients have successfully and safely dose escalated through the outpatient program since PBS approval in March. 0 patients have displayed biochemical TLS on pathology. 1 patient was deescalated from initial inpatient dose escalation to outpatient monitoring once reaching low risk stratification criteria.

The nurse consultant plays a vital role managing the outpatient dose escalation of Venetoclax including pathology monitoring and assessment, toxicity management, and psychosocial support. The Nurse-Led initiative ensures timely pathology review, assessment and early identification and intervention of biochemical TLS.

Implementation of the nurse-led dose escalation program has helped overcome many barriers including access to inpatient haematology beds, pathology wait times and enabling patient to be safely managed in the community.

This paper will also discuss future developments for this service and potential strategies for implementation in other hospital settings including regional services.

The sample size and patient clinical status including comorbidities are limitations of the study.

14. Anderson, Tam, Lew, et al, 2018.

1. Roberts, Davids, Page, et al, 2016.

2. Venclexta Product Information, Jan 2017.

3. Tam, Anderson, Pot, et al, 2018.

## **Blinatumomab neurotoxicity assessment tool for adults diagnosed with B-cell acute lymphoblastic leukaemia**

**Vanessa Donati**<sup>1</sup>, Catherine Vassili<sup>2</sup>, Jim Siderov<sup>1</sup>, Anita Edwards<sup>3</sup>, Olivia Darby<sup>3</sup>, Ing-Soo Tiong<sup>1,2</sup>, Shaun Flemming<sup>2</sup>, Emily Batterham<sup>4</sup>

<sup>1</sup>Austin Health, Heidelberg, Australia, <sup>2</sup>The Alfred, Prahran, Australia, <sup>3</sup>Barwon Health, Geelong, Australia,

<sup>4</sup>The Royal Melbourne Hospital, Parkville, Australia

Blinatumomab is a CD3/CD19 bispecific T-cell engager approved for the treatment of relapsed/refractory B-cell lymphoblastic leukaemia (B-ALL). Patients receiving blinatumomab for B-ALL should be monitored for signs and symptoms of neurological toxicity, which may be life-threatening or fatal including, headache, tremors, encephalopathy, convulsions, speech disorders, disturbance in consciousness, disorientation and co-ordination and balance disorders. (Topp et. al, 2015).

No standardised tool is available for assessing neurotoxicity in adults receiving blinatumomab leading to inconsistent practice amongst centres in Australia. There is an unmet need for a specific neurological assessment tool to consistently identify and grade neurotoxicity during the administration of blinatumomab to guide appropriate intervention. Our aim was to develop a neurological assessment tool available for centres administering blinatumomab in the adult setting, enabling a consistent approach for assessing and managing neurological toxicity.

A multidisciplinary working group of specialist haematology nurses, consultant haematologists and a cancer pharmacist were briefed with evidence based practice on blinatumomab adverse events and their management. This was followed up with robust discussion on key requirements to incorporate within the neurological assessment tool.

This collaboration allowed for creation of a neurological assessment toxicity tool based on the immune effector cell-associated neurotoxicity syndrome (ICANS) grading scale (Lee et al., 2019). The tool developed recommends a daily neurological assessment be completed during blinatumomab infusions whilst the patient is an inpatient and at each blinatumomab infusion change in the outpatient setting. By using the tool, the patient will be given an immune effector cell-associated encephalopathy (ICE) score, which contributes to the overall ICANS grade that guides appropriate neurotoxicity management to be initiated.

The tool will be evaluated across 4 major haematology centres in Victoria who are experienced with the administration of blinatumomab. The neurological assessment tool, experience and outcome of using the tool will be presented at the conference in October 2019.

Topp, M. et al. (2015). Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncology*, 16(1), 57-66.

Lee, D. W. et al. (2019). ASTCT Consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. *Biology of Blood and Marrow Transplantation*, 25, 625-638.

## **The patient experience of subcutaneous immunoglobulin programs in Victoria**

**Nadine Gilby**<sup>1</sup>, Linley Bielby<sup>1</sup>, Kaylene Bastin<sup>1</sup>, James Daly<sup>2</sup>

<sup>1</sup>*Blood Matters Program, Department of Health and Human Services Victoria and Australian Red Cross Blood Service, Melbourne, Australia,* <sup>2</sup>*Australian Red Cross Blood Service, Brisbane, Australia*

### **Aim**

To outline different models used to introduce subcutaneous immunoglobulin (SCIg) programs and provide consumer input to enhance uptake.

### **Background**

SCIg provides patients a choice to self-administer immunoglobulin replacement therapy at home, negating regular health service day-stay admissions for intravenous immunoglobulin administration. In response to consumer campaigning the Victorian Department of Health and Human Services (DHHS) commenced a SCIg access program in February 2017. Twelve health services were offered seed funding to develop SCIg access programs, 11 accepted.

Blood Matters employed a project nurse (November 2017) to support and assist health services to gain SCIg treatment centre approval, develop and implement programs and offer a choice to eligible patients.

To further enhance the implementation of SCIg programs the DHHS/Blood Matters sought consumer feedback through a facilitated focus group (November 2018). The patient experience of the access program was explored with information gained on all aspects from equipment, training, benefits, barriers and beyond.

### **Outcomes**

Seed funded sites have 20% of their eligible patients receiving SCIg. Currently 193 patients are receiving SCIg (March 19), including 3 additional sites (no seed funding).

Program models vary significantly from programs overseen by a dedicated nurse to those integrated into existing processes (i.e. allergy outpatient clinic). Consequently the consumer experience was variable, although the trend was overwhelmingly positive when well supported and flexible. SCIg treatment was described as “life changing”.

Concerns raised include:

15. SCIg is only offered in public health services within Victoria
  - Training and troubleshooting needs to be consistent
  - Pick up of supplies needs to be streamlined.

### **Conclusion**

The effectiveness and accessibility of SCIg programs influences uptake of SCIg as a treatment option. While SCIg uptake is increasing, further work is required to ensure sustainability of SCIg programs that are open to all eligible patients including those in the private health system.

O202

### **Carfilzomib: An outpatient clinic's experience**

**Jodie Charlton**<sup>1</sup>, Gabrielle Upcraft<sup>1</sup>

<sup>1</sup>*Sir Charles Gairdner Hospital, Nedlands, Australia*

**Aim:** To examine the experience of patients receiving Carfilzomib treatment in an outpatient clinic and use this data to improve future patient care.

**Method:** Retrospective data collection. It includes all patients treated with Carfilzomib between 1st of January 2017- 30th of June 2018. Trial patients excluded. Carfilzomib is a proteasome inhibitor used in combination with Dexamethasone or Lenalidomide for relapsed or refractory multiple myeloma. Patients must have received one to three lines of therapy.

**Result:** Presented will be an outpatient clinic's experience managing patients with relapsed Multiple Myeloma who had Carfilzomib. The presentation will look into the 23 patients during their Carfilzomib treatment, concentrating on main side effects and reasons for treatment omission and/or change. Case studies will be presented and discussed.

**Conclusion:** From our experience, zero of the patients have stayed on the standard regime and experienced a range of side effects. This data will be used to demonstrate how we have improved the care for patients receiving Carfilzomib post the study's completion date.

## **A systematic overview of the incidence, risk factors and trends in bortezomib-induced peripheral neuropathy**

Tiffany Li<sup>1</sup>, Hannah Timmins<sup>1</sup>, **Tracy King**<sup>2</sup>, Matthew Kiernan<sup>1</sup>, David Goldstein<sup>3</sup>, Susanna Park<sup>1</sup>

<sup>1</sup>*The University of Sydney, Camperdown, Australia*, <sup>2</sup>*Royal Prince Alfred Hospital, Camperdown, Australia*,

<sup>3</sup>*Prince of Wales Clinical School, Randwick, Australia*

Bortezomib is a proteasome inhibitor commonly used for the treatment of multiple myeloma (MM). Bortezomib-induced peripheral neuropathy (BIPN) is a disabling and common toxicity associated with this treatment, typically requiring dose reduction, delay or cessation of treatment. It commonly presents as numbness and tingling, manifesting in the extremities. This review aimed to investigate the incidence, risk factors and trends associated with BIPN.

A systematic review using Medline, PubMed, Cochrane Central Register of Controlled Trials, Embase, Scopus and Web of Science was undertaken. Additional studies were identified by investigating authors' bibliographic references cited by original and review articles. Articles reporting on neuropathy in phase III randomised control trials involving bortezomib in any treatment arm for the treatment of MM were included in this review. Extraction of articles was completed by 2 authors using predefined data fields.

A total of 43 articles met criteria, examining 23 phase III trials (N=8,218). Overall incidence of neuropathy ranged from 8.4%-80.5% (median=37.8%) and severe neuropathy (grade 3-4) ranged from 1%-33.2% (median=8%). Similar reports of overall neuropathy and severe neuropathy were observed between the newly diagnosed and relapsed cohort. Increased cumulative dosing levels and dose intensities, intravenous compared to subcutaneous administration and combination therapy with thalidomide were associated with higher rates of BIPN. BIPN is largely reversible with 64%-79% reporting improvement in 2-4 months, and 60%-68% experiencing complete resolution in 4-6 months. Resolution was more likely in patients who had dose reductions according to protocol.

This analysis investigated BIPN in phase III trials, reinforcing BIPN as a significant toxicity. The wide range of incidence between trials highlight the need for more valid and sensitive measures of BIPN. With MM survival rates steadily increasing, a better understanding of risk factors and reversibility profiles is necessary to minimise the number of cancer survivors living with residual treatment side effects.

O204

## **In their shoes – haematological malignancies in a young person's world**

**Jo Collins**

“CHALLENGING! SCARY! INSPIRING! DIFFICULT! FUN!” .... – these are some of the words often used by health professionals to describe caring for adolescents and young adults with cancer. Services that are usually focussed on the needs of the much younger or much older patient are at risk of overlooking the needs of a young person if they are not skilled to see beneath the surface and understand the effect of a diagnosis and treatment on the context of a young person's world. Drawing on the experiences of young people with malignancies, the YCS team will use creative media to walk and talk you through the impact of diagnosis, treatment and survivorship in the context of adolescence and young adulthood during this 90 minute workshop. This unique and already challenging stage of life is characterised by biopsychosocial, sexual and cognitive development and maturation. A diagnosis of cancer can have immediate, medium and long term sequelae which command expert recognition and often management to minimise these consequences and optimise the young person's chance at a full and fruitful life.

O206

## **Exercise for the transplant patient**

### **Bonnie Furzer**

The use of hematopoietic stem cell transplant (HSCT) in the treatment of haematological malignancies has increased in Australia by 25% from 2005 to 2013. This is accompanied by an increase in the overall survival rate 5 years post HSCT. As a result there is an increase in the number of patients living with a range of acute and long-term effects from this treatment including cancer-related fatigue, loss of lean muscle mass, decreased health-related quality of life and limitations to physical and social role functioning. There is a growing body of evidence in the area of exercise oncology demonstrating exercise can be a safe and effective form of adjunctive therapy to manage treatment related side effects (and general health) across all stages of the transplant process - from myeloablative conditioning, to post treatment rehabilitation. Whilst tailored programs should take into account patient preferences and presentation, various modalities of exercise including aerobic exercise (e.g. walking, jogging), strength/resistance training, and multimodal exercise programs have been shown to result in significant benefits throughout the treatment process. And importantly, even just a generalised increase in daily physical activity can demonstrate significant benefits for patients throughout this their treatment and disease process – every little bit counts!

O207

## **Lymphoma - the patient experience**

**Donna Gairns**<sup>1</sup>

<sup>1</sup>*Lymphoma Australia, Australia*

Lymphoma and chronic lymphocytic leukaemia (CLL) affects more than six thousand Australians every year, who are geographically dispersed across Australia. As a result, they are not always given the opportunity to be referred to a specialist lymphoma service, a clinical trial, receive the best treatment, reliable information, specialist education and advice.

Lymphoma Australia conducted a patient experience survey in 2019 with over 400 respondents from across the country. This follows the patient experience survey in 2017, that identified a number of key areas of unmet needs that were addressed through the introduction of services to meet the needs of lymphoma patients and their families. Patients and carers reported their experience from diagnosis, education, treatment, access to clinical trials, psychosocial concerns, barriers experienced, support from services and their health professionals.

## **Prepare for the storm: implementing CAR-T therapy education and resources for haematology nurses**

**Shuk-Yin Tsang**<sup>1</sup>, Nicole O'Leary<sup>2</sup>

<sup>1</sup>The Royal Melbourne Hospital, Parkville, Australia, <sup>2</sup>Peter MacCallum Cancer Centre, Melbourne, Australia

**Aim:** The recent approval of commercial chimeric antigen receptor T-cell (CAR-T) therapy in Australia has prompted the need to increase nurses' awareness and understanding in CAR-T therapy and toxicities management. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are common CAR-T associated toxicities requiring appropriate assessment and management. A joint clinical haematology service between two tertiary institutions in Victoria has set up a CAR-T Working Group to provide education and resources adapted from local management policy and ASTCT's consensus grading by Lee et al. (2019).

**Method:** Nurses from two haematology wards received CAR-T therapy in-services, covering topics of indication, mechanism of action and emphasis on acute toxicity management for CRS and ICANS. Nurses completed a post-education questionnaire to assess their key understanding and confidence in three areas using four-point scales: managing patients undergoing CAR-T therapy, patients with CRS, and patients with ICANS. Toxicity management guides have been developed and provided to nurses as bedside resources. Microsoft Word and Excel were used for data analysis.

**Results:** Thirty-two questionnaires received. Five key themes of understanding identified: treatment and process, assessment and management of CRS and ICANS, corticosteroid, treatment-related toxicities, and tocilizumab. "Somewhat confident" was rated the highest in all three areas of patient management (CAR-T therapy: 37.5%, CRS: 40.6%, ICANS: 46.9%).

**Conclusion:** Nurses identify assessment and management of CRS and ICANS and corticosteroid use in CAR-T therapy as their key understanding, suggesting nursing education was effective to achieve the aim of the study. Quantitative analysis reflects that nurses are less confident with ICANS management. Future initiatives include ongoing and ICANS-focused education, evaluating management guides' effectiveness, and data comparison between wards. Small sample size, years of post-registration experience, different grading scales between clinical trials and commercial access, and the use of four-point scales are limitations to the study.

**Reference:** Lee et al. (2019). ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biology of Blood and Marrow Transplantation*, 25, 625-638.

O209

## **Commercially preparing a centre for CAR T-cell therapy**

**Nicole O'Leary**<sup>1</sup>

<sup>1</sup>*Peter MacCallum Cancer Centre, North Melbourne, Australia*

Peter MacCallum Cancer Centre is an approved site to deliver Tisagenlecleucel (Kymriah) for relapsed or refractory paediatric and young adult B-ALL (up to 25years) and adult DLBCL.

Preparing a service for CAR T-Cell therapy requires a multidisciplinary approach, with mandatory engagement with multiple services.

This presentation will broadly discuss key engagements; education resources developed for toxicity management and patient flow pathways.

This session is designed to educate and guide future Haematology departments in the implementation of a CAR-T cell service.

O210

**Nursing research: Answering the questions**

**Sarah Liptrott**<sup>1</sup>

*<sup>1</sup>European Institute of Oncology, Milan, Italy*

Interested in doing a literature review to inform clinical guidelines? Want to investigate carers perceptions of the utility of discharge information? Whatever your field of interest, the masterclass is going to be led by you the participants! We will be discussing how ideas can be transformed into research questions with some worked examples, but please don't be shy! This is an opportunity to bring your ideas for future research and projects that you have ongoing to the table. Areas covered will include where to get help and support for the methodology, getting funding, and developing a research network within your centre.

O211

## **Age and gender in warfarin dosing: Comparing real world data of a tertiary hospital anticoagulation service to historical conclusions**

**Justine Burg**<sup>1</sup>

<sup>1</sup>*Sir Charles Gairdner Hospital, Nedlands, Australia*

### **Aim**

Since the 1970s, studies have suggested that warfarin doses should be reduced with increasing age and for females, however current guidelines which inform the dosing and titration of warfarin do not reflect this. This study aimed to compare historically reported trends for age and gender to current dosing requirements.

### **Methods**

A review of 3000 patients dosed by the Sir Charles Gairdner Hospital Home Anticoagulation Support Service (HASS) aimed to determine if correlations between age, gender and warfarin dose could be identified. Using real world data, a retrospective review of warfarinised patients was conducted to determine patients' gender, age and dose of warfarin at discharge from the service.

### **Results**

Although there is a statistically significant reduction in dose requirement by age, this has limited clinical significance as it relates to only an approximate 2mg per day difference from age 40 and 80 years with a broad variability of doses at all ages. Data suggests that women require less warfarin than men; however this a weak correlation and is of minimal clinical significance as it reflects an overall less than 1mg per day difference in warfarin dose.

### **Conclusions**

The data suggests that the other factors which affect warfarin metabolism may account for more difference than age and gender alone. These results support current practice as despite the acceptance that age and gender effect warfarin requirements, the current guidelines in conjunction with HASS's daily warfarin titration allow for safe warfarin dosing despite individual patient differences.

O212

## **The role of anticoagulation clinics in the age of direct oral anticoagulants**

**Allan Santiago**<sup>1</sup>

<sup>1</sup>*Sir Charles Gairdner Hospital, Nedlands, Australia*

Anticoagulation clinics were initially commenced to optimise warfarin management while minimising bleeding risks. Therapy offered by these clinics has traditionally involved; assessment, counselling and advice on warfarin's many interactions, frequent INR monitoring, and periprocedural management. Despite the reduction in warfarin prescribing at both the international and national level for various indications, anticoagulation clinics remain, and have evolved to accommodate management advice regarding direct oral anticoagulants (DOAC).

Anticoagulation management through specialised clinics is recommended by major international societies, although often at a low level of certainty, and usually in regards to warfarin therapy and perioperative procedural management, with little literature regarding their role in DOAC management. Small studies have been conducted on this topic, discussing the balance of benefits to be attained from clinics in regards to DOAC therapy being balanced against over-management and low-value services.

The Sir Charles Gairdner Hospital (SCGH) Home Anticoagulation Support Service (HASS) is an outpatient (ambulatory) anticoagulation clinic that commenced in 2008 and continues to provide outpatient care during the DOAC era. Having been involved in the commencement of DOAC therapy in over 350 patients with venous thromboembolism between January 2014 – January 2018 HASS has come across many of the concerns raised in the literature surrounding this contested area of service.

This session discusses the role HASS has played in patient care as DOAC therapies have overtaken warfarin therapy as the drug of choice, focussing on how HASS has been able to assist patients with concerns that were identified regarding DOAC prescribing, interactions, adverse reactions and compliance.

O213

## **Nursing care of patients with bleeding disorders**

**Susan Webzell**<sup>1</sup>

*<sup>1</sup>Hollywood Private Hospital, Perth, Australia*

Patients with Haemophilia, Von Willebrands and other bleeding disorders require specialist management to maintain patient safety and achieve satisfactory outcomes. There is significant variation between patients, their specific requirements and treatment plans, involvement of haematologist is required to create these personalised treatment plans. This is especially pertinent when these patients require planned surgeries.

This presentation will aim to increase staff knowledge through education to gain better understanding of bleeding disorders and potential plans or requirements when caring for this patient's cohort. This knowledge is especially important to allow nursing professionals to support patients and the staff who are following the treatment plans, who often have little experience of either bleeding disorders or the treatments required.

The presentation is to include general information on bleeding disorders with a focus on Von Willebrands. It will look at potential treatment options and specific requirements when delivering these treatments. Case scenarios/ case studies will be used to highlight clinical experiences to increase knowledge base. It will also focus on the individual plans required and potential problems that may be encountered.

O214

**Case studies in coagulation**

**Carolyn Grove**

*WA Health, Perth, Australia*

Managing disorders of coagulation is seemingly simple. The treatment is either administration of anticoagulant medications or pro-coagulant factors, depending on whether the problem is one of clotting or bleeding. However in practice things are often not so black and white. I will present a number of cases highlighting the complexity of anticoagulant management, with a focus on patients with coexistent haematological problems.

## **The Steroid Symptom Questionnaire Multiple Myeloma (SSQ-MM): Testing the psychometric properties**

**Tracy King**<sup>1,2</sup>, Jacqueline Jagger<sup>3</sup>, Judith Fethney<sup>4</sup>, Chantale Boustany<sup>2,5</sup>, Douglas Joshua<sup>1,6</sup>, Kate White<sup>2,5</sup>

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**Background:** Corticosteroids, central to the treatment for myeloma, can cause a wide range of side effects (SEs). We adapted the Dexamethasone Symptom Questionnaire Chronic (DSQ-Chronic) to report steroid SE's in a Multiple Myeloma (MM) population. The Steroid Symptom Questionnaire Myeloma (SSQ-MM) is an 18-item patient-report measure (PRM) of the incidence and severity of steroid related SEs.

**Aims:** Test the psychometric properties of the Steroid Symptom Questionnaire Myeloma (SSQ-MM) in a multi-centre cross sectional study.

**Methods:** 70 MM Patients receiving steroids were recruited from 3 hospitals. Participants completed the SSQ-MM at 2 time points 1 week apart. Analysis included descriptive statistics; feasibility and acceptability; internal consistency reliability was assessed using Cronbach's alpha, test-retest using intraclass correlation coefficient (ICC) and paired t-test to assess repeatability.

**Results:** Data from 62 participants are available for analysis. Mean (SD) age was 66.8 (12) years; 4.6 (3.2) years since diagnosis and median (min-max) 2 (0-8) prior lines of therapy. Mean (SD) dexamethasone dose per week was 24.0 (13.7) milligrams.

Completion rates at T1 & T2 were 100% with mean (SD) time to complete at T1 9.8 (6.2) and T2 8.9 (6.6) minutes. Cronbach's alpha was acceptable: 0.76 (T1) and 0.81 (T2) and the ICC was 0.91 indicating excellent consistency between the two administrations. The tool was repeatable. Mean scores at T1 were 1.92 (SD 0.35) and T2 1.87 (SD 0.40),  $p = 0.10$ . Most frequently reported symptoms  $n$  (%) were loss of energy/fatigue 58 (93.5); disturbed sleep 58 (93.5) and agitation/nervous 48 (77.4). The most bothersome symptom was disturbed sleep 27 (43.5). All patients found the SSQ-MM was an accurate and comprehensive description of the SEs relating to steroids.

**Conclusions:** The SSQ-MM demonstrates high levels of feasibility, acceptability, repeatability and internal consistency. A larger study to further test validity and associations with HRQoL is underway.

### **Developing a nursing research internship**

**Nicole Gavin**<sup>1,2</sup>, Elise Button<sup>1,2</sup>, Michael Smith<sup>1</sup>, Therese Hayes<sup>1</sup>, Jenni Leutenegger<sup>1</sup>, Tracy Glynn<sup>1</sup>, David Williams<sup>1</sup>, Veronica Percival<sup>1</sup>, Lisa Wong<sup>1</sup>, Claire Wessling<sup>1</sup>, Allannah Watling<sup>1</sup>, Patsy Yates<sup>1,2</sup>  
<sup>1</sup>Royal Brisbane & Women's Hospital, Herston, Australia, <sup>2</sup>Queensland University of Technology, Kelvin Grove, Australia

**Aims:** Cancer nurses are well placed to drive the research agenda in their workplaces, but often lack the confidence, knowledge and skills to conduct their own research. We aim to develop a 12-month Nursing Research Internship for Cancer Care Services.

**Methods:** With the support of the Nursing Leadership team and Professorial Precinct at the Royal Brisbane and Women's Hospital, the Nurse Researcher team extended the 12-week Evidence Based Practice Programme into a 12-month Internship. Nurses are released from their clinical duties one day per week to work in research. The nurses develop a Patient, Intervention, Control and Outcome question, complete a systematic review, write a research protocol, apply for funding, apply for ethics, conduct the study and disseminate their results.

**Results:** Currently, four nurses are enrolled in the Internship. The four topics are clinically relevant and driven by the needs of the service line. The first topic will determine if it is safe for patients to lay flat for less than one hour after a lumbar puncture, the second will develop a sepsis pathway for the out-patient clinics, the third will establish if using a continuous ambulatory intravenous pump will improve mobility for in-patients, and the fourth will investigate the ideal dose of local anaesthetic spray for the insertion of nasogastric tubes during a stem cell transplant. To date, one nurse has been invited to present at a national conference, the systematic reviews have been presented at national conferences, ethics has been approved, funding successfully sought and in-kind support for equipment.

**Conclusion:** The Internship is introducing nurses to research in a supportive environment. The nurses are developing new skills, growing in confidence and promoting research in their own units. The four projects involve the wider multidisciplinary team (medical, pharmacy, physiotherapy, dietetics) and collaborating with external partners.

## **Complementary therapy improves the patient experience in a group of patients receiving intensive chemotherapy for haematological malignancies**

**Wendy Risdon<sup>1</sup>**, Kate Reid<sup>1</sup>, Ray Kirk<sup>1</sup>

<sup>1</sup>University of Canterbury, Christchurch, New Zealand

The Bone Marrow Transplant Unit at Christchurch Hospital, New Zealand trialled a new initiative in 2017 involving “Healing Touch Therapy” (an energy-based complementary modality), using “hands-on” gentle nurturing touch.

### **Aim**

To evaluate the feasibility, acceptability and predictability of delivering Healing Touch (HT) sessions to patients receiving intensive chemotherapy for haematological malignancies.

To improve patient’s health related quality of life with a “hands-on” intervention which requires no energy expenditure on the part of the patient.

### **Method**

Ten inpatients were allocated to a HT practitioner (HTP) for the duration of their hospitalisation. HT sessions of 50-60 minutes occurred twice weekly and Pre/Post Treatment Evaluations were completed by the Healing Touch Practitioner (HTP). A modified Functional Assessment of Cancer Therapy, (FACT-Leu), evaluation tool was completed by the patient up to 24 hours after each session. Nursing Staff from the BMTU were also surveyed.

### **Results**

The HT intervention was well received by patients and supported by the nursing staff. Patients reported; finding the sessions helpful overall, creating a state of relaxation, reduced anxiety and muscle tension. A total of 63 HT sessions were delivered during the five month pilot project with 57 complete evaluation sets. 82 percent, found the sessions very helpful” or “quite a bit helpful” and 10 percent found them, “somewhat” or “a little bit” helpful. The data showed an increasing benefit over time, suggesting an accumulative effect took place.

### **Conclusion**

The goal for this pilot study has been met by demonstrating the ability to recruit and retain participants and to receive a high rate of positive qualitative feedback from the patients and staff suggesting a HT Programme is feasible, acceptable and predictable.

HT therapy could be offered to all Bone Marrow Transplant Unit (BMTU) patients with minor changes to delivery and funding arrangements.

### **References**

Anderson, J. G., & Taylor, A. G. . (2011). Effects of healing touch in clinical practice: a systematic review of randomized clinical trials. *Journal of Holistic Nursing American Holistic Nurses Association*, 29 (3), 221-228.

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Danhauer, S. C., Tooze, J. A., Holder, P., Miller, C., & Jesse, M. T. (2008). Healing touch as a supportive intervention for adult acute leukemia patients: A pilot investigation of effects on distress and symptoms. *Journal of the Society for Integrative Oncology*, 6(3), 89-97.

## Management of checkpoint inhibitor associated immune related adverse effects

**Johnathan Soggee**<sup>1</sup>

<sup>1</sup>*Fiona Stanley Hospital, Murdoch, Australia*

### **Introduction/ Aim:**

With the recent PBS listing of pembrolizumab for relapsed refractory Hodgkins Lymphoma and with the imminent use of immunotherapy in other haematology settings, it is important to consider the emergence of immune related adverse effects (irAE) associated with PD-1 and PD-L1 therapies and the occurrence and management of these toxicities. This free communication session will provide an interactive lecture looking at management of irAE

### **Method:**

There is currently literature and clinical guidelines such as the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines in the management of these toxicities in the oncology setting. However, with these treatments moving into the haematology setting, it is important that clinicians are aware of management strategies for PD-1 and PD-L1 aiRAE.

The lecture will cover:

- Types of immunotherapy and mechanisms
- Types of irAE and mechanisms
  - Thyroiditis
  - Hypophysitis
  - Hepatitis
  - Pneumonitis
  - Auto-immune aplastic anaemia
- Time to onset of irAE after initiating immunotherapy
- aiRA reported in the KEYNOTE-087 Trial of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma by Chen *et al.* in 2017
- Grading of adverse effects
  - Management strategies per clinical guidelines and real-world experience
    - Hydrocortisone (and other corticosteroids)
    - Calcineurin inhibitors
    - ATG rabbit

### **Conclusion:**

This lecture will look at mechanisms of toxicities, relevant investigations and treatment strategies with consideration of current guidelines and local real-world experience.

O221

## **Tele-oncology service**

**Wei-Sen Lam**<sup>1</sup>

<sup>1</sup>*WA Health, Perth, Australia*

The 2018-2022 WA Country Health Innovation Digital Innovation, Transport and Access to Care Program aims to improve service access and equity for country patients by embedding telehealth and digital services in everyday service delivery. The WA Country Health Service Cancer Implementation Strategy identified the Kimberley and Pilbara regions as a key deliverable to achieving quality cancer service.

Telechemotherapy units first originated in Queensland and is currently being developed in Western Australia. The vision is to provide telechemotherapy units in remote areas to provide treatment closer to home.

O222

## **Chimeric antigen receptor T cell therapy: Nurses - a critical link**

**Andrew Hutchison**<sup>1</sup>

<sup>1</sup>*Fiona Stanley Hospital, Perth, Australia*

Chimeric Antigen Receptor Cell Therapy (CAR-T) is a novel immunotherapy using patients' own genetically reprogramed lymphocytes, designed to target tumour cells. This approach is rapidly finding its place in the treatment of relapsed/refractory B cell malignancies. This therapeutic approach is expanding exponentially with its role being investigated in many other haematologic and solid organ malignancies. Over 300 products are currently under investigation with two products TGA approved for use within Australia. These therapies have a unique set of complications which can be severe/life threatening and require specific and timely interventions. As these treatments become more common place, nurses will be increasingly involved in the care of patients undergoing CAR-T cell therapy. This talk will give an overview of CAR-T cell therapy (including new CAR designs), its complications, monitoring & escalation procedures and focus on the critical role that nursing staff play in not only supportive care but also the education of patients, relatives and colleagues.

O223

## **Nursing minimum datasets**

**Sarah Liptrott**<sup>1</sup>

*<sup>1</sup>European Institute of Oncology, Milan, Italy*

Nursing Minimum Data Sets are defined as 'a systematic registration of the smallest possible number of unequivocally coded data, with respect to- or for the purpose of- nursing practice, making information available to the largest possible group of users according to a broad range of information requirement' (Sermeus, 1994). It has been suggested that increasing the visibility of recorded nursing care may facilitate clinical, managerial, research and educational applications (Mac Neela., 2006). This presentation will provide an overview of some of the different Nursing Minimum Datasets in use, also discussing how new technology and analysis of big data can provide insight into nursing practice and patient outcomes.

Mac Neela P, Scott PA, Treacy MP, Hyde A. (2006) Nursing minimum data sets: a conceptual analysis and review. *Nursing Inquiry*, 13(1):44-51.

Sermeus W. The Nursing Minimum Data Set in Belgium: a basic tool for the tomorrow's health care management, Katholieke Universiteit Leuven, Centre for Health Services Research. 1994.

O227

## **Elements of a CAR T-cell programme in an Australian centre – the evolving experience**

**Michael Dickinson**<sup>1</sup>

<sup>1</sup>*MacCallum Cancer Centre, Melbourne, Australia*

Gene-modified cellular therapies have been manufactured at Peter MacCallum Cancer Centre for years and chimeric antigen receptor T cells have been delivered to patients since 2010. Clinical trials provided a framework for the technical and clinical requirements of safe delivery of T-cell activating agents, which have a substantial quality assurance demand and which have foreseeable but potentially severe clinical toxicities. Safe care of patients can be extremely resource demanding and implementation of this new technology requires executive support. In this talk we will review the elements of the service as it has been established at Peter Mac, including the specific resources we have decided to employ. I will discuss the still-maturing experience of rolling out commercially available CART and an expanded trial programme. Elements of patient triage and extra-mural clinical collaboration will be discussed, as well as emerging clinical and operational dilemmas we are facing each week.

O230

## **Paediatric ITP Guidelines**

**Helen Wright<sup>1</sup>**

*<sup>1</sup>Perth Children's Hospital, Perth, Australia*

Immune thrombocytopenic purpura (ITP) is the most common cause of thrombocytopenia in childhood, and can be managed conservatively in most patients as the majority will have minor bleeding and resolve within 6 months. Patients with significant mucosal bleeding such as prolonged epistaxis, haematuria, menorrhagia or gastrointestinal haemorrhage may need treatment. Intracerebral haemorrhage (ICH) is uncommon (<1%) but can have significant morbidity and mortality. Predicting which patients should be treated is difficult, and steroids will temporarily raise the platelet count but don't alter the long term outcome of ITP. What should Clinical Practice Guidelines (CPGs) recommend?

The Paediatric ITP CPG from Perth Children's hospital in Western Australia will be presented. This was a collaboration between the emergency, general paediatrics and haematology departments at the tertiary Child and Adolescent Health Service, developed in 2011 using the American Society of Haematology (ASH) ITP Guidelines.

A case of ITP with ICH will be used to generate discussion about what ITP CPGs should recommend. Is it time to have a national consensus in Australia?

N001

## **Development of a novel haematology nurse-led post-chemotherapy assessment tool**

**Kimberley Barrow**<sup>1</sup>, Lisa Speedy<sup>1</sup>

<sup>1</sup>*Capital And Coast District Health Board, Wellington, New Zealand*

### **Aim:**

The aim was to implement a nurse-led patient assessment tool in order to mitigate patient wait times, decrease pressure on medical staff, increase autonomy of nurse-led patient reviews, increase timely recognition and management of patient deterioration, and increase patient satisfaction and streamline care.

### **Method:**

A retrospective audit of haematology patients having ambulatory care through the Wellington Blood and Cancer Centre for routine bloods and assessment review, between from 28<sup>th</sup> January-3<sup>rd</sup> March 2019. Wait times and reasons for any delays were recorded. An objective nurse-led assessment tool was developed utilising evidence-based literature pertaining to common chemotherapy side effects, and graded using the Common Terminology of Adverse Events scale. We plan to re-audit in October 2019.

### **Result:**

The average time patients remained in chairs and factors influencing wait times were reviewed. Results indicated that whilst patients were allocated 2.5 hours per booking, 78% of patients remained in the chair for equal to or greater than this time. Various factors influenced this, including: delay in laboratory results, acute presentations, neutropenic sepsis, intravenous therapies, and transfusion requirements, nursing constraints, medical constraints, and awaiting inpatient beds. The tool is currently in pilot phase, with expected outcomes including decreased pressure on medical staff by promoting autonomy of nurse-led assessment and triage, resulting in increased clinical efficiency.

### **Conclusion:**

Within an ambulatory setting, the length of time spent waiting for a review is a pertinent and modifiable aspect of patient satisfaction and outcomes. It is advantageous to utilise wait time when focussing on quality improvements due to its direct relationship with system performance, as well as its ability to be quantitatively monitored. This results in a driving-force for nurse-led reviews within a haematology setting due to a reduction in medical staff and increased clinical demands.

## Quality of life following Allogeneic Stem Cell Transplantation at Alfred Health

Bianca Cirone<sup>1</sup>, Tricia Wright<sup>1,2</sup>, David Kliman<sup>1</sup>, Daniela Klarica<sup>1</sup>, **Andrew Spencer<sup>1,3</sup>**, Tricia Sharon Avery<sup>1,3</sup>, Patricia Walker<sup>1,3</sup>

<sup>1</sup>Alfred Health, Melbourne, Australia, <sup>2</sup>LaTrobe Regional Hospital, Traralgon, Australia, <sup>3</sup>Monash University, Melbourne, Australia

**Aim:** To assess quality of life (QOL) following allogeneic stem cell transplantation (SCT) and determine what impact chronic graft-versus-host disease (cGvHD) has on QOL measures.

**Method:** Individuals who attended the late effects clinic two years and beyond SCT who were disease free from a blood cancer or its treatment completed the Functional Assessment of Cancer Therapy – Bone Marrow Transplantation (FACT-BMT) Scale. Study questionnaires were conducted and returned via hard copy following obtainment of consent. Results were analysed from a comprehensive database. The presence of cGvHD, previous or active was obtained from the SCT database.

**Results:** 151 questionnaires were analysed on 151 participants from June 2017 - June 2019. 53% of participants had a leukaemia diagnosis, 8% a myeloma diagnosis and 10% a lymphoma diagnosis. 47% of participants had documented cGvHD. In the cGvHD cohort the mean age was 51.7 years. In the non-GvHD cohort the mean age was 40.5 years. Table 1 shows the comparison of QOL domain scores between the cGvHD and non-GvHD cohort using norm-based T scores. T-scores are standardised scores with 50 representing the mean; a mean of 50 represents the mean score of the general population [1].

**Table 1:**

	Female participant %	Physical domain	Social domain	Emotional domain	Functional domain
Non-GvHD participant cohort	46%	47.9	55.7	48.1	52.5
cGvHD participant cohort	45%	40.2	53.1	44.1	48.9

**Conclusion:** Participants in the non-GvHD cohort appear to have generally favourable perceptions of their QOL post SCT. The cGvHD cohort scored significantly lower in all four domains. Both groups report poorer QOL in the physical and emotional domains. Despite this, both groups report higher QOL in the social domain relative to the norms, indicating strong support as a facilitating factor of better QOL and enhanced interpersonal relationships and thus some degree of enhanced life satisfaction. Future efforts will be directed at attempts to meet patients' educational needs and expectations at the SCT preparatory phase, particularly in relation to cGvHD and to explore outpatient services for patients living with prevalent symptoms following SCT.

### References:

1. Psycho-oncology Co-operative Research Group. PoCoG – Psycho-oncology Outcomes Database Normative Data Calculator. Queensland Cancer Risk Study, 2014. [www.pocog.org.au](http://www.pocog.org.au)

N003

## **The development of specialty haematology nurses: book smarts versus street smarts**

**Emma Cohen**<sup>1</sup>, Bernadette McCormack<sup>1</sup>, Peter Shuttleworth<sup>1</sup>, Patricia Wise<sup>1</sup>, Andrea Cameron<sup>1</sup>, Tammy Rowe<sup>1</sup>, Joanne Wooster<sup>1</sup>, Angela Mellerick<sup>1</sup>

<sup>1</sup>*Austin Health, Heidelberg, Australia*

**Aim:** To describe the barriers and facilitators to developing nurses specialty skills and knowledge since opening an allograft service in Oct 2015.

**Background:** There is increased global understanding that time spent at the bedside and specialisation in nursing leads to improve patient outcomes. In the haematology setting, specialist training for nurses most commonly involves on-the-ward experiential learning in addition to attendance at hospital designed and run education/study days. Formal post-graduate educational qualifications in haematology and stem cell transplant are limited because of a lack of availability in both university subjects and courses. Additionally, across nursing specialties, cancer nurses have been identified as having a high turnover of staff and this poses a perpetual challenge for wards and organisations in terms of maintaining a safe skill-mix.

**Method:** Survey of nurses that provide care for allogeneic stem cell transplant recipients and key nursing stakeholders in the ICU department to explore their understanding and confidence in providing care to patients undergoing allogeneic stem cell transplantation and their experience of, and opportunities to, learn about the care needs of this cohort of patient (formal and informal). Audit of nursing turnover since the service opened.

**Results:** Data collection and analysis to be completed by August 2019.

**Conclusion:** Establishing an allograft service has highlighted the need to review specialist training programs for nurses working in haematology and stem cell transplant centres. Organisational based teaching and learning initiatives have been invaluable in developing specialty knowledge, however, expertise is also shaped by experience and we are still to establish a critical mass of specialist nursing staff.

The exponential increase in new and innovative therapies e.g. CAR-T cells further highlight the need for improved sharing of policies, training resources and experiential learning opportunities for point-of-care nurses between like-units to ensure high quality, safe care that does not vary unnecessarily.

**A NIFTY intervention: empowering nursing staff to initiated pre-prescribed antibiotic order for haematology patients that develop febrile neutropenia.**

**Emma Cohen**<sup>1</sup>, Steven Walker<sup>1,2</sup>, Andrew Grigg<sup>1</sup>, Jason Trubiano<sup>1,3</sup>

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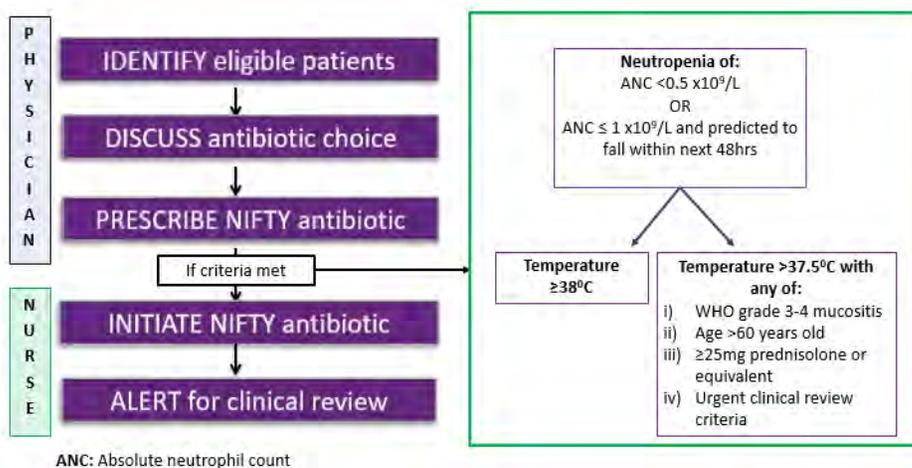
**Aim:** To evaluate the nursing experience with a pathway (Nursing-Initiated Febrile neutropenia TherapY (NIFTY)) allowing nurse initiation of pre-prescribed first dose intravenous antibiotics in febrile neutropenia (FN).

**Method:** The NIFTY pathway (implemented October 2017) involves a clinical criteria to allow nurse initiation of a pre-prescribed antibiotic order for adult (≥18 years) haematology patients that developed FN during hospital admission (see Figure 1). A retrospective chart audit (31/10/17-30/4/18) evaluated nursing compliance with the NIFTY pathway. The audit focused on the proportion of episodes; i) activated outside eligibility criteria, ii) associated with an alert for medical review immediately following initiation iii) delay despite initiation criteria being met. Impact on median (IQR) time to antibiotic administration (TTA) from first recorded fever in an included episode of FN was determined by comparing episodes in the pre- (31/10/16-30/4/17) and post-pathway implementation (31/10/17-30/4/18).

**Results:** The retrospective chart audit included 61 episodes of FN in 52 patients. A NIFTY order was nurse-initiated outside eligibility in one episode (1/61; 1.6%). Following initiation, alert for medical review occurred in all episodes (61/61; 100%). The NIFTY order was delayed despite initiation criteria being met in 11.5% (6/61) of episodes. However, this was because a NIFTY order was not pre-prescribed at the time of criteria being met rather than a consequence of nursing delay. The survey revealed a high level of nursing high satisfaction with the increased autonomy that has accompanied this pathway. Median (IQR) TTA in the pre-implementation group was significantly reduced in comparison to the post-implementation group [66 (40-100) minutes vs 29 (20-41) minutes; p<0.001].

**Conclusion:** There was a high level of nursing compliance and satisfaction with the NIFTY pathway and significant reduction in median TTA. This initiative has empowered nursing staff to make decisions about the management of patients with FN.

**Figure 1: The Nurse Initiated Febrile neutropenia TherapY (NIFTY) Flow Chart**



N005

## **Clinician knowledge, acceptance and experience of using an algorithm developed to standardise the management of mucositis pain**

**Emma Cohen**<sup>1</sup>, Clare English<sup>1</sup>, Megan Yeomans<sup>1</sup>, Chong Tan<sup>1</sup>, Ilonka Meyer<sup>1</sup>

<sup>1</sup>*Austin Health, Heidelberg, Australia*

**Aim:** To examine clinician knowledge, acceptance and experience of using a consensus-based algorithm for the management of mucositis pain in patients undergoing an autologous or allogeneic stem cell transplant.

**Background:** An assessment and treatment algorithm for mucositis has been developed using the literature and expert consensus from the anaesthetic and haematology units. The algorithm was designed to guide the management of all stem cell transplant patients who experience mucositis. The algorithm was first implemented into the inpatient haematology ward in November 2017.

**Method:** A survey was distributed to the nursing team on the inpatient haematology ward, specialist pain nurses, specialist haematology nurses as well as key medical stakeholders including haematology and anaesthetic, particularly those working in acute pain services, and consultants. The purpose of the survey was to determine: 1) awareness of the algorithm; 2) experience of using the algorithm including understanding of their individual roles/responsibilities in terms of prescribing and/or administration (as relevant); 3) perception of the algorithm's impact on patient's pain control and; 4) familiarity and acceptability of the minimum assessment requirements for patients with mucositis.

**Results:** Data collection is ongoing but will be completed in July 2019. Preliminary results indicate high awareness of the algorithm amongst point-of-care nursing and haematology registrars, however, less familiarity amongst consultant haematologists. Awareness was high in the acute pain services team.

**Conclusion:** This is the first algorithm to standardise the management of mucositis pain. Since its implementation there has been high compliance by medical registrars and nursing staff and widespread belief that it both simplifies and promotes optimal analgesia for patients. Patient pain and other mucositis related outcomes are currently being analysed and will be published.

N006

**HALT; WHINE STOPR! Development, implementation and evaluation of an individual and nursing team wellness initiative in the inpatient haematology setting**

Baccara Mahony<sup>1</sup>, Elena Tarasenko<sup>1</sup>, Jo Wooster<sup>1</sup>, Emma Cohen<sup>1</sup>

<sup>1</sup>*Austin Health, Heidelberg, Australia*

**Aim:** To develop, implement and evaluate the introduction of an end-of-shift wellness huddle and individual reflection tool for nurses working in an inpatient haematology/bone marrow transplant setting.

**Background:** Cancer nurses have been identified as having high rates of burnout, compassion fatigue and job-related stress. Haematology nurses provide care to patients at all stages of the illness and treatment trajectory. This can include providing end-of-life care to patients who have relapsed after receiving multiple different treatment regimens with curative intent. The complexity of care delivery, the emotional burden coupled with shift-work and a junior workforce puts inpatient haematology nurses at high risk of burnout and is a likely contributor to high turnover rates often seen in this setting.

**Method:** A Plan-Do-Study-Act cycle was used. This wellness initiative combined two previously described self-reflection tools. Hungry, Angry, Lonely, Tired (HALT) which has been used to promote wellness in nurses both nationally and internationally and is designed to aid nurses recognise what might be contributing to their stress. The second tool was adapted from an ED 'going home self-checklist' but renamed WHINE STOPR: Wellness Huddle Initiative for Nurses at End of Shift Supporting the Team to Observe, Pause and Reflect and designed as an end-of-shift huddle for all nurses. Evaluation included audit of attendance and nurse survey on their experiences.

**Results:** The initiative was implemented in June 2019. Preliminary findings indicate support from nursing staff, however, the practicalities of a set time for WHINE STOPR each shift is proving challenging. The first nurse survey will be conducted in the first week of August.

**Conclusion:** This wellness initiative incorporated both an individual and team component. Finding a set time in the dynamic clinical environment is a challenge, however, nurses are reporting that their self-reflection and finding positives in each day is improving.

N007

**Empowering point-of-care nurses to better assess, document and escalate patient-reported antibiotic allergies: the implementation of a validated antibiotic allergy assessment tool (AAAT) in the inpatient haematology setting**

**Emma Cohen**<sup>1</sup>, Misha Devchand<sup>1</sup>, Steven Walker<sup>1,2</sup>, Prue Andrew<sup>1</sup>, Andrea Cameron<sup>1</sup>, Patricia Wise<sup>1</sup>, Jason Trubiano<sup>1,3</sup>

<sup>1</sup>ONJ Centre, Austin Health, Heidelberg, Australia, <sup>2</sup>Monash University, Clayton, Australia, <sup>3</sup>Peter MacCallum Cancer Centre, Parkville, Australia

**Aim:** To evaluate point-of-care nursing staffs understanding, engagement and experience in the assessment and management of patient-reported antibiotic allergies post the implementation of a validated antibiotic allergy assessment tool (AAAT<sup>1</sup>).

**Background:** Patient-reported antibiotic allergies are entered in the medical record in up to 1 in 4 hospitalised cancer patients. Most often these allergies are not clarified by clinicians. This, when coupled with the fear associated with life-threatening reactions to betalactam antibiotics often results in the prescription of alternate antibiotics which has implications both for the individual patient and more broadly for antimicrobial stewardship(AMS).

Specialist haematology nurses (N=13) participated in the validation of the AAAT and were found to perform better than other key stakeholders (e.g. pharmacists, doctors) at assigning the correct allergy phenotype and management directive<sup>1</sup>. The key role of nurses in AMS and drug allergy is increasingly noted in health services program.

**Method:** A survey sent to all nursing staff on the inpatient haematology ward to explore their awareness, understanding, experience and confidence in using the AAAT and audit of completed tools and EMR allergy data.

**Results:** The data are still being collected and analysed. Preliminary findings (n = 25 patients Jan to Feb 2019) indicate that there has been an increase in the accuracy of complete antibiotic allergy document in the EMR (complete documentation 63% pre vs. 97% post), improving medication safety and enabling of point-of-care de-labelling for identified low risk allergy phenotypes.

**Conclusions:** The role of nurses in medication safety incorporating drug allergy reconciliation and AMS should not be underestimated. Nursing staff provide care to patients across the 24-hour continuum and are professionally responsible and accountable for the medications that they administer. Empowering nurses by providing them with a validated tool to assess patient-reported antibiotic allergies has had a direct impact on accuracy of the EMR and proportion of patients identified as appropriate for timely de-labelling.

Devchand JA, Urbancic K, Khumra S, Douglas A, Smibert O, Cohen E, et al. Pathways to improved antibiotic allergy and antimicrobial stewardship practice—the validation of a beta-lactam antibiotic allergy assessment tool. *J Allergy Clin Immunol Pract* 2019;7:1063-5.

N008

## **Nursing supported go-slow approach to self-administration of pegylated interferon can improve adherence and tolerability**

Jacqueline Jagger<sup>1</sup>, **Kellie Cook**

<sup>1</sup>Jacqueline Jagger, Gosford, Australia, <sup>2</sup>Kellie Cook, Gosford, Australia

### **Background & Aim:**

Pegylated Interferon alfa-2a (PEG-IFN) is now available to Australian patients with a myeloproliferative neoplasm (MPN), primarily essential thrombocythaemia (ET) and polycythaemia vera (PV). Despite the listing on the PBS in August 2018 PEG-INF has not however been the first drug of choice in the treatment of MPN's due to toxicity profile and the subsequent high drop-out rates.

We report a patient centred go-slow approach to PEG-IFN administration aimed at reducing toxicity, improving patient experience and therefore impacting drop-out rates.

### **Method:**

In collaboration with medical colleagues we developed a patient/carer education framework to support self-administration, a go-slow approach to dose escalation and management of common toxicities.

### **Results:**

24 patients commenced therapy with PEG-IFN through the Cancer Day Unit. All patients received education, administration support and guidance with management of toxicities from the cancer nurse coordinator or nurse practitioner. All patients commenced therapy on 45mcg weekly with dose adjustments depending on toxicities and efficacy. The most common reported toxicities experienced were flu-like symptoms and musculoskeletal discomfort, fatigue and occasionally mild nausea. 1 patient, with a previous history of psychological morbidity, experienced symptoms of depression resulting in cessation of drug.

Patients/carers are required to administer the correct dose from a multi-dose pre-filled syringe therefore increasing the potential for errors in administration. Minor administration errors within the cohort improved the education delivered and strategies to increase safety and accuracy. Pre-existing patient support resources from the MPN Alliance and MPN Voices provided the basis of the written education information alongside website resources.

### **Conclusion:**

PEG-IFN can be self-administered safely by patients/carers. A collaborative approach between the health care team and the patient/carer with clear information, education and strategies to manage potential toxicities improves drop-out rates. Therapy is well tolerated with a go-slow approach to dose escalation.

N009

**Not your average multiple myeloma.**

**Jo Cryer**<sup>1</sup>

<sup>1</sup>*St George Hospital, Kogarah, Australia*

Non secretory multiple myeloma is a rare condition. The literature states that 1-2% of all myeloma diagnoses are non-secretory myeloma and is reported to have a better prognosis.

KC is a married 44 year old woman who whilst surfing in Bali experienced back pain. On return to Australia she was investigated and diagnosed with multiple myeloma. It quickly became apparent that she would not follow the usual course of treatment and the team would have to reassess suitable treatment options in order to facilitate her to stem cell collection and autologous transplant. This case study will present the journey of KC from diagnosis and the challenges she faced. She had many bumps in the road but faced all of them with dignity and resilience.

N010

## **Retrospective study on bleeding rates for patient on direct oral anticoagulation (DOAC) therapy**

**Gemma Deves**<sup>1</sup>

<sup>1</sup>*Sir Charles Gairnder Hospital, Perth, Australia*

### **Aim**

To analyse if bleeding rates had improved for patients on DOACs at our hospital compared to an audit completed in 2015.

### **Method**

An audit was conducted on patients admitted to this single site tertiary hospital over a 12 month period with bleeding or who developed bleeding as an inpatient. Discharge summaries or procedure reports were reviewed for all patients. Patients were excluded from the study if there was no indication for anticoagulation therapy or if they were on subcutaneous, intravenous or warfarin anticoagulation. Only patients prescribed Rivaroxaban, Apixaban and Dabigatran were included in the audit. Demographics such as age and gender were reviewed as well as comorbidities, using the Charlson, CHA<sub>2</sub>DS<sub>2</sub>VASC and HASBLED scores and contributing factors eg. antiplatelet therapy. Patient notes were reviewed to see if they had received education on DOAC therapy. Patients were categorised as major bleeding or significant bleeding and if they required an escalation in care, critical care and/or blood transfusion.

### **Results**

Approximately 1456 patients were reviewed and 145 patients were found to be prescribed DOACs at the time of bleeding. Of these, 61% were male with 9.6% of patients being under the age of 65, 24.1% between 65-74 and 66.2% over 75 years. The bleeding rate was 9.9% of patients on DOACs. This compares to the previous hospital pharmacy audit, which demonstrated an improvement of 9%.

A number of patients had their anticoagulation ceased as result of bleeding. A small number of patients required blood transfusion, an escalation in care or critical care review or admit.

### **Conclusion**

Overall bleeding rates at this hospital have slightly improved. Ongoing patient education is required, however patients with comorbidities and risk factors for bleeding should be carefully assessed due to the risk of bleeding, hospital admission and the impact that has on individuals' lives.

## **Managing Hodgkin Lymphoma during a twin pregnancy; a case study**

**Tracey Dryden**<sup>1</sup>, Kylie Mason<sup>1</sup>

<sup>1</sup>*Victorian Comprehensive Cancer Centre, Melbourne, Australia*

Hodgkin Lymphoma is the most common lymphoma subtype diagnosed during pregnancy, occurring one in every 1,000 to 3,000 pregnancies<sup>1</sup>. Healthcare professionals involved in the care of women with Hodgkin Lymphoma concurrent to pregnancy, face the challenge of having to manage a potentially life-threatening disease whilst minimizing toxicity to the developing fetus and enabling it to reach full term<sup>1</sup>.

The evidence on managing Hodgkin Lymphoma in pregnancy is limited and based upon case-control series, retrospective reports with small numbers of patients and expert opinion. It indicates that it is possible to manage Hodgkin Lymphoma with pregnancy safely<sup>1</sup>. However, the available evidence in this setting is largely based on pregnancies involving a single fetus. Twin pregnancies are associated with a greater number of risks, including higher rates of preeclampsia, gestational diabetes mellitus, miscarriage, premature births and low birth weights<sup>2,3,4</sup>, and thus require further investigation.

This paper will discuss the experiences of a collaborative haematology and obstetric team, managing a first time mother, presenting with a large mediastinal mass confirmed to be Hodgkin Lymphoma at 12 weeks gestation with fraternal twins.

The focus of this case study is the issues and challenges faced by the team. These include disease staging and assessing treatment response in a setting where PET/CT is considered unsafe, establishing how and when to best treat, delivery of chemotherapy, facilitating a safe delivery, ensuring the emotional, social and informational needs of the patient and her family are addressed and enabling clear communication between the patient and the various healthcare professionals involved in her care.

The case study will explore the time from staging and commencement of treatment, through to the safe delivery of the twins and the subsequent restaging and completion of treatment. It aims to further inform the literature on managing Hodgkin Lymphoma in women during twin pregnancies.

1. Bachanova and Connors, 2013.
2. Coonrod, Durlin, Kangmin et al., 1995.
3. Rauh-Hain, Rana, Tamaz et al., 2008
4. Rode and Tabor, 2014

N012

## **Bringing Care Closer to Home for Subcutaneous Immunoglobulin (SCIg) Patients**

**Narelle Duncan**<sup>1</sup>

<sup>1</sup>*Canberra Health Services, Garran, Australia*

**Aim:** To further improve access, equity and 'quality of life' for patients receiving immunoglobulin in the ACT, under the National Blood Arrangements.

**Method:** Currently 41 subcutaneous immunoglobulin (SCIg) patients have their conditions managed by ACT medical specialists, 17 of which are residents from regional NSW. Our SCIg cohort of Immunology and Haematology patients is steadily expanding. Patients approved to receive SCIg must fulfil the eligibility requirements as published by the National Blood Authority (NBA) (<https://www.blood.gov.au/SCIg>). Eligible patients are then referred to the SCIg program. The SCIg nurse assesses whether the patient is physically and psychologically able to self-administer SCIg, or have a suitably competent carer to help manage their care.

The ACT SCIg nurse provides the initial one-on-one in-hospital training and induction session that introduces the patient to all aspects of their personalised SCIg therapy. The patient is discharged into the CSL Behring® Cares Program which provides a collaborative out-of-hospital clinical support of face-to-face sessions (up to 6 home visits) and phone support services. However, at all times, patients remain under the clinical oversight of the SCIg nurse and the Canberra Hospital.

**Result:** 10 patients were successfully inducted into the SCIg Pilot program in 2013/14, with 41 patients now receiving SCIg in the ACT. Since May 2019, there has been a 25% increase in enrolment of the CSL Cares Behring program.

From 1<sup>st</sup> of July 2019, we will begin piloting a free home delivery service for SCIg consumables.

**Conclusion:** Bringing care closer to home for SCIg patients will not only empower, but improve the patient's quality of life. A specialist care team monitors each SCIg patient's progress, and provides home visits and phone support where required. The introduction of the home delivery of consumables will be of particular benefit to our regional patients and we are not aware of any other SCIg program in Australia offering this.

N013

## **When malignant and non-malignant haematology collide in a complex case of primary refractory Hodgkin Lymphoma**

**Anita Edwards<sup>1</sup>**, Jenny Hempton<sup>1</sup>, Olivia Darby<sup>1</sup>

<sup>1</sup>*University Hospital Geelong, Geelong, Australia*

We report the case of a 25 year old nursing student (VL) presenting with dry cough and rash. CT chest showed bulky mediastinal lymphadenopathy causing tracheal deviation. Histology showed nodular- sclerosing Hodgkin Lymphoma (HL). Workup confirmed bulky Stage II unfavourable risk HL. Escalated BEACOPP<sup>1</sup> was commenced. Complete metabolic remission (CMR) was achieved after 2 cycles and treatment was de-escalated to 2 cycles of AVD<sup>2</sup> followed by 30Gy mediastinal radiotherapy.

PET scan performed 8 weeks post radiotherapy demonstrated recurrent disease within the radiation field. The ominous finding of primary refractory HL (PRHL) prompted consideration of novel salvage options. VL had ultra-high risk disease and her treatment pathway was underpinned by the need to offer every possible therapy advantage. VL proceeded to BeGEV<sup>3</sup> salvage chemotherapy, achieving CMR, and a consolidation autologous stem cell transplant (ASCT) with GemBuMel<sup>4</sup> conditioning followed. Brentuximab maintenance<sup>5</sup> commenced on Day 57.

With rigors of treatment now over, VL was enjoying a family break following her second cycle of maintenance Brentuximab when she presented to a rural hospital with dyspnoea and fevers. VL was transferred to us where she was admitted directly to Intensive Care Unit (ICU) with rapidly progressive respiratory failure, which continued to worsen despite intubation, broad anti-microbial cover and high dose steroids.

A two month ICU admission ensued with worsening multi organ failure, microangiopathic haemolysis and atypical haemolytic uraemic syndrome. Ventilatory, haemofiltration, and extracorporeal membrane oxygenation (ECMO) support was required, and approval to add Eculizumab was granted as the family were being prepared for VL's likely death. To everyone's relief subtle improvements were noted on day 26. By day 57 VL was transferred from ICU to the inpatient unit and subsequently finally discharged to rehabilitation 134 days after presentation.

This case study examines complex challenges faced by the multidisciplinary team involved in caring for VL during the course of her treatment and subsequent recovery, and how we can utilize knowledge gained to guide future practice.

1.Hodgkin Lymphoma BEACOPP escalated dose [www.eviq.org.au/haematology-and-bmt/lymphoma/hodgkin-lymphoma](http://www.eviq.org.au/haematology-and-bmt/lymphoma/hodgkin-lymphoma) accessed 10 June 2019

2.Johnson P et al, Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. *N Engl J Med* 2016; 374:2419-2429

3.Santoro, A. et al, Bendamustine in Combination with Gemcitabine and Vinorelbine Is an Effective Regimen as Induction Chemotherapy before Autologous Stem-Cell Transplantation for Relapsed or Refractory Hodgkin Lymphoma: Final Results of a Multicentre Phase II Study. *JCO* 2016 Sep 20;34(27):3293-9

4.Nieto y et al, Phase II Trial of High-Dose Gemcitabine/Busulfan/Melphalan with Autologous Stem Cell Transplantation for Primary Refractory or Poor-Risk Relapsed Hodgkin Lymphoma. *Biol Blood Marrow Transplant* 2018; 24:1602-1609

5.Moskowitz CH. et al. AETHERA Study Group. Brentuximab vedotin as consolidation therapy after autologous stem cell transplantation in patients with Hodgkin's Lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015;385(9980):1853-62

## Incidence of cardiac dysfunction (CD) at first visit in a dedicated allogeneic (allo) bone marrow transplant long term follow-up (LTFU) service.

**Ma Teresa Garcia**<sup>1</sup>, Yvonne Panek-Hudson<sup>1</sup>, David Ritchie<sup>1</sup>, Ashish Bajel<sup>1</sup>, David Routledge<sup>1</sup>, Ashvind Prabahran<sup>1</sup>

<sup>1</sup>Department of Clinical Haematology and Bone Marrow Transplant Services, The Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, Australia

**Background:** Studies stated an increasing number of post bone marrow transplant (BMT) survivors (estimated to be 500,000 worldwide). These patients may suffer unfavourable late effects from their treatment, such as CD, which is also described as the leading cause of morbidity and mortality post allo-BMT (Inamoto and Lee, 2017; Armenian et al., 2018).

**Aim:** To describe the incidence of cardiac dysfunction in patients at first review in a dedicated LTFU clinic.

**Method:** Using the ethics approved database of a single centre LTFU service, 438 individual patient data collected at first review from November 2014 to May 2019 was analysed to identify incidence of CD. This includes coronary artery disease, heart failure, atrial fibrillation and ischaemic heart disease, and correlated this data with TBI exposure and cumulative anthracycline dose.

**Results:** 39 (8.9 %) of these patients were found to have CD at first LTFU review. 18 (46.1%) of the 39 patients received both anthracycline and TBI; 13 (33%) received anthracycline only and 8 (20.51%) received TBI only (see Table 1 for breakdown).

Table1: Breakdown of treatment related cardiac dysfunction (allo-BMT LTFU)

Anthracycline cumulative dose (mg/m <sup>2</sup> )	Number of patients	Anthracycline + Total Body Irradiation (TBI) 12 and 13.2Gy	Number of patients
< 300mg/m <sup>2</sup>	6	< 300mg	5
300 - 500mg/m <sup>2</sup>	7	300 - 500mg	5
>500mg/m <sup>2</sup>	0	>500mg	1
No anthracycline dose	5	TBI only	7
Unknown anthracycline dose	3		

**Conclusion:** These findings provide the next steps and future opportunities to (1) compare to general Australian population, (2) modify LTFU guidelines on the frequency and modality of cardiac screening and time to specialist referral of BMT survivors, (3) modification to healthy lifestyle counselling and patient education, (4) point of care (cardiology) involvement in the LTFU model of care, and (5) future studies looking at biomarkers relevant to CD.

### References:

- Armenian, S., Yang, D., Teh, J., Gonzales, A., Wong, L., Leisenring, W., . . . Chow, E. (2018). Prediction of cardiovascular disease among haematopoietic cell transplantation survivors. *Blood Advances*, 2(14), 1756-1764. doi:10.1182/bloodadvances.2018019117
- Inamoto, Y., & Lee, S. J. (2017). Late effects of blood and marrow. *Haematologica*, 102(4), 614- 625. doi:10.3324/haematol.2016.150250

N015

## **Myeloma Australia telephone information and support line: a quality improvement project.**

**Jo Gardiner**<sup>1</sup>, Jacqui Keogh<sup>1</sup>, Nella Combe<sup>1</sup>, Hayley Beer<sup>1</sup>, Laura Jones<sup>1</sup>, Elli Foley<sup>1</sup>, Narelle Smith<sup>1</sup>, Geo Sobrio<sup>1</sup>, Kerin Young<sup>1</sup>

<sup>1</sup>*Myeloma Australia, Richmond, Australia*

### **Aim:**

- Explore experience of callers to Myeloma Australia (MA) Telephone Support Line, (TSL) focusing on met and unmet needs
1. Evaluate caller responses to guide service improvement

**Method:** over six months callers to this national service (convenience sample) were invited to complete an anonymous survey comprising 27 questions with comments available. Quantitative data underwent descriptive statistical analysis and qualitative data was thematically analysed.

### **Result:**

70 completed surveys revealed respondents' average age was 65 years, 80% had myeloma and 25% were diagnosed 3-5 years ago. 56% were receiving myeloma treatment. All states except Tasmania were represented, none from ACT or NT and 75% were from metropolitan areas. Main reasons respondents called were information about myeloma, general assistance (primarily local support groups), medications/drugs and resources. Over 50% were new callers to TSL and nearly 90% of respondents would use the service again, having had all or most of their needs met.

Main reasons for using TSL over other information sources were, access to specialist myeloma nurses and adequate time to talk. Positive comments included "*friendly, supportive, caring*"; "*an extremely valuable service, thanks you so much for being there- another key member of the team*". Comments indicating areas of improvement included "*would like service available on weekends*"; "*calls need to be returned within 24hrs*"; "*greater knowledge on integrative medicine/treatments would be helpful*".

### **Conclusion:**

TSL service is valued by respondents who were largely satisfied with their experience. This process is integral for continuous service improvement and results will guide further development. Respondents lived where MA have Myeloma Support Nurses based. Understanding who calls and why will also guide development of all MA patient resources and services. This project has confirmed the importance of TSL in helping meet needs of the myeloma community.

## **Estimating Prevalence of Impaired Skin surrounding Devices in cancer care: the preliminary results of a prospective study**

**Nicole Gavin**<sup>1,2,3</sup>, Margarette Somerville<sup>1</sup>, Amanda Ullman<sup>1,3,4</sup>, Tricia Kleidon<sup>3,4</sup>, Nicole Marsh<sup>1,3</sup>, Emily Larsen<sup>3</sup>, Jill Campbell<sup>1,2</sup>, Gabor Mihala<sup>3</sup>, Claire Rickard<sup>1,3</sup>

<sup>1</sup>Royal Brisbane & Women's Hospital, Herston, Australia, <sup>2</sup>Queensland University of Technology, Kelvin Grove, Australia, <sup>3</sup>Menzie Health Institute Queensland, Nathan, Australia, <sup>4</sup>Queensland Children's Hospital, South Brisbane, Australia

**Aims:** Skin complications caused by dressings are commonly reported in patients who have a central venous access device (CVAD). This study aims to describe the prevalence of CVAD-associated skin injury, in order to support the development of evidence-based solutions for their prevention and treatment, which includes improved site documentation.

**Methods:** A prospective, observational study of all in-patients with a CVAD in Cancer Care Services at the Royal Brisbane and Women's Hospital from April 2017 to March 2018. Patients were assessed by a research nurse twice a week.

**Results:** Three hundred and twenty-one adult patients with 422 CVADs and 627 admissions were included in this study. Three quarters (78%) of the patients were diagnosed with a haematological malignancy and the other quarter were medical oncology patients (22%). At the initial assessment patients were receiving chemotherapy (30%), radiotherapy (36%), steroids (25%) and immune suppression (1%). Half of the patients had a peripherally inserted central catheter (50%), a third had a tunnelled cuffed CVAD (35%) and the remainder had a totally implanted CVAD (15%). The patients were observed to have the following signs and symptoms: skin stripping, skin tears and blisters (6%), dermatitis (10%), bruising (12%), pressure injury (1%), itching (8%), erythema (4%) and oedema (3%).

**Conclusion:** This study is the first to report the prevalence of CVAD-associated skin injury in adults diagnosed with cancer. It has highlighted that skin complications are poorly documented by nurses and doctors in the medical record, making it difficult to ascertain which dressings and securement devices are ideally suited to individual patients. CVAD-associated skin injuries are potentially avoidable and require a cohesive approach to prevention and management.

N017

## **When Venesection Is Not An Option**

**Cassandra Hobbs**<sup>1</sup>, Jo Cryer<sup>1</sup>

<sup>1</sup>*St George Hospital, Kogarah, Australia*

Background: Hereditary hemochromatosis is a common genetic disorder affecting approx. 1 in 200 Australians. The C282Y gene fault means that individuals will have raised iron levels in their body, there is an increased absorption of iron from food, which if not treated leads to "iron overload". Organs that can be affected are Liver, Heart, Pancreas & joints. Excess iron is treated with venesection.

Mrs GS is 68yrs old. She presented to her GP with increasing fatigue. A full blood count & Liver function tests were taken. Indicating abnormal liver function. Ferritin: 643. Her father also had hemochromatosis & she is homozygous for the C282Y gene. Patient was referred to Australian Red Cross for venesection. She was referred back to St George Hospital as her venous access was too difficult. After two further failed attempts at venesection the pt was referred to the Apheresis Service for Red Blood Cell Depletion. Since referral 4 red blood cell depletions have been attended. This poster will highlight this pts response with regards to iron studies, Liver Function tests & quality of life

N018

## **Palliative Care Coffee Clinic: An Evaluation of Our Unique Service**

**Carol Hua-Yung**<sup>1</sup>, Alison Rowe<sup>2</sup>, Catherine Wood<sup>1</sup>

<sup>1</sup>Wellington Blood and Cancer Centre, CCDHB, Wellington, New Zealand, <sup>2</sup>Hospital Palliative Care Service, CCDHB, Wellington, New Zealand

**Aim:** Evidence suggests caregivers of patients undergoing allogeneic stem cell transplant experience high levels of distress. Early palliative care integration has shown to be supportive of both caregivers and patients. We initiated a unique coffee clinic. This clinic gives an opportunity for caregivers to meet up over coffee one-on-one with a palliative care nurse. An electronic questionnaire was sent to caregivers with the aim of evaluating the coffee clinic service.

**Method:** A ten question anonymous survey was sent to 50 caregivers of allogeneic stem cell transplant patients who were transplanted between 1/1/2017 to 31/12/2018 at Wellington Hospital, New Zealand. The questionnaire looked at caregiver age, gender, relationship to patient, home location, and whether they attended the coffee clinic. For those caregivers that did attend, they were asked about their clinic experience, including suggestions for improvement.

**Result:** Results will identify the impact of the clinic on caregiver distress and identify those most likely to benefit from the service. Results will also show factors which facilitate or inhibit uptake of the service.

**Conclusion:** Results will help us understand the caregiver perceptions of the clinic to guide development of the service to meet caregivers' identified needs. Results will also provide evidence of need to resource the coffee clinic appropriately.

N019

## **Take Care, the bottom Matters Too!**

**Eugenija Johnson**<sup>1</sup>

<sup>1</sup>*Alfred Health, Melbourne, Australia*

**Aim:** A significant number of patients with a haematological malignancy undergoing intensive chemotherapy treatment within the haematology and bone marrow transplant unit were experiencing distressing perianal symptoms such as discomfort, pain, burning, bleeding and tingling. Chemotherapy impairs the immune system, delays wound healing and disrupts the gastrointestinal tract which can lead to diarrhoea, mucositis and malnutrition<sup>1</sup>. Examination of the skin around the perianal region by a wound nurse consultant identified incontinence associated dermatitis as a result of the exposure of faecal fluid to the surface of the skin. The aim was to prevent and reduce perianal skin breakdown by implementing a consistent approach to perianal skin care on the unit for haematology patients undergoing intensive chemotherapy treatment.

**Method:** A nurse-led quality improvement activity was designed to gain an understanding of the impact of incontinence associated dermatitis. Current perianal care practices were reviewed and 19 patients were surveyed to evaluate their understanding and experience of this issue. An evidence-based chemotherapy care education bundle was subsequently developed and provided to patients with a specific section focusing on perianal care. Flushable wipes and sudocream were included within the care bundle.

**Results:** 28 patients were assessed following the implementation of the chemotherapy care bundle. 100% of patients reported receiving information on perianal care compared to 52% pre-implementation. There was a reduction of patients experiencing distressing perianal symptoms from 68.4% to 42% post-implementation together with a reduction of symptom severity.

**Conclusion:** The implementation of the chemotherapy care bundle with specific education around perianal care has positively impacted the patient experience with a reduction in the development and severity of perianal skin breakdown. Patients felt empowered with information and it enabled them to actively participate in preventing and managing this distressing side effect.

1. Reference: <https://www.cancer.org.au/about-cancer/treatment/chemotherapy.html>

N021

## **Collaborative communication is key to delivering better patient outcomes in acute bone marrow transplant and haematology patients**

**Amy Keating**<sup>1</sup>, Midori Nakagaki, David Williams, Peter Frederikson

<sup>1</sup>RBWH, Ascot, Australia

### **Aim:**

Acute haematology and bone marrow transplant (BMT) patients are at risk of many hospital complications secondary to disease and anticancer treatments. Haematology patients are at high risk of developing venous thromboembolism (VTE), central venous access device (CVAD) complications and experiencing falls or skin integrity incidents. Interdisciplinary communication which includes the patient is said to be a pathway to better patient health outcomes. There is often varied standards of communication used amongst healthcare teams, resulting in inconsistency and lack of standardization. The BMT unit at the Royal Brisbane and Women's Hospital (RBWH) is often under pressure to triage patient's treatments due to lack of bed availability, patient flow is an important function of an acute tertiary environment.

### **Method:**

The Haematology and BMT unit at RBWH has implemented Structured Interdisciplinary Bedside Rounds (SIBR) into their daily care routine. The routine involves members from the interdisciplinary team and occurs at the patient's bedside. A communication protocol is followed and the team arrive prepared. The round includes a customized quality safety checklist which addresses potential risks specific to haematology patients.

### **Result:**

Data was collected retrospectively twelve months pre and twelve months' post implementation based on patient and staff experience, clinical patient outcomes and patient flow effects. Results showed that staff felt patients were safer, more satisfied and clinical deterioration was detected earlier. Some staff felt that SIBR was at times underrepresented by certain disciplines. There wasn't a significant difference in falls incidence or medical emergency response calls. VTE prophylaxis compliance was significantly improved by 57 percent, medication errors decreased from 7.3 to 5.1 per month. Average length of stay for BMT patients was reduced by 11% and re-admission rates were halved.

### **Conclusion:**

Structured communication will improve staff satisfaction and patient outcomes. All healthcare teams should consider their communication approach as an avenue to better health care delivery.

## **Myeloma Special Practice Network (M-SPN): Leading best supportive care**

**Tracy King**<sup>1,2</sup>, Julija Sipavicius<sup>2,3</sup>, Daniela Klarica<sup>4</sup>, Carmel Woodrow<sup>5</sup>, Hayley Beer<sup>6,7</sup>, Kerin Young<sup>7,8</sup>, Jacqueline Jagger<sup>9</sup>

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**Background:** Patients with multiple myeloma (MM) are living longer with a chronic, complex cancer that adversely impacts health related quality of life. As part of the multidisciplinary team (MDT), specialist nurse roles incorporate patient education; delivering complex therapies; managing disease and treatment adverse effects; provision of patient support, coordination and navigation within complex environments, whilst remaining up-to-date. The Haematology Society of Australia and New Zealand (HSANZ) Nurses Group formed a Myeloma Special Practice Network (M-SPN) with a primary objective to improve nursing care quality and outcomes for individuals with MM.

**Aim:** We describe projects undertaken by the M-SPN that promote patient-centred supportive care.

**Method:** A mapping exercise identified existing MM resources. Gaps were identified, and new content prioritised for development by group consensus. Project leads and working groups were established. A successful grant application supported medical writing/formatting input. Physician colleagues and patients reviewed content and members provided feedback before final proof.

**Results:** Three nurse guidelines were written: 1. Bortezomib and 2. Daratumumab providing consensus on administration and patient management. Daratumumab guideline is published in peer review journal and referenced by eviQ. 3. The 'Myeloma Information Pathway' links to reliable up-to-date resources. A guide to implement a business case for MM Nurse Specialist roles was adapted from the Myeloma UK document. A patient resource 'Understanding Tests and Investigations' was also developed. myINTERACT platform supports the myeNURSE app enabling member access to MM resources via hand held devices or desktop. Guidelines listed accessible via HSANZ website.

**Conclusion:** MM resources were developed to support nurses working within the speciality. The myeNURSE app provides ready access at point of care to these resources; supporting nurses to remain current in a complex and changing practice environment. Future work includes an online patient treatment scheduler as a tool for education and aid medication adherence.

## **Development of the steroid symptom questionnaire – multiple myeloma (SSQ-MM): Item generation and preliminary validity**

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**Background:** Steroids play a central role in the treatment of multiple myeloma (MM), and are recognised to cause a wide range of side effects. Tools exist to measure symptoms in MM but not the impact of steroids. The Dexamethasone Symptom Questionnaire Chronic (DSQ-C) was developed to determine the burden of symptoms experienced by patients given dexamethasone for moderately emetic chemotherapy.

**Aim:** Adaption of the DSQ-C in a multiple myeloma population (DSQ-MM). Item generation and preliminary validity.

**Methods:** Phase I: Understand what is known about the impact of steroids associated with therapy for MM. Phase II: Adaption of the DSQ-C for a MM population. Phase III Test the tool in a multi-centre cross sectional study. This abstract presents findings from Phase II.

**Phase II:** Findings from phase I informed preliminary item generation/omission from original DSQ-C. Expert patient and clinician groups were utilised with purposeful sampling to form representative groups. Patient/carer group completed the draft tool then attended a focus group interview. Clinicians completed an online survey scoring each item for relevance followed by a group tele-conference. Items within the DSQ-MM were added, reworded or removed in accordance with findings.

**Results:** Clinician expert group (n=10) included nurse specialists, psychologist, pharmacists, haematologists and a nurse academic. The consumer group (n=8) included 5 patients and 3 of their spouses. There was a high level of agreement from both groups as to content of DSQ-MM. Qualitative responses lead to further refinement including the renaming of the tool to 'Steroid Symptom Questionnaire Multiple Myeloma' (SSQ-MM). All members of the expert groups were in agreement on the final content of SSQ-MM.

**Conclusions:** The development of a psychometrically sound SSQ-MM has the potential for improving steroid toxicity management and to improve treatment outcomes for this patient group. Psychometric properties are being tested in a larger multi-centre cross sectional study.

N024

## **Normal body temperature in clinical practice: A historical perspective**

**Christine Mackey**<sup>1</sup>

<sup>1</sup>*Edith Cowan University, Joondalup, Australia*

**Aim:** To identify the original research for the basis of the normal body temperature range that is used in clinical practice today.

In clinical practice body temperature is used as a key indicator or criteria in various health assessments and many clinical decisions are based on an individual's recording. Recent literature suggests that there is some debate around the normal body temperature of humans as there is not a definitive definition but rather a range of varying parameters. According to American College of Critical Care Medicine and the Infectious Diseases Society of America the normal human temperature is considered to be 37 °Celsius (C), but may vary by up to 1°C in healthy individuals, whereas other literature propose a variation of 0.5°C depending on the individual, their age and the time of day. Yet where does that figure come from and where is the evidence to support this?

### **Methods**

The researcher undertook a historical literature review to source the original evidence underpinning the accepted range for normal body temperature.

### **Findings**

On reviewing the literature it appears that the data used to base the accepted 'normal body temperature' dates back to studies undertaken in the 19th century and to date it is argued that it has not been thoroughly challenged since that time.

### **Conclusion.**

Body temperature has been an indicator of both good health and illness since ancient times and is often constitutes the basis for deciding whether or not to initiate treatment. This presentation will present the findings from this literature review highlighting some of the implications to consider in clinical practice.

### **Iron deficiency and iron infusion. A quality of life survey.**

**Shirley Nicholl**<sup>1</sup>, Claire Allen<sup>1</sup>, Kylie Elliott<sup>1</sup>, Carin Henson<sup>1</sup>, Lynne Power<sup>1</sup>, Ramdas Tampi<sup>1,2</sup>, Paul Kruger<sup>1,3</sup>, Colleen May<sup>1,4,5</sup>, Glen Lichenberger<sup>1</sup>

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Iron deficiency is the most common nutritional deficiency. It is a condition affecting people of any age, or stage in life. It is an easily rectifiable cause of anaemia. Patients often present with symptoms of fatigue or poor cognitive function that impact on their quality of life.

This iron infusion clinic designed a study to look at the impact Iron deficiency has on the patient's quality of life, rather than their ferritin and haemoglobin levels.

Patients, who were referred to the clinic, completed a questionnaire rating their physical symptoms and answered two further questions asking about their energy levels and the impact this had on every day function.

270 patients completed the initial questionnaire, and 122 patients completed the second questionnaire 4 weeks post infusion. The pre and post infusion responses were compared, and will be presented.

The response values were calculated using total sum scores and demonstrated a decrease in symptoms the patient experienced. The scores also showed a decrease when the median scores were compared.

The sample was not large enough to show a statistical difference in the outcomes for patients.

The results of the study suggest that impact on a patient's quality of life should also be assessed when addressing their iron deficiency.

A further study is to be undertaken to compare pre and post quality of life questionnaire results and haematological and biochemical parameters.

N026

## **EMPOWER: existing onsite faint prevention strategies will work if routinely implemented**

**Justine O'Donovan**<sup>1</sup>, Rena Hirani<sup>1</sup>, Barbara Bell<sup>1</sup>

<sup>1</sup>*Australian Red Cross Blood Service, Alexandria, Sydney, Australia*

**Background/Aim:** The Australian Red Cross Blood Service employs registered nurses and trained phlebotomists to collect over 1.3 million donations annually from approximately 500,000 voluntary non-remunerated blood donors. Blood donation is universally regarded as a safe procedure but is not without risk. Pre-faints and faints (vasovagal reactions (VVRs)) are the most common complication related to blood donation. In 2016/2017, 1.9% of Australian blood donors experienced a VVR. Of these, 7% experienced a loss of consciousness. VVRs most commonly occur during needle insertion, at the time of needle removal and shortly following completion. This study aimed to audit and improve implementation of evidence-based interventions to reduce VVRs.

**Methods:** A faint prevention checklist was used at 8 blood collection centres to determine which of the 72 possible interventions were being routinely implemented. The interventions analysed included donor safety signage, staff education, the application of applied muscle tension (AMT) and fluid loading. Based on the checklist findings, directed implementation of some interventions (AMT and fluid loading) was conducted for a further 4 weeks.

**Results:** Interventions such as couch position, were used routinely (~80% of the time) by the blood collection staff. Other interventions such as fall prevention strategies, education for recognising VVR onset, fluid loading and AMT were poorly used (~50% of the time). When directed interventions (AMT and fluid loading) were implemented there was an overall reduction in VVRs of 0.11%.

**Conclusions:** The use of directed intervention did improve the rate of VVRs in some centres. Staff members indicated the interventions were helpful and have continued to use them. The intervention materials are being implemented nationally for all donor centres to improve the overall blood donation experience and donor safety outcomes.

## **Integrating shared survivorship care into an Allogeneic BMT long term follow up clinic**

**Yvonne Panek-Hudson**<sup>1</sup>, David Ritchie<sup>1</sup>, Sue Hookey<sup>1</sup>, Tricia Wright<sup>2</sup>, Kylie Mason<sup>1</sup>, Sarah O'Leary<sup>3</sup>, Louise Chard<sup>1</sup>

<sup>1</sup>Peter Maccallum Cancer Centre & Royal Melbourne Hospital, Melbourne, Australia, <sup>2</sup>Latrobe Regional Hospital, Traralgon, Australia, <sup>3</sup>North Western Primary Health Network, Melbourne, Australia

**Background:** With successful developments in disease control and management of early toxicity, allogeneic bone marrow transplant (AlloBMT) outcomes continue to improve resulting in increased numbers of patients achieving eligibility for long term follow up (LTFU) care. It is recognised that survivors face a significant burden of chronic health conditions and late toxicities. These require comprehensive, and evidence- based assessment, surveillance and treatment<sup>1</sup>. Traditionally this care has been provided in quaternary centres by a dedicated LTFU team. A successful Victorian Cancer Survivorship Program grant was utilised to pilot a primary care provider (PCP) shared care model of survivorship care for eligible patients post AlloBMT.

**Aim:** 1.To assess the feasibility & acceptability of shared survivorship care after AlloBMT in an established hospital based LTFU service.  
2. To pilot a shared survivorship model for eligible patients

**Method:** 1. 250 patients and PCP pairs were surveyed to determine feasibility and acceptability of shared survivorship care. 16 patients were identified and consented to semi structured interviews focussing on acceptability of a shared care model of survivorship care. An eligibility tool based on post allograft complexity criteria was tested & implemented.  
2. 10 existing LTFU patients were identified as eligible to participate in a pilot to transition to shared survivorship care.

**Results:** 1. Application of eligibility tool, patient and PCP surveys identified approximately 60% of patients suitable for shared survivorship care.  
2. Pilot evaluation demonstrated high satisfaction with (1) quality of information provided in preparation for shared care review (2) ongoing willingness to participate in shared care (3) confidence in provision of shared survivorship care by PCP.

**Conclusions:** This paper will discuss the feasibility & acceptability by AlloBMT patients and PCPs to participate in shared survivorship care. Resource development including eligibility tool, modified care plans, education video, clinical placements and rapid access portal will be described, and resource and communication challenges will be discussed.

- Bhatia,S (2014). Caring for the long-term survivor after allogeneic stem cell transplantation. ASH education book. December 5, 2014 vol.2014 no.1 495-503

N028

## **Supporting nursing staff to care for people with a haematological malignancy who receive a lumbar puncture via development of an assessment tool**

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<sup>1</sup>Royal Brisbane and Women's Hospital, Herston, Australia, <sup>2</sup>Queensland University of Technology, Kelvin Grove, Australia

**AIM:** To develop a nursing assessment tool and patient discharge information sheet in support of nurses caring for patients with a haematological malignancy undergoing a lumbar puncture (LP) with/without intrathecal chemotherapy. The aim is to improve the detection and management of post-dural puncture headache.

**METHOD:** Using a co-design iterative process, an LP diagnostic / therapeutic nursing assessment tool and patient discharge information sheet were developed. The assessment tool was initially developed based on current clinical tools and was informed by academic literature. The tool focused on supporting nursing care of patients pre- and post-procedure, with an emphasis on patient assessment and post-dural puncture headache. The tool was refined through repeated cycles of multi-disciplinary feedback between nursing, medical, and pharmacy staff, and taken before the safety and quality unit and the hospital forms committee. The tool was piloted in a busy out-patient unit at the Royal Brisbane and Women's Hospital and data was collected on completion rates by nursing staff. The patient discharge information sheet was developed via a similar process to support patient education given by nursing staff prior to discharge.

**RESULT:** The nursing assessment tool covered the domains of pre-procedure assessment, post-procedure assessment, discharge and post-procedure assessment (by phone or in person 48-hours after lumbar puncture) and contained an itemised checklist. Preliminary data demonstrates nursing staff completed 78-100% pre-procedure assessment, 56-78% of post-procedure assessment and discharge, and 33-44% of post-procedure follow-up.

**CONCLUSION:** Early results are favourable in support of the continued use and development of the LP diagnostic / therapeutic nursing assessment tool and patient discharge information sheet. Feedback mechanisms are being used to improve documentation post-procedure, which will ultimately improve patient outcomes.

N031

## **Subcutaneous immunoglobulin (SCIg) program increases choice for regional patients**

**Debbie Regester**<sup>1</sup>, Laurie Newman<sup>1</sup>, Rosemary Parker<sup>1</sup>

<sup>1</sup>*Latrobe Regional Hospital, Traralgon, Australia*

### **Introduction:**

In Victoria over 1500 patients meet the criteria for SCIG for Immunoglobulin replacement. Blood Matters (May 2019) reported 193 patients currently enrolled in the program with 26 accessing from regional centres.

Latrobe Regional Hospital (LRH) patients currently receiving Intravenous Immunoglobulin (IVIg) identified various barriers to attending for treatment and embraced the opportunity for choice regarding their treatment.

**Aim:** To provide regional patients with equitable access to treatment for their immunodeficiency.

### **Method:**

Phase 1: LRH accredited as SCIG provider. Clinical guidelines developed. Patients provided information about SCIG and options for treatment. 'CSL Behring cares' patient support program utilised as an additional 24-hour resource and for guidance at first home treatment. Training of staff and patients commenced

Phase 2: Service expanded to patients from peripheral hospitals in the region

Phase 3: Provide dispensing service to local patients receiving SCIG at tertiary centres.

**Results:** 10 patients were identified as being eligible for SCIG. Patient's participating in the program identified greater work flexibility, increased travel opportunities and time burden associated with monthly appointments as reasons for switching treatment. Some patients chose to continue with IVIg as concurrent treatments at the hospital or enjoyed the social connection of visiting the infusion centre.

Current SCIG patients travel an average of 52km each way to LRH monthly for treatment ranging from 16-74km. Prior to offering this service, patients wishing to access SCIG would travel approximately 150km extra each way for treatment at a metropolitan SCIG approved site.

**Conclusion:** Successful commencement of SCIG program in March 2019 has 3 patients complete training and competently providing their own treatments; with ongoing interest from surrounding smaller hospitals. The program has provided patients with increased flexibility and choice, improved work attendance and interstate travel opportunities, as well as enabling the day unit to provide further services to other patients in the region.

N032

## **CLABSI Monitoring; Is it all in vein? Don't trust your gut!**

**Alexandra Rivalland**<sup>1</sup>, Hayley Page<sup>2</sup>, Laura Brunt<sup>3</sup>

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### **Aim**

This study examined the incidence of central line associated bloodstream infections (CLABSI) and mucosal barrier injury bacteraemia (MCIB) amongst acute leukaemia and allogeneic stem cell transplant (HSCT) patients, by looking at incidence of BSI in Haem/BMT patients with a long term central venous access device (CVAD). Secondly, the study compared clinical characteristics and rates of premature CVAD removal between patients identified with CLABSI and MCIB.

### **Method**

Data was collected prospectively from all patients who were treated under Haematology or Bone Marrow Transplant units at the Royal Melbourne Hospital between January 1 2018 and May 31 2019 who grew positive blood cultures. CLABSI and MCIB were determined using CDC and VICNISS definitions. In order to reduce bias, three independent reviewers appraised the data and applied the definition. CVAD insertion and removal date and reason, blood culture specimen collection date, and relevant pathology were recorded. A CVAD was defined as any peripherally inserted central catheter (PICC), a tunnelled CVAD (HICKMAN), or an implanted CVAD (Port-a-Cath). Patients without a CVAD and any organisms cultured from peripheral venepuncture sites were excluded from the analysis. A retrospective audit of electronic medical files collected demographic and clinical data of those patients identified with a bacteraemia.

### **Results**

49 CLABSI were identified over a period of 15480 Line days yielding a rate of 3.16‰ with a mean of 3 per month. The most common organisms were staphylococcus haemolyticus (n=7) and pseudomonas aeruginosa (n=13). 78 MCIB were identified with a mean of 4.5 and a median of 4. The most common organisms were Klebsiella pneumoniae (n=23) and Escherichia coli (n=18). Neutropenia and mucositis were the most common clinical feature contributing to this with a few cases of grade 3-4 graft versus host disease (n=3). Premature line removal was compared amongst these two groups.

### **Conclusion**

This study identified the significant burden of MCIB and CLABSI in this cohort of vulnerable patients. The clinical impact of premature line removal highlights the need for evidence-based prevention guidelines in this cohort.

N033

## **Current Learnings from the CSL Cares Patient Support Program for administration of Subcutaneous Immunoglobulin (Hizentra® or Evogam®) in the home setting**

**David Tognarini Tognarini<sup>1</sup>**, Kathryn Fenton<sup>1</sup>, Sherif Youssef<sup>1</sup>

<sup>1</sup>*Aesir Health, Cheltenham, Australia*

Subcutaneous immunoglobulin (SCIg) is a growing treatment option to intravenous immunoglobulin for patients with Primary Immune Deficiency (PID) or Secondary Immune Deficiency (SID). SCIg infusions are available to patients with education and training to allow for administration in the home setting. In order to support patients using SCIg (Hizentra® or Evogam®) as they transition to the home a patient support program, CSL Cares was established. Aesir Health was commissioned as an independent provider to deliver the program using qualified registered nurses.

To assess the effectiveness and quality of the program, we conducted a review on a cohort of patients initially enrolled. The program aims to ensure patient competency in SCIg self-administration through assessments such as, handling medication, aseptic technique, injection site selection and preparation and infusion of SCIg.

The group consisted of 36 patients enrolled across Australia, 19 patients with PID and 17 with SID. The average age of patients was 58.2 years (with a range 20- 80 years). Twenty-six patients had converted from IVIg treatment and 10 were started directly on SCIg. Some patients had initial training sessions by their treating hospital while others were new to SCIg administration and directly enrolled into the CSL Cares program. The average number of training sessions per patient to achieve competency with self-administration of their SCIg treatment was 2.8 visits. At the time of this analysis 9 patients had completed a feedback questionnaire focusing on knowledge of preparation and administration pre and post program training visit experience.

Analysis of a small cohort of patients in the CSL Cares program has shown effectiveness of the program in these 36 patients. A more robust analysis will be possible with further experience and will help with understanding patient needs and support ongoing convenience of home-based education for patients.

## **Integrated Management of Post Remission Leukaemia to Optimise longevity and Enhance Quality of Life: the IMPROVE longitudinal study**

**Catherine Vassili**<sup>1</sup>, Kirsty Rady<sup>2,1</sup>, Catriona Parker<sup>3</sup>, Shaun Fleming<sup>1</sup>, Andrew Wei<sup>1</sup>

<sup>1</sup>Alfred Health, Prahran, Australia, <sup>2</sup>Canberra Hospital, Canberra, Australia, <sup>3</sup>Monash University, Melbourne, Australia

Intensive chemotherapy for newly diagnosed acute myeloid leukaemia and acute lymphoblastic leukaemia is associated with considerable treatment-related morbidity and mortality, resulting from a combination of patient, disease, and treatment factors. The toxicity of acute leukaemia therapy is well appreciated, and there is now increasing interest in understanding the impacts of therapy on physical, psychological, social and financial (PPSF) functioning after completion of intensive therapy, particularly in adults not proceeding to allogeneic stem cell transplant (AlloSCT).

**Aim:** To implement a longitudinal follow-up program in the acute leukaemia cohort after intensive chemotherapy incorporating the systematic collection of clinical and patient relevant data. We hypothesise that the early identification of impaired PPSF functioning will allow risk assessment strategies such as appropriate and timely referrals for intervention/s to improve overall patient outcomes.

**Method:** A multidisciplinary team of clinicians, a nurse practitioner, physiotherapist, a social worker and a researcher have collaborated to establish this program. Patients aged  $\geq 18$  years who have completed intensive therapy, achieved complete morphological remission and are not proceeding to AlloSCT in first remission, are eligible to participate. Patients will be reviewed 3 monthly for 24 months in a dedicated IMPROVE follow-up clinic. Endpoints include the identification of; minimal residual disease, cardiotoxicity, reduced fertility and sexual well-being, osteopenia, neuropathy, metabolic dysfunction, immune dysfunction, physical fitness, patient reported outcomes (including quality of life, fatigue, sleep quality, anxiety and depression), financial toxicity, and identification of familial cancer syndrome risk.

**Discussion:** The lessons learned from establishing the IMPROVE clinic will be presented. The clinic opened for recruitment in February 2019 and to date eleven patients have consented to participate. Recruitment is ongoing. Several patients have completed review at two time points and have had significant findings which have resulted in early referral and/or clinical intervention. Preliminary findings will be available for presentation in October 2019.

N036

## **Best dosage and route of topical lignocaine to improve patient comfort and tolerability during the insertion of an enteral tube: a systematic review**

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### **Aim:**

Enteral Tube Insertion (ETI) can be an uncomfortable, painful procedure for patients particularly when patients have received myeloablative therapy and the integrity of their mucosa is compromised. Pain control during insertion is often not adequate or implemented. The aim was to review randomised controlled trials (RCT) that compared the use of topical lignocaine for ETI.

### **Method:**

Electronic databases were searched using the Medical Subject Headings. Primary outcomes were patient reported outcomes of pain and discomfort during ETI. Secondary outcomes of nasal bleeding were assessed.

### **Results:**

No studies were conducted in haematology patients; therefore, the inclusion criteria were expanded to include other populations. Eight RCTs were conducted in the emergency department: 7 in adults and 1 in paediatrics comprising of 620 patients. Seven studies reported improved patient reported outcomes of decreased pain and discomfort, when lignocaine was administered during ETI and compared to placebo. However, there was inadequate consistency of dose, route, time and method of administration. No studies compared different doses or routes. Two of the RCTs used phenylephrine nasal spray to vasoconstrict the vessels in the nasopharynx. There were no episodes of epistaxis in either the intervention or placebo group in either study.

### **Conclusion:**

The use of lignocaine is beneficial in reducing pain and discomfort during ETI. The literature is lacking evidence to determine the best dose, route and method of administration of lignocaine. The use of phenylephrine in haematology patients during ETI will potentially reduce the incidence of epistaxis and should also be considered in future studies. Consequently, this review concludes that further research and RCTs are required to determine the optimal lignocaine dose, route and method of administration to implement into clinical practice.

N037

## **Nurse Initiated Electrolyte Protocols for the Haematology inpatient**

**Trish Wise**<sup>1</sup>

<sup>1</sup>*Austin Health, Heidelberg, Australia*

**Aim:** The development and implementation of consensus-based nurse initiated electrolyte replacement protocols into a 32-bed Haematology and Bone Marrow Transplant inpatient ward.

**Background:** Electrolyte levels in this patient cohort and the potential consequences of timely replacement are well recognised by staff working in this specialty. However, despite this recognition there is variability between clinicians and like-units in how they manage electrolyte replacement in terms of ideal replacement thresholds and how replacements are prescribed.

**Method:** A prospective, single-ward examination into electrolyte administration practices in a large tertiary referral hospital in Melbourne. Clinical audit was used to allow for prospective data collection and analysis, conversations with colleagues were also used to gauge a better understanding of current organisations clinical governance and quality control systems. The objective of the audit was to identify the time of administration of intravenous Potassium and Magnesium. A re-audit will occur in early October after the protocol has been incorporated in to practice for 12 weeks.

**Result:** The findings into electrolyte administration practices indicated that 65% of Potassium and Magnesium replacement occurred during the morning nursing shift (0700-1530), with the majority of this occurring approximately seven to eight hours post the blood sample being sent to pathology. Importantly, one quarter (25%) of all electrolyte replacement was administered on the evening nursing shift. Only 11% of administrations occurred on nightshift (2100-0730) after being initiated by the availability of routine daily blood test results.

**Conclusion:** Implementation of nurse initiated electrolyte replacement protocols in the haematology specialty required the generation of consensus guidelines to standardise the clinical approach to electrolyte replacement orders. These guidelines present evidence-based recommendations for the electrolyte homeostasis management for the inpatient haematology setting with confirmation of expert opinion regarding thresholds from biochemistry and the appropriate consultants. The creation and use of nurse initiated magnesium and potassium protocols appear to be safe and effective within the public health sector.

N038

## **Incidence of viral URTI**

**Maddison Wright**<sup>2</sup>, Hannah Pahl<sup>2</sup>, Mingdi Xie<sup>1,2</sup>

<sup>1</sup>Peter MacCallum Cancer Centre, Melbourne, Australia, <sup>2</sup>Royal Melbourne Hospital, Parkville, Australia

### **Aim**

Viral upper respiratory tract infections (URTI) in patients after an allogeneic haematopoietic stem cell transplant (allo-HSCT) are common. With possible lead to lower respiratory tract infections (LRTI) and subsequent bacterial pneumonia, there is potential for readmissions, delay in recovery post allograft, and deaths.

We sought to analyse the sequelae of viral URTI in post allo-HSCT patients and their subsequent outcome in order to facilitate better patient education and preventative measures.

### **Method**

Retrospective data of 147 patients in our institution 6 months post allo-HSCT, between September 2017 and May 2019 are collected. Data collected include pathology results for viral nasal/throat swabs, number of re-admissions, length of stay (including ICU stay), treatment and outcome.

### **Results**

52 patients had positive pathology viral nasal/throat swab results returned. 22 patients had more than one positive result, 15 patients had a second or third virus isolated which is different from the virus isolated in the previous swab. Data of treatment such as Oseltamivir and/or subsequent IVIG, as well as mortality are also analysed.

### **Conclusion**

Patients with swab-positive viral URTI are associated with later pulmonary GvHD, and can affect their daily living activities in the future post allograft.

Viral URTI can largely be prevented; it could be a significant burden both medically and financially on inpatient ward and the hospital, it also puts distress on patients and their carers.

Patient education including appropriate adherence to vaccination schedule in combination with early symptom identification can aid in the better management of these infections.

N039

## **Complex care pathway: a specialist nurse-led All-In-One service**

**Mingdi Xie**<sup>1,2</sup>

<sup>1</sup>Peter Maccallum Cancer Centre, Melbourne, Australia, <sup>2</sup>Royal Melbourne Hospital, Parkville, Australia

### **Aim**

Ambulatory care for patients immediate after an allogeneic haematopoietic stem cell transplant (allo-HSCT) can be very complex. Patients and their carers spend a lot of time waiting around for blood tests, appointments and treatment, at the same time trying to juggle the transition from inpatient to ambulatory setting, the waiting time is demoralising. We thought to develop a specialist nurse led pathway, to shorten patients' waiting time and reduce confusion, thus improve patients' experience at the hospital.

### **Method**

Model of care used to be: Blood tests in pathology -> review in clinic -> treatment in day therapy unit.

Complex care pathway involves a dedicated chair/bed space within Day Therapy Unit (DTU) for an allo-HSCT patient for an extended period of time (usually 4-6 hours), who have blood tests, medical/nursing review based on complexity and clinical presentation, and any other treatment all in that time and space. It allows these patients to be observed more closely, clinical needs addressed in a more efficient way, and significant reduced time in waiting.

### **Result**

The benefits of these pathways are

- Better patient experience
  1. Reduced clinical risks
  2. Reduced stress in pathology
  3. Reduces Emergency department stress
  4. Better relationship development between OP nurses and patients& their carers;
  5. Forecast planning for DTU patient flow

Current waiting times are limited to

1. After checking in with DTU reception
2. Pathology results readiness

### **Conclusion**

Patients have reported they felt safe and much more convenient since introduction of the pathway. It could be modified and used in other complex patient groups.

The limitation of the pathway is increasing number of patients, that the chair space is blocked for other patients to use. The next step is a proposed dedicated complex care clinic/unit for these patients.

**Tandem Glycosorb®-ABO column apheresis/dialysis procedures for pre-renal transplantation patients to reduce time at hospital and therefore improve quality of life.**

**Romony Jeans**<sup>1</sup>, Justin Gerace<sup>1</sup>, Ashley Irish<sup>1</sup>, Anastazia Keegan<sup>3</sup>, Shane Gangatharan<sup>1</sup>, Marian Sturm<sup>2</sup>, Nyrene Jackson<sup>1</sup>, Marion Bamblett<sup>1</sup>, Karen Siu<sup>1</sup>, Anne Warger<sup>1</sup>

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**Background:** Glycosorb®-ABO column apheresis reduces serum anti-A and anti-B titres, facilitating blood group-incompatible kidney transplantation from living donors. Since 2016, our institution has safely and efficiently performed Glycosorb®-ABO column apheresis in tandem with renal dialysis for pre-renal transplantation patients, reducing time spent at hospital, and improving quality of life.

**Aim:**

- To monitor patient safety whilst performing pre-renal transplant Glycosorb®-ABO column apheresis in tandem with renal dialysis.
1. To confirm adequate removal of patients' blood group-specific antibodies to acceptable pre-transplant titre levels (1:8).
  2. To reduce potential for infection by reducing the frequency of accessing patients' vascaths.
  3. To observe for reduction in patients' time spent in hospital.

**Method:** The Glycosorb®-ABO column apheresis procedures were coordinated with patient's renal dialysis appointments 3 times per week, for 4-9 pre-transplant procedures. Pre- and post-apheresis anti-A/B titre levels were measured on each occasion. The apheresis nurse attended the dialysis unit and connected the Spectra Optia Apheresis System either directly into the dialysis circuit or via Y-connectors on the patient's vascath. 3-4 plasma volumes were processed via the Glycosorb®-ABO column over 3-5 hours concurrently with dialysis. An inlet speed of approximately 60mls/min was maintained, with a starting inlet:AC ratio of 25:1, progressively reducing to 50:1 as the patients were anticoagulated via the dialysis circuit.

**Results:** A total of 18 tandem procedures across 3 patients have been successfully performed to achieve required pre-renal transplantation anti-A or anti-B titre levels of 1:8 or below. No increase in adverse events have been noted with tandem procedures compared to stand-alone procedures. The apheresis and dialysis nurses safely manage the tandem procedures as a team.

**Conclusion:** In dialysis-dependant patients prior to renal transplantation, Glycosorb®-ABO column apheresis in tandem with renal dialysis is safe and efficient, reduces patient time in hospital by up to 6 hours per apheresis procedure and may improve quality of life.

**References:**

1. Fiona Stanley Hospital apheresis data
2. Glycorex Transplantation ([www.glycorex.se](http://www.glycorex.se))

N041

## **Current Nursing Workloads and Implications for the Future within Haemophilia Treatment Centres in Australia.**

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Patients with haemophilia and other bleeding disorders require specialist management. In Australia, Haemophilia Treatment Centres (HTC's) have a multidisciplinary team (MDT) to manage these patients. In a changing environment of care, these centres are constantly evolving to encompass new treatments and technologies often with little or no increase in resources.

### **Aims:**

To determine, through comparison of historical data, how HTC workloads and nursing responsibilities have changed.

Analysis of current resources, nursing responsibilities, and expectations to identify workload implications.

### **Methods:**

The Australian Haemophilia Nursing Group (AHNG) were invited to examine their centres by completing a questionnaire which was followed by more focussed questioning. Details collected included types of patients, patient numbers, working hours for nursing, medical, allied health and data administration/clerical alongside reviewing nursing roles. Adult and paediatric centres were looked at separately.

The collected data was compared with historical data to see comparison of resources and changes in workload.

Roles and responsibilities were compared to findings of a 2016 global survey of Haemophilia nurses roles and responsibilities.

### **Results:**

There is significant variation between centres, their resources, MDT involvement, and their patient numbers.

Most have significant input in surgeries with many HTC's coordinating care of patients being treated outside the HTC hospitals.

Clinical trials occur in most centres with or without input from specialist clinical trial nurses. It was also identified there was difficulty finding time for nursing led research across the centres.

The data suggests increased workloads with minimal changed resources to accommodate these increases. The current roles seen in the data collected are in keeping with those identified in a survey on global roles.

### **Conclusion:**

There have been many changes and increases in the demands to the role of the Haemophilia nurse.

Strategies to overcome the identified implications are required at both a national and international level.