Blood 2022

ABSTRACT BOOK

2022 Annual Scientific Meeting

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The combined Annual Scientific Meeting of the:

HSANZ Haematology Society of Australia and New Zealand

ANZSBT Australian & New Zealand Society of Blood Transfusion Ltd

THANZ Thrombosis & Haemostasis society of Australia and New Zealand

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Oration Presentations

Barry Firkin Oration: Platelet receptors: expression, function and shedding

Dr Robert Andrews

Extensive research over several decades has studied the structure and function of adhesion receptors expressed on anucleate platelets, and the mechanisms of how these receptors regulate bleeding and thrombus formation in flowing blood using a wide range of experimental approaches, model systems and analysis of human healthy donor and patient samples associated with a wide range of haematological diseases. As key examples, the platelet adhesive receptor glycoprotein (GP)Ib-IX-V complex, comprised of transmembrane GPIbα disulfide-linked to GPIbβ forming a complex with GPIX and GPV, is an important receptor for binding of von Willebrand factor (VWF) associated with subendothelial matrix or in plasma when exposed to high shear stress, and also the receptor, GPVI which also forms a complex with GPIb-IX-V and binds collagen and other ligands. GPIb-IX-V and GPVI are vital for normal platelet function, and defects of these receptors can cause bleeding/thrombotic complications. Detailed analysis of the biochemistry and amino acid sequences and the structure-function of these receptors using a variety of analytic methods, antibody generation, and assays for expression and platelet activation and adhesive function has identified specific domains involved in ligand binding, complex formation with other receptors, cytoplasmic domains recognizing intracellular cytoskeletal or signalling proteins, and other key interactions regulating expression or function of these receptors. In addition, additional studies have identified and purified specific proteins from rattlesnake, cobra or viper venoms that can either induce VWF binding to GPIbα, or cleave GPIbα and inhibit VWF binding, or bind to GPVI and activate platelets, or lead to shedding of GPVI from platelets. Importantly, further studies have also identified cytoplasmic amino acid sequences in GPIb, GPV and GPVI that bind to intracellular calmodulin, which was subsequently found to regulate ectodomain receptor shedding by membrane-associated A-Disintegrin-And-Metalloproteinase (ADAM) sheddases, including ADAM17 that cleaves GPIbα and ADAM10 that cleaves GPVI. Subsequent studies then investigated the ADAM10-mediated ectodomain shedding of GPVI generating soluble GPVI (sGPVI) in terms of pathways regulating this process, and developing specific reagents and assays for analysing sGPVI levels in human blood plasma and ADAM10 activity on platelets, and how these vary under conditions of elevated shear stress in experimental models and also in patient samples with platelet dysfunction and altered bleeding or thrombotic risk. Ongoing studies are continuing to investigate the regulation of GPIb-IX-V and GPVI expression, function and shedding, and future relevance as biomarkers or therapeutic targets. The recent developments regarding GPIb-IX-V and GPVI effectively illustrate how basic research based on new observations and discoveries can develop over time, leading to new insights and understanding of complex biological systems

Carl de Gruchy Oration: A Haematological Journey – Opportunity, Serendipity and Diversity

Prof P. Joy Ho

The attraction of Haematology for many lies in its diversity. As a career starts, one often aspires to incorporate all aspects – to become a "renaissance haematologist". With the explosion of knowledge, few if any can be proficient in all domains. The Red Cell, White Cell, Clotting, Clinical and Laboratory divides have become more prominent. However, proficiency and diversity are not mutually exclusive – I contend that one should aspire to make a career rewarding, for oneself, one's team as well as patients, by making it more diverse yet specialized, to have "more than one string to one's bow"; to find a meaningful and rewarding experience not only in the manifold subjects, but by "cross-fertilization" through colleagues and ideas from different sub-specialties. Serendipitously, this diversity characterized my career.

I encourage all haematologists to look for more than one "pigeon-hole". Classical Haematology in Globin research taught me the importance of opportunistic science. What is the patient asking us? Can we see the question? For me, the in vivo "patient experiments" tied in seamlessly with in vitro gene expression systems, asking questions and providing solutions in a reciprocal and complementary manner, seen in aspects of my globin work on the 5'untranslated region, RNA processing and nonsense-mediated decay. Interrogating the phenotype to genotype relationship continues to enhance our understanding and practice. In the clinical care of thalassemia, we are at the dawn of transformational change. While optimising iron chelation remains an important focus, it is evolving from "simple" chelation to targeted molecular therapy. The emphasis of my unit is moving from treating the sequelae of disease to correcting the underlying genetic defect. Major advances include gene therapy and molecules which target ineffective erythropoiesis. For the first time, on the horizon, we have therapies which aim for cure.

Serendipitously, just as I had "dived into" and became immersed in thalassemia, I then had the opportunity to join a myeloma team which I grasped with enthusiasm, and adopted as "another string to my bow". From the first analysis of IgH translocations in primary multiple myeloma (MM) samples, we expanded to gene expression and now to massive parallel sequencing. Immunologically, we have extended clonal T cell analysis by flow to mass cytometry and single cell RNA sequencing. We have shown that the balance between CD69- and CD69+ Terminal effector T cells (T_{TE}) may regulate anti-MM responses and contribute to clinical heterogeneity. We found in newly diagnosed MM that skewing of bone marrow memory T cells towards the effector (T_{TE}) phenotype is restricted to an infiltrating CD69- subset which may affect anti-MM immunity. In clinical care, we must not refrain from examining those difficult patients with the greatest need and the highest risk in clinical trial eg. patients with renal failure exhibiting suboptimal response. It is necessary to overcome the "one-size-fits-all" pathways even if unpopular. Setting up a robust minimal residual disease assay by next generation flow cytometry has led to the investigation of circulating MM cells as an early marker of disease response, and hopefully, risk-adapted therapy. As we re-expand our molecular capacity, noting the findings of molecular "triple hit MM", we have developed a novel 34-gene massive parallel sequencing panel incorporating clinically significant mutations, including those recently detected by whole genome and exome sequencing, to identify patients with the worst prognosis, for whom novel therapies may be of the greatest benefit.

One of the significant highlights of my career has been the advent of Chimeric antigen receptor-T (CAR-T) cell therapy. I have been privileged to lead a world-class Haematology team as one of the first units in Australia to perform this therapy in clinical trial, and to continue this transformational therapy as a standard of care. In continuing state-of-the art clinical trials, and to be able to offer patients a therapeutic option where there had previously been none, must be the most precious opportunity and deeply meaningful experience, for both doctor and patient, in any haematological journey.

In my opinion, the greatest satisfaction in professional life comes from service - first and foremost, service to patients as the primary objective, and to colleagues and the team. For me, the opportunities to serve in diverse collegial settings have been a highlight – in HSANZ, Joint specialist advisory committee for training of the next generations of haematologists, ALLG for clinical trials, Myeloma Australia, International Myeloma Society and Foundation, International Members' committee for the American Society of Hematology, and in government working groups, I have experienced the beauty of altruistic efforts working towards a common goal.

Opening Symposium

Factors associated with outcomes of CAR-T cell therapies for B cell malignancies

Prof Cameron Turtle

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. Using data from a large phase I/II clinical trial of CD19 CAR-T cell immunotherapy (NCT01865617) we will discuss factors associated with outcomes of CAR-T cell therapy in adult B cell malignancies. The impact of lymphodepletion chemotherapy on CAR-T cell engraftment and immune rejection, mechanisms of failure of CAR-T cell immunotherapy, and ex vivo leukapheresis T cell and manufactured product characteristics associated with outcomes will be presented.

Creating customised iPSCs with rare blood group antigen combinations as renewable sources of red cell reagents

Dr Stella Chou

Red blood cell (RBC) transfusion is a common therapy for individuals with sickle cell disease (SCD) and thalassemia. Alloimmunization to foreign Rh proteins (RhD and RhCE) on donor RBCs remains a challenge for transfusion effectiveness and safety. With hundreds of *RH* variants now known, precise identification of Rh antibody targets is hampered by the lack of appropriate reagent RBCs with uncommon Rh antigen phenotypes. Using a combination of human induced pluripotent stem cell (iPSC) reprogramming and gene editing, RBCs derived from these iPSCs (iRBCs) can be a renewable source of cells with unique Rh profiles to facilitate the identification of complex Rh antibodies. These incude Rh null RBCs or those that express specific Rh antigens such as RhD alone (D--), Go^a+, or DAK+. The iRBCs are compatible with standard laboratory assays and can determine the precise specificity of Rh antibodies in patient plasma. These renewable red cell reagents have the potential to provide a valuable diagnostic tool for use as an adjunct to current antibody identification panels, particularly for patients with SCD.

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Combined Symposiums

Access to viral specific T cells in Australia (with David Gottlieb)

Dr Andrea Henden

Adaptive immune control of viral infection in the immunocompromised state is impaired through functional and numeric cellular perturbations. Effective viral immunity requires contribution from both humoral and cellular compartments including B cell and T cell populations, both of which are impaired in the immunosuppressed state. Restoration of T cell dependent immunity can be achieved through infusion of virus specific T cell preparations, derived from patients or from third party matched banked T cells. Clinically, access is available in Australia to numerous virus specific products through both academic and commercial channels. The range of products routinely available and their clinical use and utility will be discussed in addition to novel clinical trials providing access to COVID-19 specific T cells for patients at risk of severe COVID-19 disease.

Obstetric iron deficiency, why the controversy?

Dr Lisa Clarke

Anaemia is the well-recognised, widely accepted consequence of untreated iron deficiency. The two diagnoses however are not synonymous with the effects of tissue iron deficiency felt long before the development of anaemia. Unfortunately, iron deficiency in the absence of anaemia remains underappreciated and goes largely undiagnosed and untreated. In adults iron deficiency is associated with both physical and neuropsychological manifestations such as lethargy, altered mood, poor concentration and diminished wellbeing. Fetal and neonatal iron deficiency has been associated with impaired neurocognitive development with lasting effects despite iron replacement in early life. This session focuses on the pathophysiology of obstetric iron deficiency, highlighting the non-erythropoietic roles of iron, the detrimental effects of tissue iron deficiency to both mother and infant and the need for widespread iron optimisation in pregnancy.

Gene and targeted therapies in the haemoglobinopathies: are we heading towards a cure?

Prof P. Joy Ho

The management of beta-thalassemia and sickle cell disease over past decades have mainly concentrated on the treatment of disease sequelae of these single gene diseases. For many years, transfusion and iron chelation were the main therapeutic modalities in beta-thalassemia, while in sickle cell disease, hydroxyurea was the only available agent that could modulate the pathophysiology of sickling. While stem cell transplantation provided some patients with the chance of cure, this was restricted in application due to demographics (especially age), co-morbidities and resources. In recent years, tremendous progress has been made in therapies directed towards the genetic cause and pathophysiology. Most prominently, gene addition and gene editing have led to the correction and modulation of the effects of genetic mutations in beta-thalassemia and sickle cell disease. While significant risks can be associated with gene therapy such as the impact on fertility, the potential risk of insertional mutagenesis and the financial risk to the community, these must be weighed against potential benefits. Our experience in gene therapy by gene addition in two patients with beta-thalassemia major has provided an important understanding of both the transformational nature of the therapy as well as its risks. Molecular and other therapies are being developed at great pace, targeted at multiple mechanisms in disease pathophysiology. Some have already been evaluated in clinical trials, and are approved in some jurisdictions, such as the erythroid maturation agent Luspatercept for thalassemia; and for sickle cell disease, Crizanlizumab (antibody to P-selectin), Voxeletor (inhibitor of HbS polymerization) and L-glutamine to reduce oxidative stress. Many others are in the process of development with diverse actions. For example, while agents such as hepcidin mimetics, allele-specific nucleotides to TMPRSS6, and ferroportin small molecule inhibitors have been designed to modulate iron metabolism, this may lead to the amelioration of ineffective erythropoiesis, the primary pathogenic mechanism in thalassemia. Mitapivat, an allosteric activator of red cell-specific pyruvate kinase, has been shown to have activity in both thalassemia and sickle cell disease, through the increase of ATP, with the additional mechanism of reduced 2,3-DPG and improved oxygen affinity in preventing sickling. Molecules targeting the upregulation of HbF (eg phosphodiesterase-9 inhibitors, benserazide and others) are at different stages of development with varying success. This session provides the opportunity to describe some of these exciting developments including our experience, and evaluate their possible impact on thalassemia and sickle cell disease.

Beyond factor replacement in haemophilia

Prof Huyen Tran

Until recently, intravenous factor concentrate was the only available therapy for the treatment of haemophilia. Though effective, this is associated with 1) an increased risk of inhibitor development, where immune tolerance induction failure is not uncommon and effective treatment for patients with chronic inhibitors was lacking; 2) significant inconvenience as prophylaxis resulting in suboptimal adherence among some patients leading to breakthrough bleeds and potentially damaging haemophilic arthropathy. Emicizumab, a humanised bi-specific FIXa/FX antibody recently became the first non-factor replacement therapy (NFRT) available in Australia that is administered subcutaneously and effective for haemophilia A patients with or without inhibitors. Other NFRTs that aims to “recalibrate” haemostasis and appears to be effective for both haemophilia A and B are currently under evaluation in clinical trials. Adeno-associated viral (AAV) vector haemophilia gene therapy targeting hepatocyte expression of FVIII or FIX, aims to provide durable factor expression and long-term bleed prevention offer a once off therapy.

Difficult transfusion cases in individuals with sickle cell disease

Dr Stella Chou

Difficult transfusion cases in individuals with sickle cell disease

Red cell therapy remains a key intervention in the acute and chronic management of patients with sickle cell disease (SCD). While transfusion therapy reduces SCD-associated morbidity and mortality, alloantibody formation and associated acute and delayed hemolytic transfusion reactions (DHTR) can pose significant challenges in transfusion management, and thus, prevention is key. Prophylactic Rh and K, or more extended antigen matching decreases the rate of alloimmunization but does not completely eliminate new alloantibody formation. We will address the prevention and management of red cell alloimmunization in patients with SCD including the role of molecular diagnostics for red cell antigen typing, donor matching, and transfusion support of alloimmunized patients. Lastly, the transfusion management of patients at high risk or experiencing an acute or delayed HTR will be discussed.

Management of pregnancy in the patient with sickle cell disease

Assoc Prof Kylie Mason

Pregnancy in a woman with sickle cell disease carries a high risk for complications for both mother and infant that range across the spectrum of perinatal complications including pre-eclampsia, IUGR, placental insufficiency and abruption. Optimum management starts with planning including genetic counselling and optimisation of maternal health and continues through pregnancy with coordinated multidisciplinary care. Our experience demonstrates that with careful management, successful pregnancy outcomes can be achieved in the majority of patients

Closing Symposium

Non-invasive prenatal testing (NIPT) - RhD immunoprophylaxis and beyond

Dr James Daly

Since 2019, the Lifeblood Red Cell Reference Laboratory has government approval to provide Non-Invasive Prenatal Testing (NIPT) for fetal RHD genotype in alloimmunised pregnant women. In these women, the test determines if the fetus is at risk of haemolytic disease of the fetus and newborn (HDFN) and guides the management of the pregnancy. Following successful development of a droplet digital PCR assay by the Lifeblood R&D team, this NIPT testing service is now being expanded to include testing for other fetal blood group genotypes including RhC, c, E, K, Fy^a, Fy^b for pregnant women with the corresponding red cell alloantibodies. Lifeblood R&D are currently investigating the use of Next Generation Sequencing of cell free DNA using a customised panel to enable fetal blood group genotyping of other blood groups or multiple blood groups.

NIPT for RHD can also be used more broadly to screen all RhD negative pregnant women after 11 weeks of pregnancy to enable targeted rather than universal RhD-immunoglobulin prophylaxis. Targeted antenatal RhD-Ig prophylaxis would avoid 2 antenatal injections of RhD-Ig at 28 and 34 weeks pregnancy (and following potentially sensitising events) in the approximately 37% of women who are shown to be carrying an RhD negative fetus.

Current evidence (and Australian Guidelines) supports the safety and cost effectiveness of a targeted antenatal RhD-Ig prophylaxis program in Australia and NIPT for RHD has been added to the Medicare Benefits Schedule (MBS) from 1st July 2022. However, the test is not yet widely available for pregnant women in Australia.

HSANZ Invited Speakers

Improving therapeutic response to hypomethylating agents

Prof John Pimanda

Hypomethylating agents (HMAs) are the backbone of pharmacotherapy for the treatment of myelodysplastic neoplasms (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia when patients are unfit for intensive chemotherapy. HMA therapy is not curative and clinical improvement is not accompanied by clearance or major shifts in mutant clones in the bone marrow of patients with MDS and CMML. I will show evidence that suggests that these therapies act predominantly as differentiation agents that are permissive to productive haematopoiesis from mutant clones and discuss combinatorial strategies to improve response to HMA therapies.

Molecular landscape in aggressive B cell lymphomas

Dr Colm Keane

Diffuse Large B cell lymphoma (DLBCL) was one of the first cancers to have a molecular classification described. These initial steps indicated a basic separation into ABC and GCB subtypes over 20 years ago. Up until recently this was still the main classification for defining the molecular basis of DLBCL but had limited clinical utility.However, advances in genomic sequencing have recently provided new insights into the biology of the disease and there is emerging evidence that these will be important in the future management of DLBCL. This talk will discuss these new classifications and how this will impact the diagnostic classification and treatment stratification moving forward

Sequencing therapies in relapsed Chronic Lymphocytic Leukaemia

Dr Mary Ann Anderson

The advent of novel agent therapy for CLL has transformed patient outlook over the last decade with less toxic and in many cases more effective treatment options available for patients. With the proliferation of new treatment modalities open questions remain regarding the best ways to sequence these new therapies to buy the patients the longest possible period of good quality life. In Australia treatment decisions are often impacted by PBS re-imbursement for novel agents. The novel agents currently reimbursed in Australia include the: Burtons Tyrosine kinase inhibitors (BTKi) ibrutinib and acalabrutinib (relapsed / refractory [RR] CLL); the Pi3 kinase inhibitor (Pi3Ki) idelalisib (RR CLL) and the BCL2 inhibitor venetoclax (upfront and RR).

In the front-line treatment of CLL Resonate 2 demonstrated a clear benefit in terms of progression free survival (PFS) for ibrutinib over chlorambucil (*Burger, Leukemia, 2020*). Ibrutinib in combination with rituximab also has a superior PFS to fludarabine, cyclophosphamide and rituximab (FCR) (*Shanafelt, NEJM, 2019*) in the front-line setting. The value of rituximab when added to ibrutinib however remains unclear with data suggesting that it does not significantly prolong response (*Burger, Blood, 2019*). Among older patients with treatment naive disease and co-existing morbidity venetoclax + obinutuzumab (VO) confers a superior progression free survival over chlorambucil + obinutuzumab (*Fischer, NEJM, 2019*). For younger fit patients FCR remains an effective long-term option for those without adverse genetic features (*Thompson, Blood, 2016; Eichorst, Lancet Oncol, 20166; Rossi, Blood, 2015*). However, the toxicities of FCR in particular myelodysplasia and infection alongside the relatively short PFS seen with adverse genetics mean that its role is diminishing. For patients with adverse genetics novel agent therapy is preferred wherever available to FCR.

In RR CLL Venetoclax + rituximab (VR) is superior to chemoimmunotherapy (CIT) (*Seymour, NEJM, 2018*). Similarly, BKTi therapy is superior to CIT in RR CLL (*Ghia, JCO, 2020*). In RR CLL Venetoclax and the BTKi have similar PFS and overall survival (OS) (*Eyre, Haematologica, 2021*) which is clearly superior to the PFS seen with idelalisib based therapies (*Mato, Ann Oncol, 2017; Ghia, JCO, 2020*). As a result of which idelalisib tends to be reserved for patients who have previously been exposed to venetoclax and BTKi and CIT is generally avoided where possible for the management of RR CLL. There is a paucity of good data to guide the choice of BTKI vs venetoclax in the treatment of RR CLL and generally the choice of product is guided by patient co-morbidities and the toxicity profile of the drugs. Patient preference for time limited (venetoclax) vs continuous (BTKi) therapy is also a relevant consideration. Importantly however given that venetoclax is successful in salvaging BTKI failure (*Byrd, JCO, 2021*) and BTKis are effective at salvaging venetoclax failure (*Lin, Blood, 2020*) the sequence of venetoclax / BTKi is less important.

We are fortunate to now have access to an array of effective treatments for CLL and sequencing decisions are directed by evidence (table 1).

Table 1: *Potential approach to sequencing in CLL.*

	Young and fit	Older and Comorbid
Front line	FCR reasonable if good genetics features. Novel agent therapy has favourable early efficacy and toxicity to FCR in this group. Access off clinical trials can be challenging. If adverse genetics novel agent therapy is preferred	Venetoclax + obinutuzumab BTKi therapy is also reasonable where available
Second line	Venetoclax may be preferred for patients with hypertension or on anti platelet / anti coagulants. May also be preferred if desire for time limited therapy. BTKi may be preferred for patients with bulky disease	
Third line	Venetoclax if previously BTKI exposed BTKi if previously venetoclax exposed	
Beyond third line	Idelalisib is an available option Clinical trials are appropriate Consideration of Allograft	

Upfront treatment of myeloma

Dr Georgia McCaughan

Upfront treatment of myeloma

The treatment landscape for multiple myeloma is evolving rapidly. This presentation will review the treatment of newly diagnosed multiple myeloma with a focus on the Australian therapeutic context.

ANZSBT Invited Speakers

Reducing transfusion errors

Ms Rachel Moss

In 1996 the first annual report was published from SHOT (Serious Hazards of Transfusion), a newly established haemovigilance scheme for the UK. Although safety measures within the blood manufacturing process had made substantial improvements in the 1990s, during the same time period less progress had been achieved in maintaining patient safety during the transfusion process. That initial report was a milestone for transfusion practice both in the UK and internationally, as it triggered not only a whole new focus on transfusion safety for the patient receiving the transfusion, but it was a driving force for the Transfusion Practitioner role. Fast forward to 2022 where SHOT has celebrated their silver jubilee and published their 2021 report. The report addresses that in 25 years there has been a substantial reduction in the number and severity of incidents which is attributed to learning from incidents and dissemination of information. Yet SHOT state that there remains “a low but persistent, fluctuating level of both errors and near-misses”
This talk will consider the current thinking on approaching errors in healthcare, and some practical ideas for some of the more persistent transfusion problems.

Rachel Moss, Senior Transfusion Practitioner
Great Ormond Street hospital for Children NHS Foundation Trust, London, UK

Washed red cells for neonatal transfusion – Where to Next?

Assoc Prof Michael Stark

Washed red cells for neonatal transfusion – Where to Next?

Packed red blood cell (PRBC) transfusion exposure increases the incidence of significant morbidity and mortality in preterm newborns. Historically, this was thought to relate to co-morbidities in the transfusion recipient. We, and others, have shown that even following leukodepletion, PRBCs remain biologically active. Our data has shown increases in both pro-inflammatory cytokines and measures of endothelial activation post-transfusion, effects that increase with repeated transfusion exposure. Critically, we have shown that these pro-inflammatory immune responses to transfusion in preterm infants can be modified when PRBCs are washed prior to transfusion. It has also been recognised that donor characteristics such as sex impact prognosis, including potentially outcomes for preterm newborns exposed to PRBCs. These observations have been largely based on retrospective data, with little attention given to the biologically plausible mechanistic pathways that could underlie these associations. The next step is to undertake a large, Australia wide data linkage study to confirm if donor sex is related to neonatal outcome following PRBC transfusion. This will then inform a series of coordinated studies both in vitro and within the clinical setting to investigate if donor sex influences the immune response to PRBC exposure in the preterm newborn, and whether this was modifiable by the use of washed versus unwashed PRBCs.

Challenges in plasma self sufficiency: the Dutch experience and future plans

Dr Cynthia So-Osman

Challenges in plasma self sufficiency- the Dutch experience and future plans

Due to the growing demand of immunoglobulins, which is the main driver of the need for donor plasma, there is an ongoing need to increase donor plasma collection worldwide, including the Netherlands. The ultimate goal is to reach 100 % self-sufficiency, which presently is up to 60% in the Netherlands, varying widely between countries. In this presentation Dr Cynthia So-Osman will discuss the challenges to expand plasma supply on a national basis, and will share new initiatives on expanding plasma collection, on how to gain more insight in plasma demand, and to create more awareness among clinicians in usage of this valuable resource from preferably non-remunerated donors.

The Monocyte Monolayer Assay (MMA): predicting when clinically significant really is clinically significant

Miss Alison Badger

The Monocyte Monolayer Assay (MMA) is an in vitro procedure used to assist in predicting if incompatible blood can be transfused safely to a patient. This testing is useful for antibodies to a high incidence antigen or antibodies for which a specificity cannot be determined, or for those with variable reports of clinical relevance. It can be particularly relevant in cases where antigen negative blood is in limited supply or unavailable.

A particular focus for NZBS implementing the MMA is the effective use of rare red cells. With the incidence of anti-Jk3 in New Zealand being reasonably high, and the supply of Jk(a-b-) red cells being requested globally, it would be pertinent to know if the use of Jk(a-b-) red cells is required on all occasions or if this rare blood supply could be utilised more efficiently.

Evidence of changing demographics – glycophorins and MNS

Prof Robert Flower

Evidence of changing demographics – glycophorins and MNS
Prof Robert Flower, Clinical Services and Research, Australian Red Cross Lifeblood

The 50 antigens of the MNS system are found on Glycophorin A, Glycophorin B and hybrid glycophorins such as GP.Mur. The system includes 4 polymorphic, 10 high prevalence and 36 low prevalence antigens. The complex genetics are a result of gene duplication followed by crossing over and gene conversion. Demographic changes in the distribution of MNS antigens has occurred previously in Australia as Indigenous Australians have a considerably higher frequency of homozygous N than Caucasians. The B-A-B hybrid GP.Mur is most prevalent in East Asia and many Australians were born overseas or have a parent from an East Asian country. In screening for individuals carrying a hybrid glycophorin anti-Mi^a is the most useful antisera as it is found on most hybrids of interest. In Australia 0.22% of donors were found to be Mi^a pos with GP.Mur the most frequently detected. In Asian donors in the USA a rate of 2.2% was found. In addition, hybrid glycophorins have been found in India but at a much lower rate that East and SE Asia. GP.Dantu, a GP(B-A) hybrid found mainly in African ethnic groups, confers natural resistance against Plasmodium falciparum infection with a 40% reduction in the risk of severe malaria. Genotyping MNS hybrid glycophorins is complex as the genetic changes in homologous genes can be difficult to interpret. In summary, hybrid glycophorins previously highest frequency in East Asian ethnic groups now have a wide distribution. As a result of these changing demographics availability of Mi^a positive RBC (Gp.Mur) is an increasing requirement to assist in identification of antibodies of unknown specificity.

Evidence of changing demographics - Australian ABO/RhD types and demand for phenotyped red blood cell units

Dr Rena Hirani

Australian Red Cross Lifeblood has seen an increased demand for O negative red blood cell units and phenotyped units over the last 5 years. We have also released some data on the changing blood group demographics nationally, which shows that Australia is becoming more Rh(D) positive. Having accurate national data to understand blood demand enables supply forecasting so what does this all mean for future collections and supply of blood products to match patients?

The transfusion medicine research roadmap

Dr Cynthia So-Osman

EHA roadmap/research priorities in adults

In 2016, the European Hematology Association (EHA) published the EHA Roadmap for European Hematology Research aiming to highlight achievements in the diagnostics and treatment of blood disorders, and to better inform European policy makers and other stakeholders about the urgent clinical and scientific needs and priorities in the field of hematology, written by experts in the field. In the 5 years that have followed, advances in the field of hematology have been plentiful. Dr Cynthia So-Osman will provide an overview including some highlights of the research priorities in adult Transfusion Medicine, defined in this recently updated and published roadmap [1].

References:

1. The EHA Research Roadmap: Transfusion medicine. S. J. Stanworth et al. HemaSphere 2022;6:2 (e670). *http://dx.doi.org/10.1097/HS9.0000000000000670.*

Patient blood management redux: a vagabond scholar's perspective

Prof James Isbister

Patient blood management (PBM) ensures a patient's blood is acknowledged and managed as a goal directed standard of clinical care in all medical and surgical settings thus contributing to optimising individual patient outcomes. As a corollary to PBM allogeneic blood transfusion is minimised or avoided. Stewardship of altruistically donated blood ensures a valuable and costly human and community resource is used ethically and appropriately.

PBM is not a specific intervention but a multidisciplinary bundle of clinical care that is a parallel and iterative component of a patient's clinical pathway for all disciplines of medicine and surgery. PBM addresses the questions, "*What is the status of the patient's blood*?" "*If abnormal, what is the diagnosis and management*?" and "*If allogeneic blood transfusion is considered, are there no effective and safe alternatives*?" There are valid reasons to implement non-transfusion default policies when there is clinical uncertainty and debatable evidence for effectiveness for allogeneic blood transfusion.

PBM is not new, it was addressed and practiced towards the end of the 19th century. William Harvey had earlier emphasised in his 1628 treatise, *De Motu Cordis*, the importance of blood above all other body systems. John Snow, James Simpson and William Morton introduced anaesthesia in the 1840's. Louis Pasteur discovered germ theory in 1861 and Joseph Lister researched inflammation in 1857, haemostasis in 1891 and introduced antisepsis in 1865. These were the precursors to the recognition of the importance of PBM.

By the end of the 19th century PBM was a clinical focus as manifest by several 1899 publications: *"The importance of blood examinations in reference to general anaesthetization and operative procedures"*, "*Post-partum haemorrhage: its treatment, anticipatory and actual" and "The saving of blood in gynaecological operations"*. William Osler advocated examination of the blood and integrated routine pathology laboratories into hospitals. What is now referred to as the three pillars of PBM were already being addressed and implemented in perioperative care prior to Karl Landsteiner's discovery of the ABO blood groups and subsequent development of allogeneic blood transfusion.

Role of the Transfusion Practitioner in patient blood management

Ms Rachel Moss

The Transfusion Practitioner (TP) role was born from both a safety and haemovigilance culture, where the greatest identified risk to the patient undergoing a transfusion was human error. From this initial trigger for improved safety, the TP role has evolved into a multifaceted, highly specialised role, involved in both patient blood management (PBM) and transfusion processes. As the transfusion paradigm shifted from product to patient, the TP role evolved to include PBM, with an emphasis on the patients and the impact transfusion has on them. A multidisciplinary team is required to drive both PBM and transfusion, and the TP is now recognised as a critical link within that team. They are a driving force for change, bridging the gap between the laboratory and the clinical arenas. This talk outlines the vital role that the TP plays in helping establish and embed PBM that then improves patient and safety outcomes.

Rachel Moss, Senior Transfusion Practitioner
Great Ormond Street hospital for Children NHS Foundation Trust, London, U

Towards a systematic approach for (de)implementation of patient blood management strategies

Dr Cynthia So-Osman

Being up to date with current research is important for all institutions. However, it may be a challenging to incorporate patient blood management (PBM) recommendations from evidence based guidelines into daily practice. Dr. Cynthia So-Osman will discuss implementation strategies to incorporate PBM recommendations into hospital practices including the effectiveness of these options in changing medical practice. Dr. So-Osman will furthermore apprise the audience of her own experience in evaluation implementation strategies using a cluster RCT approach.

THANZ Invited Speakers

Platelet gene expression and functional responses during COVID-19

Prof Matthew Rondina

Thrombotic complications in patients with COVID-19 are common and contribute to organ failure and mortality. Patients with severe COVID-19 present with hemostatic abnormalities that mimic disseminated intravascular coagulopathy associated with sepsis, with the major difference being increased risk of thrombosis rather than bleeding. Dr. Rondina will present data on the altered platelet gene expression and functional responses in patients infected with SARS-CoV-2. RNA sequencing demonstrates distinct changes in the gene-expression profile of circulating platelets of COVID-19 patients. Pathway analysis revealed differential gene-expression changes in pathways associated with protein ubiquitination, antigen presentation, and mitochondrial dysfunction. The receptor for SARS-CoV-2 binding, angiotensin-converting enzyme 2 (ACE2), was not detected by messenger RNA (mRNA) or protein in platelets in some, but not all, studies. As mRNA from the SARS-CoV-2 N1 gene can be detected in some platelets from COVID-19 patients or during infection, platelets may take-up SARS-COV-2 mRNA independent of ACE2. Resting platelets from COVID-19 patients had increased platelet activation and platelet-leukocyte interactions, compared with healthy donors. Furthermore, platelets from COVID-19 patients aggregated faster and showed increased spreading on both fibrinogen and collagen. The increase in platelet activation and aggregation could partially be attributed to increased MAPK pathway activation and thromboxane generation.

Why do we need to diagnose Bleeding Disorder of Unknown Cause (BDUC)?

Prof Ross Baker[1,2,3] and James S. O' Donnell [3,4,5]
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Recent studies have demonstrated that only 30% of patients referred for assessment of a possible bleeding tendency will eventually be diagnosed with a recognised mild bleeding disorder (MBD) such as von Willebrand disease or platelet function defect. Instead, many such patients will be diagnosed with Bleeding Disorder of Unknown Cause (BDUC).

Objective assessment of bleeding phenotype using a standardised bleeding assessment tool (BAT) is the fundamental first step in diagnosing BDUC. Importantly, BAT scores suggest that patients with BDUC display identical bleeding phenotypes comparable to those seen in patients either with the unequivocal diagnosis of VWD or PFD.

Despite the prevalence of BDUC, diagnosis and management of these patients frequently pose significant laboratory, scientific and clinical dilemmas. BDUC is a prominent but unrecognised woman's and infant health issue contributing to heavy menstrual bleeding and iron deficiency. With innovations in genomics, transcriptomics, proteomics, or metabolomics in diagnostic testing in haemostasis, further insights into the underlying pathobiological mechanisms in some BDUC patients will emerge over time. First, the global haemostasis community must unite to address this neglected area by conducting adequately powered prospective studies. The data is essential if we are to develop an evidence base for clinical decision-making in BDUC patients. Furthermore, the knowledge gained from discovering the scientific basis behind BDUC will apply to understanding the variation in the clinical phenotype of other well-established bleeding and thrombotic disorders.

Platelet MHC I regulates CD8+ T cell responses in sepsis

Prof Matthew Rondina

Circulating platelets interact with leukocytes to modulate host immune and thrombotic responses. In sepsis, platelet-leukocyte interactions are increased and have been associated with adverse clinical events, including increased platelet-T-cell interactions. Sepsis is associated with reduced CD8+ T-cell numbers and functional responses, but whether platelets regulate CD8+ T-cell responses during sepsis remains unknown. Dr. Rondina will present data that both human and murine platelets internalize and proteolyze exogenous antigens, generating peptides that are loaded onto MHC-I. The expression of platelet MHC-I, but not platelet MHC-II, is significantly increased in human and murine platelets during sepsis and in human megakaryocytes stimulated with agonists generated systemically during sepsis (e.g., interferon-γ and lipopolysaccharide). Upregulation of platelet MHC-I during sepsis increased antigen cross-presentation and interactions with CD8+ T cells in an antigen-specific manner. Platelet MHC-I regulates antigen-specific CD8+ T-cell proliferation in vitro, as well as the number and functional responses of CD8+ T cells in vivo, during sepsis. Loss of platelet MHC-I reduces sepsis-associated mortality in mice in an antigen-specific setting. These data identify a new mechanism by which platelets, through MHC-I, process and cross-present antigens, engage antigen-specific CD8+ T cells, and regulate CD8+ T-cell numbers, functional responses, and outcomes during sepsis.

Autoimmune HIT

Dr Ashwini Bennett

This presentation will discuss autoimmune HIT pathophysiology, diagnosis and management. Autoimmune HIT (aHIT) is a relatively recently recognised entity, and involves anti-platelet factor 4-polyanion antibodies which can activate platelets, despite no heparin being present in the test system. Although the clinical manifestations of aHIT can bear similarities with classical HIT, one key difference is that the patients have not had any proximate exposure to heparin. Subtypes of aHIT that have been described include spontaneous HIT, delayed-onset HIT and fondaparinux-associated HIT. In 2021, the entity of vaccine-induced thrombotic thrombocytopenia (VITT) was described during the global COVID vaccination campaign. Although the pathophysiology of VITT has not yet been fully determined, intriguingly an autoimmune-HIT like phenomenon has been implicated in many cases of VITT.

NETosis and Thrombosis in HIT and HIT-like Conditions

Prof Beng H. Chong
NSW Health Pathology, St George Campus. NSW, Australia.

Heparin-induced thrombocytopenia (HIT) is a strong immune reaction to heparins, characterized by thrombocytopenia and usually severe thrombosis with high morbidity and mortality. HIT is mediated by IgG antibodies with specificity for heparin/platelet factor 4 (PF4) complexes. The antigen/antibody complexes activate platelets and neutrophils via Fc□RIIa receptors leading to thrombocytopenia and thrombosis.
Our research showed that the thrombosis in HIT is driven mainly by NETosis, a process in which activated neutrophils release highly thrombogenic net-like DNA structures called neutrophil extracellular traps (NETs). NETs also provide the framework for clot formation. We demonstrated *in vitro* using a blood flow microfluidics system (venaflux) and *in vivo* using a murine HIT model, that NETosis inhibitor (GSK 484), DNAse and PAD4 knock-out suppressed thrombosis, but did not prevent thrombocytopenia. In contrast, anti- Fc□RIIa monoclonal antibody IV.3 completely inhibited both thrombosis and thrombocytopenia. Altogether these findings suggest that NETosis is a major driver of thrombosis in HIT, and thrombocytopenia and thrombosis are distinct Fc□RIIa-dependent processes.
Recently, HIT-like thrombotic and thrombocytopenic conditions have emerged such as vaccine-induced thrombocytopenia and thrombosis (VITT) and COVID-19 associated thrombosis. In VITT, the mechanism is slightly different as the IgG antibody is directed against platelet factor 4(PF4) alone, and not PF4-heparin.
In conclusion, HIT and HIT-like conditions are serious thrombotic conditions that lead to serious clinical outcomes. NETosis is a major driver of thrombosis. Current and future research will increase our understanding of the complex pathogenesis and will lead to better treatment.

Nursing Invited Speakers

Global impact of COVID-19

Dr Rebecca Davis

COVID-19 has impacted all of us in a myriad of ways. We will focus on the timeline of the pandemic and impact on health systems. Our patients and staff contend directly with COVID-19 infection but also suffer indirect effects due to service interruption, supply chain difficulties, delayed treatment and anxiety, amongst others issues.

Impact of COVID-19 on Blood & Marrow Transplant Service and Outcomes

Prof Jeff Szer

The onset of the COVID-19 pandemic has had a profound and ongoing impact on the management of patients planned to undergo stem cell transplantation. The direct impact on institutions was obvious with restriction on visitor access, and required viral testing of patients, donors and visitors all impacting on patient flow and care with the frequent requirement for rescheduling. Of particular importance in the Australian setting was our heavy reliance on international donations of stem cells. The severe disruption of international (and interstate) travel meant that our model of commencing conditioning and timing the arrival of the freshly donated product for day 0 was no longer possible. The move to cryopreserved product was near universal and this required a national coordinated effort and collaboration with our international colleagues. In Australia a body was formed under the aegis of the Australasian Bone Marrow Donor Registry called the Coronavirus Australian BMT Group (or CABG). This group developed policy and procedures to provide guidance to centres to ensure that the maximum number of patients requiring transplantation still had access. Collections had to be completed, product had to be delivered and quality control of the cryopreserved product ensured prior to commencing conditioning. While one may have anticipated worse outcomes after the use of cryopreserved product, it is not clear that this was so. Despite reopening of commercial air travel, there is to this day, a heavy reliance on cryopreserved stem cell products and it will be interesting to see whether, in the future this goes back to the original model or a more hybrid mode of operations results.

‘Hope for the best; prepare for the rest’: a risk management approach in palliative care integration 0

Dr Maura Dowling

‘Hope for the best; prepare for the rest’: a risk management approach in palliative care integration

It is widely reported that people living with haematological cancer are referred later to palliative care when compared to the referral patterns of people living with non-haematological cancer. The reasons are complex, including the heterogeneous disease range with obvious variations in disease trajectories and curability, challenges of individual prognostication, the intensity of treatment and the speed of change to a terminal phase. Moreover, continuing advances in treatment for haematological cancers present additional prognostic uncertainties. However, an increasing number of trials on the early integration of palliative care in haematology highlight the growing interest in meeting the palliative care needs of haematology patients.

Palliative care specialists advocate a risk management approach to address the unmet palliative care needs of haematology patients. A risk management approach is based on a philosophy of integration of palliative care at diagnosis which continues in tandem with treatment, whether that be for curative or life-prolonging intent.

This approach moves away from an ‘either-or-situation’ where the focus is either quantity of life or quality of life to ‘both/and’ care; two faces of the same coin. Its goal is to address each patient’s individual needs, which can be towards death and bereavement care or cure and survivorship care.

This approach is not for every patient and depends on their expected illness trajectory and unmet needs. It requires health care professionals in haematology to use professional compassion, active listening and knowledge of patients’ history and disease awareness in their engagement and shared decision-making with patients and families. It also requires that palliative care professionals have an enhanced understanding of haematology, in particular prognostic models and novel therapeutic options in order to appropriately counsel patients about their treatment.

The end-of-life journey for people with haematological cancer: Patterns of ED attendance, hospital admission and place of death in the Central Coast Local Health District.

Dr Thomas Osborne

Title: The end-of-life journey for people with haematological cancer: Patterns of ED attendance, hospital admission and place of death in the Central Coast Local Health District.

Biography: Dr Osborne is a palliative medicine specialist working in the Central Coast of New South Wales. He trained in the London (UK), where he completed a PhD at King's College London investigating the quality of life of people with multiple myeloma. In early 2020 he relocated from the UK to the Central Coast of New South Wales. His research interests include the supportive and end of life care of people with haematological cancer, and supporting preferred place of care at the end-of-life.

Abstract: Studies have suggested that patients with haematological cancer are more likely to die in hospital than other disease groups, yet this may not be always be aligned with their preferences. This talk presents local data from the Central Coast Local Health District, outlining patterns emergency department use, hospital admission and place of death, exploring how people with haematological cancer may differ from other disease groups.

Symptom management at the end of life

Dr Amy Waters

In this session, Amy will explore the unique challenges in caring for haematology patients at the end of life'.

Are we there yet? The long journey to maximise outcome with Car-T therapy

Prof Simon Harrison

Chimeric Antigen receptor Car T cell therapy has emerged as an Australian standard of care for B cell ALL in those aged 26 and under, and relapsed and refractory diffuse large B cell lymphoma. Internationally there are now approvals for refractory follicular lymphoma and multiple myeloma. I will discuss this complexities of delivering this emerging technology, updates on results and the supportive care required to deal with the toxicities associate with this therapy such as Cytokine release syndrome, Immune effector cell-associated neurotoxicity syndrome (ICANS), cytopenia and infection risk.

Clinical Nursing Update: CAR T Cell Toxicities

Ms Karen Maddock

Immune effector cell (IEC)therapy is used for the clinical treatment of relapsed haematological malignancies, with promising outcomes. Although different forms of immune effector cells are used, they share the same potential for immune-related toxicities that require specific management to ensure the safety of the recipients. There are now six commercial Chimeric Antigen Receptor cell (CAR T cell) products offered for administration in America and Europe, two currently available in Australia, and many trials proceeding in multiple countries. As a result of this global experience and the American Society for Transplant and Cellular Therapy (ASTCT) Consensus toxicity guidelines, produced in 2019, we now have more knowledge diagnosing and grading the expected toxicities and their management.
Cytokine Release syndrome (CRS) and Immune effector cell-associated neurotoxicity syndrome (ICANS) are the most the most documented adverse events. However, infections, long term cytopenias and hypogammaglobulinaemia are also common. Acute toxicities are managed by the specialist (IEC) centres and together with the referring centres manage the long-term adverse events and nursing care following CAR T cell Therapy. Both groups of toxicities require accurate monitoring by skilled staff to maximise the benefit of the therapy whilst managing safely the complications.
This presentation updates the clinical toxicities experienced post CAR T Cell therapy and the management.

Reference

Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J., Brudno, J. N., . . . Pavletic, S. (2019). ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biology of Blood and Marrow Transplantation, 25*(4), 625-638.

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BMT in the elderly – should we keep doing it?

Ms Julija Sipavicius

BMT in the elderly – should we keep doing it?
Acute Myeloid Leukaemia (AML) is the largest indication for adult Allogeneic Haematopoietic Stem Cell Transplantation (alloHSCT). The medium age of AML onset is 68 years of age and historically patients ≥ 60 years were not considered for alloHSCT due to unacceptable high toxicity and non-relapse mortality - based on age alone. Recent advances in alloHSCT including reduced intensity conditioning regimes, and improved supportive care have enabled older fit patients to proceed with alloHSCT with data reporting similar outcomes to younger patients. Older patients however have higher incidence of comorbidities, poor performance status and are more vulnerable to treatment toxicities. This presentation will discuss the considerations for alloHSCT in patients ≥ 60 years, and present local experience in undertaking alloHSCT in patients ≥ 70 years of age.

Making connections and managing disruptions and crucial events: Carers' work in 'redefining normal'

Dr Maura Dowling

Continued treatment developments in chronic haematological malignancies (CHMs) have resulted in patients living for many years, often between periods of being acutely unwell, relapses and remission. Informal carers play a major role in supporting patients through their often uncertain and long illness trajectory.

Informal carers of patients living with CHMs pursue connections as they seek information from the time of diagnosis and throughout the disease trajectory. The language of haematology is complex and they try to put the pieces of the puzzle together.

Carers' fear for the future is borne out of the incurable nature of CHMs, its cycle of relapses and remission and possible sudden deterioration at end of life. Their fear for the future is closely linked with patients' fear of cancer recurrence illustrating the complex interactions within a patient-carer dyad. However, to be 'effective' carers means having to mask any negative emotions.

In the context of CHMs, carers' priority is on patients' quality of life over quantity of life. However, end-of-life discussions often do not occur until a sudden deterioration in a patient's condition. Carers' experience is often dominated by doctors' reluctance to discuss end of life before a rapid deterioration in the patient's condition and urgent unplanned transfer to hospice care or re-admission to hospital.

Building the Haematology Nursing Workforce – tools, tips and tiaras!

Discussion facilitated by Tracy King. Panel approach to answering some of the key questions regarding haematology nursing work-force , where we are now, where we would like to be and how we can get there.

Creating and sustaining Haematology NP roles

Mrs Jacqueline Jagger

Creating and sustaining Haematology NP roles

Development of a haematology nurse practitioner role in NSW is complex. The session will focus on fundamental principles underpinning role development such as identifying service gaps, pathway to NP and endorsement, business case and funding, scope of practice, champions and mentors, ensuring sustainability and governance models. The session aims to highlight common pitfalls, debunk myths and share some ‘pearls of experience’.

Next Gen sequencing and monitoring MRD - implications for AML management

Prof Harry Iland

The classification of acute myeloid leukaemia (AML) has evolved considerably since the French-American-British classification was first presented in 1976. Iterations of classification systems encompassing diagnosis and prognosis published in 2022 by the World Health Organization, the International Consensus Classification, and the European LeukemiaNet have highlighted the fundamental need to characterise the pattern of genomic variation in AML at initial presentation. This requirement to obtain comprehensive genetic data in a timely and cost-efficient manner has contributed to a shift from single gene assays to massively parallel sequencing (MPS), also known as next generation sequencing. Although methodology for whole genome and whole exome sequencing is available, the most practical and clinically useful MPS strategy employed by the majority of diagnostic laboratories is sequencing of panels of limited numbers of genes that have been recurrently implicated in myeloid malignancies, including those that that have the potential to influence the choice of therapy.

The use of sensitive genetic assays that are able to identify and quantitate measurable residual disease (MRD) is standard-of-care for some haematological malignancies, such as acute promyelocytic leukaemia and acute lymphoblastic leukaemia, but their role in the management of AML in general is less well established. As the proportion of patients whose AML cells carry an identifiable molecular target expands, the ability to utilize MRD testing to alter management is assuming increasing importance, both in the day-to-day care of patients with AML, and in clinical trials of novel therapeutic agents.

The evolving landscape of AML

Dr Yee-May Ling

Whilst there are many similarities across patient presentations with acute myeloid leukaemia (AML), there is considerable genetic heterogeneity within the disease. The World Health Organisation, International Consensus Classification and European Leukaemia Net have updated diagnostic systems in 2022, with greater incorporation of cytogenetic and molecular lesions in the diagnostic categories of AML, reflecting an increased recognition of the dominant role of genetics in determining disease characteristics, responses to therapies, including targeted therapies and prognosis. Preceding clonal haematopoiesis, progression from preceding myelodysplastic or myeloproliferative neoplasms and cytotoxic therapy-related disease introduces an additional layer of genetic complexity. Significant clonal evolution throughout treatment, allows survival of chemoresistant clones and presents as refractory or relapsed disease, which portends dismal survival and represents a particularly challenging area of unmet need. Improved understanding of the evolving genetic landscape of AML, through the leveraging of precision technologies, will help inform novel treatment strategies to improve patient outcomes.

Oral Abstract Presentations

Presidential Sessions

Platelet receptor levels can differentiate patients with ITP or isolated thrombocytopenia

Dr Sidra Ali[1], Ms Sarah Hicks[1], Dr Lucy Coupland[1,2], Dr Robert Andrews[1], Dr. Philip Choi[1,2,3], Dr. Elizabeth Gardiner[1,2]

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Aim: Platelet count remains the key diagnostic criteria for immune thrombocytopenia (ITP) however often patients present with severe thrombocytopenia, making platelet functional assessment difficult. Flow-cytometric analysis of platelet adheso-signalling receptor levels and function is a powerful tool in the setting of thrombocytopenia which may provide valuable information about bleeding propensity and treatment responses. We compared levels of platelet surface proteins and platelet function in patients diagnosed with primary ITP against patients with thrombocytopenia due to other causes (non-ITP).

Method: A single-centre study was conducted on 74 cases with platelet counts below 100 x 10^9/L. Patient data were compared to healthy controls acquired contemporaneously. Whole blood cell counts, rotational thromboelastometry (ROTEM), platelet receptor quantification, and aIIbb3-activation assays were performed using citrate- or EDTA-anticoagulated blood.

Results: Both ITP and non-ITP patient groups exhibited reduced levels of adheso-signalling receptors GPIbα (p=0.0008; 0.0142 respectively), GPVI (p=0.0007, <0.0001) and □IIb integrin (<0.0001, 0.0006) which were unrelated to platelet count. P-selectin levels in patients with primary ITP were significantly higher than in healthy donors (p=0.0001) and non-ITPs (p=0.0089) indicating platelet activation. Non-ITP platelets demonstrated reduced □IIb□3-activation relative to ITP platelets in response to agonists of GPVI (p=0.0010), thrombin receptor (p<0.0001) or ADP receptor (p=0.0381). All patients had reduced extrinsic and intrinsic clot amplitudes (A10) (p<0.0001) in ROTEM. ITP platelet tetraspanin CD9 levels weakly correlated with intrinsic (r^2=0.3013, p=0.0122) and re-calcified (NATEM) (r^2=0.3473, p=0.0101) clot size as well as with extrinsic (r^2=0.3751, p=0.0041) and fibrinogen specific (FIBTEM) (r2=0.3309, p=0.0080) clotting times.

Conclusion: Platelet receptor levels evaluated in combination with functional assays such as ROTEM and a GPVI-mediated □IIb□3 activation assay can help distinguish primary ITP from other types of thrombocytopenia. Diminution of platelet receptors may contribute to haemostasis dysregulation observed in thrombocytopenia that is not explained by platelet coun

Glofitamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and ≥2 prior therapies: pivotal Phase II expansion results

Assoc Prof Michael Dickinson[1], Carmelo Carlo-Stella[2], Franck Morschhauser[3], Emmanuel Bachy[4], Paolo Corradini[5], Gloria Iacoboni[6], Cyrus Khan[7], Thomasz Wróbel[8], Fritz Offner[9], Marek Trněný[10], Shang-Ju Wu[11], Guillaume Cartron[12], Mark Hertzberg[13], Anna Sureda[14], David Perez-Callejo[15], Linda Lundberg[15], James Relf[16], Emma Clark[16], Kathryn Humphrey[16], Martin Hutchings[17]

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Aim: For the first time, we present pivotal results from Phase II expansion study (NCT03075696) of glofitamab in patients with R/R-DLBCL and ≥2 prior therapies.

Methods: All patients received IV-obinutuzumab (1000mg) 7 days before IV-glofitamab step-up dosing (2.5/10/30mg) on D1, D8 of C1 and on D1 of C2–12 (21-day cycles), respectively. The primary endpoint was IRC assessed CR rate.

Results: As of Sep 14, 2021, 107 patients had received ≥1 dose of study treatment (Table 1). After a median follow-up of 9 months (0.1–16), ORR and CR rates by IRC were 50.0% and 35.2%, respectively. CR rates were consistent in patients with and without prior CAR-Ts (32% vs 37%). Median time to CR was 42 days (95% CI: 41–48). The majority of complete responders (33/38; 87%) were ongoing at data cut. An estimated 84% of complete responders and 61% of responders remained in response at 9 months. The projected 12-month OS rate was 48% and 92% of complete responders were alive. CRS occurred in 68% of patients, was primarily associated with the initial doses, and was mostly Gr-1 (51%) or Gr-2 (12%); Gr-3 (3%) and Gr-4 (2%) events were uncommon. All but 2 CRS events were resolved at data cut. Glofitamab-related neurologic AEs potentially consistent with ICANS occurred in 3 patients (all Gr-1/2). No glofitamab-related Gr-5 (fatal) AEs occurred. Glofitamab-related AEs leading to discontinuation were uncommon (3 patients, 3%).

Conclusions: Fixed-duration glofitamab induces durable complete remissions and has favorable safety in patients with R/R-DLBCL and ≥2 prior therapies, including exposure to CAR-Ts. Glofitamab is a promising new therapy for patients with heavily pretreated and/or highly refractory DLBCL.

Table 1: Baseline demographics

Characteristic	N = 107
Median age, yrs (range)	66 years (21–90)
DLBCL NOS (%)	74
Ann Arbor stage III–IV disease (%)	74
IPI score ≥3 (%)	54
Prior therapies, median (range)	3 (2–7)
≥3 prior therapies (%)	59
Prior CAR T-cells (%)	35
Refractory to a prior aCD20 Ab-containing regimen (%)	85
Refractory to most recent regimen (%)	85
Refractory to initial therapy (%)	59
Refractory to prior CAR-T (%)	32

Integrating single cell transcriptional and genotyping analysis to identify mutational drivers of leukemic transformation in myeloproliferative neoplasm (MPN)

Dr Julian Grabek[1], Dr Jasmin Straube[1,2], Mrs Leanne Cooper[1,2], Ms Ranran Zhang[1,2], Dr Claudia Bruedigam[1,2], Prof David Ross[4], Dr Megan Bywater[1,2], Prof Steven Lane[1,2,3]
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Aim: There is strong evidence that the acquisition of mutations in chronic phase MPN haematopoietic stem cells (HSC) is a key driver of leukemic transformation. To date, there is limited understanding of how clonal evolution is mediated at the transcriptional level and how this relates to clinical progression. We therefore sought to develop a pipeline that enables concurrent mutational profiling and transcriptome analysis of HSCs from patients with MPN at the single cell level. We used this method to assess the effect of mutational heterogeneity on transcriptional lineage priming and stem cell composition.

Method/ Results: To validate accurate genotyping of transcripts we created a heterogenous mix of genetically well-characterised human AML cell lines with 10X chromium barcodes and used concurrent short read (Illumina) gene expression analysis together with Oxford Nanopore (ONT) long read sequencing. The ONT method was optimised by target enrichment for 30 genes commonly mutated (such as JAK2, TP53, ASXL1) in myeloid blood cancers. We were able to successfully deconvolute the individual cell lines and identify their pathogenic mutations based on combined gene expression and genotyping analysis.

We then examined 12 primary human samples from patients in paired samples of chronic phase MPN and leukemic transformation. 10X Chromium single cell separation and cDNA barcoding was performed on CD34+ HSC-enriched populations isolated from bone marrow. Transcriptomic analysis was performed using Illumina sequencing with concurrent mutational profiling by the ONT method. Individual cell mutational profiles were mapped to their corresponding transcriptome through matching of cell barcodes.

We were able to identify discrete clusters of transcriptionally similar cells within both chronic phase and leukemic samples that showed clonal progression. Disease progression was associated with loss of stem cell heterogeneity, lineage bias and differentiation block.

Conclusions: We have developed a novel MPN specific pipeline that can identify the clonal evolution of high molecular risk MPN stem cells during disease progression. This is the first time that MPN HSC mutational and transcriptional heterogeneity can be interrogated at such a comprehensive level

Procoagulant platelet assay for the diagnosis and monitoring of platelet-activating antibodies in vaccine-induced immune thrombotic thrombocytopenia (VITT) – Australian cohort

Dr Christine Lee[1], Dr Lisa Clarke[2,4], Dr Hai Po Liang[1], Dr David Capraro[2], Mayuko Kondo[10], Dea Donikian[10], Dr David Connor[12,13], Heather Campbell[1], Dr Timothy Brighton[10], Dr Emmanuel Favaloro[7,8,9], Associate Professor Sanjeev Chunilal[11], Professor Huyen Tran[5,6], Associate Professor Vivien Chen[1,2,3]
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Aim: The putative mechanism for VITT following ChAdOx1 nCoV-19 vaccination involves pathological anti-platelet factor 4 (PF4) antibodies driving thrombosis and thrombocytopenia. We developed a novel functional assay for detection of vaccine-induced platelet-activating antibodies (Lee et al, Blood Advances) and aim to report the utility in the Australian VITT cohort at diagnosis and follow-up.

Method: 381 patients referred for functional testing after vaccine associated thrombosis underwent flow cytometry VITT testing. 98 confirmed VITT patients identified by clinic-pathological adjudication (confirmed thrombosis within 4-42 days of ChAdOx1 nCov-19 vaccination, D-dimer >5x ULN, platelets $<150x10^9$/L or falling platelet count) after screening on PF4/heparin ELISA (Stago Asserachrom HPIA IgG or Hyphen Zymutest HIA IgG) were included. Platelet-activating antibodies in patient plasma were assayed using whole blood procoagulant platelet flow cytometry assay. Clinical correlation was obtained.

Results: VITT flow cytometry successfully identified 91 of 98 VITT cases. Three cases returned equivocal results while 4 cases had no serological support. 32 confirmed VITT patients (18 females, 14 males; median age 57.5 years [range, 27-80]) underwent follow-up testing with a median follow-up of 24 weeks (range, 8-36). Median time to a negative functional test was 16 weeks with platelet-activating antibodies persistent at 36 weeks in one patient. 93% of patients received a documented second vaccination (Comirnaty, median interval 16 weeks [range, 11-28]) and 71% have received an mRNA booster with no reported adverse events.

Conclusion: Our procoagulant platelet flow cytometry assay accurately identified VITT cases and has been adopted as part of a national diagnostic algorithm. Anti-PF4 antibodies persist longer than functional platelet-activating antibodies in VITT but did not appear to warrant avoidance of subsequent vaccinations. Whether the decline in platelet-activating antibodies allows withdrawal of anticoagulation in these patients is unclear but could be a useful guide.

Autologous stem cell transplantation for autoimmune diseases at St Vincents Hospital, Sydney – 25 years and over 150 patients: An analysis of disease specific outcomes and safety.

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Aim: To describe the patient cohorts treated with autologous haematopoietic stem cell transplantation (HSCT) for severe autoimmune diseases (ADs) from 1997 to 2022.

Method: All studies were approved by the St Vincents Hospital ethics committee (HREC: 96/014,00/03,99/102,08/106,10/206,16/221). Data collected included clinical and quality of life (QOL) data pre HSCT and 3, 6, 12 months post HSCT then yearly. Safety was the primary endpoint (as measured by Transplant Related Mortality - TRM) with disease specific efficacy as secondary endpoints (skin score/change in FVC for scleroderma, NEDA for MS, ACR criteria for RA and Visual analogue scales/DMARD use for other diseases).

Results: Between Jan 1997 and February 2022, 159 patients received HSCT for severe ADs. The major indications were systemic sclerosis (SSc – 65 patients), multiple sclerosis (MS- 64 patients), rheumatoid arthritis (RA – 14 patients) and other conditions (16 patients). TRM in SSc patients was 7.7% (5/65) at D100 with one TRM in the other ADs, confirming an overall TRM of 3.8%. Overall survival at 5 years was 85.4% for SSc, 100% for MS, 100% for RA and 85.7% for other indications. Response rate at 3 years was 86% for SSc, 76% for MS, 0% for RA and 50% for others. There were five late malignancies – Hodgkin Lymphoma, PTLD, lung carcinoma, renal cell carcinoma and melanoma. QOL was significantly improved in most conditions post HSCT particularly in physical well-being.

Conclusion: HSCT for autoimmune conditions provides meaningful long term disease free survival for the vast majority of patients (except RA). Data from our centre mirrors the world experience in both phase II and III trials suggesting that HSCT can be considered in patients who fail conventional therapies. Further work is required to improve short term safety in SSc and to elucidate the mechanisms of action of the procedure.

Third-generation anti-CD19 CAR T-cells incorporating a TLR2 domain for relapsed or refractory B-cell lymphoma: A phase 1 clinical trial (ENABLE)

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Aim: Toll-like receptor (TLR) 2 signalling promotes T-cell expansion and memory formation[1]. We assessed safety, manufacturing feasibility and efficacy of WZTL-002, comprising autologous third-generation chimeric antigen receptor (CAR) T-cells combining TLR2 and CD28 CAR costimulatory domains, for relapsed or refractory B-cell non-Hodgkin lymphomas (B-NHL).

Method: A first-in-human phase I dose escalation trial is underway at Wellington Hospital[2]. WZTL-002 CAR T-cells manufactured at the Malaghan Institute of Medical Research are administered after cyclophosphamide/fludarabine lymphodepletion. The primary outcome is safety. Secondary outcomes include manufacturing feasibility and 3 month response rate. Exploratory outcomes include pharmacokinetic and pharmacodynamic assessments. At abstract submission, 19 subjects have been enrolled. Analyses are descriptive. Registration: ClinicalTrials.gov NCT04049513.

Results: Of the first 19 enrolled subjects: 11 are male; 15 NZ European, 3 Māori, and 1 Asian; age range 23 to 70 years; 15 had aggressive B-NHL, 4 indolent B-NHL. Four were withdrawn before CAR T-cell administration (2 progressive disease, 1 received commercial CAR T-cells, 1 manufacturing failure). Subjects received 5×10^4 (n=3), 1×10^5 (n=3), 2×10^5 (n=3), or 5×10^5 (n=6) WZTL-002 cells/kg. One dose-limiting toxicity (neutropenia) occurred at 5×10^5/kg. Eight subjects (53% of recipients) had grade 1 or 2 CRS. No grade 3 or 4 CRS, and no ICANS of any grade, occurred. Of 14 assessable recipients, 3 month overall response rate was 57% (50% complete, 7% partial). CAR T-cells expanded in all recipients. At day 90, both transgene DNA and B-cell aplasia persisted among all assessable recipients of ≥ 2×10^5/kg WZTL-002.

Conclusion: This preliminary experience suggests acceptable safety with promising efficacy at doses of 5×10^4 to 5×10^5 WZTL-002 CAR T-cells/kg. Trial enrolment continues.

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Blood Donor, Component and Recipient-Specific Factors Associated With Venous Thromboembolism in Transfused Hospitalized Adult Patients: Data from the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)

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Objective: Growing evidence suggests multiple pathophysiological mechanisms linking RBC transfusions to thrombotic outcomes. This study aims to assess various donor, blood component and recipient-specific factors which may be associated with thromboembolic outcomes following RBC transfusions.

Methods: Recipient Epidemiology Donor Evaluation Study-III (REDS-III) database on patients transfused in 12 academic hospitals across different geographic regions of the United States between 2013-2016 was used. Linkage analysess of associations of donor and component modification characteristics on the outcomes of patients transfused RBC units were performed using stratified Cox proportional hazards regression models with time-dependent exposures.

Results: 59,603 patients were transfused 229,500 RBC units during the course of 79,298 hospitalizations with VTE occurring in 1,869 (2.4%) of patients. In adjusted regression analyses, female donor sex, storage duration greater than 5 weeks, gamma irradiation, AS-1 storage solution, and apheresis-derived collections were associated with VTE. Among recipient factors, pre-transfusion anemia, obesity, and primary diagnoses including malignancy, cardiovascular risk factors and sepsis were associated with VTE in adjusted regression analyses. ($p<0.01$ for all associations). The dose-dependent association of the donor and component factors on VTE was modest in contrast to those of recipient-specific risk factors.

Discussion: We identify several donor, component and recipient-specific factors associated with VTE in transfused hospitalized adult patients. Studies identifying mechanistic pathways linking these factors with thrombotic outcomes are needed. Identifying some of the modifiable variables can be critically important in future precision transfusion medicine-based decisions in accounting for donor and component modifications specific variation in choosing the optimal units for transfusion.

RBCeq: A robust and scalable algorithm for accurate genetic blood typing at population level

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Aim: Repetitive blood transfusion increases the risk of red cell alloimmunisation in patients which can impact on the timeliness antigen negative blood provision to prevent adverse transfusion outcomes. The International Society of Blood Transfusion (ISBT) currently recognise over 350 blood group antigens represented at varying frequencies in world populations. This level of blood group diversity challenges SNP-array genotyping platforms which target fewer red cell antigens (35). Comprehensive blood group profiles have been accurately determined from Next Generation Sequence data in the research setting, however a user-friendly automated interpretation pipeline application is lacking. To address this unmet need, we have developed RBCeq, a novel genetic blood typing algorithm.

Method: Blood groups profiling is divided into three steps 1) Extract single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) from NGS data; 2) Genotype and phenotype predictions of known blood groups alleles using novel algorithm; 3) Detection of rare and novel blood group variants by In-silico prediction. All three steps are integrated into a user-friendly web application called RBCeq (https://www.rbceq.org/).

Results: RBCeq is an automated web server-based (https://www.rbceq.org/) software with advanced visualization capabilities and the ability to address the computational and storage challenges associated with large NGS data processing. It profiles 36 blood groups and identifies genomic alterations like indels and CNVs. The RBCeq algorithm was validated on 403 serologically tested samples which include 58 complex serology cases from Australian Red Cross LifeBlood, 100 samples from The MedSeq Project and a further 239 from Indigenous Australian dataset. The final blood typing data from RBCeq was 99.40% concordant for 402/403 samples (85 different antigens in 21 blood group systems) with that listed from the ISBT database. The RBCeq has extensively redefined blood group profiles in 5757 whole genome sequencing samples from different multi-ethnic cohort.

Conclusion: This platform has the potential to overcome methodological limitation, reduce pre-transfusion testing time and to increase sample processing throughput, ultimately improving the quality of patient care

Making decisions about platelet transfusions in patients with myelodysplastic syndromes (MDS): a clinician survey to inform future clinical trials

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Aim: Thrombocytopenia and bleeding are common in MDS but optimal management and current practice, including prophylactic platelet transfusions (PLT) or tranexamic acid (TXA) use, is unclear. We conducted a survey aiming to describe current use of PLT and TXA to inform future trial design on management of MDS-related thrombocytopenia.

Method: Following ethics approval, a 25-question survey was developed and piloted within the ALLG Supportive Care group, then distributed to all 436 ALLG members in December 2020 and July 2021.

Results: 64 clinicians across Australia, New Zealand and Singapore responded (response rate 15%); including 60 (94%) specialists, 2 (3%) registrars, 2 (3%) nurses. Clinicians treated a median of 15 MDS patients annually, including median 5 patients receiving disease-modifying therapies and median 2 with thrombocytopenic bleeding.

Guidelines Institutional guidelines for PLT and PLT thresholds varied (Table 1). Only 45% of respondents reported guidelines for prophylactic PLT, and 10% for TXA prophylaxis.

Table 1: Institutional guidelines

Does your institution have guidelines for:	Yes n(%)	PLT threshold if yes (x10^9/L)				
		<10	<20	<30	<50	Other
Prophylactic PLT in stable MDS patients	29 (45%)	24/29 (83%)	1/29 (3%)	0	0	4/29 (13%)
Therapeutic PLT in bleeding MDS patients	36 (56%)	0	16/36 (44%)	5/36 (14%)	7/36 (19%)	8/36 (22%)
Prophylactic PLT prior to bone marrow biopsy	13 (20%)	2/13 (15%)	4/13 (30%)	3/13 (23%)	1/13 (7%)	3/13 (23%)
Prophylactic PLT prior to Hickman/PICC line	41 (64%)	1/41 (2%)	5/41 (12%)	6/41 (15%)	26/41 (63%)	3/41 (7%)

Clinical practice A median of 80% of patients did not need regular treatment for thrombocytopenia; 5% received prophylactic PLT, 5% regular TXA, 0% received both TXA and prophylactic PLT. Three scenarios involving MDS patients with thrombocytopenia were presented (Table 2); respondents were more likely to give prophylactic PLT during disease-modifying therapy (e.g. azacitidine) (76%, commonest platelet threshold<10x10^9/L) or to patients with minor bleeding (50% transfusing at platelet threshold <20x10^9/L; 35% at platelet threshold <10x10^9/L). For stable patients not on treatment, responses varied; 45% would not give PLT and 50% would give PLT.

Table 2: Clinical scenarios

Scenario	**PLT threshold (x10^9/L) for prophylactic transfusion**					
	<5	<10	<20	<50	Would not give PLT	Other
Stable patient, not on disease-modifying therapy, no history of bleeding	6(9%)	25(39%)	1(2%)	0	29(45%)	2(3%)
Stable patient, on azacitidine, no history of bleeding.	4(6%)	45(70%)	0	0	6(9%)	1(2%)
Minor bleeding already taking TXA	1(2%)	22(34%)	32(50%)	3(5%)	3(5%)	3(5%)

Clinical trials 72% were interested in recruiting patients to trials in this area. Potential barriers included resource limitations, funding, patient and clinician acceptance.
Conclusion: This survey suggests marked variability in the management of MDS-related thrombocytopenia management, and a need for clinical trials to inform practice

Assembling a reference RHD gene to personalise transfusion management for the Indigenous Australian population

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Aim: Accurate RhD typing is clinically important, but the *RHD* gene is highly polymorphic. The suitability of the current Reference Sequence (RefSeq) *RHD* gene used to detect gene variants in Indigenous Australians has yet to be defined. This study aimed to investigate the *RHD* gene sequence of Indigenous Australians and compare with RefSeq *RHD* gene (*RHD*01*).

Method: Whole blood samples from 247 Indigenous Australians in Queensland were collected with informed consent. Genomic DNA was extracted and the *RHD* gene was amplified. Amplicons were sequenced on the Illumina custom, targeted Massively Parallel Sequencing (MPS) panel to identify *RHD* zygosity and exonic/intronic variants. Hemizygous *RHD* samples were then selected for whole *RHD* gene sequencing (n=2). Amplicons spanning the whole *RHD* gene were generated by long-range (LR) techniques and then sequenced as 250bp reads on Illumina MiSeq. Reads were mapped to RefSeq *RHD* (NG_007494.1) using QIAGEN CLC Genomics Workbench for variant detection.

Results: In 247 Indigenous Australians, MPS identified 21 as *RHD*-negative and 226 as *RHD*-positive (122 homozygotes and 104 hemizygotes). Of 226, 21 carried *RHD* gene variants associated with known but rare weak D and partial D phenotypes.

In two *RHD*01* hemizygote samples, LR amplicon analysis detected 60 intronic variants; 12 were common to the two samples and 48 were not. Of these 48 variants, six had not been reported in the Caucasian population[1]: rs28445757 delG, rs1643944507 AAdel, rs376450364 G>A, rs201200089 A>G, rs181068505 G>C, rs145383442 delC.

Conclusion: This study showed a pattern of unusual but clinically significant gene variants associated with weak and partial D phenotypes. There was a contrasting pattern of *RHD* gene variants detected in the exons and introns compared to the reference *RHD* gene. These preliminary findings require further investigation to assemble a reference *RHD* gene for Indigenous Australians.

Acknowledgements:
We thank the ANZSBT for the research grant support.

References:

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Predicting the severity of cardiac iron-overload in transfusion dependent thalassemia (TDT) patients through deep learning.

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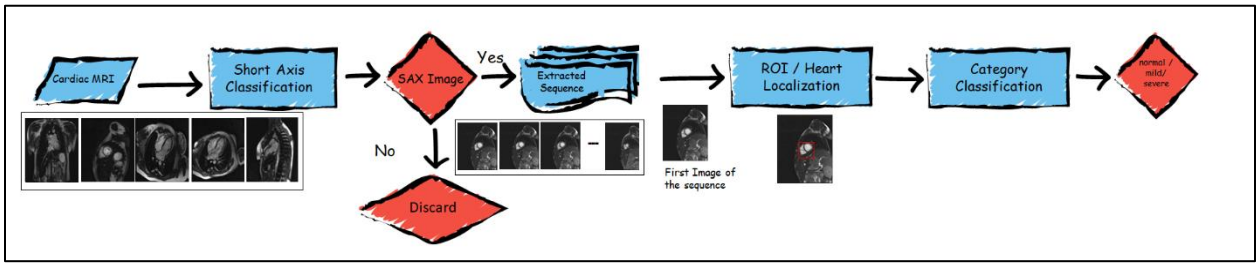
Aim: Cardiac iron overload is among the leading causes of morbidity and mortality in TDT. The detection of cardiac iron overload requires Cardiac Magnetic Resonance Imaging (CMR) along with an expensive software and a highly trained interpreter. The objective of this study is to develop a deep learning algorithm on CMR images to identify myocardial iron overload in TDT patients, thus bypassing the need for a costly specialized software and highly trained professionals.

Method: For this study, the CMR data of 661 TDT patients (from May 2014 – June 2019) was provided by Aga Khan University Hospital, Karachi, Pakistan. The images included apical 2 chamber view, apical 4 chamber view, left and right ventricular view, and short axis view of the heart. The short axis view was the image of interest which was used to calculate the severity of iron overload.

After extracting short axis sequences from the CMR images through classification model, we localized the heart from the first image only and treated it as the ROI, contrary to the conventional manual delineation of septum which is time consuming and prone to error. This ROI was given as input to Convolutional Neural Network (CNN) for predicting the severity of iron overload (normal, mild/moderate and severe). Since the category classification model uses ROI from the first image only, therefore, this technique can be easily used for free breathing short axis images. The dataset was divided into 80% training, 10% validation and 10% testing sets. The model was evaluated based on accuracy, precision, recall and f1 score for all three classes.

Results:



The severity of distribution of data for the 3 target classes was 39% normal, 19% mild and 42% severe. With our algorithm, for all three classes on average we were able to achieve; 90% accuracy with precision, recall and f1 score being 0.89, 0.90 and 0.88 respectively.

Conclusion:
Management based on accurate estimation of iron overload using CMR has improved the survival of TDT patients. However, in resource limited settings, access to interpretation of CMR is limited. This study reports that a deep learning algorithm was able to identify the category with > 85% accuracy without the need of software or trained personnel. If implemented, this algorithm has the potential to improve health outcomes in TDT patients in a resource efficient manner

Sequential Blinatumomab with Reduced Intensity Chemotherapy for Treatment of Older Adults with Newly Diagnosed Ph-Negative B-Precursor Acute Lymphoblastic Leukaemia – Interim Analysis of Australasian Leukaemia and Lymphoma Group ALL08 Study

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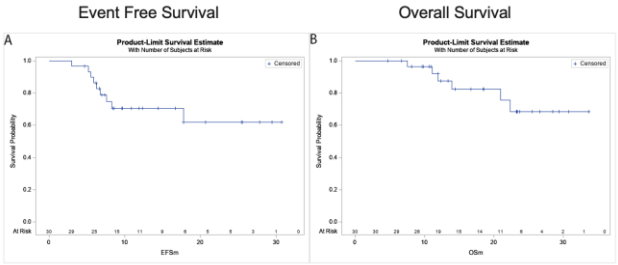
Aim: While paediatric-inspired regimens have improved ALL outcomes in younger adults, their intensity limits their application in older adults. We explored the efficacy of reduced-intensity chemotherapy and Blinatumomab in adults aged >40 years with newly diagnosed B-ALL.

Method: Patients received a pre-phase of corticosteroids (Prednisolone 100mg/d, 5 days) followed by low-intensity chemotherapy debulking (Cyclophosphamide 150mg/m^2 BD D1-3, Vincristine 2mg IV D1, 11 and Dexamethasone 10mg/m^2 D1-4 D11-14). Patients received Blinatumomab at 9mcg/d D1-7 and 28mcg/d D8-28. A B-cycle of Hyper-CVAD (Cytarabine 3g/m^2 BD x 4 and Methotrexate 1g/m^2 D1 with Methylprednisolone 50mg BD D1-3). Patients then received 3 alternating cycles of Blinatumomab (28mcg/d D1-28) and B-cycles of Hyper-CVAD then 2-years of POMP maintenance. We performed a pre-specified interim analysis.

Results: 30 patients were enrolled, median age of 51.7(39.5 – 66.5 years). All attained CR. Of 26 evaluable for MRD, 70% achieved a complete MRD response after cycle 1B and 83% after 2B. At data cut-off, the 24 month estimated event-free survival (EFS) was 61.8% (95% CI 36.3 – 84.2%) and median EFS was not reached (95% CI 8.3 months – NA). Similarly, overall survival (OS) at 24 months was estimated as 68.6% (95% CI 41.5 – 85.1%) and median OS not reached (95% CI 21.0 months – NA). The predicted EFS was greater than pre-specified stopping rule. 2 episodes of cytokine release syndrome were recorded (1 grade 2, 1 grade 3). 7 episodes of neurological toxicity were demonstrated (1 myelopathy,4 peripheral neuropathy and 2 encephalopathy). 4 patients had proceeded to alloHSCT.

Conclusion: The combination of Blinatumomab with chemotherapy was tolerable and efficacious with a high rate of remission and deep MRD responses observed. Responses appeared durable. Future developments from this protocol will emphasise further reduction in cytotoxic chemotherapy through incorporation of further novel agents.



Factors Associated with Poor Outcome in High Body Mass Index Patients in the Australasian Leukaemia and Lymphoma Group ALL06 Study

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Aim: BMI ≥30kg/m2 (BMI^{hi}) was associated with inferior DFS and OS in ALL06. Our aim was to identify variables that may be associated with poor outcome in this cohort.

Method: Retrospective analysis of the ALL06 cohort. Patients were divided into BMI^{hi} and BMI^{lo} (<30kg/m^2). BMI cohorts were compared with regards to risk stratification (RS), induction mortality (IM), time to protocol M or HR1, MRD negativity at day 79 (MRD^{neg}) and diagnostic genomic classifiers where available.

Results: 86 patients were registered to ALL06, 82 were eligible. Median follow up 44 (1.2-95.7) months. Mean BMI was 25.9 (range 14.9-50.6) kg/m^2. N=16 patients were BMI^{hi} and n=66 BMI^{lo}. In BMI^{hi} mean age 26.4 (sd=8.0) vs 24.5 (sd=6.2) years, (p=0.32). RS was MR/SR 50% in BMI^{hi} vs 47% BMI^{lo}, (p=0.87). For BMI^{hi}, IM was 2/16 (12.5%) vs 1/66 (1.5%), (p=0.09). Time to protocol M/HR1 was 100 (96-103) vs 94 (86-103) days (p=0.22), MRD^{neg} was 58% vs 59% (p=0.99). At last follow up, 3yr DFS was 53.3% (28.1-78.6) vs 77.5% (67.1-87.9), (p=0.023) and 3yr OS was 49.2% (24.3-74.1) vs 81.1 (71.4-90.8), (p<0.001) for BMI^{hi} vs BMI^{lo} respectively. Genomic classifiers were available in 42 patients, n=10/16 in BMI^{hi} and n=32/66 BMI^{lo} and not tested, n=40. For BMI^{hi}, genomic classifiers were good risk in n=3/10, intermediate n=1/10, poor n=5/10, other n=1/10 vs n=12/32, n=6/32 n=10/32, n=4/32 respectively in BMI^{lo}.

Conclusion: BMI^{hi} is associated with inferior DFS and OS in ALL06. However, small cohort size limited our capacity to identify factors which significantly increased risk for BMI^{hi} on this protocol. A pooled analysis of ALL06 and ALL09 may provide insights that could be taken forward to improve outcome for this high risk group in future stud

Characteristics and outcomes of patients with acute promyelocytic leukaemia and extreme hyperleukocytosis at presentation – a multinational experience.

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Aim: In acute promyelocytic leukaemia (APL), the white cell count (WCC) at presentation is the most important predictor of failure due to early death (ED) or relapse. Approximately 25% of patients have high-risk disease (WCC > $10x10^9$/l), but only 1.5% present with extreme hyperleukocytosis (defined as WCC > $100x10^9$/l).[1,2] We sought to characterise the presentations and outcomes of this previously unreported rare subgroup of APL.

Methods: Haematologists in Australia, UK and North America provided data on APL patients presenting with extreme hyperleukocytosis regardless of management, clinical trial participation or outcome. The protocol was approved by the Sydney Local Health District HREC. Patients were stratified according to (i) presentation in the early vs late era (before or after January 2012 as a surrogate for the intensity of supportive care), (ii) treatment paradigm (± arsenic trioxide (ATO) during induction and/or consolidation), (iii) age (above or below the median), and (iv) differentiation syndrome (DS) prophylaxis (± corticosteroids). Time-to-event outcomes were estimated using the Kaplan-Meier product limit method and compared with the log-rank test.

Results: Data from 37 patients spanning 25 years were collected from 17 institutions in 6 countries. Median age was 43 years (1-73), median WCC $124.0x10^9$/l (96.7-297.0), haemorrhagic and thrombotic manifestations in 74% and 24% respectively, and 73% had FLT3-ITD. Cohorts included late presentation (59%), ATO-based therapy (41%), age ≤ 43 (51%), and corticosteroid prophylaxis (65%). ED (≤ 30 days) occurred in 7 patients (19%), 29 achieved haematological CR (78%), and molecular CR was documented in 26 (70%). Outcomes at 5 years with 95% confidence intervals (CI) were 76% (58%-87%) for overall survival (OS), and 81% (55%-93%) for both disease-free and relapse-free survival. In univariate analysis (Table 1), improved OS was associated with both ATO-based therapy and late era of presentation, although these parameters were closely correlated (p=0.0002). Age ≤ 43 was of borderline significance.

Conclusion: These data reinforce the need for aggressive supportive care and ATO-based therapy. When managed in that way, APL patients with extreme hyperleukocytosis have OS that is comparable with published data for conventionally defined high-risk disease (Table 2).

Table 1: Univariate analysis of OS				
Parameter		**Hazard ratio**	**95% CI**	**p-value**
ATO-based therapy	Yes vs No	5.9	1.7-20.0	< 0.005
Presentation era	Late vs Early	5.7	1.6-19.9	< 0.007
Age	≤ 43 vs > 43	3.2	1.0-10.4	< 0.06
Corticosteroid prophylaxis	Yes vs No	1.7	0.5-6.1	> 0.3

Table 2: Comparison with published data for APL and WCC > $10x10^9$/l				
Cohort	**Subgroup**	**Endpoint**	**OS**	**95% CI**
Current study	Presentation after Jan 2012	OS (5 years)	91%	68%-98%
MD Anderson [3]	ATRA + ATO + GO	OS (5 years)	86%	not reported
ALLG APML4 [4]	ATRA + ATO + idarubicin	OS (5 years)	87%	65%-96%
NCRI AML17 [5]	ATRA + ATO + GO	OS (4 years)	87%	68%-95%
	ATRA + idarubicin + mitoxantrone	OS (4 years)	84%	63%-94%

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Lenalidomide as maintenance therapy post-allogeneic haematopoietic stem cell transplantation for patients with acute myeloid leukaemia or myelodysplastic syndromes at high risk of relapse (MicroLEN)

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Aim: Relapse of acute myeloid leukaemia (AML) or myelodysplastic syndromes (MDS) is a major cause of mortality after allogeneic transplantation (alloSCT). Post-transplant strategies that promote the graft-versus-tumour effect need to be balanced with the risk of graft-versus-host disease (GVHD). In prior studies, lenalidomide at 10mg/d post alloSCT resulted in an excessively high rate of GVHD. We conducted a phase I dose escalation study to investigate the safety of low-dose lenalidomide in combination with accelerated immunosuppression withdrawal for patients with high-risk (HR) AML or MDS.

Method: A dose escalation study design was used commencing with a lenalidomide dose of 2.5mg weekly up to 10mg alternate daily in five distinct dose cohorts. Immunosuppression withdrawal commenced at day 40-45 post-alloSCT with intention to cease immunosuppression by day 100. Inclusion criteria included HR AML (defined as adverse risk cytogenetics, FLT3-ITD, detectable MRD prior to transplant, short duration of CR1, transformation from prior myeloid neoplasm) or MDS with adverse cytogenetics or greater than 10% bone marrow blasts. Patients with grade 2-4 acute GVHD or with persistent disease post-transplant were excluded. Dose limiting toxicities (DLTs) were defined as grade 3-4 acute GVHD, moderate to severe chronic GVHD or grade 3-4 cytopenias within 120 days from the commencement of lenalidomide.

Results: Of the 55 patients with HR AML/MDS identified, only 15 were enrolled. Post-alloSCT organ toxicity, disease relapse and patient preference were the main reasons for screen failure. Median age was 53 (range 18-63) and 60% were males. Most participants were HR AML (87%) with a median HCT-CI score 3 (range 0-6) and baseline ECOG 1 (range 0-2). Myeloablative conditioning was used in 40% of participants. Protocol directed immunosuppression withdrawal was completed in 5 participants (33.3%) and 4 (26.7%) completed the whole study protocol. Disease relapse was the main reason for trial discontinuation (33.3%) followed by acute GVHD (20%). The dosing cohort of lenalidomide 5mg alternate days was reached without any DLTs encountered. For the entire cohort, at 1 year, the overall survival (OS) was 60% (95% CI 35.2-84.8%), relapse-free survival (RFS) 60% (95% CI 35.2-84.8%) and GVHD, relapse-free survival (GRFS) 53.3% (95% CI 25.1-78.6%). The cumulative incidence of relapse at 1-year and 5-years were 33.3% (95% CI 16.3-68.2%) and 40.7% (95% CI 21.9-75.7%), respectively.

Conclusion: Maintenance low-dose lenalidomide and early immunosuppression withdrawal are challenging to deliver post-alloSCT for patients with HR AML/MDS due to a high incidence of early disease relapse and GVHD.

Preliminary safety and efficacy of BGB-11417, a potent and selective B-cell lymphoma 2 (BCL2) inhibitor, in patients with acute myeloid leukaemia (AML)

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Aim: BCL2, a key apoptosis regulator, is aberrantly expressed in many hematologic malignancies. The highly selective BCL2 inhibitor, BGB-11417, demonstrated more potent antitumor activity than venetoclax in preclinical studies. Here, preliminary results for BGB-11417+azacitidine in AML are presented.

Method: BGB-11417-103 (NCT04771130) is an ongoing, phase 1b/2, global, dose-escalation/expansion study. Eligible patients have treatment-naïve (TN) AML (unfit for intensive induction chemotherapy) or relapsed/refractory (R/R) AML (no prior azacitidine or BCL2 inhibitors). Patients received 40mg (Cohort 1), 80mg (Cohort 2), or 160mg (Cohort 3) BGB-11417 for 10 days + azacitidine (75mg/m^{2}x7 days). Cycle 1 had a 4-day BGB-11417 ramp-up. Dose-limiting toxicity (DLT) through Day-28 (nonhematologic) and Day-42 (hematologic), treatment-emergent AEs, and responses (2017 European LeukemiaNet criteria) were assessed.

Results: As of 10Jan2022, 27 patients were treated (Cohort 1=6; Cohort 2=15; Cohort 3=6). Median age was 80 (TN n=18) and 70 (R/R n=9) years; 44% had adverse karyotype. At median follow-up of 2.1 months and median treatment duration of 1.8 months (range 0.3-7.6), 2/23 evaluable patients had DLTs: Grade [Gr]4 neutropenia and Gr4 thrombocytopenia (Cohort 2) which did not meet safety stopping criteria. 1 patient (Cohort 3) with chronic kidney disease had asymptomatic laboratory tumour lysis syndrome. Most common nonhematologic AEs: constipation (37%) and azacitidine injection-site reaction (33%). Most common Gr≥3 hematologic AEs: neutropenia (44%), thrombocytopenia (41%), and anaemia (37%). No patients had BGB-11417 dose-reductions. 10 patients discontinued treatment: AEs (n=3), proceeding to transplant (n=3), withdrawal (n=2), disease progression (n=2). CR/CRh rates: 56% (TN) and 44% (R/R). 7/9 CRs occurred by the end of Cycle 1.

Conclusion: Preliminary data suggest that 10-day BGB-11417+azacitidine treatment was well-tolerated with promising activity in AML. Most AEs were low-grade in severity. 2 DLTs occurred across 3 dose levels tested. BGB-11417+azacitidine resulted in a majority of CR by the end of Cycle 1 and was well-tolerated in AML.

Clinical and biological markers associated with long-term overall survival (OS) for patients with acute myeloid leukemia (AML) in remission after chemotherapy in the QUAZAR AML-001 trial of oral azacitidine (Oral-AZA)

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Background: In the randomized, phase-3 QUAZAR AML-001 trial, Oral-AZA significantly prolonged OS vs placebo (median 24.7 vs 14.8 months) in patients ≥55 years of age with AML in remission after intensive chemotherapy (IC). At a Sep-2020 data cutoff, 34.9% and 24.4% of patients in the Oral-AZA and placebo arms, respectively, survived ≥3 years from randomization.

Aim: Assess clinical and biological variables associated with long-term survival (LTS) in QUAZAR.

Methods: 472 patients received Oral-AZA 300-mg or placebo for 14d/28d cycles within 4 months of CR/CRi. The LTS cohort comprised patients who survived ≥3 years from randomization; the Non-LTS cohort included patients who died or were censored before 3 years. Variables assessed for association with LTS included AML subtype, cytogenetic risk, *NPM1* and *FLT3* mutations at diagnosis (^{mut}); response to IC (CR/CRi), receipt and number of consolidation cycles; baseline patient characteristics and MRD status; and post-baseline variables (MRD response [baseline MRD+ to MRD− on-study], timing of MRD− [baseline vs on-study], and transplant after treatment discontinuation). Variables were compared within treatment arms in univariate analyses, and for all patients using a Cox multivariate analysis comprising select covariates.

Results: The LTS cohort included 83/238 patients (34.9%) and 57/234 patients (24.4%) in the Oral-AZA and placebo arms, respectively. Within both arms, factors significantly associated with LTS were intermediate-risk cytogenetics and *NPM1*^{mut} at diagnosis, and MRD response on-study. Factors significantly associated with LTS only in the placebo arm were baseline MRD− status and transplant after treatment discontinuation.

In the multivariate analysis, Oral-AZA was independently and significantly predictive of LTS vs placebo; other significant covariates were intermediate-risk cytogenetics, *NPM1*^{mut}, and baseline MRD−.

Conclusion: In the univariate analysis, intermediate-risk cytogenetics and *NPM1*^{mut} at diagnosis, and MRD response on-study, were prognostic for LTS in both treatment arms. Multivariable analysis confirmed that Oral-AZA was significantly associated with LTS vs placebo.

CTX-1 levels can predict individuals at high risk of progression from smouldering myeloma to multiple myeloma

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Aim: To guide clinical management, biomarkers are needed to differentiate smouldering myeloma (SMM) patients who will rapidly progress to multiple myeloma (MM) from those with stable disease. Osteolytic lesions are characteristic of MM, with increased bone resorption being a common feature of SMM to MM progression. We investigated whether the bone resorption marker C-terminal telopeptide 1 (CTX-1; β-Crosslaps) can be used to identify SMM patients at risk of progression to MM.

Method: We conducted a retrospective analysis of disease progression in SMM patients (n=63) seen at the Royal Adelaide Hospital (RAH) between 2/4/2008-29/6/2020 with serum CTX-1 levels assessed at diagnosis. Additionally, CTX-1 levels were assessed in serum samples from SMM patients (n=32) from the Myeloma and Related Diseases Registry (MRDR) M1000 Biobank. SMM progression to MM was defined as per IMWG diagnostic criteria[1]. Kaplan Meier, log-rank and Cox proportional hazards analyses were used to assess risk of progression in CTX-1^{hi} and CTX-1^{lo} groups.

Results: In the RAH cohort, risk of progression was significantly higher in CTX-1^{hi} patients (≥425 ng/L, defined by ROC analysis) compared with CTX-1^{lo} patients (median time to progression [TTP], CTX-1^{hi}:1.1 years [n=29]; CTX-1^{lo}:3.1 years [n=34]; p=0.008, HR=3.0). In multivariable analyses, CTX-1 retained its predictive value when corrected for risk factors in the 2/20/20 model[2,] with any 3 of CTX-1 ≥425 ng/L, paraprotein >20 g/L, sFLCr >20, and/or BMPC >20% identifying a group with 80% risk of progression by 2 years. In the MRDR cohort, CTX-1^{hi} patients (≥188 ng/L) were more likely to progress to MM (p=0.04, HR= 6.3), with 5/15 (33%) CTX-1^{hi} patients progressing compared with 0/12 (0%) CTX-1^{lo} patients (median TTP not reached).

Conclusion: CTX-1 is a prognostic biomarker which can differentiate SMM patients at risk of progression. CTX-1 is a well-established clinical diagnostic test and hence could be rapidly integrated into standard of care testing for SMM patients.

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Subcutaneous daratumumab (D) with bortezomib, cyclophosphamide, and dexamethasone (VCd) in patients with newly diagnosed light chain (AL) amyloidosis: 18-month analysis of the phase 3 ANDROMEDA study

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Aim: Light chain (AL) amyloidosis is a plasma cell disease characterized by the deposition of insoluble amyloid fibrils into organs, leading to organ dysfunction and death. Here we present 18-month update from the ANDROMEDA phase 3 study, having previously reported the 6/12-month analysis.

Methods: Patients were randomized to D-VCd or VCd for six 28-day cycles (C). Bortezomib (1.3 mg/m2), cyclophosphamide (300 mg/m2 up to 500 mg per week), and dexamethasone (20–40 mg) were administered weekly. Subcutaneous daratumumab (1800 mg co-formulated with recombinant human hyaluronidase PH20 in 15 mL) was administered once weekly in C1 and C2, and Q2W in C3–6. Patients in the D-VCd arm received only subcutaneous daratumumab after C6, Q4W (up to a total of 24 cycles from first dose). Primary endpoint was overall hematologic CR rate. Secondary endpoints included PFS, organ response rate, time to hematologic response, overall survival, and safety.

Results: 388 patients were randomized to D-VCd or VCd alone (Table). Median duration of treatment was 21.3 months for D-VCd and 5.3 months for VCd. In the D-VCd arm, 149 patients (77.2%) received daratumumab alone after 6 cycles; of those, 17 (11.4%) had ongoing treatment. Rates of deep hematological responses favored D-VCd and more patients achieved a very-good-partial-response. At 18-months, greater cardiac: (D-VCd [53%]/VCd [24%]) and renal (D-VCd[58%]/VCd [26%]) response rates were achieved with D-VCd vs VCd. 79 deaths occurred (D-VCd [N=34]/VCd [N=45]). Grade 3/4 adverse events occurred over 18 months vs 12 months (119 [61.7%] vs 118 [61.1%] patients) and no additional infusion-related reactions were reported.

Conclusions: These results demonstrate the sustained clinical benefits of D-VCd vs VCd in terms of hematologic and organ responses with longer follow-up and support the use of D-VCd over VCd in patients with newly diagnosed AL amyloidosis, representing a new standard of care for these patients.

Table. Hematologic response rates by treatment group at any time

n (%)	**D-VCd**	**VCd**		
	(N=195)	**(N=193)**	**Odds ratio (95% CI)**	***P*-value**
CR	116 (59.5)	37 (19.2)	6.03 (3.80, 9.58)	<0.0001
VGPR	38 (19.5)	60 (31.1)		
PR	25 (12.8)	52 (26.9)		
NR	8 (4.1)	37 (19.2)		
NE	8 (4.1)	7(3.6)		
≥VGPR	154 (79.0)	97 (50.3)	3.74 (2.39, 5.86)	<0.0001
ORR	179 (91.8)	149 (77.2)		

CI, confidence interval; CR, complete response; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; NE, not evaluable; NR, no response; ORR, overall response rate; PR, partial response; VCd, bortezomib, cyclophosphamide, and dexamethasone; VGPR, very good partial response.

RG6234, a novel GPRC5DxCD3 T-cell engaging bispecific antibody, induces rapid responses in patients with relapsed/refractory multiple myeloma (RRMM): preliminary results from a first-in-human trial

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Aim: RG6234 is a GPRC5DxCD3 T-cell engaging bispecific antibody with a novel 2:1 format. We present preliminary dose-escalation results from a Phase I trial (NCT04557150) of RG6234 in patients with RRMM.

Method: Eligible patients received RG6234 IV at escalating QW step-up doses followed by a Q2W target dose for up to 1 year. CRS was graded per ASTCT criteria (Lee et al. 2019).

Results: As of 31 January 2022, 41 patients had received RG6234 (0.006–10mg). Median age was 63 years (range: 27–78) and 58% of evaluable patients had high-risk cytogenetics. Median number of prior therapies was 5 (range: 2–15); 14.6% had received prior anti-BCMA therapy.
CRS (85.4% of patients) was generally confined to Cycle 1 and was mostly Grade 1 (56.1%) or Grade 2 (24.4%). RG6234-related CNS toxicity occurred in 3 patients (Grade 1 and Grade 3 headache; Grade 1 confusion). Grade 3–4 neutropenia, thrombocytopenia and anaemia occurred in 9.8%, 19.5% and 12.2% of patients, respectively; infections occurred in 46.3% (Grade ≥3: 14.6%). One patient died of an E. coli sepsis that was considered unrelated to RG6234.
AEs related to target expression included skin-related events (any Grade: 66%; Grade 3: 7.3%) and Grade 1–2 dysgeusia/ageusia (36.6%), dry mouth (36.6%), dysphagia (17.1%) and nail changes (12.2%). No RG6234-related AEs leading to discontinuation occurred. MTD was not reached.
At cut-off, median follow-up was 3.5 months (range: 0.03–11.7). The ORR among 34 evaluable patients was 68%. The ≥VGPR rate was 50% and included 2/6 patients with prior anti-BCMA therapy. Median time to first response was 1.3 months (95% CI: 1.1, 1.6). Responses were ongoing in 18/23 (78.3%) patients at cut-off (longest DoR: 10 months).

Conclusion: RG6234 is clinically active and has manageable safety in patients with heavily pre-treated RRMM. IV and SC dose escalations are ongoing.

Continuing poor outlook for relapsed Australian Multiple Myeloma (MM) patients: Impact of limited available therapies

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Aim: To describe the characteristics and outcomes of relapsed refractory multiple myeloma (RRMM) patients participating in the Australia & New Zealand Myeloma and Related Diseases Registry (MRDR) matched to eligibility criteria for the CARTITUDE-1 study.

Method: Two cohorts were analysed. CARTITUDE-1 eligible MRDR(CE-MRDR): 28 patients ≥3 lines of therapy (LOT) including an immunomodulatory drug (IMID), proteasome inhibitor (PI) and anti-CD38 monoclonal antibody (CD38mAb) with ECOG Performance Scale (ECOG PS) 0-2 at diagnosis. Modified(m)CE-MRDR: 132 patients with ≥3 LOT, including an IMID and PI but not a CD38mAb. Moreover, all patients had to have demonstrated progressive disease within 12 months of commencing their most recent LOT. Significance tests for categorical variables were calculated using the chi-squared tests and Wilcoxon rank-sum test for continuous variables. Survival was analysed using a Kaplan-Meier approach, and comparisons between groups, the log-rank tests.

Results: Median age 65.2 and 67.6 years, median time from diagnosis 3.2, 2.1 years and median LOT of 4.0, 3.0 ($p<0.001$), CE-MRDR and mCE-MRDR, respectively. 61% and 43% of CE-MRDR were triple class refractory and penta-exposed, respectively, 68% had undergone autologous stem cell transplant. Responses to next treatment: CE-MRDR: overall response rate (ORR) 23%, complete response (CR) 0%, very good partial response (VGPR) 17%, partial response (PR) 6% with 61% progressive disease (PD). mCE-MRDR, ORR 30% - CR 4%, VGPR 5%, PR 21% and PD 36%. Response to subsequent treatment: CE-MRDR: ORR 0%, stable disease (SD) 33% and PD 67%. mCE-MRDR ORR 31% CR 3%, VGPR 3%, PR 25%, minor response (MR) 25%, SD 19% and PD 25%. PFS1 were comparable at 2.4, 3.4 months ($p=0.219$), as were PFS2 at 3.7, 6.6 months ($p=0.306$), CE-MRDR, m-CEMRDR, respectively. PFS at 12 months CE-MRDR 18%, mCE-MRDR 23% versus 77% in the CARTITUDE-1 study, median overall survival of 5.4, 9.5 months ($p=0.531$), for CE-MRDR and mCE- MRDR, respectively compared to not reached at 12.4 months follow-up with 89% OS rate in CARTITUDE-1(1).

Conclusion: This study confirms the dismal outcome for Australian RRMM patients who have exhausted currently available PBS treatment and highlights their critical need for improved accessibility to newer treatments.

1. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-24.

Ciltacabtagene autoleucel (cilta-cel), a B-cell maturation antigen-directed chimeric antigen receptor T (CAR-T) cell therapy, in relapsed/refractory multiple myeloma (RRMM): CARTITUDE-1 results 2 years post last patient in (LPI)

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Aim: To report updated results from the phase 1b/2 CARTITUDE-1 study (NCT03548207) evaluating cilta-cel in heavily pretreated patients with RRMM. Results 2 years post LPI (~30-month median follow-up [MFU]) will be presented; here we report results at 21.7-month MFU.

Method: Eligible patients with RRMM had ≥3 prior lines of therapy (LOT) or were refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD) and had received a PI, IMiD, and anti-CD38 antibody. After apheresis, bridging therapy was allowed. A single infusion of cilta-cel (target dose 0.75×10^6 CAR+ viable T cells/kg) was administered 5–7 days after lymphodepletion. Safety and efficacy were the primary objectives. Response and minimal residual disease (MRD) negativity (10^{-5} by next-generation sequencing) were assessed.

Results: 97 patients (59% male; median age 61 years) received cilta-cel as of July 22, 2021. Median number of prior LOT was 6 (range 3–18). Overall response rate was 97.9% (94.9% very good partial response; 82.5% stringent complete response). Median times to first response, best response, and ≥complete response were 1.0, 2.6, and 2.9 months, respectively. Median duration of response was not reached (NR). Among MRD-evaluable patients (n=61), 92% were MRD negative (10^{-5}), sustained for ≥6 months in 44% and ≥12 months in 18%. Progression-free survival (PFS) at 2 years was 60.5%. Median PFS and overall survival were NR. PFS rates at 2 years in patients with sustained MRD negativity for ≥6 months and ≥12 months were 91% and 100%, respectively. No new safety signals, new events of CAR-T cell neurotoxicity, movement and neurocognitive treatment-emergent adverse events, or treatment-related deaths have occurred since 1-year MFU. Over ~2 years MFU, 15 second primary malignancies were reported in 11 patients.

Conclusion: At ~2 years MFU, a single cilta-cel infusion resulted in deepening and durable responses and manageable safety in heavily pretreated patients with RR

Daratumumab plus Bortezomib and Dexamethasone (D-Vd) versus Bortezomib and Dexamethasone (Vd) alone in previously treated multiple myeloma patients: Overall survival (OS) results from the phase 3 CASTOR trial

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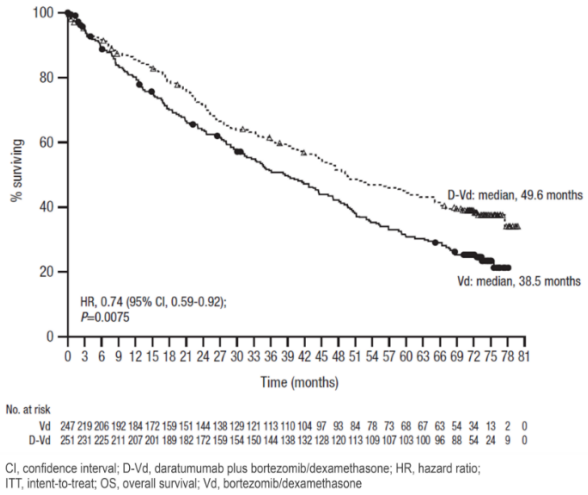
Aim: In the phase 3 CASTOR study, D-Vd significantly prolonged progression-free survival (PFS) versus Vd alone in patients with relapsed/refractory multiple myeloma (RRMM). Here, we report final OS and updated minimal residual disease [MRD]-negativity and safety results after ~6 years of follow-up.

Method: Pts with RRMM and ≥1 prior line of therapy (LOT) were randomized 1:1 to receive 8 (21-day) cycles of D-Vd/Vd. Primary and secondary endpoint: PFS and OS.

Results: Overall 498 pts (D-Vd [251], Vd [247]; median [range] age 64 [30-88] years) receiving a median (range) of 2 (1-10) prior LOT were randomized. At a median (range) follow-up of 72.6 (0.0-79.8) months, a statistically significant/clinically meaningful improvement in OS with D-Vd versus Vd (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.59-0.92; *P*=0.0075 [crossing the prespecified stopping boundary of *P*=0.0323]), representing a 26% reduction in the risk of death with D-Vd was noted (**Figure**). Prespecified subgroup analyses showed an OS improvement with D-Vd across most subgroups (pts ≥65 years/pts receiving 1–2 prior LOT/pts with International Staging System stage-III disease/high-risk cytogenetic abnormalities/prior bortezomib treatment/pts refractory to last prior LOT). The most pronounced OS benefit of D-Vd was seen in pts with 1 prior LOT (HR,0.56; 95% CI,0.39-0.80). D-Vd achieved significantly higher rates of MRD negativity(10^{-5}) versus Vd (15.1% vs 1.6%; *P*<0.0001). The most common (≥10%) grade 3/4 treatment-emergent adverse events (TEAEs; D-Vd/Vd) were thrombocytopenia(46.1%/32.9%)/anemia(16.0%/16.0%)/neutropenia(13.6%/4.6%)/lymphopenia(10.3%/2.5%)/pneumonia(10.7%/10.1%). Discontinuation rates due to TEAEs were low and similar between D-Vd(10.7%) and Vd(9.3%).

Conclusion: D-Vd significantly prolonged OS than Vd alone. These results, together with the OS results in the phase 3 POLLUX study, demonstrate for the first time an OS benefit with DARA-containing regimens in RRMM (greatest benefit of D-Vd observed in pts with 1 prior LOT), supporting early use of D-Vd to maximize pt benefit.

Figure: OS in the ITT population.



CI, confidence interval; D-Vd, daratumumab plus bortezomib/dexamethasone; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Vd, bortezomib/dexamethasone

A phase 1 study with the novel B-cell lymphoma 2 (BCL2) inhibitor BGB-11417 as monotherapy or in combination with zanubrutinib in patients with B-cell malignancies: Preliminary data

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Aim: BCL2 is aberrantly expressed in many hematologic malignancies and promotes tumorigenesis. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study evaluating safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose of oral BGB-11417, a potent, highly selective BCL2 inhibitor, alone or in combination with zanubrutinib, a BTK inhibitor, in patients with relapsed/refractory (R/R) B-cell malignancies.

Method: BGB-11417 (40, 80, 160, 320, or 640mg once daily [QD]) with weekly or daily ramp-up to target dose) was given as monotherapy or combined with zanubrutinib (320mg QD or 160mg twice daily) 8-12 weeks before BGB-11417. Dose-limiting toxicity was evaluated by Bayesian logistic regression. Adverse events (AEs) were reported per CTCAE v5.0.

Results: As of 17Dec2021, 58 patients received BGB-11417 (monotherapy=32; combination=26). Of patients receiving monotherapy, 26 with non-Hodgkin lymphoma (NHL) received ≤640mg and 6 with CLL/SLL received ≤160mg; for those receiving combination treatment, 19 with R/R CLL/SLL received BGB-11417 ≤160mg and 7 with R/R MCL received ≤80mg. MTD has not been reached. Median follow-up was 3.9 months (range=0.1-20.4). Two grade ≥3 AEs (neutropenia=1, autoimmune haemolytic anaemia=1) occurred in combination cohorts. 20 patients discontinued treatment (disease progression=17; AE=1; other=2). One high-risk patient with CLL (monotherapy) had laboratory tumour lysis syndrome (<2%) that resolved without intervention. Early data show that most patients had reduction in sum of product of perpendicular diameters; 2 patients with NHL (monotherapy) had responses (complete response=1). Patients with CLL/SLL had notable reductions in absolute lymphocyte counts at doses ≥1mg; 2 responses (≥partial response) occurred with monotherapy and 12 with combination (≥partial response + lymphocytosis).

Conclusion: Preliminary findings suggest BGB-11417 has promising efficacy and is tolerable at ≤640mg as monotherapy and ≤160mg combined with zanubrutinib. Dose escalation continues as MTD has not been reached. Enrolment is ongoing, data for Waldenström macroglobulinemia and treatment-naïve CLL/SLL are forthcoming

Fixed-duration (FD) ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL) in patients with high-risk genetic features: a subgroup analysis of the phase 2 CAPTIVATE study

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Aim: To report efficacy and safety of first-line, fixed-duration (FD) ibrutinib + venetoclax in patients with high-risk genetic features from CAPTIVATE (NCT02910583), an international, multicenter, phase 2 study that demonstrated deep, durable responses in patients with CLL (Ghia, ASCO 2021; Wierda, *J Clin Oncol* 2021).

Methods Patients aged ≤70 years with previously untreated CLL received orally 3 cycles of ibrutinib then 12 cycles of ibrutinib + venetoclax (ibrutinib 420 mg/day, venetoclax ramp-up to 400 mg/day). After receiving this FD regimen, patients in the FD cohort received no further treatment; patients in the Minimal Residual Disease (MRD) cohort were randomized to subsequent treatment according to MRD status, including a placebo treatment. Outcomes from patients with high-risk features (del(17p), *TP53* mutated, or unmutated IGHV) from the FD cohort and MRD cohort placebo arm were pooled and analyzed.

Results: Of 202 patients (FD cohort: n=159; MRD cohort, placebo arm: n=43), 129 (64%) had high-risk features. Median time on study was 28.7 months (range 0.8-45.1) and 94% of patients completed planned treatment. Median treatment duration for ibrutinib was 13.8 months (range 0.7-24.9) and 11.1 months (range 9.9-22.1) for venetoclax. Best response rates of CR and undetectable MRD in peripheral blood and bone marrow were high (Table). The 18-month landmark estimate for duration of CR was 95%. The 24-month PFS rate was 94%, similar to that of patients without high-risk features (97%). Three percent of patients discontinued ibrutinib or venetoclax due to adverse events. No new safety findings were observed in this analysis of high-risk patients treated with FD ibrutinib + venetoclax. (Table).

Conclusion: First-line ibribrutinib + venetoclax for a fixed duration provides durable treatment-free remissions and sustained PFS in patients with CLL. These clinical outcomes are maintained in patients with high-risk features, with PFS rates that were similar to patients without high-risk features.

Table. Efficacy and safety outcomes in patients with high-risk features treated with FD ibrutinib + venetoclax

	Patients with high-risk features, n=129
Efficacy outcomes	
Overall response rate, n (%)	126 (98)
CR, n (%)	76 (59)
18-mo DOCR, % (95% CI)	95 (85-98)
uMRD $<10^{-4}$ by flow, n (%)	
Peripheral blood	114 (88)
Bone marrow	93 (72)
24-mo PFS rate, % (95% CI)	94 (88-97)
24-mo OS rate, % (95% CI)	98 (93-99)
Safety outcomes	
Grade 3/4 AEs in ≥5% of pts, n (%)	
Neutropenia	38 (29)
Hypertension	12 (9)
Neutrophil count decreased	9 (7)

[a]Defined as ≥3 abnormalities by CpG-stimulated cytogenetics.

SEQUOIA: Results of a phase 3 randomized study of zanubrutinib versus bendamustine+rituximab (BR) in patients with treatment-naive chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)

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Aim: The Bruton tyrosine kinase (BTK) inhibitor, zanubrutinib, was designed for high BTK specificity and minimal toxicity. SEQUOIA (NCT03336333) is a global, open-label, randomized phase 3 study in treatment-naive patients with CLL/SLL without del(17p) who were unsuitable for fludarabine/cyclophosphamide/rituximab.

Method: Patients were randomized to receive zanubrutinib (160 mg twice daily) or bendamustine (day 1-2: 90 mg/m^2) and rituximab (cycle 1: 375 mg/m^2; cycles 2-6: 500 mg/m^2); stratification factors were age (<65 years vs ≥65 years), Binet Stage, IGHV mutation, and geographic region. Primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS) in Cohort 1. Secondary endpoints included investigator-assessed (INV) PFS, overall response rate (ORR), overall survival (OS), and safety.

Results: From 31Oct2017–22Jul2019, 479 patients were enrolled into Cohort 1 (zanubrutinib=241; BR=238). Baseline characteristics (zanubrutinib vs BR): median age, 70.0 years vs 70.0 years; unmutated IGHV, 53.4% vs 52.4%; del(11q), 17.8% vs 19.3%. With median follow-up of 26.2 months, PFS was significantly prolonged with zanubrutinib by IRC (HR 0.42; 2-sided P<.0001), and INV (HR 0.42; 2-sided P=.0001). Zanubrutinib treatment benefit occurred across age, Binet stage, bulky disease, del(11q) status and unmutated IGHV (HR 0.24; 2-sided P<.0001), but not mutated IGHV (HR 0.67; 2-sided P=.1858). For zanubrutinib vs BR, 24-month PFS-IRC=85.5% vs 69.5%; ORR-IRC=94.6% vs 85.3%; complete response rate= 6.6% vs 15.1%; ORR-INV=97.5% vs 88.7%; and 24-month OS=94.3% vs 94.6%. Select adverse event (AE) rates (zanubrutinib vs BR): atrial fibrillation (3.3% vs 2.6%), bleeding (45.0% vs 11.0%), hypertension (14.2% vs 10.6%), infection (62.1% vs 55.9%), and neutropenia (15.8% vs 56.8%). Treatment discontinuation due to AEs (zanubrutinib vs BR)=20 patients (8.3%) vs 31 patients (13.7%); AEs leading to death=11 patients (4.6%) vs 11 patients (4.8%). No sudden deaths occurred.

Conclusion: Zanubrutinib significantly improved PFS-IRC vs BR and was well tolerated, supporting the potential utility of frontline zanubrutinib in treatment-naive CLL/SLL.

Venetoclax with rapid post-apheresis dose escalation is a safe bridge to brexucabtagene autoleucel (brexu-cel) in patients with Mantle Cell Lymphoma (MCL).

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Aim: Prognosis of patients with MCL who fail BTK inhibitors is very poor[1]. Such patients are eligible for CAR-T treatment with brexu-cel in the UK. Poor prognostic features (blastoid/TP53-mutated/high Ki67) are common in real-world datasets[2] so bridging strategies which avoid conventional cytotoxic chemotherapy appear preferable. We assess venetoclax as a bridging strategy.

Method: We reviewed records of all MCL patients who underwent leukapheresis for brexu-cel at King's College Hospital, London until March 2022. We analysed bridging response based on pre-lymphodepletion PET and evaluated incidence of CAR-T toxicity, tumour lysis syndrome (TLS) and infections up to D28 post-infusion.

Results: Seven of 16 patients were bridged with venetoclax. Median age was 61 years. Six patients (86%) were male, six (86%) had stage 4 disease pre-bridging and all seven had high-risk features. Venetoclax was given alone (n=4) or with continued ibrutinib (n=3) and was dose-escalated either weekly (n=3) or using a rapid escalation strategy (n=4) [fig 1]. Grade 3+ neutropenia occurred in two patients (28%). There was one Gd3 infection and one Gd3 TLS, both in a single venetoclax-bridged patient who died of progression pre-infusion. One venetoclax patient vs two non-venetoclax patients could not receive brexu-cel due to bridging failure (14% vs 22%, p=0.6). One venetoclax patient could not be infused due to manufacturing failure (had bendamustine but no venetoclax exposure pre-leukapheresis). There was a trend to shorter bridging time with venetoclax (p=0.06).

CRS/ICANS incidence was similar between groups. Bridging responses and toxicity data are displayed in table 1.

Conclusion: Venetoclax alone, or with a BTK inhibitor may be an effective bridging strategy to brexu-cel in MCL. The rapid dose-ramping strategy as described here appears safe and well-tolerated and can be delivered predominantly through ambulatory care.

First interim analysis of ALPINE study: Results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)

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Aim: CLL/SLL treatment has been transformed with Bruton tyrosine kinase inhibitors (BTKi) such as ibrutinib. Zanubrutinib, a next-generation BTKi, was designed to maximize BTK occupancy and minimize toxicity. ALPINE (NCT03734016) is a global, randomized, phase 3 study of zanubrutinib vs ibrutinib in patients with R/R CLL/SLL; presented here is a preplanned interim analysis conducted ~12 months after 415 patients enrolled between 5Nov2018–20Dec2019.

Method: Patients were randomized 1:1 to zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily), stratified by age (<65 years vs ≥65 years), geographic region, refractory status, and del(17p)/*TP53* mutation. Primary endpoint was investigator-assessed overall response rate (ORR) per 2008 IWCLL guidelines or Lugano criteria; noninferiority of zanubrutinib-to-ibrutinib response ratio was evaluated at noninferiority margin of 0.8558. If noninferiority was demonstrated, superiority of zanubrutinib vs ibrutinib in ORR was tested.

Results: Baseline characteristics (zanubrutinib vs ibrutinib): age ≥65 years: 62.3% vs 61.5%; male: 68.6% vs 75%; >3 prior therapies: 7.2% vs 10.1%; del(17p): 11.6% vs 12.5%; *TP53* mutation without del(17p): 8.2% vs 5.8%. With median follow-up of 15 months, ORR was 78.3% vs 62.5% for zanubrutinib vs ibrutinib (2-sided *P*=.0006, prespecified α=0.0099). ORR was higher for zanubrutinib vs ibrutinib in patients with del(11q) (83.6% vs 69.1%) and del(17p) (83.3% vs 53.8%); zanubrutinib had higher overall 12-months progression-free survival (PFS; 94.9% vs 84.0%) and overall survival (97.0% vs 92.7%). Significantly fewer patients had atrial fibrillation/flutter (AF) with zanubrutinib vs ibrutinib (2.5% vs 10.1%, 2-sided *P*=.0014, prespecified α=0.0099). Zanubrutinib had lower rates of major bleeding (2.9% vs 3.9%), adverse events leading to discontinuation (7.8% vs 13.0%), and death (3.9% vs 5.8%). Zanubrutinib had higher neutropenia rate (28.4% vs 21.7%) while grade ≥3 infections (12.7% vs 17.9%) were lower.

Conclusion: This interim analysis showed zanubrutinib had a superior ORR, improved PFS, and lower AF rate compared with ibrutinib

Utility of FDG-PET in predicting the histology of rebiopsy obtained for suspected relapse/refractory (R/R) non-Hodgkin lymphoma (NHL)

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Aim: FDG-PET is used universally in NHL staging and response assessment. Rebiopsy is the gold standard to confirm suspected R/R disease and its histology. We correlated FDG-PET parameters (SUVMax, SUVMean and Tumour Volume (TV)) with rebiopsy histology (benign pathology versus R/R NHL, indolent versus aggressive NHL). We explored whether any FDG-PET parameter predicts transformation when initial diagnosis was indolent.

Method: This was a retrospective single-centre analysis from 2008-2019 of NHL cases with at least one rebiopsy for suspected R/R disease (N=223). Data collected included baseline clinical, histopathological factors, initial staging FDG-PET parameters (is-PET), rebiopsy timepoint histology and FDG-PET (r-PET). Chi-squared test and Mann-Whitney U Test were used to identify correlating factors and Receiver Operating Curve (ROC) Analysis was used to identify optimal cut-offs.

Results: Out of 346 re-biopsied cases, initial NHL diagnosis was indolent in 40% (FL being 28%) and aggressive in 60% (DLBCL being 39%). Rebiopsy histology was benign in 13% and R/R disease in 79% (58% concordant and 21% discordant NHL histology). No baseline clinicopathological factors correlated with discordant histology. Presence of R/R NHL compared to benign pathology was associated with higher r-PET SUVmax, SUVmean and TV values. Using ROC analysis, TV had the best performance to predict R/R disease (Table 1). Higher SUVmax and SUVmean correlated with aggressive histology compared to indolent histology (Table 1). In sub-group analysis of cases where initial diagnosis was indolent NHL and low grade FL, 70% increase in SUVMax from is-PET to r-PET (ΔSUVMax%) reliably predicted transformation (Table 2).

Table 1: Mean r-PET and optimal cut-off values in benign versus R/R rebiopsy histology and indolent versus aggressive rebiopsy histology

	Benign	R/R NHL	P value	ROC AUC	Optimal Cut-offs (sensitivity, specificity)	Indolent NHL	Aggressive NHL	P value	ROC AUC	Optimal Cut-offs (sensitivity, specificity)
SUVMax	8.9	14.6	<0.001	0.70	≥12 (51%, 87%)	12.4	15.9	0.012	0.62	≥12 (59%,63%)
SUVMean	3.6	5.5	0.001	0.69	≥5 (47%, 90%)	4.7	6.0	0.016	0.63	≥5 (54%, 66%)
TV (ml)	42	352	<0.001	0.80	≥90 (56%, 90%)	427	312	0.239	n/a	n/a

Table 2: Using ΔSUVMax% to predict transformation to aggressive histology

ΔSUVMax % Cut-offs	Indolent NHL (N=116, AUC=0.71, P value=0.027)		Low grade FL (N=69, AUC=0.72, P value=0.039)	
	Sensitivity	Specificity	Sensitivity	Specificity
+25%	71%	61%	67%	69%
+70% (Optimal)	50%	83%	58%	77%
+150%	29%	94%	33%	92%
+200%	21%	100%	25%	100%

Conclusion: r-PET parameters can predict R/R disease, aggressive NHL histology and transformation with moderate reliability but cannot replace rebiopsy in clinical practice. Doubling of SUVmax almost always indicates transformation to aggressive NH

Updated 96 week results from ASCEMBL, a phase 3 study of asciminib vs bosutinib in patients with chronic myeloid leukemia in chronic phase after ≥2 prior tyrosine kinase inhibitors

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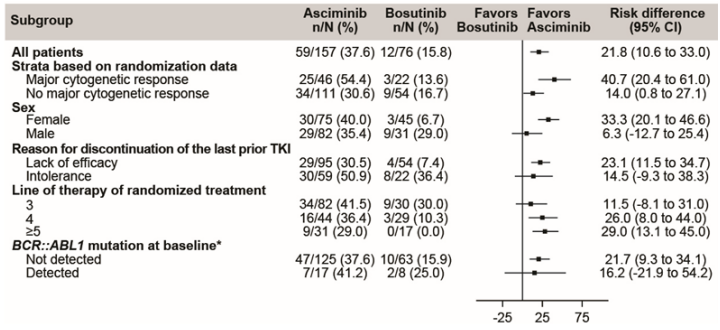
Aim: In the ASCEMBL primary analysis, week (wk) 24 cutoff, asciminib had superior efficacy and better safety/tolerability vs bosutinib (BOS) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) after ≥2 prior tyrosine kinase inhibitors (TKIs). We report updated efficacy and safety results after 2.3 years of median follow-up (cutoff: October 6, 2021). The key secondary objective was to compare MMR rate at wk 96 on asciminib vs BOS.

Method: Adults with CML-CP after ≥2 prior TKIs, with intolerance/failure were randomized 2:1 to asciminib 40 mg twice daily or BOS 500 mg once daily, stratified by baseline major cytogenetic response (MCyR) status.

Results: 233 pts were randomized to asciminib (n=157) or BOS (n=76). MMR rate at wk 96 (per ITT) was 37.6% on asciminib and 15.8% on BOS (difference adjusting for baseline MCyR was 21.7%), meeting the key secondary objective, and was consistently higher with asciminib in all demographic/prognostic subgroups (Figure). At wk 96, more pts on asciminib than BOS had *BCR::ABL1*^{IS} ≤1% (45.1% vs 19.4%) (Table 1). Median time to treatment failure was 24 months on asciminib and 6 months on BOS. Despite asciminib's longer duration of exposure (median: 103.1 wk vs 30.5 wk), its safety/tolerability continued to be better than that of BOS (Table 2). Most frequent (>10%) grade ≥3 AEs on asciminib vs BOS were thrombocytopenia (22.4%, 9.2%), neutropenia (18.6%, 14.5%), diarrhea (0%, 10.5%), and increased alanine aminotransferase (0.6%, 14.5%).

Conclusion: After >2 years of follow-up, asciminib continued to show clinically and statistically significant, superior efficacy with durable response and better safety/tolerability vs BOS. The difference in MMR rates between the 2 arms increased from 12.2% at wk 24 to 21.7% at wk 96. These results further support the potential of asciminib to transform current standard of care in CML.

Figure. Risk Differences (95%CI) for MMR at wk 96 From Subgroup Analyses



IS, international scale; MMR, major molecular response (BCR::ABL1^{IS} ≤0.1%); TKI, tyrosine kinase inhibitor.
Patients with T315I and V200L BCR::ABL1 mutation or a non-evaluable mutation were excluded from the subgroup analysis

Table 2. Safety Results From ASCEMBL

Safety, n (%)	Wk 24[a]				Wk 96[b]			
	Asciminib (n=156)[c]		Bosutinib (n=76)		Asciminib (n=156)[c]		Bosutinib (n=76)	
	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3
AEs	140 (89.7)	79 (50.6)	73 (96.1)	46 (60.5)	142 (91.0)	88 (56.4)	74 (97.4)	52 (68.4)
AEs leading to discontinuation	9 (5.8)	8 (5.1)	16 (21.1)	12 (15.8)	12 (7.7)	12 (7.7)	20 (26.3)	15 (19.7)
AEs leading to dose adjustment/interruptions	59 (37.8)	53 (34.0)	46 (60.5)	37 (48.7)	66 (42.3)	57 (36.5)	49 (64.5)	39 (51.3)
AEs requiring additional therapy	103 (66.0)	44 (28.2)	67 (88.2)	31 (40.8)	112 (71.8)	52 (33.3)	68 (89.5)	35 (46.1)

AE, adverse event.
[a]Data cutoff: 25 May 2020
[b]Data cutoff: 06 Oct 2021
[c]one patient on asciminib developed cytopenia after randomization and was not treated per investigator's decision.

Table 1. Efficacy Results From ASCEMBL*

Efficacy, (%)	Asciminib (n=157)	Bosutinib (n=76)	Asciminib (n=157)	Bosutinib (n=76)
	At wk 24		At wk 96	
MMR	25.5	13.2	37.6	15.8
CCyR[a]	40.8	24.2	39.8	16.1
BCR::ABL1^{IS}≤1%[b]	44.4	20.8	45.1	19.4
MR^{4}	10.8	5.3	17.2	10.5
MR$^{4.5}$	8.9	1.3	10.8	5.3
	By wk 24		By wk 96	
Cumulative incidence of MMR[c]	24.9	11.9	41.2	22.6
Cumulative incidence of BCR::ABL^{IS}≤1%[b,d]	41.5	25.2	53.7	33.7
	≥ 24 wk		≥ 72 wk	
Probability of maintaining MMR, % (95% CI)[e]	98.4 (89.3-99.8)	100 (NA)	96.7 (87.4-99.2)	92.9 (59.1-99.0)
Probability of maintaining *BCR::ABL1*^{IS}≤1%, % (95% CI)[f]	94.6 (86.2-97.9)	95.0 (69.5-99.3)	94.6 (86.2-97.9)	95.0 (69.5-99.3)
	Long-term outcomes (by 1 year)		Long-term outcomes (by 2 year)	
Estimated rates of PFS	95.1	88.6	94.4	91.1
Estimated rates of OS	98.0	98.6	97.3	98.6

CCyR, complete cytogenetic response; IS, international scale; MMR, major molecular response (BCR::ABL^{IS}≤0.1%); MR^{4}, BCR::ABL^{IS}≤0.01%; MR$^{4.5}$, BCR::ABL^{IS}≤0.0032%; NA, not applicable; OS, overall survival; PFS, progression-free survival; pt, patient

*Data cutoff: 06 Oct 2021
[a]In pts without CCyR at baseline (asciminib, n=103; bosutinib, n=62)
[b]In pts with BCR::ABL1^{IS} >1% at baseline (asciminib; n=142; bosutinib, n=72)
[c]Adjusted by competing risks, including discontinuation from treatment for any reason without prior achievement of MMR
[d]Adjusted by competing risks, including discontinuation from treatment for any reason without prior achievement of BCR::ABL^{IS}≤1%
[e]In pts who achieved MMR (asciminib, n=69; bosutinib, n=18)
[f]In pts who achieved BCR::ABL^{IS}≤1% (asciminib, n=78; bosutinib, n=24)

Identification of DDX41 mutations through routine molecular testing in patients undergoing assessment for myeloid malignancy

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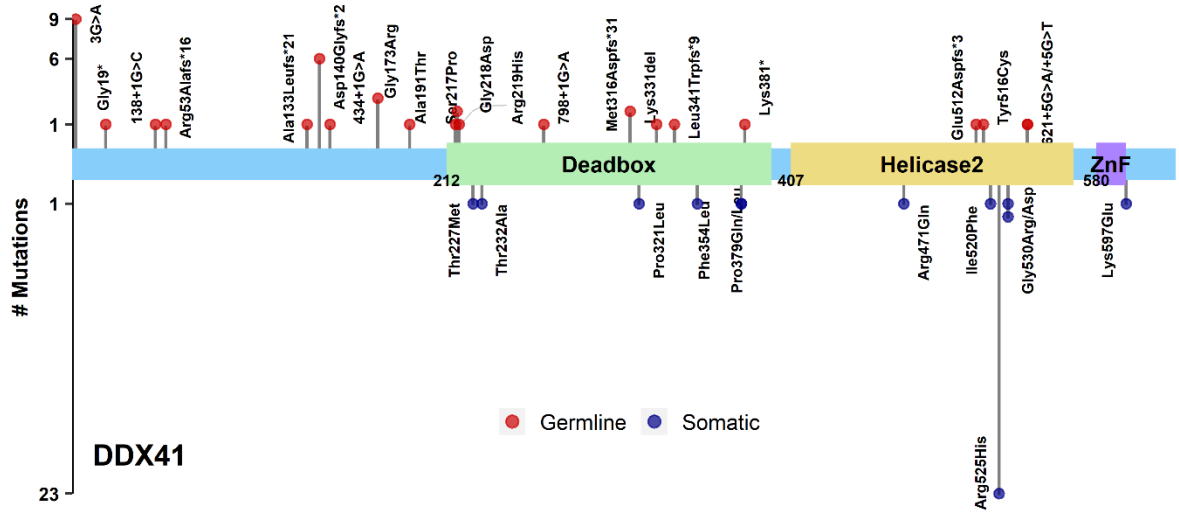
Aim: To characterise the incidence and clinical implications of deleterious germline *DDX41* mutations in patients (pts) undergoing molecular testing as part of routine multi-gene panel testing.

Method: Data were aggregated from consecutive samples between October 2021 and April 2022 referred for NGS multi-gene panel clinical sequencing to the Peter MacCallum Cancer Centre Molecular Haematology Laboratory.

Results: 960 pts underwent testing for myeloid malignancy or reassessment of previously diagnosed myeloid malignancy during the seven-month study period. In 38 pts (4%), a deleterious mutation in *DDX41* was detected (see figure); median age was 67 years (range 33-84 years) and male:female ratio was 1.7:1. Indication for testing included cytopenias for investigation (n=26), MDS reassessment (n=7), AML reassessment (n=2), and reassessment following allogeneic stem cell transplant (alloSCT, n=3). Of the 26 pts with cytopenias, bone marrow biopsy diagnosed AML (n=9), MDS (n=14) and was non-diagnostic with mild dysplasia only in 3 pts. 8/38 (21%) pts harboured novel *DDX41* mutations not previously reported in the literature. 33 (87%) pts had a somatic 'second hit' mutation in *DDX41* (see figure) and 31 (82%) pts had a somatic mutation detected in a non-*DDX41* gene (range 1-4 mutations/pt) including *DNMT3A* (n=8), *SRSF2* (n=7), *ASXL1* (n=6) and *CBL* (n=6). Three pts had *DDX41* mutations detected for the first time post alloSCT from a related donor with two of these pts developing donor-derived clonal haematopoiesis. 24 at-risk family members have undergone predictive testing to date by our service as a result of identification of these 38 probands.



Conclusion: Our large real-world Australian cohort has identified germline *DDX41* mutations in 4% of patients undergoing testing for myeloid malignancy. Whilst recognition of this entity is important for treatment planning, testing of at-risk family members and transplant decision making, the potential resource requirement by this patient group is significant.

Senolytics can restore function of profoundly senescent tMN bone marrow stroma

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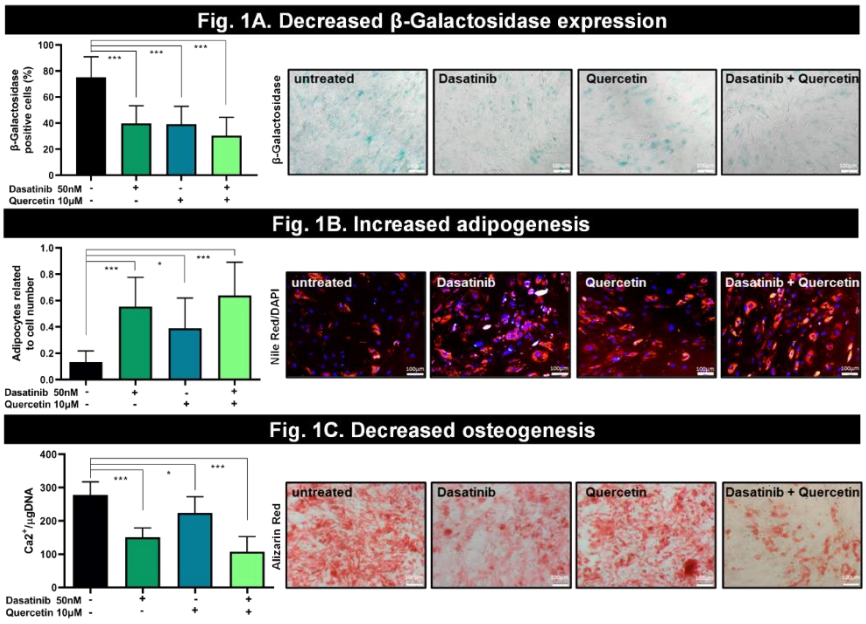
Background: Therapy-related myeloid neoplasm (tMN) is considered a direct consequence of cytotoxic therapy induced DNA damage in hematopoietic stem cells. Despite increasing recognition that altered stroma can also drive leukemogenesis, the functional biology of the tMN microenvironment remains unknown.

Aims and Methods: We performed multi-omic (transcriptome, DNA damage response, cytokine secretome and functional profiling) characterization of bone marrow stromal cells from tMN patients. Critically, we also compared (i) patients with myeloid neoplasm and another cancer but without cytotoxic exposure, (ii) typical primary myeloid neoplasm, and (iii) age-matched controls to decipher the microenvironmental changes induced by cytotoxics versus neoplasia.

Results: Strikingly, tMN exhibited a profoundly senescent phenotype with induction of *CDKN1A* and β-Galactosidase, a characteristic flattened morphology, and impaired proliferation. Moreover, tMN stroma showed delayed DNA repair and defective adipogenesis. Despite their dormant state, tMN stromal cells were metabolically highly active with a switch towards glycolysis, and secreted multiple pro-inflammatory cytokines indicative of a senescent-secretory phenotype that inhibited adipogenesis. Critically, senolytics not only significantly reduced senescence burden of tMN stroma (Fig.1A), but also restored adipogenesis as reflected by a six-fold increase in adipogenic potential (Fig.1B) and reduced aberrantly excessive osteogenic potential to near normal (Fig.1C). Finally, sequential patient sampling showed senescence phenotypes were induced within months of cytotoxic exposure, well prior to the onset of secondary cancer.

Conclusion: Our data underscores a role of senescence in the pathogenesis of tMN and provides a valuable resource for future therapeutics.



Treatment-free remission (TFR), after a defined duration of tyrosine kinase inhibitor (TKI), should be the goal of every newly diagnosed patient with CML: A single centre experience with long-term follow-up.

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Aim: Prior to TKIs, CML was a uniformly fatal disease unless the patient underwent allogeneic-HSCT. It is now well accepted that some patients can achieve long-term TFR – either cured or functionally cured. We present a single centre experience, with long-term follow up, of a cohort of CML patients undergoing TFR attempts.

Method: We searched our database of 173 patients diagnosed with CML between 1994 and 2022 for those who could be eligible for TFR: CML diagnosed in 1st chronic phase (CP1); no allogeneic HSCT in CP1; >3 yrs of treatment with TKI; adequate follow-up.

Results: Of the 173 patients, 120 fulfilled the criteria above and was the cohort analysed. 68 (57%) achieved the generally accepted criteria to attempt TFR: >3 years of TKI treatment; a deep molecular response (MR4 or better). 37 (54%) remain in TFR with median follow-up of 39 months (range 1-180 months). 2 patients with acquired mutations and 1 with an acquired cytogenetic abnormality are long-term TFR successes.

All patients who had CML recurrence (bcr-abl >0.1%) restarted TKI and rapidly returned to a major molecular response (MMR) or better. No patient developed accelerated or blast phase.

11 (35%) of the 31 failed TFR patients had a 2nd attempt at TFR (if MR4 or better was obtained for >5 yrs). Currently, 6 (55%) remain in TFR.

17 patients (25%) developed a withdrawal syndrome. All but 4 patients had resolution over a median of 11 months (range 1-25 months). Some patients benefitted from a course of prednisolone.

Conclusion: Most patients with newly diagnosed CML will at some stage be eligible for a TFR attempt, and a majority of those will achieve long-term TFR – hence, ~30% will be actually or functionally cured. TFR is safe with no cases of disease progression, although the withdrawal syndrome can be temporarily troublesome.

Discovery and Optimisation of Neoepitope Directed Immunotherapy for Myelofibrosis with Calreticulin Mutation

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Aim: Mutations within calreticulin (*CALR*) are the second most common genetic aberration associated with myelofibrosis (MF), observed in 70% of non-JAK2, non-MPL cases. Patients with *CALR* mutations respond poorly to JAK inhibitors and currently no mutation-specific approach exists. Virtually all *CALR* mutations are indels within exon 9 leading to a neoepitope believed to activate the thrombopoietin receptor (TpoR) by an undefined mechanism. Here we engineered neoepitope-specific monoclonal antibodies that have mutation-specific biological activity.

Method: Rats immunised with the CALR mutant peptide were screened by ELISA for a strong immunogenic titre. Engineered TF-1 cells expressing TpoR and $CALR^{mut}$ were cultured in the presence of mAbs and downstream signalling was assessed. Primary MF CD34+ cells from CALR mutant patients were differentiated into megakaryocytes in the presence of mAbs or IgG. *CALR*-dependent in vivo models were established in NSG mice.

Results: We engineered rat mAbs after immunisation with the mutant-CALR neoepitope peptide and clones 4D7 and 9H11 showed superior activity, in addition to binding to different epitopes. 4D7 inhibited cell proliferation of TF-1 TpoR $CALR^{mut}$ cells, compared to TpoR alone ($p<0.0001$). Additionally, 4D7 reduced TpoR phosphorylation, blocked constitutive phospho-STAT5 and phospho-ERK signalling and induced an apoptotic response in $CALR^{mut}$ cells. We tested activity in primary *CALR*^{mut} CD34+ cells through megakaryocyte differentiation in liquid culture and colony formation and 4/5 patient samples showed inhibition of megakaryocyte progenitors by mAb treatment by at least 60% ($p<0.0001$). Additionally, both bone marrow engraftment and chloroma models in NSG mice showed significantly prolonged survival with 4D7 treatment and a reduction of human CD33+ in the peripheral blood or tumour size in comparison to controls. Data showing humanised versions and combinatorial strategies with and without ruxolitinib is also present.

Conclusion: These results underscore the potential for an effective immunotherapeutic approach with clinical utility in *CALR*-driven myeloproliferative neoplasms and in *CALR*-mutant patients that develop ruxolitinib-resistance.

Clinical and patient-reported outcomes (PROs) in a phase 3, randomized, open-label study evaluating axicabtagene ciloleucel (axi-cel) vs standard-of-care (SOC) in elderly patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) (ZUMA-7)

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Aim: In a preplanned subgroup analysis of the Phase 3 ZUMA-7 study, we assessed outcomes, including PROs, of second-line axi-cel (an autologous anti-CD19 CAR T-cell therapy) versus SOC in elderly patients with R/R LBCL.

Method: Patients aged ≥65 years with R/R LBCL ≤12 months after 1L chemoimmunotherapy were randomized 1:1 to axi-cel or SOC. PRO instruments, including the EORTC QLQ-C30 (Global Health [GH] and Physical Functioning [PF]) and the EQ-5D-5L VAS, were administered at specified timepoints. The QoL analysis set included all patients who had a baseline and ≥1 PRO measure at Day (D) 50, D100, or D150.

Results: As of 03/18/2021, 51 and 58 patients were randomized to axi-cel and SOC, respectively, with median ages (range) of 70 years (65-80) and 69 years (65-81). At baseline, more axi-cel versus SOC patients had second-line age-adjusted IPI 2-3 (53% vs 31%) and elevated LDH (61% vs 41%). EFS was superior with axi-cel versus SOC (HR, 0.276, descriptive *P*<.0001), with higher CR rates (75% vs 33%). Grade ≥3 treatment-emergent adverse events (AEs) occurred in 94% and 82% of axi-cel and SOC patients, respectively, and Grade 5 treatment-related AEs occurred in 0 and 1 patient. In the QoL analysis set (46 axi-cel and 42 SOC patients), there were clinically meaningful differences in mean change of scores from baseline at D100 favoring axi-cel for EORTC QLQ-C30 GH (*P*<.0001) and PF (*P*=.0019) and EQ-5D-5L VAS (*P*<.0001). For all 3 domains, scores also favored (*P*<.05) axi-cel over SOC at D150. Mean estimated scores numerically returned to or exceeded baseline scores earlier with axi-cel (by D150) but never equaled or exceeded baseline scores by Month 15 with SOC.

Conclusion: Axi-cel demonstrated superiority over second-line SOC in patients ≥65 years with improved EFS, manageable safety profile, and meaningful improvement in QoL over SOC.

An open-label phase 1/2 study of favezelimab (MK-4280; anti–LAG-3) and pembrolizumab co-blockade in patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) who progressed after anti–PD-1 therapy

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Aim: The MK-4280-003 study (NCT03598608) evaluated favezelimab plus pembrolizumab in R/R hematologic malignancies. Cohort 2 included patients with anti–PD-1–refractory R/R cHL.

Method: Patients had R/R cHL after receiving or were ineligible for autologous stem cell transplantation, and disease progression after ≥2 doses of anti–PD-1 therapy. Safety lead-in (part 1; all cohorts) using modified toxicity probability interval design to identify recommended phase 2 dose (RP2D) was followed by dose-expansion (part 2). Patients received pembrolizumab 200 mg + favezelimab 200 mg or 800 mg IV Q3W in part 1. In part 2, patients received pembrolizumab + favezelimab at RP2D for ≤35 cycles. Primary end point: safety. Secondary end point: objective response rate (ORR). Exploratory end points: duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Results: Only 1 dose-limiting toxicity (DLT; autoimmune hepatitis [grade 4]) occurred with favezelimab 200 mg; no DLTs occurred at 800 mg (established as RP2D). Cohort 2 included 34 patients. At database cutoff (March 21, 2022), median follow-up was 18.2 months. Treatment-related adverse events (TRAEs) occurred in 28 patients (82%); most commonly (≥15%) hypothyroidism (18%), fatigue (15%), and nausea (15%). Grade 3/4 TRAEs occurred in 6 patients (18%); 6 (18%) discontinued treatment due to TRAEs. No treatment-related deaths occurred. ORR for patients with opportunity for postbaseline assessment (n=33) was 30% (95% CI, 16-49; 2 complete responses/7 partial responses); median DOR was 19.4 ([95% CI, 0.0+ to 19.4 months). 70% of responders received anti–PD-1 as most recent therapy. Median PFS for cohort 2 was 9.4 months (95% CI, 5.1-14.7); 12-month PFS was 39%. Median OS was 25.7 months (95% CI, 21.2-not reached); 12-month OS was 91%.

Conclusion: Favezelimab 800 mg + pembrolizumab 200 mg Q3W was well tolerated and demonstrated antitumor activity in anti–PD-1–refractory R/R cHL, suggesting combination may reinduce response

Outcome of patients with disease progression post CAR T-cell therapy for large B-cell lymphoma (LBCL)

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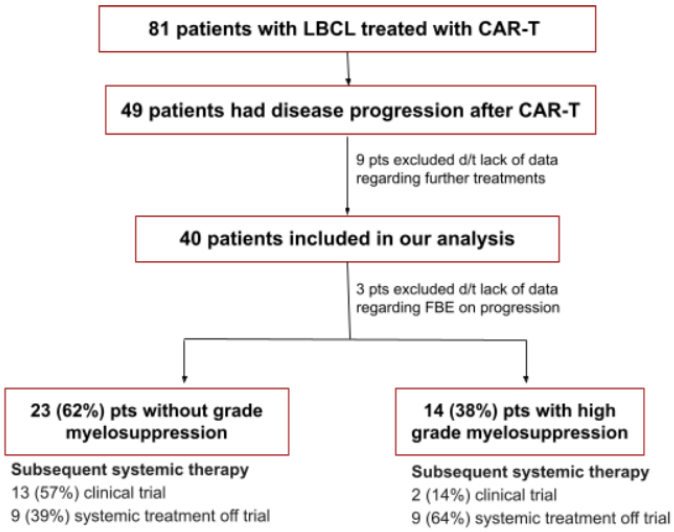
Aim: Patients with disease progression after CAR T-cell therapy for aggressive lymphoma has a poor outcome. We sought to describe our institutional experience of patients with progressive disease after CAR T–cell therapy, including subsequent lines of therapy and outcomes.

Method: We performed a retrospective cohort study of patients with LBCL treated with CAR T-cell therapy in third-line or beyond at our centre between June 2016 and May 2022 that subsequently progressed. Data were collected on toxicities, including haematological parameters, during the first month and at time of progression, first subsequent line of systemic therapy, use of radiotherapy and subsequent transplant, and survival.

Results: Eighty-one patients with LBCL treated with CAR T-cell therapy (62 tisa-cel, 19 axi-cel) were identified. Forty-nine patients with progressive disease after CAR T-cell therapy were included. Nine patients had insufficient data regarding subsequent treatments and/or survival and were excluded from subsequent analyses. The median time to progression after CAR-T was 63 days (range 13-533 days). At a median follow-up of 141 days from progression, 21 patients had died. The median overall survival (mOS) from first progression was 203 days. At the time of progression, 14/37 (38%) patients had at least one grade 3/4 cytopenia (8/37 (22%) neutropenia, 11/37 (30%) thrombocytopenia). 36/40 (90%) patients received subsequent systemic therapy. The mOS from progression was 84 days vs 319 days for patients with and without high-grade cytopenias at progression (p=0.14).

Conclusion: In our institutional experience, the majority of patients with progressive disease after CAR-T therapy for aggressive lymphoma were able to receive further systemic therapy, including a high proportion that enrolled in clinical trials, despite high rates of cytopenias. Despite further treatment the outcome was poor, including short overall survival. Prospective trials targeting disease progression post CAR T-cell therapy are needed to improve the outcome of this high-need group.

	First subsequent line of therapy for patients who progressed post CAR-T
Number of patients	N=40
Median time to progression	63 days
Subsequent systemic treatment	16 (40%) clinical trial 9 (23%) lenalidomide +/- rituximab 4 (10%) bispecific off trial 4 (10%) chemoimmunotherapy 3 (8%) palliation 2 (5%) checkpoint inhibitor off trial 1 (3%) second CART infusion + lenalidomide
Radiotherapy	7 (18%) prior to systemic therapy 4 (10%) concurrent to systemic therapy 1 (3%) as sole treatment for local recurrence
Haematopoietic cell transplantation (HCT)	1 (3%) autologous HCT 1 (3%) allogeneic HCT



Phase I clinical trial of place-of-care manufactured CD19 CAR T cells for the treatment of relapsed / refractory B cell cancers

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Aim: CD19 CAR T cells are currently approved and funded but not all patients who may benefit from the treatment are eligible or are able to be safely bridged. The aim of this study is to investigate the safety and feasibility of CD19 CAR T cell therapy using on-site manufacturing within an academic tertiary hospital setting.

Method: This study is open to adults (aged □ 18 years) with relapsed or refractory CD19+ B cell cancers who are ineligible for TGA-approved CAR T cells. CAR T cells are manufactured from fresh leukapheresis collection using a semi-automated closed system (Miltenyi Biotec, Germany) within the Cellular Therapy Laboratory at Royal Brisbane & Women's Hospital. Participants received 3 days of fludarabine / cyclophosphamide lymphodepletion chemotherapy followed by an infusion of non-cryopreserved CAR T cells at a dose of 0.5x10e6/kg (if high-risk for cytokine release syndrome, CRS) or 2x10e6/kg (if standard risk for CRS). Trial ID: ACTRN12621000762853

Results: Seven participants were recruited between July 2021 and May 2022, including one currently in manufacture. Of the 6 evaluable participants, the diseases were: B-ALL (2), follicular lymphoma (2), mantle cell lymphoma (1) and Burkitt Lymphoma (1). All had successful manufacture of an infusible product and 5 of 6 met the target cell dose. Median time from apheresis to infusion was 13 days (range 12 – 13). Three patients had CRS, all grade □ 2. None had neurotoxicity. Of the evaluable patients, there were 3 complete remission, 1 stable disease, 2 progressive disease. B cell aplasia was documented in all 5 patients who survived >30 days. Two patients with B-ALL had loss of B cell aplasia at 3 and 6 months.

Conclusion: CAR T cells can be manufactured within a routine cell processing laboratory with short turnaround time. Early data demonstrates safety. The study is ongoin

Efficacy of Ibrutinib, Rituximab and mini-CHOP in Very Elderly Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma: Final Results from the Australasian Leukaemia & Lymphoma Group NHL29 Study

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Aim: The optimal treatment strategy for very elderly pts with DLBCL remains unclear. We conducted a prospective Phase II study of ibrutinib-R-mini-CHOP in pts ≥75yrs with newly diagnosed DLBCL 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, the latter being presented here.

Method: Pts received six 21-day cycles of ibrutinib 560mg daily and R-mini-CHOP (Rituximab 375mg/m2, cyclophosphamide 400mg/m2, doxorubicin 25mg/m2, vincristine 1mg on day 1 & prednisone 40mg/m2 or 100mg/d x 5) followed by an additional two 21 day cycles of rituximab + ibrutinib (or high dose methotrexate for CNS prophylaxis). The efficacy primary endpoint was 2yr OS. Sample size calculations were made using a one-sample two-sided approach to detect a 15% improvement on the fixed reference OS (59%) and PFS (47%) rates[1].

Results: Eighty pts were recruited from Nov 2015 to Dec 2018. One died prior to receiving treatment and is excluded from the analysis. Baseline demographics are shown in Table 1. Two-year OS was 68% (95% CI 55-78%), not differing significantly from the null hypothesis of 59% (p=0.11), (Figure 1A). Two-year PFS was 60% (95% CI 49-72%), significantly different from the reference 47% (p=0.03), (Figure 1B). 30/79 pts (38%) have died. 67% pts experienced an SAE. Most common AEs were infections & diarrhoea (majority grade 1-2).

Conclusion:
The addition of ibrutinib to R-mini-CHOP was deliverable with an improved 2-yr PFS compared to R-mini-CHOP alone. While there was a trend towards improvement in 2-yr OS, our target 15% increase was not achieved in this small sample size. Despite considerable and not unexpected toxicity in this elderly cohort, the QOL and functional improvements in survivors are also promising. These data support further study of the addition of BTK inhibitors to R-mini-CHOP in elderly patients with DLBCL.

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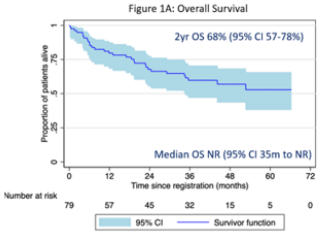
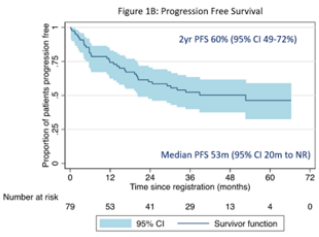
Table 1: Baseline Demographics

Sex	Male	39 (49%)
	Female	40 (51%)
Median Age (years)		81.5 (range 75-95)
		65% >80yrs
Stage (Ann Arbor)	I (bulky)	1 (1%)
	II	14 (18%)
	III	17 (22%)
	IV	47 (59%)
IPI Risk Score	Low Risk (1)	9 (11%)
	Low-Intermediate Risk (2)	20 (25%)
	High Intermediate Risk (3)	23 (29%)
	High Risk (4&5)	27 (34%)
Cell of Origin (Centralised IHC: Hans)	Non-GCB	45 (57%)
	GCB	34 (43%)
	Double Expressor	26 (33%)
CIRS-G	< 6	42 (53%)
	≥ 6	37 (47%)
Follow-up (months) Data cut-off 26 October 2021	median	34.3 (0.2, 66.3)





Real-world data on lymphoma in adolescents and young adults (AYA) - report from the Lymphoma and Related Diseases Registry (LaRDR).

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Background: Lymphoma in adolescents and young adults (AYA) accounts for 20-25% of cancer diagnosis in the age group[1]. Studies in AYA patients lag behind reported improvements in treatments and outcomes in childhood and adult lymphomas[1-2].

Method: We analysed data from the Lymphoma and Related Diseases Registry (LaRDR) to compare disease features, therapeutic approaches and outcomes between AYA (aged 18-39) with older patients ('adults' aged 40-60). Differences in Diffuse Large B-cell Lymphoma (DLBCL), Burkitt Lymphoma (BL), Primary Mediastinal B-cell lymphoma (PMBCL) and Hodgkin Lymphoma (HL) were analysed between the 2 populations using Chi-squared tests and Wilcoxon rank-sum tests.

Results: 922 lymphoma diagnoses were analysed, with 461 in each age group. Classical HL was the predominant lymphoma in AYA (65.2% vs 23.2%) and DLBCL in adults (16.8% vs 66.2%) (overall p<0.001). PMBCL and BL accounted for 8.5% vs 2.6% and 4.8% vs 3.5% in AYA and adults, respectively. Adults with HL had poorer HL-IPS and higher stage compared to AYA (p<0.001). Prognosis and disease-stage for DLBCL, BL and PMBCL did not differ significantly.

No difference was observed in time to treatment. Treatment for HL differed between AYA and adults (p=0.012), likely reflecting the poorer prognosis and disease-stage in the latter. There was no difference in treatment regimens for other lymphomas across the 2 groups.
Overall survival (OS) was higher for AYA (p<0.001) at median follow up of 34.7 months. Overall combined hazard ratio (HR, adult vs AYA) of 5.4 (95%CI 2.6-11.0; p<0.001) for OS lost significance when adjusted for diagnosis (HR=2.1, 95%CI 0.96-6.68; p=0.063).

Conclusion: AYA lymphoma patients differ from adults in disease subtypes, prognosis and outcomes, and this is consistent with other lymphoma studies acknowledging AYA as a distinct population[3-4]. Mature long-term registry data are required to assess differences in rarer lymphoma subtypes and evaluate long-term toxicity.

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High-throughput sequencing of immunoglobulin genes for measurable residual disease testing in Australian patients with lymphoid malignancy

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Aim: To assess the ClonoSEQ assay in a real-world Australian cohort across a range of B-cell malignancies and clinical contexts.

Methods: We analysed baseline and remission samples from patients with B-ALL, CLL, PCM and MCL using the ClonoSEQ NGS assay (Adaptive Biotechnologies). DNA extraction, library preparation and sequencing (Illumina NextSeq500) was performed at the Peter MacCallum Cancer Centre in Melbourne, Australia. NGS MRD results were correlated with standard-of-care MFC MRD (≥8 colour) and *BCR::ABL1* RT-qPCR results.

Results: A clonotype was identified in 98% (121/124) of baseline samples. An MRD result was obtained for 118/123 remission samples from 97 patients (52 B-ALL, 29 PCM, 23 CLL and 14 MCL). Treatments included chemotherapy, cellular, immuno- and targeted therapies. The DNA input for MRD analysis strongly correlated with total nucleated cell count. The median DNA input for samples that achieved a sensitivity of $1x10^{-4}$, $1x10^{-5}$, $1x10^{-6}$ was 1340ng, 7500ng and 19825ng respectively ($p<0.0001$). Of 117 samples with correlative MFC, 24% (28/117) had a discordant MRD result. 93% (26/28) of the discordant results were NGS^{POS} but MFC^{NEG}, with 73% (19/26) of these attributable to greater sensitivity achieved by NGS compared to MFC. MRD discordance was similar across the four diseases. A higher degree of MRD discordance between NGS and MFC was seen in cases with disease biology and/or treatment factors known to cause challenges in MFC gating (*KMT2A* rearrangement, recent anti-CD19 CAR T-cell therapy, blinatumomab, daratumumab) compared to those without (42% vs 17%, $p<0.05$). 45% (5/11) Ph+ B-ALL samples had discordant NGS MRD and *BCR::ABL1* transcript results including two samples NGS^{POS} without detectable *BCR::ABL1* transcript and three samples with detectable transcript but NGS^{NEG}.

Conclusion: Real-world ClonoSEQ data from Australian patients demonstrate superior sensitivity and ability to detect MRD when compared to MFC, particularly in those receiving antigen-directed therapies. High quality DNA samples should be prioritised for NGS MRD testing.

Asciminib enhances efficacy of dexamethasone in treatment of ABL fusions in acute lymphoblastic leukaemia

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Intro: Asciminib is a novel allosteric inhibitor of the Bcr-Abl kinase. Asciminib is in Phase III trials for treatment of chronic myeloid leukaemia and *BCR::ABL1*+ (Ph+) acute lymphoblastic leukaemia (ALL).

Aim: We assessed efficacy of asciminib in treating Ph-like ALL, a disease with gene expression similar to Ph+ ALL but lacking the hallmark *BCR::ABL1* fusion gene.

Method: Ba/F3 cells were transduced with different *ABL1* fusions and asciminib efficacy evaluated in AnnexinV/7-AAD cell death assays. Cells from a relapsed *NUP214::ABL1* T-ALL patient were injected into NSG mice to establish a patient-derived xenograft (PDX) model. STAT5/CRKL phosphorylation and hCD45 levels were investigated by flow cytometry. Once mice reached 5% hCD45+ cells in PB, treatment was commenced: citric acid control, dexamethasone, dasatinib, asciminib, combination asciminib+dexamethasone. At experimental endpoint (>50% hCD45+ cells in PB) mice were humanely killed and organs harvested for analysis.

Results: Transduced Ba/F3 cells demonstrated varying sensitivity to asciminib (Table 1) with Ba/F3 *NUP214::ABL1* cells most sensitive, LD_{50}=8.7 µM (p=0.0086 compared with control). Following asciminib treatment, Ba/F3 *NUP214::ABL1* cells demonstrated reduced phosphorylation of STAT5 (MFI=1820 to 790) and CRKL (MFI=2069 to 951), confirming asciminib inhibits kinase signalling. No phosphorylation of STAT5/CRKL was observed in control cells.

Asciminib treatment significantly increased murine survival outcomes compared with control mice (84 vs 46d, p=0.01) by a time comparable to that of dasatinib treatment (93 vs 46d, p=0.0046). Results were confirmed in two additional *NUP214::ABL1* B-ALL PDX models demonstrating asciminib's potential to treat *NUP214::ABL1* patients. Furthermore, survival of combination$^{asciminib+dexamethasone}$ treated mice was significantly greater than observed in mice receiving dexamethasone alone (p=0.0026). Asciminib treatment reduced spleen and liver weights to that of healthy mice and resolved the leukaemic immunophenotype of blood and bone marrow cells.

Conclusion: Ph-like ALL is associated with high rates of treatment failure and relapse. We demonstrate the efficacy of asciminib in this high risk disease for the first time. These data support addition of asciminib to the treatment regimen for patients with *NUP214::ABL1* ALL, the most common ABL class gene fusion observed in Ph-like ALL.

Table 1: LD_{50} values from cell death assays using asciminib to target different *ABL1* fusion genes identified in ALL. LD_{50} values represent a minimum biological replicate of n=3. Note the steady state C_{max} of asciminib (ASC) in patients treated with 200 mg BID is 15.2 µM

	Control	*NUP214::ABL1*	*RCSD1::ABL1*	*ZMIZ1::ABL1*	*SNX2::ABL1*
LD_{50}^{ASC} (µM)	48	8.7	34	32	42

Treatment naïve follicular lymphoma is associated with dysregulated peripheral blood immunity

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Aim: Inter-tumoral T cell dysfunction in follicular lymphoma (FL) has been well established. However, few studies have examined peripheral blood immunity. We hypothesised that immune dysregulation in peripheral blood would be present in treatment naïve FL.

Method: Baseline PBMC samples from 34 untreated FL patients enrolled in the 1st FLOR clinical trial (First-line treatment for grade 1-3A follicular lymphoma using opdivo [nivolumab] plus rituximab, NCT03245021) and 12 healthy donors were analysed using a single-tube 29 antibody FACS panel on an Aurora spectral flow cytometer. Follicular lymphoma international prognostic index (FLIPI) was used to stratify patients into low/intermediate risk (FLIPI = 0-2, n=26) and high risk (FLIPI ≥3, n=8) for correlation to immune profile.

Results: Compared to healthy donors, there was increased proportions of TRegs ($P<0.0001$) and NK cells ($P<0.05$) in FL patients at diagnosis with a 2 fold increase in TIM3 expression ($P<0.01$) on NK cells. Patients with a FLIPI ≥3 had reduced CD8 Naïve cells with a reciprocal increase in CD8 effector memory cells ($P<0.05$). Expression of PD-1, TIM3, HLA-DR and 4-1BB were significantly increased in both CD4 and CD8 T cells from FL patients with higher expression correlating with a higher FLIPI. By contrast, B cell and monocyte populations were unchanged.

Conclusion: Treatment naïve FL is associated with significant dysregulation of peripheral blood T and NK cells which correlates with disease prognosis. This may impact on responses to immune targeted therapies and correlation of immune profile with patient response to nivolumab ± rituximab will be performed in future analyses

Profiling the genomic landscape of multiple myeloma in Victoria and the importance for widespread application of chromosomal microarray analysis

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Background: Conventional karyotyping (CGEN) and fluorescence in situ hybridisation (FISH) are the cornerstone of genomic profiling of MM, informing prognosis and guiding therapy. Here we review genomic aberrations detected by CGEN and FISH and highlight the benefits of CMA.

Method: From 01/Sep/2020 until 30/Nov/2021, the Victorian Cancer Cytogenetics Service received samples from 800 patients with newly diagnosed MM (NDMM). Samples with ≥5% bone marrow plasma cells (PC) were investigated by G-banded chromosome analysis of unsorted, overnight cultures and interphase FISH on CD138 enriched PCs. Twenty cases were additionally assessed by microarray using high-resolution Illumina Infinium Screening Array-24, v3.0. CMA was interpreted and reported according to genome build GRCh37 and consensus recommendations from the American College of Medical Genetics and Genomics.

Results: Karyotype analysis was successful in 640 (79.9%) cases; with abnormal karyotype identified in 175 (21.9%), 31.4% of which had age-related -Y as sole abnormality. Of the 121 abnormal karyotypes, common recurrent aberrations were -13 (41.3%), +15 (35.5%), +9 (34.7%), +19 (31.4%) and +5 (28.9%). Cases with a normal karyotype were likely to have lower PC% (20.9□22.3% vs. 37.3□24.9%; p<0.0001). Chromosome 1 abnormalities were identified by FISH in 42.7% cases (deletion 1p in 7.45%, gain of 1q in 32.1% and amplification of 1q in 11.9%). *IGH* was rearranged in 55.5% with partner gene identified in 61.6% cases including *FGFR3* (6.7%), *CCND1* (21.7%), *MAF* (4.2%) and *MAFB* (1.8%). *TP53* deletion was detected in 7.4% cases in an average 65% of cells scored (range 12-100%). Microarray analysis was successful in 19/20 (95%) cases; 17/19 (89.5%) identified an abnormal karyotype (range 3-35 copy number variations). 10/12 (83.3%) cases normal by cytogenetics were abnormal by microarray. All cases abnormal by CGEN had a complex karyotype by microarray including cytogenetically cryptic chromoanasynthesis. The combination of FISH and CMA demonstrated genomic abnormalities in 100% cases assessed.

Conclusions: Conventional karyotype analysis is uninformative in 80% of cases while microarray in combination with comprehensive FISH assessment identifies relevant genomic aberrations in all patients with myeloma and should become the new gold standard of genomic profiling in this disease.

Age-related mesenchymal stromal cell senescence is associated with progression from MGUS to multiple myeloma

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Aim: The risk of progression of monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma (MM) increases with advancing age and may be driven by age-related changes to the bone marrow (BM) microenvironment. Notably, senescent mesenchymal stromal cells (MSCs) accumulate in the BM with age and display an altered secretory phenotype, which includes the key MM growth factor interleukin-6 (IL-6). We hypothesise that age-related increases in BM-MSC senescence will lead to increased proliferation of plasma cells in MGUS patients, resulting in progression to MM.

Method: We assessed BM-MSCs isolated from BM trephine biopsies from MGUS (median age: 67.5 [range: 42-84]; n=28) and MM (age: 70 [52-84]; n=8) patients and aged (age: 88 [68-94]; n=11) and young (age: 21 [17-26]) healthy subjects by evaluating senescence-associated-β-galactosidase activity, proliferation and cellular morphology. We also evaluated whether the induction of BM-MSCs senescence via irradiation or replicative exhaustion could promote 5TGM1 and KMM1 MM cell line proliferation in co-culture.

Results: We show that, like BM-MSCs from aged healthy subjects, MM and MGUS patient BM-MSCs exhibit a senescent phenotype characterised by increased β-galactosidase activity, flattened cellular morphology and decreased proliferation compared with BM-MSCs from healthy young individuals. The percentage of senescent cells correlated with MGUS and MM patient age. Notably, the risk of progression to MM is significantly elevated in MGUS patients with increased BM-MSC senescence (p=0.048, HR: 5.8) or *IL6* expression (p=0.012, HR: 10.7; log-rank test). Induction of senescence in young healthy BM-MSCs also increased expression of *IL6* and the proliferation of MM cell lines in co-culture.

Conclusion: Collectively, we show for the first time that the accumulation of senescent BM-MSCs precedes progression from MGUS to MM and that BM-MSC senescence promotes MM proliferation. Moreover, elevated BM-MSC senescence at MGUS may be associated with more rapid progression to MM, which may be mediated by IL-6.

CX3CL1/CX3CR1 chemokine signalling plays role in disease progression and dissemination in t(14;16) multiple myeloma

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Aim: In the plasma cell malignancy multiple myeloma (MM), the chromosomal translocation t(14;16) is associated with increased circulating tumour cells and poor survival. Notably, transcriptomic analyses suggest that elevated expression of the chemokine receptor CX3CR1 is characteristic of this subgroup of patients. We hypothesised that CX3CR1 may promote tumour dissemination, leading to aggressive presentation and poor outcomes. Accordingly, we aimed to evaluate the role of CX3CR1 in proliferation, migration, and adhesion of MM cells in vitro and tumour growth and dissemination *in vivo*.

Method: We constitutively expressed Cx3cr1 in the murine MM cell line 5TGM1 and generated CRISPR/Cas9-mediated CX3CR1 knockouts in the human MM cell line RPMI-8226. The role of CX3CR1 in MM cell proliferation (WST-1), migration (transwell assay), and adhesion to bone marrow endothelial cell was assessed *in vitro*. Cx3cr1-overexpressing or empty vector 5TGM1 cells were injected intratibially in C57BL/KaLwRij mice and tumour growth and dissemination was assessed using flow cytometry.

Results: CX3CR1 overexpression or knockout, in the presence or absence of CX3CR1 ligand CX3CL1 or the CX3CR1 inhibitor AZD8797, had no effect on cell numbers *in vitro*. Overexpression of CX3CR1 in 5TGM1 cells led to increased adhesion to BM endothelial cells, compared with empty vector controls ($p=0.046$), which was inhibited by treatment with AZD8797 ($p=0.044$, two-way ANOVA). In transwell assays, CX3CL1 significantly increased the migration of RPMI-8226 cells ($p=0.024$), which was abrogated by CX3CR1 knockout ($p=0.015$) or by pre-treatment with AZD8797 ($p=0.035$, two-way ANOVA). In mice, CX3CR1 overexpression significantly increased MM PC dissemination to the contralateral limb ($p=0.042$, Mann-Whitney test), but not primary tumour growth within the injected tibia.

Conclusion: CX3CR1 plays a role in MM dissemination through increasing migration and endothelial cell adhesion, without affecting tumour growth. Further investigation is required to determine whether therapeutic targeting of CX3CR1 could prevent MM tumour dissemination in t(14;16) M

SH2B3 (LNK) mutations represent an inherited cause for myeloproliferative disease

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Background: *BCR-ABL*-negative myeloproliferative neoplasms (MPN) arise from dysregulation of the JAK-STAT signalling cascade. SH2B3 is an important negative regulator of this pathway and mutations within this gene have been implicated in MPN.

Aim: To validate germline *SH2B3* mutations associated with MPN by characterising affected families and a murine model of human disease.

Method: Clinical history, full blood examination and targeted amplicon sequencing data was obtained from the families of individuals with an MPN and germline *SH2B3* mutation, and pedigrees have been modelled. A mouse with a human *SH2B3* point mutation, E395K (corresponding to E367K in mouse), was developed using CRISPR/Cas9 gene editing. Peripheral blood, spleen and bone marrow from wildtype, heterozygous and homozygous mice was examined by cytology, histology, immunohistochemistry, and flow cytometry. Non-competitive bone marrow transplantation was undertaken. Statistical analysis was performed using a Mann-Whitney test; a *P* value of <.05 was considered significant.

Results: Three families were found to harbour germline mutations in *SH2B3*, and all were missense variants within the SH2 domain of the protein (the region responsible for biological effects via interaction with phosphorylated signalling partners). In two cases, inheritance was autosomal recessive; the proband was either homozygous (for E395K) or compound heterozygous (for E395K and E400K), whilst heterozygous family members were either unaffected carriers or had subtle blood count abnormalities. The proband in the third family had a heterozygous mutation only (T404A), suggesting T404A may cause more severe disease than the other variants, E395K and E400K. *Sh2b3*-E367K homozygous mice have an MPN phenotype (see Figure 1) with peripheral blood cytoses, splenomegaly and fibrosis. Platelets have increased phospho-STAT3 levels consistent with hyperactive JAK-STAT signalling. The cell-intrinsic nature of this phenotype was confirmed through bone marrow transplantation experiments.

Conclusion: Germline *SH2B3* SH2 domain missense mutations can cause an inherited form of MPN.

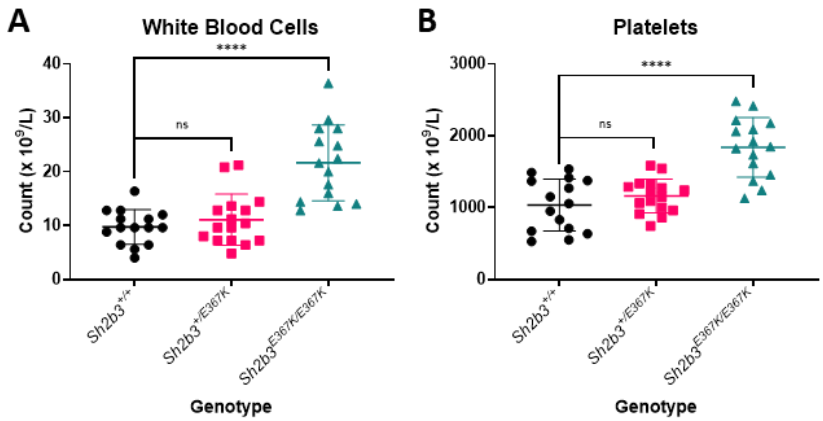

Figure 1: *Sh2b3*-E367K homozygous mice have an MPN phenotype.
(A) White blood cell count in *Sh2b3*$^{+/+}$ (n=15), *Sh2b3*$^{+/E367K}$ (n=16) and *Sh2b3*$^{E367K/E367K}$ (n=15) mice. (B) Platelet count in *Sh2b3*$^{+/+}$ (n=15), *Sh2b3*$^{+/E367K}$ (n=16) and *Sh2b3*$^{E367K/E367K}$ (n=15) mice. ****, $P \leq .0001$; ns, not significant.

ABO incompatibility does not significantly influence infusion, transfusion or survival outcomes after peripheral blood allogeneic progenitor cell transplantation irrespective of whether incompatible products are washed prior to infusion.

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Aim: ABO incompatibility between donor and recipient has been associated with haemolytic transfusion reactions and delayed red cell engraftment following allogeneic haemopoietic progenitor cell (HPC) transplantation. Some centres attempt to reduce the risks of minor and bidirectional ABO mismatch through HPC product washing prior to infusion. Our centre recently abandoned this practice due to uncertain benefit of this time-consuming procedure. We sought to assess the effects of ABO mismatch on infusion, transfusion and survival outcomes, and to determine whether product washing influenced these outcomes at our centre.

Method: We reviewed 237 peripheral blood stem cell (PBSC) transplants undertaken between 2015 and 2019 by data collection from patient medical records and transplant database.

Results: 237 PBSC transplants were conducted (Table). Median age was 52 years with 39% female recipients and 37% related donor grafts. Median follow-up was 36 months.

There was no significant difference in platelet or PRBC transfusion requirement at 30 or 90 days, rate of infusion reaction, time to platelet or neutrophil engraftment or overall survival between groups (Table). Infusion reactions included mostly transient chest tightness, rigors, breathlessness or throat discomfort.

26 (52%) of the minor and bidirectional mismatch transplants were washed. There was no significant difference in rate of infusion reaction (p=0.069) or in platelet or red cell transfusion burden at 30 or 90 days (p=0.777 platelet 30 days, p=0.991 platelet 90 days, p=0.794 PRBC 30 days, p=0.407 PRBC 90 days) in washed versus non-washed transplants.

Conclusion: In our unit ABO mismatch was not associated with transfusion burden, infusion reaction rate or overall survival. Furthermore, washing HPC products to remove isohaemagglutinins prior to infusion did not influence transfusion outcomes.

		Matched	Major mismatch	Minor/bidirectional mismatch	
Number (total 237)		135	52	50	
Age (median)		51	55	53	p=0.439
Patient sex – female		54 (40%)	18 (35%)	20 (40%)	p=0.367
Donor	Matched related	61 (45%)	13 (25%)	16 (32%)	p=0.024
	Matched unrelated	74 (55%)	39 (75%)	34 (68%)	
Conditioning	High intensity myeloablative	75 (56%)	22 (42%)	24 (48%)	p=0.238
	Reduced intensity	60 (44%)	30 (58%)	26 (52%)	
Infusion reaction reported - Yes		24 (17%)	12 (24%)	9 (18%)	p=0.668
RBC transfused to d30 (median, range)		3 (0-24)	3.5 (0-22)	4 (0-37)	p=0.779
RBC transfused to d90 (median, range)		4 (0-48)	7 (0-30)	5 (0-41)	p=0.197
Plt transfused to d30 (median, range)		4 (0-28)	6 (0-35)	4.5 (0-26)	p=0.090
Plt transfused to d90 (median, range)		4 (0-54)	6 (0-42)	5 (0-61)	p=0.242
Time to neutrophil recovery, days median (95% CI)		15 (14-16)	16 (14-18)	16 (15-17)	p=0.345
Time to platelet recovery >20x10^9/L, days median (95% CI)		16 (14-18)	20 (18-22)	20 (16-24)	p=0.667
Overall survival at 1 year		73%	75%	71%	p=0.747
Graft washed - yes		N/A	N/A	26 (52%)	

Lenalidomide, bortezomib and dexamethasone (RVd) in transplant eligible patients with newly diagnosed multiple myeloma (NDMM): an update of the NSW Harmonisation study

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Aim: We proposed the use of the GRIFFIN[1] RVd protocol in all NDMM patients eligible for transplant in NSW. We aim to evaluate efficacy, toxicity, patterns of dose modification, mobilisation and transplantation in a real world setting.

Method: All transplant eligible NDMM patients across 9 NSW sites were prospectively registered. Data was collected including demographics, disease characteristics, induction, mobilisation, transplantation and conditioning. Post-transplant response and consolidation data was further collected.

Results: At time of abstract, a total of 90 patients were registered. 48 patients were male with a median age of 61 (38-73). 78 patients had a calculated R-ISS score (I in 25, II in 40, III in 13). 79 patients had completed induction. 88 patients received the GRIFFIN protocol. The median number of induction cycles was 4. Treatment was prematurely ceased in 8 cases, primarily due to toxicity (7). Dose modifications occurred in 16/79 for lenalidomide, 17/79 for bortezomib and 4/79 for dexamethasone. Peripheral sensory neuropathy was the main cause for bortezomib reduction/cessation in 12/16 cases (28 Grade 1; 7 Grade 2; 1 Grade 3). Hospitalisation occurred in 32 patients. 51 patients achieved □ VGPR response post induction. Mobilisation occurred in 71 patients. Median cycles prior to mobilisation was 4 and median collection days 1. Unplanned plerixafor occurred in 10 and 1 failed to mobilise. The mean CD34+ cell count/kg was $7.36x10^6$. 58 patients have undergone transplantation. At 100 days post-transplant, 40/50 achieved □ VGPR, 8 PR, 1 SD and 1 PD.

Conclusion: This study demonstrates feasibility of treatment harmonisation in NSW. Peripheral neuropathy continues to be a primary non-haematologic toxicity. Ongoing recruitment will improve understanding of toxicity to guide future treatment direction in the real world Australian setting.

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The case for erythrocytapheresis to replace venesection for the treatment of JAK2+ polycythaemia.

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Aim: To compare erythrocytapheresis with venesection as treatment for JAK2+ polycythaemia by assessing the average hematocrit drop, time interval between sessions, number of sessions required, and cost-funding models.

Method: 116 patients with JAK2+ polycythaemia who received treatment with erythrocytapheresis or venesection at Barwon Health between 2014 to 2021 were identified. The median hematocrit drop after each treatment session, intertreatment time interval and number of sessions required to achieve a haematocrit < 0.45 were compared with an independent t-test. A cost-funding analysis was done by assessing the Weighted Inlier Equivalent Separation (WIES) and National Weighted Activity Unit (NWAU) funding models, as well as the cost of each procedure according to the manufacturer's marketing.

Results: 61 patients were treated with venesection only, 20 patients with erythrocytapheresis only and 30 patients with venesection followed by a transition to erythrocytapheresis. Patients treated with erythrocytapheresis achieved a greater median hematocrit drop per session (0.075 vs 0.03, p<0.01) and required fewer sessions to achieve a hematocrit < 0.45 (1 vs 4, p<0.01) than those treated with venesection (Figure 1). The median intertreatment time was 1.5 times longer for erythrocytapheresis than venesection. Cost-funding analysis demonstrated the cost of erythrocytapheresis was $461 compared to $176 for venesection. However, due to increased government funding per treatment session, erythrocytapheresis was more financially viable with a surplus of $297 compared to a deficit of $176 with venesection (Table 1). Even if funding for venesection is restored, erythrocytapheresis may still be more cost-effective than venesection due to a lower mean number of procedures performed per treatment year (3.8 vs 5.3, p<0.01).

Conclusion: Erythrocytapheresis is more efficacious than venesection for the treatment of JAK2+ polycythaemia, allowing for a greater fall in hematocrit in fewer sessions. It is also more financially viable for haematology units under the WIES and NWAU funding models.

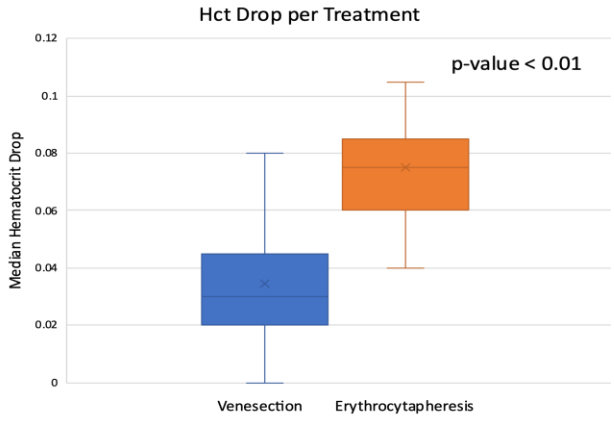

Figure 1: Median drop in hematocrit after each session of Erythrocytapheresis or Venesection.

	Erythrocytapheresis	Venesection
COST	**$461.00**	**$176.14**
Consumables	$273	$82
Machine	$15.63	$0
Maintenance	$36.06	$0
Nurse	$128.04	$85.36
Reception	$8.78	$8.78
FUNDING	**$757.87**	**$0**
WIES Funding	$757.87	$0
NET	**SURPLUS OF $296.87**	**DEFICIT OF $176.14**

Table 1: Cost-funding analysis of Erythrocytapheresis and Venesection per treatment session

Next-generation sequencing in elderly diffuse large B cell lymphoma aged > 75 years identifies new targetable mutations

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Aim: We aimed to map the genetic landscape of diffuse large B cell lymphoma (DLBCL) related mutations in elderly patients ≥ 75 years and compare it to patients that are non-elderly < 75 years using both cell-free DNA (cfDNA) and genomic DNA (gDNA). The ALLG Ibrutinib with R-mini-CHOP (IRiC) study, a prospective multicentre single arm phase II study in elderly (≥ 75 years) DLBCL patients provided an opportunity to genotype this uncommon cohort.

Method: Using next generation sequencing, we assessed 35 DLBCL-associated genes for mutations at diagnosis in 64 *elderly* patients [55 IRiC trial patients + 9 non-trial patients] with a median age of 81 years (75-91 years). Similarly, for comparison, 42 *non-elderly* non-trial DLBCL patients (median 65 years, 29-91 years) were also genotyped.

In addition, mutations in an expanded panel of 150 genes in cfDNA samples were assessed pre and post treatment after cycle 4 on IRiC trial elderly patients (n=36/55) to investigate treatment related mutational changes. Mutations were also evaluated for correlation with survival.

Results: We found that mutations in DTX1 (p=.041), MYC (p=.016), NOTCH2 (p=<.001), PTEN (p=.018) and TET2 (p=.001) were more frequent in the elderly. Presence of mutations in CDKN2A from cfDNA samples, but not gDNA samples, in elderly patients was associated with poor overall survival (p=.008, n=55). Preliminary data for cfDNA analysis in IRiC trial patients (n=36) showed mutations in 27 out of 150 DLBCL related genes to be significantly altered post treatment compared to pre-treatment samples.

Conclusion: Our study has found that the mutational profile of elderly DLBCL patients aged ≥ 75 years is enriched for targetable mutations in DTX1, MYC, NOTCH2, PTEN and TET2 compared to those < 75 years. CDKN2A mutations predicted for poor survival outcomes in elderly DLBCL. Mutational profile was altered by treatment with Ibrutinib and R-mini-CHOP.

Australasian Leukaemia and Lymphoma Group (ALLG) Laboratory Science Study LS21: Molecular Correlates of Response in Relapsed/Refractory Marginal Zone Lymphoma (rrMZL) Patients Treated with Zanubrutinib in the MAGNOLIA Trial

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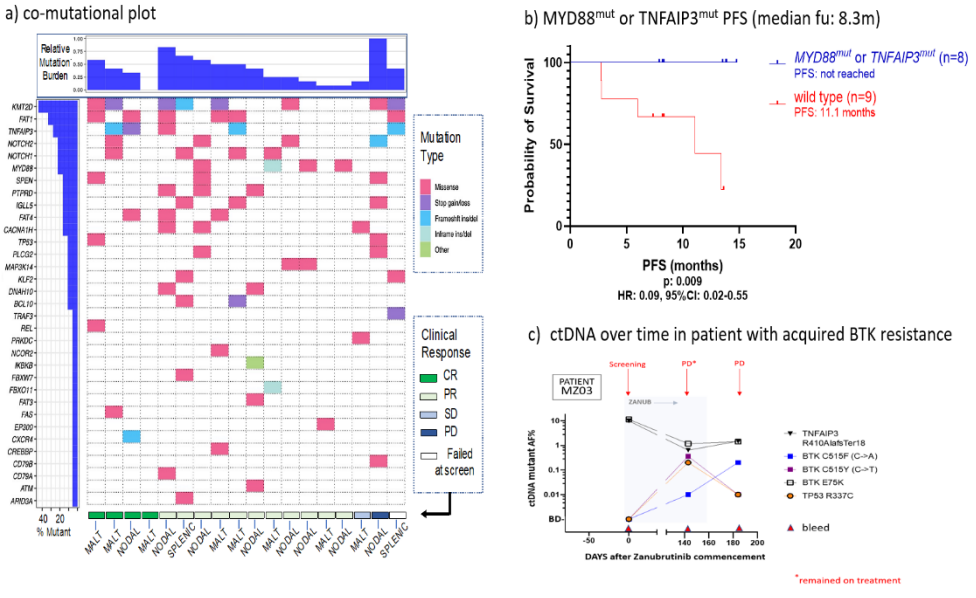
Aim: To identify molecular correlates of response to Zanubrutinib in patients with rrMZL using whole exome sequencing (WES) and determine if emergence of resistance mutations in circulating tumour DNA (ctDNA) heralds clinical progression.

Method: WES (Agilent, Ver7) was performed on 19/25 baseline tumour samples obtained from 18 patients with adequate DNA. For 7 patients, plasma DNA was harvested pre-treatment and at several timepoints during therapy. Plasma DNA was subject to a bespoke hybrid-capture NGS assay for 48 targeted genes. Library synthesis included molecular barcoding that allowed for digital error suppression within the analysis pipeline. NGS assay sensitivity for ctDNA was 0.1%. Mutations (primarily SNVs and indels) were correlated with clinical data and survival analysis using the Kaplan-Meier (log-rank) method.

Results: Baseline WES identified mutations in 33/48 (69%) genes, with a median of 5 affected genes per sample (range: 0-8) (Fig. a). NFkB, NOTCH or BCR pathway genes were implicated in 16/18 (89%) patients. *KMT2D* mutations (n=8) were most common followed by *NOTCH1, NOTCH2, TNFAIP3* and *MYD88* (all n=4). Patients with mutated *MYD88* or *TNFAIP3* had improved PFS (not reached (NR) vs 11.1 months, p: 0.009, HR: 0.09, 95% CI: 0.02-0.55) (Fig. b); patients with *KMT2D* mutations trended to worse outcome (PFS: 13.40 months vs NR, p: 0.06, HR 6.5, 95%CI: 1.06-38.76). 8/14 (57%) mutations detected in WES were present within ctDNA. 40 mutations present in ctDNA were not detected on baseline WES. Two patients had persistent *MYD88* mutations detectable in ctDNA 15 months after treatment commencement. Acquired resistance mutations *PLCG2* (R665W/R742P*)* and *BTK* (C515Y/515F) were detected in 2 patients who progressed (Fig. c).

Conclusion: *MYD88*, *TNFAIP3* and *KMT2D* mutations correlate with response to Zanubrutinib in rrMZL patients. Detection of acquired *BTK* and *PLCG2* mutations in ctDNA while on therapy is feasible and may herald clinical disease progression.



CRISPR gene editing of KLF1 to cure sickle cell disease

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Background: Sickle cell disease (SCD) is characterized by recurrent, vaso-occlusive crises, end-organ dysfunction, and premature death. Until recently, allogeneic stem cell transplant offered the only chance of cure. However, an increased understanding of 'haemoglobin switching' mechanisms in association with advancing molecular editing techniques has made gene therapy an achievable alternative. Krüppel-like factor (KLF1) is an essential, erythroid-specific, transcription factor that binds the β-globin gene promoter to upregulate its expression, whilst regulating the expression of transcription factors such as *BCL11A* and *LRF* that directly repress γ-globin gene expression. Heterozygosity for loss of function mutations in KLF1 leads to elevated HbF and clinical improvement in beta-hemoglobinopathies, whereas homozygosity leads to *hydrops fetalis* (1).

Aim: To modify *KLF1* in the HUDEP-2 cell line (triploid for KLF1) by CRISPR-based gene editing and examine transcriptome changes, differentiation capacity and HbF reactivation (2).

Method: We designed two separate guide RNAs with corresponding homology directed repair templates to target the second exon of *KLF1* and ablate its function. We optimised transfection protocols and tested the on-target specificity of our guide RNAs using Sanger sequencing and the web tools, TIDE and CRISPR-ID. Globin gene expression was assessed by qRT-PCR and RNAseq was employed to examine other transcriptome changes. We examined differentiation potential and HbF cells by flow cytometry, and haemoglobin type by HPLC.

Results: We show HUDEP-2 cells require at least one copy of KLF1 for survival. Heterozygous clones differentiate normally. Gamma-globin is upregulated 10-fold and *BCL11A* down-regulated 3-fold in clones that harbour 2/3 edited alleles. HbF was markedly induced (by HPLC) and HbF cells were present in many of these clones. *ICAM-4* and *BCAM*, both cellular adhesion molecules, are down-regulated. We anticipate their reduced surface expression may provide additional benefit in reducing endothelial adhesion of sickled red cells.

Conclusion: KLF1 is an exciting target for future gene editing studies in SCD.

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Assisted reproductive technology required to achieve high conception rates, despite low rates of hypogonadotrophic hypogonadism in transfusion dependent Thalassaemia and Sickle Cell Disease patients

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Aim: Improved iron chelation has altered the natural history of transfusion dependent thalassemia (TDT) and sickle cell disease (SCD). Fertility challenges and pregnancy complications have historically limited reproductive options in this group, however improved disease management has made subfertility a chronic disease complication deserving increased attention. Despite this, there are very few reports and no Australian data describing fertility and pregnancy outcomes in this population.

Method: A 20 year retrospective analysis (1997 – 2017) at an Australian centre identified 14 women with TDT and SCD who tried to conceive. Conception rates, use of assisted reproductive technologies (ART), and pregnancy outcomes were assessed by medical record audit.

Results: The median age at conception was 28 years (range 21-35). A total of 28 pregnancies were reported. Fifteen of the 28 pregnancies (54%) were spontaneous. Amongst pregnancies achieved with ART, 69% were in patients without underlying hypogonadotrophic hypogonadism (HH). No association was seen between serum ferritin and ART use. There was a trend between maternal age and use of ART. Two thirds of primiparous women underwent caesarean section, with prematurity complicating 20% of births. Intrauterine growth restriction (IUGR) occurred in 28% of live births. Post-partum haemorrhage occurred after four deliveries. There were no neonatal or maternal deaths.

Conclusion: Our data is the first analysis of fertility and pregnancy outcomes in Australian TDT and SCD patients. Although high conception rates were observed, ART was required for almost half of pregnancies. Only 30% of assisted conception occurred in women with HH, indicating that other factors are involved in subfertility in this patient population. Guidelines around pregnancy management in this population abound, however large prospective studies are needed to identify those at risk of sub- and infertility, even in the era of effective chelation. Our data also highlight the importance of affordable ART access for this population

Benchmarking paediatric sickle cell care in Australia.

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Sickle cell disease (SCD) is a multisystem vasculopathy, associated with reduced life expectancy and high carer burden. SCD in Australian children has been increasing and disproportionately affects migrant families with socio-economic challenges. Local models of care are still evolving and there is a need for service benchmarking to define consensus best practice. Key issues include access to affordable Hydroxyurea (HU) paediatric formulations, red cell exchange (RCE), antenatal/newborn screening policy and consideration of indications for curative bone marrow transplantation (BMT).

Aim: To survey health care service delivery for paediatric SCD at specialist centres in Australia.

Method: Lead clinicians at six centres were surveyed to determine: basic demographics, availability of current treatment modalities, transfusion practices, service integration, care pathways and access to support services and transition services. Current challenges to optimal health care delivery were identified.

Results: 285 cases were identified. Variations in care included: inequity of funding for HU formulation, access to RCE as recommended transfusion method, screening protocols for stroke prevention, SCD pain management pathways. Identified challenges to optimal care delivery were consistent across the centres, with common themes identified: difficulty accessing support services (social work, mental health) and care co-ordination; limited ability to provide comprehensive care such as educational resources/neuropsychology testing; financial restrictions (variations in funding for paediatric HU formulations, (liquid HU is a special access product often requiring patient co-payment despite PBS coverage of capsules); limited networks of clinicians to provide multi-disciplinary care models ; poorly defined transition pathways for young adults.

Conclusion: This survey has identified key challenges in access to RCE, affordable HU formulations, as well as allied health support/care co-ordination for this disadvantaged population. We recommend the need for the development of consensus recommendations for standards of care for SCD services in Australia, to provide a benchmark for advocacy and interactions with policymakers.

Patient No.	54	13	18	53	52	95
Staffing: Medical /CNC	Y/ 0.5 EFT	Y/No	Y/No	Y/Shared 0.7 EFT	Y/1.0 EFT	Y/0.7EFT
DMT -HU % cohort prescribed, funding	68% $$ not funded	70% $ partial funded	78% Fully funded	45% Fully funded	85% $$ not funded	66% $$ not funded
% Transfused Type: RCE	19% Preferred	23% Preferred	17% No access	19% Available	15% No access	20% Preferred
Transition Access	Annual	Co located	Annual	In development	Difficult ++	Difficult ++

Molecular testing in antenatal haemoglobinopathy screening: Validation of an implemented algorithm and implications for everyday practice.

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Aim: To review change in outcomes following implementation of a prescriptive screening algorithm in 2 large Sydney multi-ethnic maternity units in September 2018 and to assess impact on workflow and upcoming MBS requirements. The goals of the algorithm were to optimise referrals for molecular testing (including to detect ≥2 alpha thalassaemia gene deletion), to assist clinicians with interpretation of individual and couple haemoglobinopathy screening results, and to streamline referral pathways.

Method: Retrospective analysis of FBC, haemoglobinopathy screening tests and genetic tests for women and their partners. Comparison of current results (Sept 2018-Dec 2020) with results prior to implementation of the screening algorithm (January 2015-August 2018) and also comparison with maternity units not following the algorithm ('External Referrers'). Review of FBC and HbEPG thresholds in algorithm. Analysis of proposed MBS criteria for molecular testing.

Results: 1029 molecular tests were included over the 6 year period. Adoption of the algorithm led to a 48% reduction in referral for molecular testing, despite an increase in samples from External Referrers. Despite the reduction in laboratory referral numbers, the yield of significant antenatal results (2 gene *cis* alpha deletions, 2 gene *trans* alpha deletions, beta thalassaemia variants) was not reduced. The number of 1 gene HBA1/2 deletions was reduced by 50% with a relative increase in detection of 2 gene *in cis* deletions by 15%, which resulted in a higher diagnostic yield for sites with the algorithm. Implications for clinical, laboratory and MBS pricing will be discussed.

Conclusion: The collaboration between molecular and haematology laboratories and antenatal services has resulted in enhanced diagnoses and optimisation of laboratory resources. This antenatal haemoglobinopathy screening algorithm is demonstrated to be effective for this population of Sydney and could be considered for evaluation in other regions of Australia and New Zealand.

Prevalence of anaemia and somatic myeloid gene mutations in outpatients attending Inner Sydney geriatric clinics - a prospective study

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Aim: Anaemia affects >10% of adults over the age of 60 and increases by 5% per decade. Furthermore, anaemia is associated with increased mortality, cardiovascular events, dementia, and frailty. We aimed to prospectively evaluate anaemia prevalence and its correlation to somatic myeloid gene mutations in the blood of individuals attending 2 geriatric clinics in Sydney.

Methods: Individuals referred to geriatric clinics for frailty assessment at St Vincent's and War Memorial Hospitals (September 2017 to October 2019) were invited to participate (HREC approval 2019/ETH03362). Standardised clinical and blood test data were collected. Somatic gene mutations in blood were detected by ultra-high depth NGS (limit of detection 0.001 VAF) using the VariantPlex Myeloid (Invitae) 75 gene panel and analysed with Archer Analysis 4.01 and parametric and non-parametric statistical tests. Clonal haematopoiesis of indeterminate (CHIP) mutation is defined by variant allele frequency (VAF) of ≥ 2%.

Results: 216 participants were recruited (mean age 82.5, range 64-100), 40% were male and 18% (*n*=38) were found to be anaemic. Chronic kidney disease and iron deficiency were the main causes of anaemia. Seventeen patients (8%) were diagnosed with unexplained anaemia (UA). The mean numbers of CHIP mutations with VAF ≥ 0.02 found was 5.8 per subject, with mutation numbers positively correlated to age and male gender. The most prevalent observed somatic mutations were EZH2 (60%), ATRX (55.6%), and U2AF2 (44.4%), and these mutations were 1.4–1.7 fold more frequently in subjects with UA compared to non-anaemic subjects.

Conclusion: Anaemia was detected in nearly 20% of subjects attending geriatric clinics, and approximately 10% were diagnosed with UA. A small number of recurrent mutations were more commonly observed in subjects with UA than non-anaemic subjects, suggesting somatic mutations may be drivers of the disease in some cases. This may inform the management of anaemia in this population.

Categorised haematologic response to pegcetacoplan and correlations with quality of life in patients with paroxysmal nocturnal haemoglobinuria: post-hoc analysis of data from phase 1b, phase 2a, and phase 3 trials.

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Aim: These post-hoc analyses aim to categorise haematologic response to pegcetacoplan (PEG) in the PADDOCK (NCT02588833), PALOMINO (NCT03593200), and PEGASUS (NCT03500549) trials, and assess correlation between improved haematologic response, and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores in patients with paroxysmal nocturnal haemoglobinuria (PNH).

Method: Haematologic response was assessed via manual categorisation (Risitano A, et al., Front Immunol, 2019;10:1157) at Days 113/337in the PADDOCK/PALOMINO trials (N=24) and at Weeks 16/48 for PEGASUS (N=80, Hillmen P, et al, NEJM, 2021; 18;384(11):1028-1037). Statistical significance for response categories within arms at Week 16 vs. 48, and between arms at Week 48, was evaluated using Wilcoxon-Signed-Rank and Chi-square testing. FACIT-Fatigue scores for PEGASUS patients, summarised using descriptive statistics, were correlated to haematologic category using Wilcoxon-Mann-Whitney and Chi-square testing.

Results: Most PADDOCK/PALOMINO patients achieved at least a good haematologic response at Weeks 16 and 48. At Week 48, most patients in both PEGASUS arms achieved a good/major/complete haematologic response (inter-arm p=0.4390), with a significant increase in the percent of patients switching from eculizumab to PEG at Week 16 achieving at least a good response (Week 16 vs. 48: intra-arm p<0.0001). In PEGASUS, patients with better haematologic response categories had higher FACIT-Fatigue scores when compared to the rest of the cohort (Week 16: p<0.001, Week 48: p=0.028).

Conclusion: In these post hoc analyses of PADDOCK, PALOMINO, and PEGASUS trial data, a substantial proportion of patients achieved and maintained good, major, or complete haematologic responses to PEG, suggesting that PEG can lead to sustained improvements in haematologic parameters. PEGASUS data also demonstrated correlation of improved haematologic response category with clinically meaningful improvements in quality of life, as measured by FACIT-Fatigue, suggesting that achieving at least a good categorised haematological response could be an important comprehensive treatment goal in PNH.

Interventions to reduce infections in patients with haematological malignancies: A systematic review and meta-analysis

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Aim: Acquired hypogammaglobulinaemia is common in patients with CLL, NHL and MM. No previous systematic reviews (SR) have compared different approaches to infection prevention. We aimed to assess the efficacy and safety of prophylactic immunoglobulin (Ig), antibiotics and vaccinations in these patients.

Method: SR and meta-analysis of RCTs (PROSPERO CRD42017070825) evaluating the efficacy and safety of prophylactic Ig, antibiotics and vaccinations in adult patients with haematological malignancies commonly associated with acquired hypogammaglobulinaemia, specifically CLL, NHL and MM. We searched Pubmed (MEDLINE), EMBASE and Cochrane Registry to 01/09/2021. Results for dichotomous data were expressed as relative risks (RR) with 95% confidence intervals (CI) and pooled using a random effects model.

Results: From 10,576 studies screened, there were 21 completed RCTs and one ongoing RCT. Of these, eight studies evaluated prophylactic Ig (n=370, seven published before 2000); five evaluated prophylactic antibiotics (n=1587), seven evaluated vaccinations (n=3996) and one compared Ig to antibiotics (n=60). Prophylactic Ig reduced the risk of ≥1 clinically documented infections (CDIs) by 28%, (n=2 trials; RR 0.72 [95% CI 0.54 to 0.96]; Figure 1) and vaccinations reduced the risk of CDIs by 63%, RR 0.37 (95% CI 0.30 to 0.45; Figure 2). Prophylactic antibiotics did not reduce the risk of CDIs, and none of the interventions reduced risk of all-cause mortality. Prophylactic Ig and antibiotics increased risk of adverse events. Findings should be interpreted with caution given low patient numbers and high risk of bias in many studies. There was significant variability in reporting infection outcomes, limiting the pooling of studies in the meta-analysis.

Conclusion: There is a clear need for high-quality contemporary trials to establish the effectiveness of different approaches to preventing infection. Future studies should compare different interventions, specifically Ig vs. antibiotics given rising costs and increasing demand for Ig globally, and evolving changes to cancer treatment.

Figure 1: Prophylactic Ig vs. standard care, Outcome: Patients with ≥1 CDIs

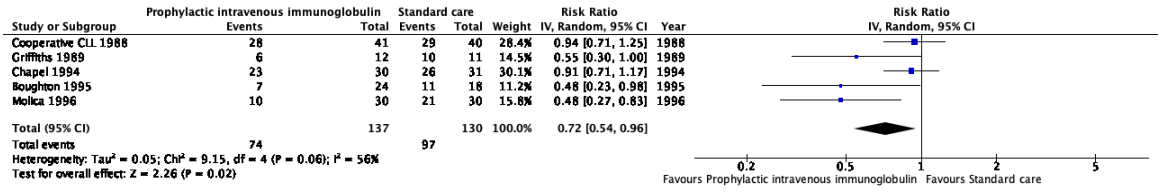
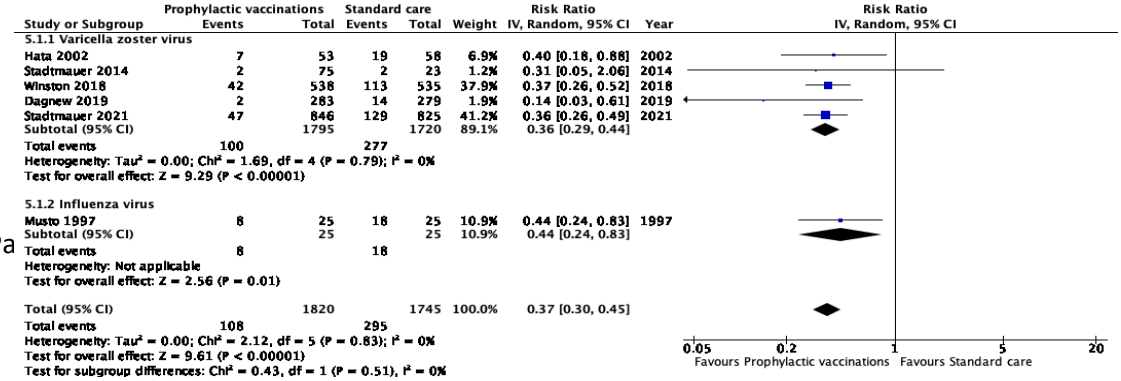


Figure 2: Prophylactic vaccinations vs. standard care, Outcome: Patients with ≥1 CDI



Infection patterns and outcomes in patients with newly diagnosed CLL and NHL – Preliminary results from the Immunoglobulin use and Outcomes in CLL and NHL (ICAN) study

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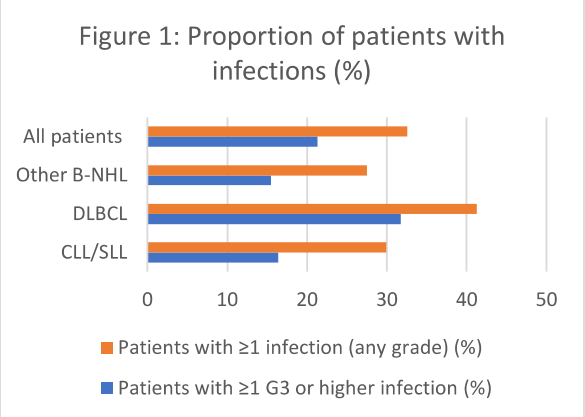
Aim/Method: Interim descriptive analysis of baseline characteristics, infection prophylaxis (including immunoglobulin use), infection patterns and outcomes in patients with newly diagnosed CLL/NHL in the ICAN substudy of the Lymphoma and Related Diseases Registry (LaRDR).

Results: 540 patients (67 CLL/SLL, 189 DLBCL, 284 other B-NHL) from 10 ANZ sites with median follow-up duration of 20.1 months are included. Median age was 67.35 years and 56% patients were male (Table 1). Of 186 patients with baseline Ig levels available, median IgG levels were 10.2g/L (IQR 7.8-11.9g/L). 15.1% patients had hypogammaglobulinaemia (IgG<7g/L) and 2.1% had severe hypogammaglobulinaemia (IgG<4g/L). Ig therapy was administered to 24 patients (4.4%). Most patients (447/540, 82.8%) received chemotherapy during follow-up, most commonly R-CHOP21. 260 infection episodes were detected (0.29 infections per patient-year). Infections were more frequent in patients with DLBCL (Figure 1). From 189 DLBCL patients, 41.3% developed ≥1 infection and 31.7% had ≥1 more grade (G) 3 or higher infection (requiring IV antimicrobials, hospital/ICU admission or resulting in death) (2 deaths). From 67 CLL/SLL patients, 29.9% had ≥1 infection and 16.4% had ≥1 G3 or higher infection. From the other 284 patients (other B-NHL), 27.5% had ≥1 infection and 15.5% had ≥1 G3 or higher infection. Respiratory infections were the most common infection site (28%). Most infection episodes (71.9%) had no organisms identified. Of 73 microbiologically-documented infections, 60.2% were bacterial, 28.8% viral (none with SARS-CoV-2) and 9.6% fungal.

Conclusion: Infections are frequent in Australian and NZ newly diagnosed CLL/NHL patients and up to one third result in serious consequences. Improved prevention and surveillance strategies are required. Further analysis will follow on study completion in late 2022, and a parallel study in myeloma is underway (the IMPROVE study).

Table 1: Patient Demographics and Ig prophylaxis

Patient characteristics	All patients (n=540)
Age at diagnosis (years), median (IQR)	67.4 (57.2, 74.6)
Male, n (%)	305/540 (56.4%)
ECOG 2-4, n (%)	51/457 (11.2%)
Co-morbidities (Cardiac), n (%)	115/531 (21.7%)
Co-morbidities (Pulmonary), n (%)	44/531 (8.3%)
Co-morbidities (Renal), n (%)	21/531 (4.0%)
Co-morbidities (Diabetes), n (%)	90/531 (16.9%)
Chemotherapy received, n (%)	447/540 (82.8%)
Baseline hypogammaglobulinaemia (IgG<7g/L), n (%)	28/186 (15.1%)
Severe hypogammaglobulinaemia (IgG<4g/L), n (%)	4/186 (2.1%)
Ig therapy received at any timepoint, n (%)	24/540 (4.4%)



Clinical and radiological assessment of cardiovascular risk in aggressive lymphoma requiring anthracycline-based chemotherapy

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Background and Aims: High survival rates in aggressive lymphoma necessitate effective management of late therapy-related adverse effects. Anthracycline-related cardiotoxicity is established, increasing with cardiovascular risk factor (CVR) burden. Guidelines advocate CVR optimization, however tools ensuring comprehensive evaluation and management are unavailable. CT coronary calcium score (CTCS) is feasible using lymphoma staging, predicts cardiovascular risk, and may identify new patients requiring CVR modification.

We aimed to determine CVR and incidence of major adverse cardiac events (MACE) in patients undergoing chemotherapy for aggressive lymphoma, and assess the role for CTCS in CVR stratification.

Method: A single-centre retrospective audit of patients undergoing chemotherapy (2019-2021) for aggressive lymphoma (Austin Health, Heidelberg). CTCS was calculated from CT component of baseline PET/CT. CVR factors were elucidated from medical records, including hypertension, dyslipidaemia, increased BMI, smoking, diabetes, and chronic kidney disease (eGFR<45). MACE included myocardial infarction, cardiac failure, or arrhythmia.

Results: 107 patients were eligible. Median age was 66 years (range 19-93), and follow-up 486 days (68-1051). 75% did not have comprehensively documented CVR factors before treatment.

Median CVR factor burden was 2, with 57(53%) having $\geq$2 risk factors. CVR modification strategies were not documented in any case.

Prior MACE were identified in 25(23%). Thirteen(52%) were referred to cardiology. Ten(40%) received full-dose anthracycline, with 15(60%) undergoing anthracycline dose reduction or omission.

Moderate/high-risk CTCS (ischaemic risk >10% in 10 years), was identified in 30(28%) patients. 15(50%) had no cardiac history, with 5 having <2 CVR factors, and 2 experiencing MACE during follow-up.

Overall, 9(8%) had MACE during follow-up, 7 with no cardiac history.

Conclusion: *CVR burden is significant, but underreported in lymphoma, and there is no consistent approach to management. Development of lymphoma-specific risk management tools is crucial. CTCS may improve recognition of high-risk patients and reduce adverse cardiac events. Further assessment of CTCS within a prospective cohort is warranted and planned (HREC/79155/Austin-2021).*

A pilot study of continuous temperature monitoring for the early recognition of febrile neutropenia in haematological malignancies: THERMAL

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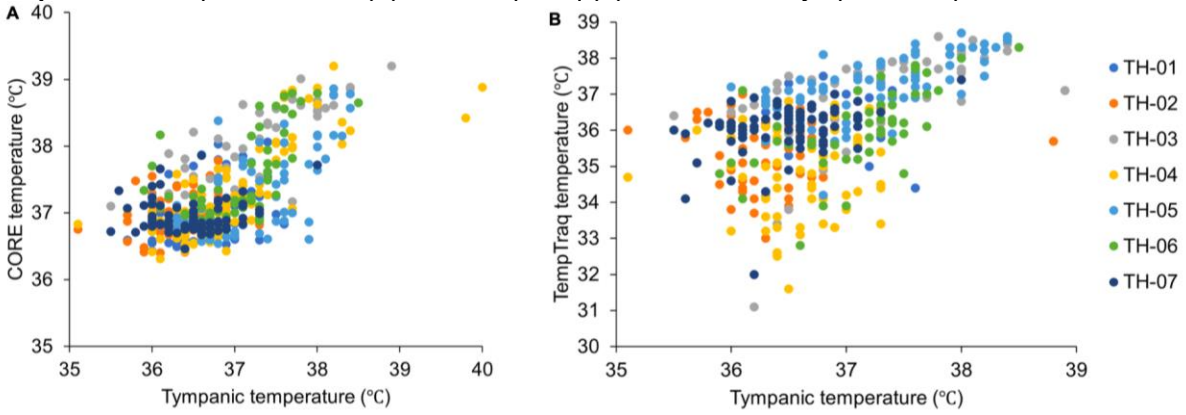
Aim: To explore the acceptability and feasibility of two wearable temperature-monitoring devices, CORE® and TempTraq®, for fever detection in patients at high risk of neutropenic infection.

Method: We recruited 15 inpatients at Wellington Hospital, New Zealand with leukaemia, lymphoma or myeloma undergoing intensive chemotherapy, stem-cell transplantation or chimeric antigen receptor (CAR) T-cell therapy. Both CORE® (GreenTEG) and TempTraq® (BlueSpark Technologies) devices were worn concurrently by participants for up to 14 days. Continuous temperature data were collected using a cloud-based system; tympanic temperature was monitored 4 hourly; and a questionnaire was applied to identify device preferences. Descriptive statistics were used to assess time worn for device; correlation between measurements from devices and tympanic thermometer; and device preferences.

Results: The 15 participants had a median age of 57, and ethnicities included 9 NZ European and 3 Māori. Treated diseases were lymphoma (8), leukaemia (5) and myeloma (2), and treatment included intensive chemotherapy (8), CAR T-cells (3), allogeneic transplant (2) and autologous transplant (2). CORE was worn and recording for a mean 89.2% of available time (IQR 8.2), and TempTraq for 89.8% (IQR 11.9). An interim analysis of the first 7 participants (see graph 1) shows positive correlation between tympanic readings and both CORE ($r^2 = 0.476$) and TempTraq ($r^2 = 0.256$). 10 participants preferred TempTraq and 5 preferred CORE (p=0.302).

Conclusion: This pilot study suggests that both CORE® and TempTraq® wearable devices have potential utility for detection of fevers among patients at risk of post-chemotherapy infection, and were considered tolerable by patients undergoing treatments with a high febrile neutropenia risk. No clear preference for a device was seen. If future studies determine suitability for detection of post-chemotherapy fevers, they would represent potential alternatives to inpatient monitoring.

Graph 1: Scatter plot of CORE (A) and TempTraq (B) correlation to tympanic temperature



Immune response to COVID-19 vaccination in adult patients with haematological malignancies: preliminary results from SerOzNET

Dr Jeremy Ong[1,2], Dr Amy Body[1,2], Dr Elizabeth Ahern[1,2], Dr Michael Leahy[3], Dr Marat Gallyamov[3], Dr John Balendra[3], A/Prof Nada Hamad[4], Cindy Ho[1,2], Luxi Lal[1,2], Hesham Abdulla[1], Professor Stephen Opat[1,2], Professor Eva Segelov[1,2]
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Patients with haematological malignancy that experience COVID-19 infection are at increased risk of severe disease and death. Several COVID-19 vaccines have been shown to be highly effective in disease prevention in the general population; however, less is known about vaccine responses in patients with immunocompromising haematological malignancies, who were excluded from early trials.

Aim: To determine the immune response following COVID-19 vaccination in adult patients with haematological malignancies.

Method: SerOzNET (ACTRN 12621001004853) is a multicentre prospective study examining the immune response following COVID-19 vaccination in patients with solid and haematological malignancies. Neutralising antibody titre and T-cell response was measured at baseline and after each dose of vaccine and correlated with disease characteristics.

Results: SerOzNET included 129 adult patients with haematological malignancy. Median age was 62 years (IQR 47-70), with 46% female. 101 patients (78%) were receiving anti-cancer treatment at the time of vaccination, most commonly chemotherapy (40 patients), chemoimmunotherapy (31), BTK inhibitor (12) and immunotherapy (9).

Antibody (Ab) titres were available for 87 patients following 2 vaccine doses, and for 60 patients following 3 doses. Neutralising Ab titre ≥20 was detected in 41% after the 2nd dose, and 73% after the 3rd dose ($p<0.001$). The Ab response in 20 patients exposed to rituximab in the preceding 12 months was low, with adequate titres present in only 5% and 35% after 2 and 3 doses respectively. In contrast, Ab response in 14 patients not receiving anti-cancer therapy at the time of vaccination was 79% and 93% after 2 and 3 doses respectively. Further analysis of serological and T-cell response will be available.

Conclusion: Humoral immune response following COVID-19 vaccination is reduced in patients with haematological malignancies. The response is improved following a third dose, though remains low in patients receiving anti-B-cell directed therapy

Multiple Sequential COVID-19 Vaccine Doses in Chronic Lymphocytic Leukaemia (CLL) and Monoclonal B-Lymphocytosis (MBL): High Seroconversion and T-cell Response Rates but Reduced Neutralisation of Recent Variants

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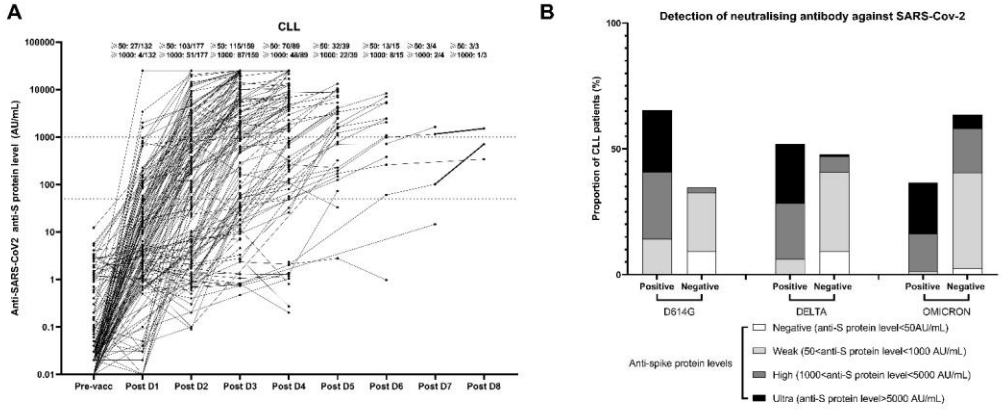
Aim: CLL and MBL patients have impaired response to Covid19 vaccination with >50% and 10% failure respectively after 2 initial vaccine doses (Shen BJH 2022). We sought to assess the immune response to multiple sequential vaccine doses.

Method: Patients were evaluated for anti-spike seroconversion ("positive" ≥50AU/ml), and level, with Abbott Diagnostics assay. Subsets had neutralisation assays against D614G, Delta and Omicron variants, and T-cell responses with IFN□/IL-2 Fluorospot.

Results: From 1.3.2021 to 1.4.2022, there were 211 CLL and 39 MBL, 250 patients, for analysis with anti-S level after >2 doses. Median age was CLL 72 years and MBL 73 years; males were CLL 55.9% and MBL 35.9%. The ultimate seroconversion rate (□50AU/ml) was 82.0 % for CLL and 97.4% for MBL. Post-D2 in 250 patients, 44.0% of CLL and 8.3% MBL failed seroconversion. Post-D3 in 159 CLL, 27.7% failed seroconversion, 17.6% anti-S level 50-999AU/mL, and 54.7% anti-S >1000AU/ml. Of those seronegative post-D2, 71 received D3, and 37.9% seroconverted. Sequentially if seronegative after prior dose, seroconversion occurred post-D4 in 41.9% (13/31), post-D5 53.8% (7/13), but 0% after D6 (0/3), D7 (0/1) and D8 (0/1) (Figure 1). For those who seroconverted, most had a progressive increment in anti-S level with sequential doses (Figure 1). 24/39 MBL received D3; all 24 patients responded; 6 (25.0%) anti-S level 50-999AU/mL, and 18 (75.0%) >1000AU/mL. Neutralising antibody against D614G, Delta and Omicron typically required an anti-S level of >1000, >2500, and >20,000 respectively. T-cell responses to spike peptide resulted in high IFN□ and IL-2 production when anti-spike levels were >5,000AU/ml.

Conclusion: Multiple sequential Covid19 vaccine doses ultimately seroconvert 82% of CLL, and 97.4% of MBL; 18% of CLL failed seroconversion. Given the current lack of approved Covid-prophylactic antibody therapy for CLL in Australia, the immune response obtained with additional vaccine doses may be very important.

Figure 1. Sequential post vaccination anti-spike protein IgG levels in CLL (A). An anti-S level >50AU/mL is classified as positive response and an anti-S level >1000AU/mL is classified as strong positive response. (B) Bar chart shows the proportion of samples with positive or negative neutralisation and were split into four stratifications of anti-S responses.



State-wide review of O positive blood for emergency transfusion and rates of alloimmunisation to red cell antigens

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Aim: Analysis of emergency transfusions after implementation of a policy to use O positive blood in female patients ≥ 50 years of age and male patients >16 years of age. Secondary aim of defining rates of alloimmunisation before and after emergency transfusion.

Method: Retrospective review of emergency transfusions at Queensland public health Hospital between June 2020 and June 2021. Demographic details of the patients transfused emergency blood, indications for transfusion, usage of O positive and O negative blood and rates of alloimmunisation were investigated.

Results: There were 2354 red cell units transfused to 1013 patients during the 12-month period. Most patients were male (n=599, 59%) with the average age being 53 years (IQR 34-72 years). Patients were mostly transfused for trauma (n=408, 39.8%) and gastrointestinal bleeding (n=338, 33%). O positive units accounted for 46.9% (1103 units) of emergency transfusions. However, a significant number of patients were transfused with O negative blood without a recommended indication (n=737 units, 31.3%). Twenty-eight patients (2.9%) had a red cell alloantibody prior to transfusion with the most common being anti-E (n=10), anti-D (n=4) and anti-K (n=4). There was one episode of mild delayed haemolytic transfusion reaction in a patient with prior anti-D. There were 19 patients (4.3%) who developed a red cell alloantibody after emergency transfusion at a median follow up of 22 days with the most common being anti-E (n=11), anti-D (n=7) and anti-C (n=5).

Conclusion: The use of O positive blood for emergency transfusion has resulted in 1103 O negative red cell units being saved with no detriment to patient outcome. Rates of alloimmunisation before and after transfusion were low. There remains further potential to optimize use of O positive blood in emergency transfusion and to understand alloimmunisation rates in a prospective fashion.

Recovery of organ-specific oxygen delivery at restrictive transfusion thresholds after crystalloid treatment for massive haemorrhage and shock in sheep.

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Aim: Massive transfusion is indicated for massive uncontrolled haemorrhage, but is this appropriate once haemorrhage is controlled? Current guidelines recommend fluids to restore blood volume and packed red blood cells (PRBC) if haemoglobin <70g/L (restrictive transfusion threshold). Microcirculatory flow and tissue oxygen delivery are critical for organ and patient survival, but infrequently assessed. Our aim was to evaluate the utility of non-invasive tissue-specific measures to guide Patient Blood Management, and determine physiological outcomes of fluid treatment (PlasmaLyte or novel crystalloid) compared to PRBC transfusion.

Method: A model of massive haemorrhage and shock in sheep, an intensive care setting, with controlled haemorrhage (40-60% blood volume) to pressure (mean arterial pressure (MAP): 30-40mmHg) and oxygen debt (lactate >4mM) targets. Outcomes were analysed by ANOVA; recovery of haemodynamic parameters, non-invasive sublingual microcirculatory flow, regional tissue oxygen saturation, and arterial lactate, were benchmarked against invasive organ-specific measures of microvascular perfusion, oxygen tension and lactate in brain, kidney, liver, and skeletal muscle. Organ function outcomes were defined by inflammatory and biochemical markers, and post-mortem assessments after 4hrs treatment.

Results: Recovery of primary haemodynamic (MAP >65mmHg and cardiac index >2.5L/min/m^2) and tissue oxygen delivery (muscle oxygen saturation >50% and lactate <2mM) parameters were equivalent ($p>0.05$) between treatments after 4hrs, despite haemodilution after crystalloid infusion to <70g/L ($p<0.001$). Recovery of invasive organ-specific perfusion, oxygen tension and lactate occurred shortly before non-invasive measures indicated recovery. The novel crystalloid supported rapid peripheral vasodilation ($p=0.014$) and tended to achieve tissue oxygen delivery targets earlier. PRBC supported earlier renal oxygen delivery ($p=0.012$) but delayed peripheral perfusion ($p=0.034$). Organ function markers were equivalent.

Conclusions: The outcomes confirmed that restrictive transfusion thresholds support tissue oxygen delivery and recovery[1]. Non-invasive tissue perfusion and oximetry technologies merit further clinical appraisal to guide treatment for massive haemorrhage in the context of Patient Blood Management.

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Transfusion practices in Australian and New Zealand intensive care units: a point prevalence study

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Aim: To describe current blood transfusion practices in intensive care units (ICU), compare them against national guidelines, and describe how point-of-care testing (POCT) is used in guiding transfusion decisions.

Method: We performed a prospective, multicentre point-prevalence study of all adult patients admitted to participating ICUs in Australia and New Zealand (ANZ) on either of two study days in June 2021. Transfused patients were compared to non-transfused patients; multivariate regression was used to assess effects of transfusions on outcomes after adjusting for confounding variables. Clinical reasons and triggers for transfusion were compared to ANZ patient blood management guidelines.

Results: Out of 712 adult patients from 51 ICUs, 10% of patients received a transfusion. Compared to patients not transfused, these patients had higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores (18.9 versus 16.7, $p = 0.02$), and a greater proportion were mechanically ventilated (49.3% versus 37.3%, $p < 0.05$), received vasopressors (53.5% versus 30.7%, $p < 0.01$), and had systemic inflammatory response syndrome (70.4% versus 51.3%, $p < 0.01$). Most transfused patients (8.9% of all patients) received red blood cell (RBC) transfusions, and only 1.4% received platelets, 0.8% fresh frozen plasma (FFP), and 0.7% cryoprecipitate. POCT was available in 82.4% of sites but only used in 9.5% of transfusions involving platelets, FFP or cryoprecipitate. Alignment with guidelines was found for all RBC transfusions, but disagreement was up to 53.8% for platelet transfusions, 57.1% of FFP transfusions, and 80.0% of cryoprecipitate transfusions. In both univariate analysis and after adjustment for confounding, blood transfusion was not significantly associated with mortality or length-of-stay.

Conclusion: RBC transfusions in ICU are aligned with guidelines, but non-RBC transfusion decisions are often not. POCT is commonly available but not often the reason for transfusion decisions.

Thromboelastography-Guided transfusion algorithm reduces transfusions in complex cardiac surgery.

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Aim: The present study aimed to compare transfusion rates, the main associated cardiac surgery complications and other clinical outcome parameters, in order to assess the impact of the implementation of rotational thromboelastometry (ROTEM) viscoelastic point-of care tests with algorithm-based coagulation management in cardiac surgery with cardiopulmonary bypass.

Method: Retrospective cohort study including 675 patients who underwent cardiac surgery with cardiopulmonary bypass. The incidence of allogeneic blood transfusions and clinical postoperative complications were analyzed before and after ROTEM implementation.

Results: Following viscoelastic testing and the implementation of a specific algorithm for coagulation management, the incidence of any allogeneic blood transfusion decreased (41.4% vs 31.9%, p=0.026) during the perioperative period. In the group monitored with ROTEM,decreased incidence of transfusion was observed for packed red blood cells (31.3% vs 19.8%, p=0.002), fresh frozen plasma (9.8% vs 3.8%, p=0.008), prothrombin complex concentrate administration (0.9% vs 0.3%, p=0.599) and activated recombinant factor VII (0.3% vs 0.0%, p=0.603). Increased incidence was observed for platelet transfusion (4.8% vs 6.8%, p=0.530) and fibrinogen concentrate (0.9% vs 3.5%, p=0.066), tranexamic acid (0.0% vs 0.6%, p =0.370) and protamine administration (0.6% vs 0.9%, p=0.908). Similar results were observed in the postoperative period, but with a decreased incidence of platelet transfusion (4.8% vs 3.8%, p=0.813). In addition, statistically significant reductions were detected in the incidence of postoperative bleeding (9.5% vs 5.3%, p=0.037), surgical reexploration (6.0% vs 2.9%, p=0.035), and length of Intensive Care Unit (ICU) stay (6.0 days vs 5.3 days, p ¼ .026).

Conclusion: The monitoring of hemostasis by ROTEM in cardiac surgery, was associated with decreased incidence of allogeneic blood transfusion, clinical hematologic postoperative complications and lengths of ICU stay.

Introduction of Fibrinogen Concentrate for Critical Bleeding in South Australia

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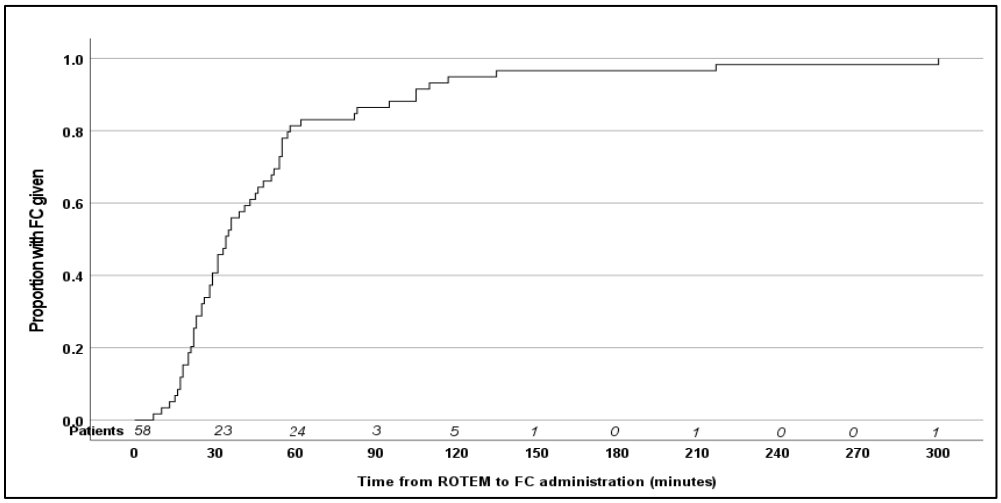
Aim: Fibrinogen Concentrate (FC) use in critical bleeding is not currently available through national blood supply. SA Health independently purchased FC as part of COVID-19 contingency planning. FC doses were allocated to SA public hospitals and the MedSTAR Retrieval service based on historical cryoprecipitate use. Protocols developed by the State Critical Bleeding Advisory Group included a threshold of FIBTEM levels ≤ 6 and ≤ 8 for use in critical and obstetric bleeding where thromboelastometry (ROTEM) testing available. A single dose (4g) was used, patients requiring additional doses were transfused with cryoprecipitate. The aim of this study is to examine use of FC in first 22 months of availability.

Method: RedCAP Database was[i] used to capture the use of FC. Data collected included patient demographics, physiological, laboratory + ROTEM, blood and blood product use and patient outcomes.

Results: 64 patients used 246 grams of FC between July 2020 to April 2022 and of those 40 received hospital trauma activations. Median time (interquartile [IQR]) from the start of ROTEM measurement to commencement of FC infusion was 34(22-55) minutes. Median time from start of ROTEM measurement to dispensing FC from laboratory or Emergency Department Blood fridge was 18 (10-41) minutes. Median time from dispensing FC to commencement of patient administration was 14(8.5-20) minutes. Median FIBTEM A5 was 5 mm (IQR 4-6) pre-FC and 11mm (IQR 9-13) post FC administration. Patients received a median of 5(2-10) red cell units, 4(3-8) FFP units, 2(1-3) platelets units and 1(1-2) adult doses of cryoprecipitate. Overall, in-hospital mortality was 15.6%.



Conclusion: About 40% of FC doses commenced within 30 minutes of ROTEM testing. Considering a longer median time to administration of cryoprecipitate, we have identified a patient cohort with severe coagulopathy who may benefit from rapid access to fibrinogen replacement in the form of FC.

Understanding the biology of the Kidd blood group protein in the erythroid cells of control and Jk-null individuals.

Dr Genghis Lopez, Ms Fenny Chong, Ms Glenda Millard, Ms Tanya Powley, Prof Catherine Hyland, **Dr Rebecca Elizabeth Griffiths[1]**
[1]*Australian Red Cross Lifeblood, Kelvin Grove, Australia*

Aim: To identify and characterise the molecular basis for the Jk(a–b–) phenotype in Australian blood donors and decipher the biological consequence using our ex vivo model of erythropoiesis to help inform clinical transfusion practice.

Kidd (Jk) blood group antigens are present on the red blood cell (RBC) membrane urea transporter (UT-B) glycoprotein. In many populations the Jk(a–b–) phenotype is absent or rare, making provision of blood for patients requiring this phenotype challenging.

Method: DNA was extracted from routine EDTA blood samples and analysed using whole exome sequencing to determine the molecular basis of the Jk phenotype (n=6)[1].

To characterise UT-B expression during erythropoiesis, haematopoietic stem cells were isolated from the Jk(a–b–) donor whole blood collection's buffy coat and differentiated to RBCs using an established erythropoiesis model [2]. The expression of the UT-B protein and other erythroid proteins were examined throughout erythroid differentiation by flow cytometry and confocal microscopy.

Results: DNA sequencing showed all 6 donors with the Jk(a–b–) phenotype were homozygous for *JK* c .342-1G>A polymorphism resulting in the *JK*02N.01/*02N.01* genotype.

Preliminary data suggest that the UT-B protein is produced in the Jk(a–b–) phenotype during erythropoiesis but does not appear to sort correctly to the plasma membrane. As the Jk(a–b–) erythroid cells mature, the UT-B protein is cleared from the cells.

Conclusion: RBCs with the *JK*02N.01/*02N.01* genotype exhibit a null Kidd blood group phenotype attributed to the c.342-1G>A splice site variant that is predicted to generate a truncated protein due to exon skipping in protein synthesis. Our data suggest the production of a misfolded protein which is cleared by the RBCs during erythroid maturation and not integrated onto the membrane.

Understanding the biological basis and consequence of genotype variants may enhance the ability to predict the potential clinical significance enabling better informed transfusion management when supply of serological compatible blood is limited.

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Intertwining roles for genomics and international data sharing defines a novel low prevalence Kell antigen in a blood donor

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[1]Australian Red Cross Lifeblood, Brisbane, Kelvin Grove, Australia, [2]Faculty of Health, Queensland University of Technology, Kelvin Grove, Australia, [3]Australian Red Cross Lifeblood, Melbourne, Melbourne, Australia, [4]School of Health and Behavioural Sciences, University of the Sunshine Coast, Sippy Downs, Australia

Aim: To date the KEL blood group system comprised 37 antigens. The most recently discovered KEL antigen, named KHIZ, was acknowledged in 2022 by the International Society of Blood Transfusion (ISBT) Working Party (WP) on Red Cell Immunogenetics and Blood Group Terminology; the ISBT WP responsibilities include accepting, registering and curating all red cell antigens and alleles.

The KHIZ antigen was reported because of an investigation of a patient who presented with an antibody to a high-prevalence antigen.[1] Genomic whole exome sequencing studies revealed the patient was homozygous for a c.1538G>A change on exon 14 of the *KEL* gene, predicting a p.Arg513Gln on the Kell glycoprotein. This has been recognised as defining a high-prevalence antigen involving the p.Arg513. We will present a case study of a patient with an antibody to a proposed antithetical low-prevalence antigen to KHIZ.

Method: Standard serological techniques were used to investigate the antibody specificity. Blood samples from a red cell incompatible donor were provided for genomic sequencing using the TruSight One panel and Massively Parallel Sequencing (MPS).

Results: Serological investigation of the patient following a transfusion reaction suggested the antibody specificity was directed to an antigen in the KEL system. Sequencing showed that the incompatible donor was heterozygous for *KEL* c.1538G/A (GenBank accession number MG818162) predicting p.Arg513/p.Gln513. There were no other significant *KEL* gene blood group variants.

Conclusion: The p.Gln513 is responsible for a low-prevalence antigen on the Kell glycoprotein, with the proposed name KHOZ. The International data and our genomic-based study suggest that the KHIZ and KHOZ are antithetical antigens on the Kell glycoprotein. Both were defined by genomic studies but in previous years such cases may have remained unresolved for many decades. This study shows the value of involvement and data sharing through presentations with the ISBT Working Parties.

Reference:

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The use of multi-colour imaging flow cytometry to identify platelet subpopulations during extended cold-storage

Dr Lacey Johnson[1], Mr Christopher Roan[1], Miss Pearl Lei[1], A/Prof Denese Marks[1,2]
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Aim: Platelets for transfusion are stored at room-temperature (RT), limiting their shelf-life to 7 days. Cold-storage (refrigeration) of platelets is attractive as it could extend the shelf-life to 21 days, whilst providing a haemostatic advantage to the platelets. Cold-storage induces the progressive externalisation of phosphatidylserine, which is a feature of both procoagulant and apoptotic platelet subpopulations. As such, the aim of this study was to identify the subpopulations present in platelet components during extended cold-storage.

Method: Platelets from fresh components (n=6) were either unstimulated or stimulated with thrombin and collagen, calcium ionophore (A23187) or ABT-737 to generate resting, aggregating, procoagulant or apoptotic platelets, respectively. In parallel, platelet components (n=6) were stored for 21 days under RT (20-24°C) or cold (2-6°C) conditions. Multi-colour fluorescent marker panels were designed to identify platelet subpopulations by the presence ($^+$) or absence ($^-$) of staining with: annexin-V (AnnV), CD61, PAC-1, CD42b, GPVI, CD62P and tetramethylrhodamine ethyl ester (TMRE). The phenotypic profile of platelets was determined by imaging flow cytometry (Amnis ImageStreamX Mark II).

Results: Both procoagulant and apoptotic platelets were AnnV$^+$, CD61$^+$, GPVI$^-$, PAC-1$^-$ and TMRE$^-$, making identification of the subpopulations difficult when these markers were used in isolation. However, the combination of AnnV, CD42b and PAC-1 separated resting, aggregating, procoagulant and apoptotic platelet subpopulations. Using this panel, a greater proportion of procoagulant (AnnV$^+$/CD42b$^+$/PAC-1$^-$) platelets was evident during cold-storage by day 7; whereas RT-storage promoted the appearance of apoptotic (AnnV$^+$/CD42b$^-$/PAC-1$^-$) platelets (see Table). This trend continued throughout 21 days of storage.

	Day 1	Day 7		Day 21	
	Pool	RT	Cold	RT	Cold
Procoagulant (%)	0.4±0.2	0.9±0.2	4.3±1.8*	12.0±2.2	20.4±5.8*
Apoptotic (%)	0.3±0.2	0.4±0.1	0.2±0.1*	9.1±5.1	0.9±0.7*

Data represents mean±SD; * indicates $p<0.05$ compared to RT at same time-point

Conclusion: Storage temperature differentially drives the development of procoagulant and apoptotic platelet sub-populations. This data suggests that the enhanced haemostatic potential of cold-stored platelets may be due to the preferential development of procoagulant platelets.

Concordance analysis between genetically and clinically determined blood cell antigen types using the two array formats developed by the Blood transfusion Genomics Consortium (BGC).

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on behalf of the Blood transfusion Genomics Consortim

Aim: To perform concordance analysis between clinically and genetically determined blood cell antigen types obtained using the UK Biobank_v2.2 array (UKBB_v2.2) and Universal Blood Donor Typing (UBDT_PC1) developed by the BGC.

Method: The BGC is an international partnership between blood services, research institutions and industry leaders with the aim to improve the safety and efficiency of blood and platelet transfusion by introducing cutting-edge genomics technology into routine clinical practice. Seven blood services have come together to share DNA samples and antigen typing data on 14,000 donors to deliver a validation study on a powerful array platform. So far half (n=6,952) of the samples have been tested, with 1,974 in 4 labs, 4,512 samples have been tested in 3 labs and all 6,952 have been tested in two labs to compare the performance of two array formats with antigen typing data held on Electronic Donor Record. The arrays and interpretation workflow can type all clinically relevant Human Erythroid Antigen (HEA) systems (except ABO) and can also type Human Leukocyte Antigen (HLA), Human Platelet Antigen (HPA) and markers for iron homeostasis and restless leg syndrome. The UBDT_PC1 array is currently being assessed by Lifeblood in Brisbane with the aim to evaluate its performance on the Australian population.

Results: Preliminary results show concordance of 99·85% with Human Erythroid Antigen (HEA) typing data with only a small number of discordances. This is the largest multi-centre study to date comparing performance of a new genotyping array between four laboratories testing samples from an ethnically diverse panel.

Conclusion: The results obtained for the concordance analysis confirmed the high accuracy of the array and interpretation pathway for typing all clinically relevant HEA systems. Access to accurate and cost-effective typing such as provided by these arrays, can revolutionise treatment for patients where better-matched blood can prevent alloimmunisation and simplify long-term transfusion support.

Type of anti-human neutrophil antigen 3a antibody and potential impact on transfusion-related acute lung injury development

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Aim: Antibodies against human neutrophil antigen (HNA)-3a, expressed on choline transporter-like protein 2 (CTL2), cause severe and fatal transfusion-related acute lung injury (TRALI). Epitope mapping suggests there are two types of HNA-3a antibodies. This study aimed to evaluate the activity of type I and type II anti-HNA-3a antibodies in an in vitro TRALI model.

Method: Granulocyte agglutination test (GAT) and granulocyte immunofluorescence test (GIFT) tested anti-HNA-3a activity in two sera (Q49 and Q50). Flow cytometry tested antibody binding to human or mouse neutrophils. The monoclonal antibody immobilization of granulocyte antigen (MAIGA) assay was modified to include a rabbit polyclonal antibody (i.e. PAIGA) against an epitope in the third extracellular loop of CTL2, and tested antibody binding to human neutrophils. To model TRALI, human lung microvascular endothelial cells (HLMVECs) were treated with lipopolysaccharide (LPS). Freshly isolated HNA-3aa homozygous neutrophils were added, along with Q49, Q50, or control sera. HLMVEC cytotoxicity and ROS production were measured.

Results: GAT/GIFT confirmed Q49 and Q50 contained anti-HNA-3a antibodies. Flow cytometry showed that Q49 and Q50 bound to human neutrophils, but only Q49 bound to mouse neutrophils. PAIGA showed binding for Q49 but not Q50. These results suggested that Q49 contained type I anti-HNA-3a antibodies that bind an epitope on CTL2's first extracellular loop of CTL2 and that Q50 contained type II anti-HNA-3a antibodies that bind to an epitope spanning CTL2's first three extracellular loops. In the TRALI model, HLVMEC cytotoxicity was observed with both Q49 and Q50, although damage was greater with Q49 treatment compared to Q50.

Conclusion: In this model, differences in HLMVEC cytotoxicity severity were observed between sera containing either type I or type II anti-HNA-3a antibodies. This highlights the importance of further research into anti-HNA-3a-mediated TRALI.

Increasing safety and awareness of RhD immunoglobulin through haemovigilance reporting

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RhD immunoglobulin (RhDIg) use in Australia is likely to have significantly reduced infant mortality from haemolytic disease of the newborn; however, errors in RhDIg use occur.
Blood Matters Serious Transfusion Incident Reporting (STIR) system has collected RhDIg administration incidents since 2015. To further enhance our understanding of RhDIg issues, STIR commenced reporting of RhD isoimmunisations in 2020.

Aim: Increase safety and reduce risks, by understanding errors associated with RhDIg administration.

Method: Reporters notify STIR of the event and are sent an investigation form to complete, which is then reviewed by members of the STIR expert group.
An annual report of all validated reactions and incidents is made available and de-identified information from investigations is used to support education and audit.

Results: From January 2015 – June 2021, STIR validated 92 events: These included (% of RhDIg incidents)

1. 30%, dose omitted

- 26%, inappropriate administration including use in RhD positive women, RhD negative woman with RhD negative infant, women with pre-formed immune anti-D
- 7%, wrong dose
- 7%, delayed administration >72hours
- 30%, other (near miss, storage and handling)

Most errors occur in the maternity clinics or wards, with a small number happening in emergency departments or theatre.
RhD isoimmunisations: Currently there is one confirmed report, in a woman who appears to have received all appropriate prophylaxis, however was likely isoimmunised and not fully investigated at the start of her pregnancy. Full details of prophylaxis in a previous pregnancy were not available.

Conclusion: These incidents indicate multi-faceted process problems. Recommendations for improvement include appropriate education for health professionals involved in maternity care, standardised reporting of maternal RhD status, positive patient identification, and regular auditing to identify areas for improvement. Blood Matters continues to work with maternity care providers to improve practice, including education of the updated RhDIg guidelines.

Keeping it Safe from Transfusion to Transport: The development of tailored transfusion resources for regional and remote Western Australia

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Aim: To understand the unique challenges and educational requirements of clinicians who care for patients requiring transfusions across regional and remote WA and develop tailored clinical support tools to empower them to deliver safe transfusion practices.

Method: The project team used active research methodology to engage with stakeholders across regional and remote WA (online questionnaire) and invited key stakeholders to participate in 1.5 days workshop to understand and define their learning needs. Based on this information, the project team created a suite of innovative clinical support tools tailored to these needs. A post implementation evaluation (online questionnaire) will assess the impact of the project.

Results: 87 clinicians from across WA Country Health Service participated in the online questionnaire. 82% received training on safe transfusion but only 38% had received it within the last 2 years. 62% felt "completely confident" to transfuse red cells however 9% felt "either somewhat", "a little" or "not confident at all". Adverse transfusion reactions (90%) and blood administration (77%) were the leading learning needs identified as well as specific requests for training on regional blood transport. Clinicians preferred to receive their transfusion education via e-learning (87%), scenario-based learning (46%), checklists (44%) or lanyard cards (39%).

The project team created a suite of innovative clinical support tools including 1) printed resource illustrating key steps in the safe administration of red cells based on local policies with QR code to improve accessibility to the ANZSBT guidelines, 2) scenario-based e-learning module for recognising and responding to adverse transfusion reactions and 3) printed resources with QR code to a video demonstrating the key steps to safely transporting blood to prevent wastage.

Conclusion: Clinicians who care for patients requiring transfusions across regional and remote WA appeared to welcome the opportunity to guide the development of tailored resources to allow them to deliver safer transfusion practices.

Culturally safe blood transfusion and blood donation for Aboriginal and/or Torres Strait Islander peoples.

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Aim: Aboriginal and/or Torres Strait Islander peoples, and indeed, Indigenous peoples globally, tend to experience a higher than average burden of chronic illnesses that may require treatment with a blood transfusion. Minimal research has been undertaken that focuses on Indigenous perspectives of blood, blood transfusions and donation. An understanding of the cultural connections blood may represent is helpful to provide culturally safe healthcare.

Method: The researcher, an Nganyaywana (Anaiwan) and Wiradjuri woman, used well-known Indigenous research method 'Yarning' to allow participants to share their experiences through stories. The researcher's community connections aided the recruitment of participants despite Covid. The yarns were recorded, transcribed and analysed using Thematic Analysis with themes identified and collated for analysis. Eleven Aboriginal and/or Torres Strait Islander peoples, with family connections to eighteen different communities 'yarned' with the researcher as well as twelve Health Practitioners who have Indigenous patients.

Results: Two-thirds of the transcripts have been analysed, with the following themes identified so far:

1. Blood is a sacred substance and the connection for Indigenous peoples to their to family, land and community.
    - Long standing distrust of the health system due to historic poor treatment of Aboriginal peoples by European colonisers has caused delays in seeking or accepting treatment.
    - This distrust has been passed on to future generations, causing delays in accessing health care until sometimes it is too late to intervene and save a life.
    - Half the Indigenous participants would prefer to know that the blood they are receiving is from an Indigenous person.

Conclusion: Understanding the thoughts, feelings and beliefs that Aboriginal and/or Torres Strait Islander peoples have about blood, blood donation and transfusion will provide invaluable information for Health Practitioners to provide culturally safe healthcare.

The prevalence of alloantibodies in a cohort of Indigenous and non-Indigenous cardiac surgery patients

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Aim: There is very limited evidence on prevalence and specificity of red cell (RC) antibodies in Aboriginal and Torres Strait Islander peoples (herein respectfully referred to as Indigenous). We examined the prevalence of RC antibodies in Indigenous and non-Indigenous patients undergoing cardiac surgery at a South Australian (SA) tertiary hospital that is the referral centre for Northern Territory (NT) patients.

Method: Indigenous and non-Indigenous patient's ABO & RhD blood groups and RC antibodies at the time of surgery and up until 2021 were retrospectively analysed for all consecutive patients undergoing cardiac surgery at Flinders Medical Centre between January 2014 and June 2019.

Results: 2327 patients were included, 420 (18.0%) Indigenous and 588 (25.3%) from the NT. Indigenous patients had higher prevalence of ABO group O (59.5% vs 43.6%) and RhD positive (98.8% vs 83.6%) blood groups. 132 patients had RC alloantibodies detected, 63/420 (15%) Indigenous versus 69/1907 (3.6%) non-Indigenous ($p<0.0001$). Lewis, P1 and M IgM alloantibodies were more common in Indigenous patients (Fig 1). 101 patients had antibodies detected at time of surgery. 16 NT patients (15 Indigenous, 1 non-Indigenous) with previously detected alloantibodies, on average 7.7 years prior to surgery, presented with a negative antibody screen at time of surgery in SA. These included anti-Kell, C, E and e alloantibodies.

Conclusion: We found a high prevalence of alloantibodies, particularly IgM class in Indigenous patients undergoing cardiac surgery. Such antibodies, though not necessarily clinically significant, may cause delays in finding crossmatch compatible blood, particularly in rural and remote settings. Our subset of NT patients with previously identified clinically significant alloantibodies not present at time of surgery in SA support the need for a national antibody transfusion register.

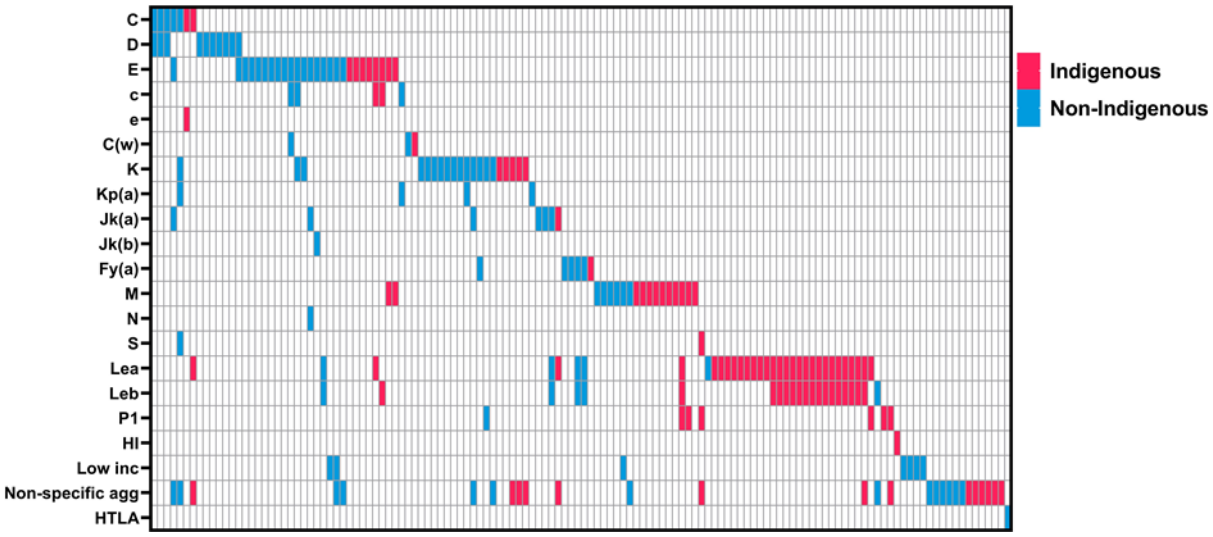

Fig 1 Alloantibodies detected in Indigenous versus non-Indigenous patients (columns represent individual patient data)

Mapping South Australia's laboratory and satellite blood stocks – uncovering surprise stocks of O Neg red cells

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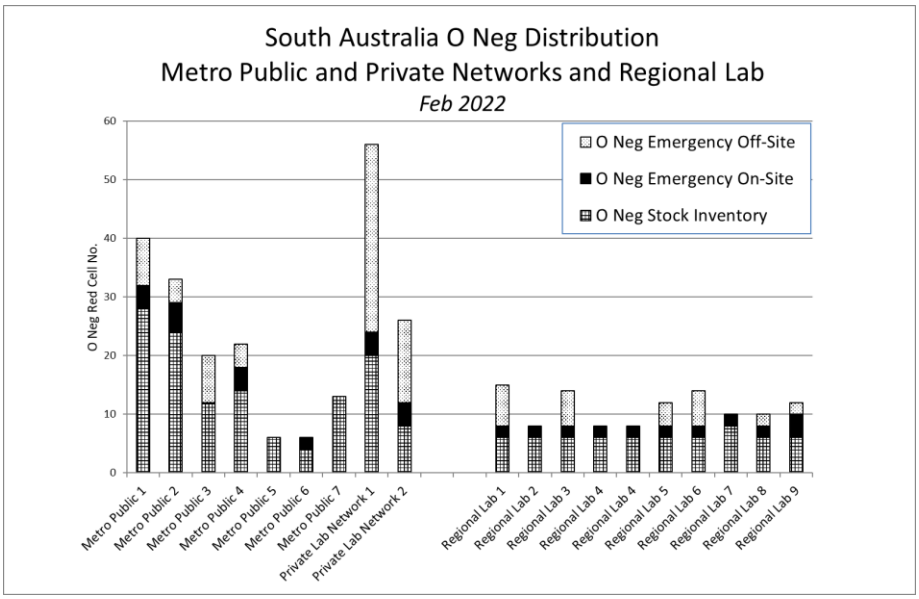
Aim: Map the O Neg red cell (ONegRC) holdings in the transfusion laboratories and partnered satellite hospital sites in South Australia (SA).

Method:An audit was conducted on all SA public, private, metropolitan, regional hospital and laboratory sites to determine their ONegRC holdings that were classified as unallocated stock and/or allocated on-site as emergency standby blood ie. ONegRC ready for emergency issue usually as part of a massive transfusion pack or similar standby in lab or emergency department stock. Off-site emergency ONegRC stocks were also audited to determine levels and locations.

Results:



For metropolitan and regional labs, the ONegRC stock inventory was commonly supplemented by a small no. of on-site emergency standby ONegRC plus varying amounts of off-site ONegRC holdings. The off-site arrangements were in place to deal with concerns regarding potential lab supply delays often linked to geography.
Conversely, a large amount of off-site ONegRC were observed with the hospitals supported by private lab networks. These off-site holdings were generally larger than their own lab stock inventory. Possible reasons are the adoption of the group and hold protocols for surgical procedures with a low crossmatch to transfusion ratio with a parallel reduction in the matched blood held. Holding ONegRC provides some assurance of blood being available for transfusion in cases of unexpected peri-operative bleeding.
Not unexpectedly, a large portion of ONegRC in SA are located in various public and private hospitals without on-site labs as emergency standby blood.

Conclusion: Mapping the ONegRC inventories, together with an assessment of historical usage and clinical risk, will inform targeted supply and threshold adjustments as well as support discussion on the adoption of possible alternative practices such as the transferring to holding O Pos red cells as emergency inventory

THANZ Oral Presentations

Regulation of proplatelet production by endoplasmic reticulum protein 5 (ERp5)

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Aim: Megakaryocytes undergo a unique differentiation process involving endomitosis to produce proplatelets which eventuate into platelets. Part of the regulation of platelet formation involves the synthesis of granule proteins within the endoplasmic reticulum [ER] of megakaryocytes [1]. Increased protein synthesis can cause ER stress in megakaryocytes during proplatelet formation [2]. In response to ER stress, cells upregulate ER chaperone proteins, such as ER protein 5 (ERp5) [3]. However the role of ERp5 in the development of ER stress in megakaryocytes is unknown. The aim of this study was to determine the role of ERp5 in megakaryocyte ER homeostasis and proplatelet production.

Methods: To study the role of ERp5 in platelet production, we generated mice with megakaryocyte lineage deficient in ERp5 (PF4Cre+Pdia6 fl/fl) using CRISPR-Cas9 technology. Platelet count and platelet clearance was measured after intravenous injection of an anti-platelet labelled antibody. Megakaryocytes were cultured from ERp5 deficient and control mice for assessment of proplatelet formation with or without treatment with ER stress inducers (thapsigargin, tunicamycin). Immunostaining of fixed frozen bone marrows was performed for the measurement of platelet formation and ER stress markers.

Results: Mice with ERp5 deficiency in the megakaryocyte lineage had mild macrothrombocytopenia compared with controls. Platelet clearance was normal in ERp5 deficient mice. On the contrary, ERp5 deficient mice showed evidence of a platelet production defect. Cultured ERp5 deficient megakaryocytes had decreased proplatelet formation in culture, with or without induction of ER stress. Bone marrows of ERp5 deficient mice had decreased number of megakaryocyte fragments compared with ERp5 replete mice. Additionally, ERp5 deficient megakaryocytes showed increased phosphorylation of the ER stress sensor IRE1 compared with controls.

Conclusion: Our results demonstrate that ERp5 plays an important role in maintaining platelet endoplasmic reticulum homeostasis during platelet formation. ERp5 deficiency or dysfunction may underly conditions of decreased platelet formation.

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Shear stress and Factor Xa promote amyloid precursor protein (APP) processing platelets

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Aim: APP proteolysis can generate deleterious pro-aggregatory APP fragments (Aβ) that contribute to cerebral plaque formation. Platelet APP may alternatively undergo α-secretase (ADAM10)-mediated cleavage, producing a soluble, non-aggregatory, 33-kDa fragment (sAPPα). ADAM10 also cleaves glycoprotein (GP) VI from shear- or FXa-activated platelets to produce soluble GPVI (sGPVI). We assessed whether FXa could regulate platelet APP proteolysis.

Methods: Platelet-rich plasma (PRP) or washed platelets (WP) were isolated from healthy donor blood and exposed to GPVI receptor agonists (convulxin and collagen-related peptide), FXa (by adding Russell's Viper Venom) or 5,000 – 15,000 s^{-1} continuous shear stress for 5 min in a cone/plate viscometer. Some samples contained rivaroxaban (FXa-inhibitor), hirudin (thrombin-inhibitor), or GI254023X (ADAM10-inhibitor). Levels of GPVI, integrin αIIb, granule marker TLT-1, and APP were quantified by flow cytometry, and western blotting of platelet lysates. sGPVI and sAPP levels were quantified by ELISA, and by western blot of platelet supernatant. Platelet ADAM10 activity was quantified using a fluorescence resonance energy transfer (FRET) assay.

Results: Platelet membrane APP levels increased 5-15-fold (relative to resting platelets) when PRP or WP were treated with GPVI agonists or shear stress (triggering platelet degranulation). Integrin αIIb levels remained stable. Platelet GPVI and APP were shed from convulxin-treated WP, with concomitant appearance of sGPVI and sAPP, by western blot. When PRP was recalcified and subsequently exposed to FXa, sAPP release was increased 3-fold independent of thrombin activity but inhibited by inclusion of GI254023X or rivaroxaban. Resting platelet ADAM10 activity did not significantly change upon recalcification, shear exposure, coagulation (FXa), or addition of GPVI agonists.

Conclusion: Activated platelets expose membrane APP and improve access of active ADAM10, promoting GPVI and APP cleavage. Upon coagulation, sAPP generation is enhanced. FXa contribution to platelet APP regulation may be disrupted by inhibitors of FXa (rivaroxaban, apixaban) potentially increasing the generation of pro-aggregatory Aβ fragments

High sensitivity proteomics identifies a platelet ER stress response in type 2 diabetes mellitus

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Aim*: Platelets in patients with type 2 diabetes are "hyperactive" resulting in decreased efficacy of antiplatelet agents in the prevention of cardiovascular events [1]. Platelet proteomics allows quantitative analysis of mediators of platelet hyper-reactivity. However, a dedicated study of the platelet proteome in patients with diabetes and cardiovascular disease (CVD) has not been performed previously.*

We aimed to identify alterations in platelet protein pathways from patients with or without diabetes, and to correlate these with functional platelet assays and cardiovascular risk.

Method: Forty-two patients with type 2 diabetes (DM) and 34 patients without diabetes (non-DM), matched by sex and age, were recruited at Royal Prince Alfred Hospital, Sydney. Isolated platelets were separated into lysate and releasate fractions (with or without stimulation with low dose thrombin 0.025 U/ml). Platelet function was assessed by platelet aggregation and mobilisation of P-selectin and PAC-1 after stimulation. Platelet proteins were identified by LC-MS/MS using a Thermo Lumos Tribrid Orbitrap instrument [2]. Protein identification and quantification was performed by MaxQuant software and by Western blot.

Results: The expression of cell surface activation markers P-selectin and PAC-1 in response to thrombin (IIa) were not different between DM and non-DM cohorts. However there were significant differences in endoplasmic reticulum (ER) stress and inflammatory pathways between DM and non-DM platelets. DM platelets had significantly increased phosphorylation of the ER stressor IRE1 (Fig. 1A) at rest and upon IIa stimulation. DM platelets secreted higher amounts of chemokines, e.g. CXCL3 (Fig. 1B) and lower amounts of cardioprotective proteins, e.g. superoxidase dismutase 2 (SOD2) after IIa stimulation.

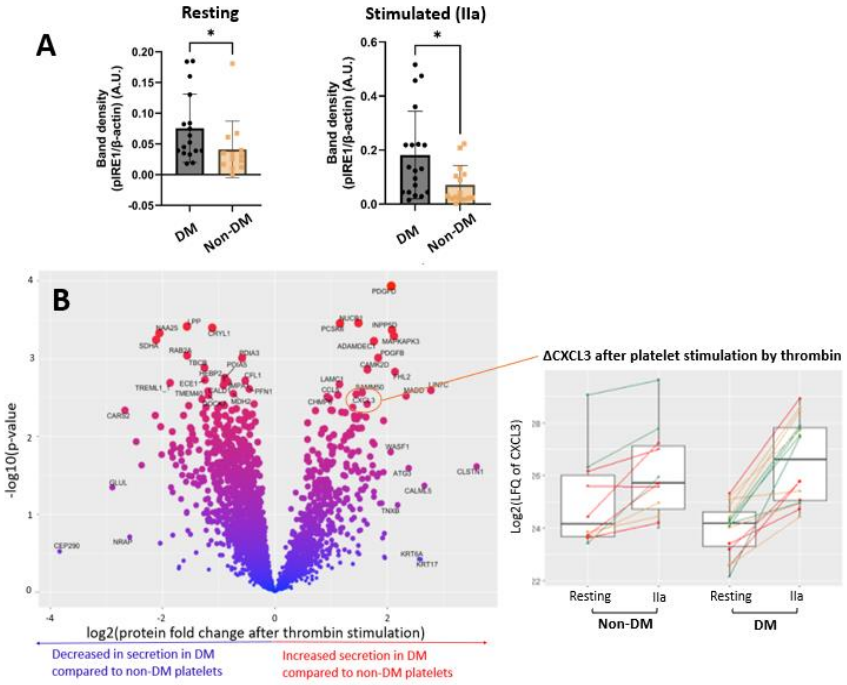

Figure 1. A. Increased phosphorylation of the ER stress sensor IRE1 in platelet lysates from resting and IIa stimulated platelets. **B.** (left) Volcano plot of secreted proteins from resting and IIa stimulated proteins. The differential secretion of platelet proteins is shown, as determined by anti-correlation between IIa-stimulated vs resting proteomes. Scatterplot (right) demonstrating differential secretion of CXCL3 patients with or without diabetes. DM=diabetes mellitus, Non-DM=without diabetes mellitus; n=16 (DM) and 13 (non-DM) for proteomic analysis.

Conclusion:
We have identified a novel pathway, platelet endoplasmic reticulum stress, in patients with diabetes which may contribute to platelet hyperactivity and increased secretion of inflammatory mediators.

Development of targeted CD39 as a therapy of stroke

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Aim: Stroke is caused by obstructed blood flow (ischaemia). Endothelial dysfunction largely underpins ischaemia pathogenesis, leading to aggravated inflammatory response and increased oxidative stress, culminating in thrombo-inflammatory response. Purinergic signaling is an endogenous molecular pathway, where CD39 and CD73 catabolize extracellular adenosine triphosphate (eATP) to adenosine. After ischemia, eATP is released, triggering thrombosis and inflammation. In contrast, adenosine is anti-thrombotic, protects against oxidative stress, and suppresses the immune response. Our group developed a bifunctional compound - αVCAM-CD39 that targets dysregulated endothelium and promotes adenosine generation in site of infarct, localising antithrombotic and anti-inflammatory effects of CD39. The aim was to demonstrate that αVCAM-CD39 will improve stroke outcome in murine models of stroke (middle cerebral artery occlusion MCAo) when given as a single agent, will maximise the benefit of tPA in ischaemic stroke, as well as reduce tPA-related neurotoxicity.

Method: Transient MCAo was utilised as model of stroke. Test drugs αVCAM-CD39 and controls were given 3h after 30min ischaemia. Assessments at 24h included neurological function, infarct volume, perfusion, albumin extravasation.

Results: We showed that there was overall improvement in neurological deficit in treated mice after MCAo. MRI revealed treated mice had significantly smaller infarcts compared to saline and control treated mice. It was further found that blood flow in the brain was increased after drug treatment. There was less albumin extravasation in treated mice after MCAo, suggesting αVCAM-CD39 conferred neuroprotection in the brain through preservation of BBB permeability. We also found that our drug not only did not perturb haemostasis after tPA treatment, but also further mitigated tPA-related blood brain barrier permeability and infarct volume.

Conclusion:
αVCAM-CD39 is a novel therapeutic that can promote neuroprotection, reduce tissue damage and inflammation in the brain after stroke in mice. These findings suggest that αVCAM-CD39 could be a new avenue of stroke therapy and could potentially be used in other cerebrovascular diseases where endothelial dysfunction is a constant underlying pathology.

Myeloproliferative neoplasm (MPN) patients show increased platelet mitochondrial mass with abnormal distribution and impaired mitochondrial function

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Aim: MPN patients demonstrate increased procoagulant platelet responses to agonist stimulation and remain at risk of thrombosis despite optimal management. Procoagulant phenotype may relate to mitochondrial bioenergetics. We aimed to determine if platelets from MPN patients demonstrate quantitative and qualitative platelet mitochondria differences with associated altered platelet reactivity.

Method: MPN patients and healthy controls were recruited from three hospitals. Platelet mitochondrial number and distance from plasma membrane were measured by confocal or electron microscopy (MPN, n=37, healthy n=16, 50 platelets per individual). Platelet mitochondrial mass (mito-DR integrated intensity corrected for platelet size) relative to membrane potential (ΔΨm) (TMRE) in unstimulated platelets was assessed in JAK2+ET (n=12), JAK2+PV (n=8) and healthy (n=9) individuals. Change in platelet ΔΨm with agonist stimulation in essential thrombocythaemia (ET; n=36), polycythaemia vera (PV; n=11) and healthy individuals (n=20) was measured by flow cytometry. Data were analysed using one-way ANOVA and Tukey's multiple comparison or mixed-effects model for repeated measures.

Results: JAK2+ ET patients demonstrated increased platelet mitochondrial mass (x vs y, **p=0.0035) but reduction in ΔΨm relative to mitochondrial mass (0.57 versus 0.96, *p=0.02) in unstimulated platelets. No difference was demonstrated in PV patients. Following stimulation with collagen (10ug/mL), but more marked with increasing doses of thrombin or thrombin/collagen, ET and PV platelets demonstrate significantly greater loss of ΔΨm compared to controls (Figure 1). We also noted that platelet mitochondria were located significantly closer to plasma membrane in MPN compared to healthy platelets (0.03 vs 0.4µm, ***p<0.001) and spontaneous mitochondrial extrusion was observed in ET platelets.

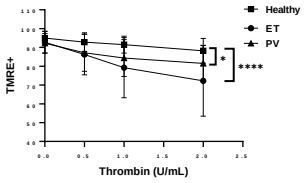

Figure 1: Flow cytometry analysis of TMRE staining of functional mitochondria within healthy donors (n=20), ET (n=36) and PV (n=11) patients following stimulation with various concentrations of thrombin (****p<0.0001 by mixed-effects model).

Conclusion: We demonstrate a mitochondrial dysfunctional platelet phenotype in MPN, more marked in ET than PV. This occurs despite increased mitochondrial numbers in MPN platelets and may relate to multiple mechanisms including mitochondrial extrusion and sensitisation to mitochondrial membrane depolarisation. We speculate that these phenomena may be linked to excess thrombotic risk in MPN.

Overall Haemostatic Potential (OHP) assay can risk stratify for venous thromboembolism recurrence in anticoagulated patients

Dr Julie Wang[1,2], Dr Hui Yin Lim[1,2], Dr Rowena Brook[1], Professor Harshal Nandurkar[3], A/Prof Prahlad Ho[1,2,3]

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Aim: Assessing the risk of recurrent venous thromboembolic (VTE) events, particularly when patients remain on anticoagulation, remains a major challenge largely due to lack of biomarkers. We aimed to investigate the use of the OHP assay in newly diagnosed patients following VTE and explore its role in the risk stratification of VTE recurrence, including in patients whilst receiving anticoagulation.

Method: Adult patients following VTE were recruited between January 2018 and September 2020. Platelet-poor plasma was obtained whilst patients remained on therapeutic anticoagulation. Overall haemostatic potential (OHP) assay, which evaluates fibrin formation with and without tissue plasminogen activator (tPA), was performed on all plasma samples. Time-to-event analysis was performed with recurrent VTE or recurrent unprovoked VTE as endpoints.

Results: OHP assay results were obtained from 196 patients (52.6% male) with a mean age of 57.1 years. Compared to healthy subjects, VTE patients displayed significantly higher overall coagulation potential (without tPA) (39.6 v 34.5 units, p< 0.001) and OHP (with tPA) (9.3 v 6.4 units, p< 0.001) as well as lower overall fibrinolytic potential (OFP) (75.6 v 81.1%, p< 0.001). There were 16 VTE recurrences including 11 unprovoked, all of which occurred above an OCP cut-off of 40th percentile (recurrence rate 4.32 per 100 patient-years, 95% confidence interval (CI) 2.39-7.80, p=0.002). Of 97 patients who subsequently ceased anticoagulation (FigA&B), all unprovoked VTE recurrences (n=9) occurred above the 40th OCP percentile (recurrence rate 9.10 per 100 patient-years, 95% CI 4.74-17.49, p=0.005) and the 40th OHP percentile (recurrence rate 8.46 per 100 patient-years, 95% CI 4.40-16.25, p=0.009). OCP performed better than D-dimer at predicting unprovoked VTE recurrence (AUC 0.72 vs 0.43).

Conclusion: Our pilot study demonstrates that the OHP assay can detect a hypercoagulable and hypofibrinolytic state in anticoagulated VTE patients and may be able to risk stratify for VTE recurrence, allowing for more individualised targeting of long-term anticoagulation.

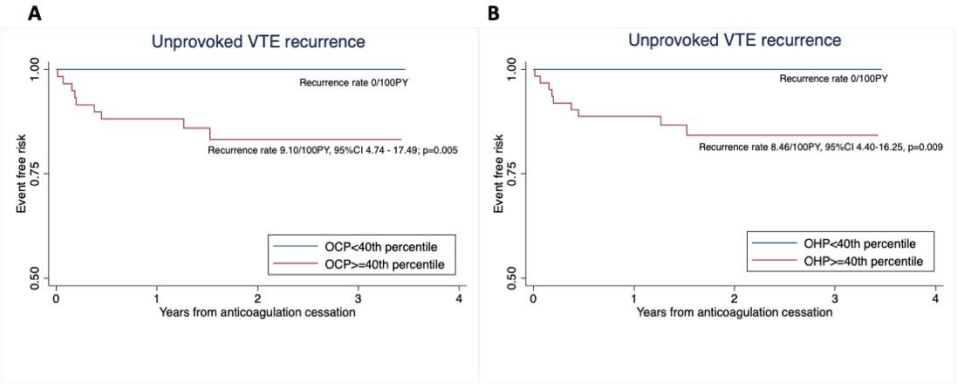

***Fig.A&B**. Kaplan-Meier curves of unprovoked recurrent VTE (n=9) in patients without long-term anticoagulation prophylaxis (n=97).*
***A** – OCP threshold at 40th percentile; **B** – OHP threshold at 40th percentile*

COVID-19 vaccinations and ITP: experience from Australia

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Aim: Immune thrombocytopenia (ITP) has been reported following COVID-19 vaccination. From a population of over 20 million eligible vaccine recipients in Australia, over 32 million doses have been administered: 19,600,000 Pfizer BNT162b2 (BNT), 12,600,000 AstraZeneca ChAdOx1 nCoV-19 (ChAd), and 397,000 Moderna mRNA-1273.

Method: We collected data on ITP diagnosed in Australia within six weeks of COVID-19 vaccination doses, and compared to a cohort of ITP prior to the pandemic. We analysed outcomes using international consensus (Mann-Whitney continuous variables, Fisher's exact categorical and contingency, $p < 0.05$, two-tailed).

Results: Data collected on 50 ITP cases diagnosed after COVID-19 vaccinations (37 *de novo*, and 13 relapsed prior ITP; 40 after ChAd, and 10 BNT).

Bleeding mostly minor: 35/50 (70%) WHO score <2. Compared to relapses of prior ITP, new presentations of ITP significantly associated with ChAd over BNT (OR 7.1: 95% CI 1.7 to 25.7, P=0.0124*). None presented thrombosis.
Most responded quickly and deeply: median TTR 4 and TTCR 7 days, RR 45/47 (96%), CR 40/45 (89%). Gender, age, antecedent influenza vaccination, and severity of thrombocytopenia had no impact on bleeding, RR, CR, TTR.
Cohort comparison with 47 chronic ITP patients monitored prior to COVID-19 pandemic confirmed distinctly more severe thrombocytopenia in relapse after vaccination than baseline fluctuation in unstable chronic ITP (median nadir 6 vs 27×10^9/L, P=0.005**).

Conclusion: ITP was diagnosed more frequently after ChAd than BNT (3.2/million vs 0.5/million doses), occurring *de novo* after 1st doses. Ascertainment bias cannot be excluded due to heightened thrombocytopenia concerns.
Standard first-line ITP therapies highly effective for both *de novo* and prior ITP (96%), but second-line therapies often required (34%).
Our data reaffirms safety vaccinating pre-existing ITP, as bleeding mild (92% WHO <2) and platelets respond quickly (TTCR 5 days) when relapsed after vaccination

Vaccine-induced Immune Thrombotic Thrombocytopenia post Dose 2 ChAdOx1 nCoV19 vaccination: less severe but not void of catastrophic outcomes

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Aim: To describe the clinicopathological features of clinically suspected VITT post 2nd dose AZD1222 vaccination in Australia, highlighting the significance of this entity and its unique characteristics in contrast to VITT post dose 1 AZD1222.

Method: 35 cases of clinically suspected VITT post dose 2 AZD1222 vaccination underwent immunoassay and antibody mediated platelet activation testing. Clinicopathological features were adjudicated by an expert advisory committee. Cases with evidence of anti-PF4 antibody on immunoassay or antibody mediated platelet activation on functional testing were classified as VITT.

Comparative analysis was performed on confirmed cases of VITT post 1st and 2nd dose of AZD1222.

Results: Cases of clinically suspected VITT were predominantly male (66%) with PE/DVT (74%) and presented at a median of 14days IQR 9,18) with platelet count 116 x10^9/L (IQR 92, 139) D-dimer fold change 14.5xULN (IQR 9.4, 28.8) and 84days (IQR 42, 85) between doses of AZD1222.

16 patients with clinically suspect VITT post dose 2 AZD1222 had evidence of PF4 antibodies via immunoassay (4/16) or antibody mediated platelet activation on functional testing (16/16) and were classified as confirmed VITT. In comparison to cases post 1st dose the median platelet count was higher; 121x10^9/L (IQR 89, 140) vs 71x10^9/L (IQR 37, 125), p=0.02 and plasma D-dimer elevation lower; 14.5xULN (IQR 0, 24) vs 40xULN (IQR 16, 45), p=0.003. 2 fatalities occurred in the context of concomitant factors including dosing interval less than 30 days.

Conclusion: VITT is a complication of dose 2 AZD1222 vaccination. Whilst laboratory findings are more modest compared to VITT post 1st dose, fatalities occurred. Concomitant factors likely contributed to outcome severity, with short dosing interval implicated in all catastrophic cases. Antibody-mediated platelet activation remained the hallmark of the disease however the low level of detection of anti-PF4 antibodies raises the question of alternative pathways for platelet activation warranting further research.

Multi-centre evaluation of a rapid screening test for ADAMTS13 activity - report from the rapid assessment of plasma in microangiopathic thrombocytopenia (RAPMAT) study

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Introduction: Thrombotic thrombocytopenia purpura (TTP) is a rare, life-threatening disease, and a timely diagnosis is critical. An ADAMTS13 activity level of <10IU/dl is essential to differentiate TTP from other causes of Thrombotic Microangiopathic Thrombocytopenia (TMAT). Current test iterations are FRET, automated chemiluminescence and ELISA assays which can take hours to days at specialised laboratories.

Aim: To evaluate the TECHNOSCREEN ADAMTS13 Activity test (Technoclone) and compare it to an ELISA and a chemiluminescence method.

Method: Suspect and confirmed TTP patient plasmas (n=120) from 6 diagnostic laboratories in Australia and New Zealand were collected for the study and sent to WACTH Murdoch University for further testing. Institutional ethics approval was obtained to collect samples for assay development and calibration. (Permit No. 2013/131). Local and central measurements of ADAMTS13 activity were conducted using: 1. Technozym ELISA assay and 2. TECHNOSCREEN test. The central site also included a chemiluminescence Hemosil assay. The semi quantitative screening test indicates if ADAMTS13 is at one of four level indicator points equivalent to: 0, 10, 40 and 80 IU/dl.

Results: ADAMTS13 activity levels from local and central sites were comparable, r^2= 0.78, as were the chemiluminescence levels with ELISA, r^2= 0.86. TECHNOSCREEN results were interpreted either above or below 10 IU/dl, the TTP diagnostic clinical threshold. From all the 0 TECHNOSCREEN results reported, all but 1 gave quantitative ELISA results <10 IU/dl. There were 2 screening results of 40 IU/dL that were <10 IU/dL and no results at 80 IU/dl resulted in activity levels less than <10 IU/dl.

Conclusion: The screening test provides a time critical semi-quantitative ADAMTS13 evaluation. The screening test value of 80 IU/dl does not require an urgent quantitative assay performed and the patient is unlikely to have TTP. The simple assay operation makes it suitable for all laboratories, especially remote and regional laboratories where quantitative levels are not available.

Characteristics and outcomes of Australian adults with immune thrombocytopenia (ITP): the Melbourne Adult ITP (MA-ITP) Registry

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Aim: ITP is a rare disorder, diagnosis is difficult, treatment varies and many patients require subsequent lines of therapy. The aim of this study was to develop and future-proof a registry that details the natural history and outcomes of patients with ITP, and to provide a resource for collaborative ITP research.

Method: A retrospective and prospective registry was established with consumer support (ITP Australia) of all patients aged 18 years and older with newly diagnosed or relapsed ITP managed at the Royal Melbourne Hospital (RMH), Peter MacCallum Cancer Centre (PMCC) between 01/01/2008 and 28/02/2022.

Results: 158 patients were enrolled. Median age was 42.5 years (interquartile range [IQR], 26-62.75). 55.7% were female. 45% had secondary ITP. At presentation, 64.6% had severe thrombocytopenia (platelet count <20 x 10^9/L), 25.1% had grade 1-2 cutaneous bruising or petechiae only and 49.6% had clinically significant bleeding (28.1% oral cavity, 17.0% epistaxis, 8.0% gastrointestinal bleeding and 3.0% intracerebral haemorrhage). Bone marrow biopsy was performed in 43.5% (median age 55 years vs 39 years p=0.021), however contributed additional information in only 9%. 126 patients received first line therapy, consisting of single-agent prednisolone in 50.7%. Intravenous immunoglobulin (IVIG) was used in 39.7% (p <0.0001 for platelet count <20 x 10^9/L). Rates of complete (CR) and overall (OR) response were 65.5% and 94.9%, respectively. 59.5% of those treated had second or subsequent lines of therapy. Median time until first relapse was 46.8 months (IQR, 7.6-98.8 months). 26.5% received a TPO agonist, predominately at first relapse. Splenectomy was preformed in 11.3%, median age 31.5 years vs 43 years, p=0.05. All- cause mortality was 5.1%, median time from diagnosis to death 8.2 years.

Conclusion: This registry illustrates contemporary ITP diagnosis and management at a major Victorian teaching hospital. It sets a foundation for future collaborative opportunities for registry expansion and ITP research agendas.

Insights into thrombotic risk in patients with ITP: An Australian experience

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Aim: Patients with ITP are at increased risk of thrombosis. This study aimed to investigate the incidence and risk factors of thrombosis in patients with ITP whilst describing events and management.

Method: This was a retrospective cohort study of ITP patients identified from the Melbourne Adult ITP registry, a prospective registry of adult patients with ITP treated at Peter MacCallum Cancer Centre and Royal Melbourne Hospital. These patients have extensive documentation and were included if diagnosed or relapsed beyond 01/01/2008. Any thrombotic event was recorded. Incidence was calculated in person-time (years). Descriptive statistics were used to characterise the association between risk factors alongside past and present therapies. Comparisons were made to known meta-analyses and global estimates of thrombosis alongside the cohort itself.

Results: By the 31/12/2021 we identified 162 eligible patients in the registry, of which 21 (12.9%) developed thrombosis beyond diagnosis (8 with primary ITP, 13 with secondary ITP). 28 thrombotic events were documented, 20 venous events (VE) and 8 arterial events (AE), with 1 death from thrombosis. Incidence of thrombosis was 27.6 events per 1,000 person-years, 19.7 for VE and 7.9 for AE. Patients had a mean of 1.15 thrombotic risk factors for VE and 2.88 cardiac risk factors for AE. 89.3% of patients were receiving therapy at thrombosis. Corticosteroids, IVIG, splenectomy and TPO-RAs were associated with 60.7%, 32.1%, 28.5% and 25.0% of events respectively. Of those who received IVIG, TPO-RA or underwent splenectomy, 10.3%, 21.2% and 23.5% respectively developed thrombosis. 19 of 20 VE received anticoagulation with 4 bleeding events occurring on anticoagulation.

Conclusion: To our knowledge this is the largest cohort study detailing thrombotic risk within a cohort of Australian ITP patients. Our cohort of ITP patients not only had an increased incidence of thrombosis, compared to the general population, but had strikingly high rates of thrombosis post therapy

Endochip for the assessment of thromboinflammation in vaccine-induced immune thrombotic thrombocytopenia (VITT)

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Aim: Vaccine induced thrombosis thrombocytopenia (VITT) syndrome is a rare complication of ChAdOx1 vaccination for COVID19 [1]. VITT shares similarities with heparin induced thrombocytopenia (HIT). In both VITT and HIT, patients develop antibodies against platelet factor 4 (PF4) which promote platelet activation and thrombosis. Involvement of the endothelium in the pathogenic process has been described for HIT. Binding of HIT antibodies to PF4/glycosaminoglycan complexes on the surface on endothelial cells leads to their activation and increased procoagulant activity [2]. However, the role of the endothelium in VITT has not been described. Here, we evaluate the use of an endothelial biochip [3] to study the thrombo-inflammatory effect of serum from patients with VITT.

Method: Serum samples were received from patients with clinical criteria of VITT [1] and from healthy, age and sex matched, ChAdOx1 vaccinated individuals within timeframe (controls) (Ethics SLHD X21-0160 and X20-0177). Microfluidic straight channels were fabricated from polydimethylsiloxane. The channels were endothelialised with human umbilical vein endothelial cells (HUVECs). HUVECs were treated with VITT or control serum (n=6 per group) and compared with tumour necrosis factor-a treatment. The surface expression of activation markers intercellular adhesion molecule 1 (ICAM-1) and von Willebrand factor (vWF) were measured by immunostaining. Thromboinflammation was measured by fluorescence area of adhered platelets, neutrophils and fibrin on the Endochip after perfusion of antibody-containing, recalcified blood from controls.

Results: Endothelial surface expression of vWF and ICAM-1 was increased after 4 or 12h incubation with 25% VITT serum respectively, compared with control serum. Treatment of the Endochip with VITT serum significantly increased the adhesion of platelets (2.4-fold), neutrophils (2.4-fold) and fibrin (7.1-fold) compared with control serum ($p<0.02$, Mann Whitney test).

Conclusion: Endothelial inflammation contributes to the prothrombotic tendency in VITT in *an in vitro* model of thromboinflammation. Endothelialised biochips have diagnostic potential for detecting immune prothrombotic tendencies.

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Thromboprophylaxis in the restrained patient

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Aim: To investigate the risk of VTE in mechanically restrained patients, comparing psychiatric and non-psychiatric presentations.

Method: In a database of 4,000 cases of patients restrained from October 2019 to November 2020 at a Melbourne metropolitan tertiary referral hospital, 150 cases were screened as part of a pilot study. Data including type of presentation (psychiatric or non-psychiatric) based on ICD-10 codes, duration and location of restraint, and use of pharmacological thromboprophylaxis, were investigated to examine risk of forming a VTE. Risk ratios were used to compare outcomes for the type of presentation (psychiatric vs non-psychiatric presentations) and the prescription of thromboprophylaxis. Fisher's exact test was utilised for categorical variables. A p-value <0.05 was considered statistically significant.

Results: Of the 150 restrained patients identified, 48.6% (n=73) received thromboprophylaxis during their admission. No significant difference was identified between those receiving thromboprophylaxis and those who did not in developing a VTE (relative risk 2.12, 95% CI 0.58 – 7.80, p-value 0.2999). However, patients with psychiatric presentations were less likely to receive thromboprophylaxis than their non-psychiatric presentation counterparts (relative risk 0.28, 95% CI 0.16 – 0.52, p-value 0.0001). Whilst not statistically significant, a trend appeared to illustrate that patients with non-psychiatric presentations were more likely to develop VTE than patients with psychiatric presentations (relative risk 0.28, 95% CI 0.06 – 1.26, p-value 0.0676).

Conclusion: Restrained patients with psychiatric presentations do not appear to be at increased risk of developing VTE as compared to patients with non-psychiatric presentations, although the sample size investigated is small. It should be noted, patients with non-psychiatric presentations are more likely to require thromboprophylaxis as their mobility is reduced and potentially have other medical risk factors for VTE in comparison to inpatients with psychiatric presentations.

Efficacy of capped dose Desmopressin in patients with haemophilia A and von Willebrand disease: South Australian experience

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Aim: To compare desmopressin (DDAVP) test response between capped 15mcg subcutaneous (SC) dosing and historical 0.3 mcg/kg intravenous (IV) dosing in patients with mild to moderate haemophilia A (HA) and von Willebrand disease (VWD).

Method: A retrospective chart audit was performed using data from the Australian Bleeding Disorders Registry (ABDR). South Australian patients with HA or VWD with DDAVP challenge results entered in the ABDR from 2009 to 2022 were examined. Coagulation test results, demographic details and diagnostic information (including genetic mutation where known) were collected. Data was analysed to detect a difference between capped 15mcg SC dosing and weight-based (0.3 mcg/kg) IV dosing in each group of patients using descriptive statistics.

Results: Data for 135 patients were analysed. In patients with mild HA, 25/33 (76%) patients achieved a complete response (CR) to capped dosing and 16/21 (76%) to weight-based dosing. No patients (N= 9) with moderate HA achieved CR to either capped or weight-based dosing. In patients with Type 1 VWD, 34/39 (87%) achieved CR with capped dosing and 18/19 (95%) with weight-based dosing. In Type 2 VWD, 3/6 (50%) patients achieved CR with capped dosing, while 4/6 (67%) achieved CR with weight-based dosing. Data will be analysed for other potential predictors of response to DDAVP including weight, gender and disease severity.

Conclusion: This study shows that there is no difference in DDAVP test results for patients having capped 15mcg SC dosing compared to 0.3 mcg/kg IV dosing in patients with mild haemophilia A.

Obstetric Outcomes of Women with Inherited Antithrombin Deficiency: The Western Australian Experience

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Inherited antithrombin deficiency is a rare, high-risk thrombophilia associated with obstetric and neonatal morbidity and mortality. The use low molecular weight heparin (LMWH) and antithrombin concentrate (AT3) appears to improve maternal and fetal outcomes; however, there is a lack evidence-based recommendations to guide clinicians in the management of these complex pregnancies.

Methods: We undertook a multicentre, retrospective cohort analysis of all pregnancies (≥20 weeks gestation) in women with known inherited antithrombin deficiency across Western Australia from January 2015 to May 2022. Analysis was performed based on predefined maternal characteristics, LMWH dosing (weight-based vs anti-Xa guided), AT3 use and maternal, obstetric, and neonatal outcomes.

Results: Eight women with known inherited antithrombin deficiency delivered eight live infants (one ongoing pregnancy). The average maternal age was 33 years and 50 % of pregnancies were conceived on LMWH. LMWH was initially weight-based (1mg/kg BD) then up-titrated to achieve an anti-Xa level between 0.6 -1.0. The average dose of LMWH was 1.39mg/kg BD however wide variation in LMWH dosing was noted (1.03-1.90mg/kg BD). All women received AT3 at induction followed by an additional dose 24 hours later. There was marked variation in the dosing (amount and duration) of AT3 based on clinicians' prescribing preferences and clinical need. One woman had a large volume postpartum haemorrhage, two women developed wound haematomas and one woman developed a sagittal sinus thrombosis on day 19 postpartum. Four pregnancies were affected by significant placental insufficiency including severe preeclampsia and intrauterine growth restriction. Two neonates required admission to Neonatal Intensive Care.

Conclusion: We are the first to describe the Western Australian experience with the management of inherited antithrombin deficiency in pregnancy. Maternal and fetal morbidity remains significant despite the use of LMWH and AT3 supporting the need for the development of evidence-based guidelines for the management of these high-risk pregnancies.

Plasma angiotensin converting enzyme 2 (ACE2) activity in healthy controls and patients with cardiovascular risk factors

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Aim: Angiotensin converting enzyme 2 (ACE2) is a key regulator of the renin-angiotensin system, with effects to degrade angiotensin II. We reported that increased circulating ACE2 activity confers adverse cardiovascular outcomes. In this study, we aim to investigate the factors which can influence ACE2 activity and how levels correlate with global coagulation assays.

Method: Blood samples were collected from healthy controls and patients with cardiovascular risk factors (CVRF) for plasma ACE2 activity and global coagulation assays such as thromboelastography, thrombin and fibrin generation.

Results: Plasma ACE2 activity was measured in 123 healthy controls and 260 patients with CVRF. Fifty-nine controls had ACE2 levels ≤0.02ρmol/ml/min (lowest detectable limit). Male controls had higher ACE2 levels than female controls (1.8 vs 3.9ρmol/ml/min, p=0.014) with minimal differences in baseline investigations. Controls with plasma ACE2 activity >5ρmol/ml/min had lower maximum amplitude on thromboelastography (57.3 vs 62.0mm, p=0.008) but higher fibrin generation parameters and no differences on thrombin generation.

Patients with CVRF had higher ACE2 levels compared to controls (11.3 vs 2.5ρmol/ml/min, p<0.001). Patients with higher Framingham Heart Score (FHS) had higher ACE2 levels (FHS<10 4.9ρmol/ml/min vs FHS10-20 7.4ρmol/ml/min vs FHS>20 12.2ρmol/ml/min, p<0.001). Those with higher ACE2 levels (tertile 3 vs tertile 1) had significantly higher HbA1c (6.6 vs 6.0%, p=0.011). Patients with extremes of ACE2 level (>30ρmol/ml/min) also paradoxically demonstrated lower maximum amplitude on thromboelastography (65.3 vs 68.6mm, p=0.013) and endogenous thrombin potential (1211.6 vs 1335.4nM.min, p=0.038) despite higher fibrin generation (35.5 vs 42.4units, p=0.004) and tissue factor pathway inhibitor (TFPI, 62.5 vs 40.5ng/mL, p=0.006).

Conclusion: Plasma ACE2 levels are higher in patients with CVRF compared to controls. Those with higher levels of ACE2 demonstrate less procoagulant thromboelastography and thrombin generation but increased fibrin generation and TFPI. These contradictory findings highlight the complexity of the pathogenesis of cardiovascular disease and its intricate interactions with coagulation.

Rapid release of IL-1β from platelets stimulated by ADP, thrombin receptor agonists and collagen

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Aim: Platelets as first responders to sites of vascular injury play a pivotal role in both thrombosis and inflammation. We examined the early release of platelet IL-1β in response to soluble platelet agonists and investigated whether this is controlled by caspase-1, as occurs with leukocytes.

Method: Blood samples from healthy donors recruited from Concord Repatriation General Hospital (n=3-5/test), were assessed for: platelet expression/location of IL-1β (Western blot, confocal and electron microscopy); platelet IL-1β release (ELISA) over time after activation (ADP, collagen, and thrombin receptor agonists (SFLLRN/AYPGKF-NH_2); the effect of inhibitors on release (including caspase-1, NLRP3, translation and phospholipase inhibitors); and platelet activation (flow cytometry). Paired t-tests (+/- stimulation/inhibition), repeated measures 2-way ANOVA with uncorrected Fisher's least significant difference analysis (time courses) were used to identify significance.

Results: Platelets have pre-stored active IL-1β (cytosol, open canalicular system, α-granules) that is released rapidly in response to stimulation by platelet agonists. Significant release was observed after 2 minutes (in response to ADP 20.6±11.4 pg/10^9 platelets, p=0.005; collagen 15.8±10.8 pg/10^9 platelets, p=0.02; or PAR-1/4 agonist SFLLRN/AYPGKF-NH_2, 98.9±26.5 pg/10^9 platelets, p=0.008). Release was dependent on plasma but independent of traditional IL-1β release mechanisms involving caspase-1 and the NLRP3 inflammasome and not directly correlated with traditional markers of platelet activation. Additionally, while release of IL-1β after $P2Y_{12}$ receptor stimulation was phospholipase dependent, IL-1β release after PAR stimulation was not.

Conclusion: We have identified mature IL-1β in resting platelets which is rapidly released in plasma-containing media after stimulation of platelets with soluble ADP or PAR-1/-4 agonists. Acute IL-1β release from platelets may trigger downstream inflammatory effects in vascular microenviron

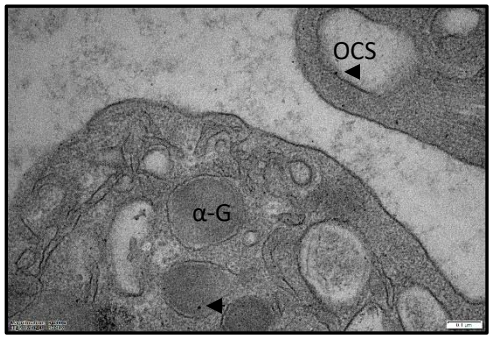

Figure: Active IL-1β is present in resting platelets in the α-granules (α-G), open canalicular system (OCS) and the cytosol. Arrows indicate positive mature IL-1β immunogold-labelling in a representative platelet ultrathin section.

Novel Prothrombotic Genetic Variants, TSPAN15 rs78707713 and SLC44A2 rs2288904, are associated with an increased risk of Cancer-associated Thrombosis

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Background: Cancer-associated thrombosis (CAT) is diagnosed in up to 20% of patients with cancer. Clinical prediction models cannot accurately identify patients at high risk of CAT, and new methods to risk stratify patients are highly sought-after. The recently described genetic variants, TSPAN15 rs78707713 and SLC44A2 rs2288904, are associated with an increased risk of venous thromboembolism (VTE) in a non-cancer cohort, but their role in CAT remains unknown.

Aim: To determine the association between the genetic variants, TSPAN15 rs78707713 and SLC44A2 rs2288904, and CAT.

Methods: Prospective cohort study utilising the UK Biobank identifying a cancer cohort and a non-cancer cohort defined by ICD-10 coding. Within the cohorts, we established the rate of VTE and performed Cox Regression analysis to determine the association between TSPAN15 rs78707713 and SLC44A2 rs2288904 and CAT. We report hazard ratios (HR) with 95% confidence intervals (CI) for these outcomes.

Results: Overall, 369,990 participants were included, with 69,029 in the cancer cohort and 300,960 in the non-cancer cohort **(Figure 1)**. The rate of VTE was 3.6% in the cancer cohort, and 1.3% in the non-cancer cohort (p<0.0001). When compared with the non-cancer cohort with 0 risk alleles, the heterozygous and homozygous forms of TSPAN15 rs78707713 and SLC44A2 rs2288904 were associated with an increased risk of CAT **(Figure 2).** The HR for the homozygous states were 4.25 [95% CI 3.16–5.72] and 4.05 [95% CI 3.41–4.83], respectively **(Figure 2).** Additionally, when evaluating specific cancer types associated with highest risk of VTE (pancreatic, gastro-oesophageal and lung), homozygous TSPAN15 rs78707713 and SLC44A2 rs2288904 were strongly associated with CAT (HR 29.40 [95% CI 21.66-39.92] and 29.39 [95% CI 24.27-35.59], respectively).

Conclusion: We identify for the first time an association between TSPAN15 rs78707713 and SLC44A2 rs2288904 with an elevated risk of CAT. Consequently, these variants may improve current risk stratification methods for predicting risk of CAT.

Figure 1. Study Design

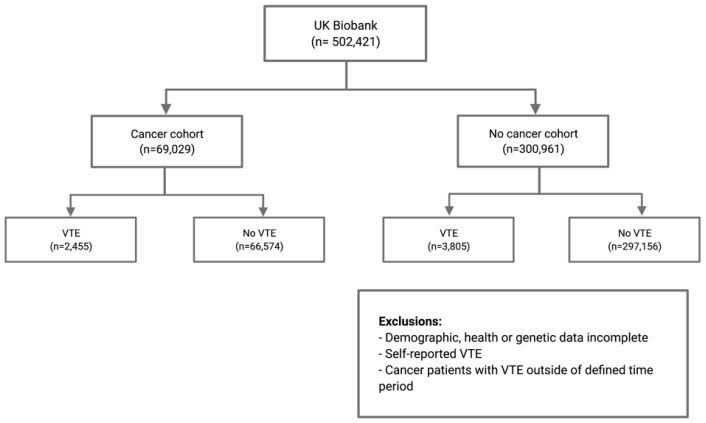
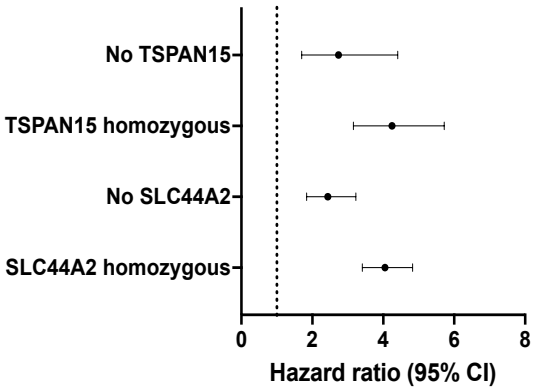


Figure 2. Association between novel genetic variants and cancer-associated thrombosis



Commercial CAR-T in Queensland: Royal Brisbane and Women's Hospital (RBWH) Nursing Review

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Aim: To review patient outcomes and processes related to CAR-T therapy in Queensland to inform future practice.

Method: This analysis will review all patients who received commercial CAR-T cells, either Tisagenlecleucel (Kymriah) or Axicabtagene ciloleucel (Yescarta), from July 2020 to August 2022.

We will examine various timelines including referral to infusion, needle to needle, and the steps in between. Incidence of adverse events such as CRS, ICANS and cytopenia's will be reviewed and follow up treatment analysed. Numerous comparisons will be made including variances between the specific product used, interstate versus local referrals, and various barriers that can influence the patient journey throughout their treatment will be identified.

Results: Review of the data has identified various pain points that can influence referral to leukapheresis, leukapheresis to delivery time, and needle to needle time. Difficulties surrounding logistics of interstate referrals, the impact of COVID-19 and subsequent challenges will be discussed.

Strategies to manage adverse events such as CRS, ICANS and cytopenia's will be evaluated and assessed to determine the effectiveness of patient education and carer engagement practices utilised.

Conclusion: Ongoing collection of CAR-T therapy data from the RBWH Commercial CAR-T Program has allowed continuous appraisal of RBWH CAR-T nursing practices. Inefficiencies have been identified which has resulted in adjustments to our policies, procedures and patient education strategies to help streamline the treatment process to ensure best patient outcomes and experie

Nursing Oral Presentations

Cheers to seven years and beyond. A snapshot of long term follow up (LTFU) reviews in a dedicated allogeneic bone marrow transplant (AlloBMT) LTFU service.

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Background: Studies show that the number of BMT survivors is expected to increase 5-fold by the year 2030, with most of them living beyond 2 years, and are at risk of developing a multitude of complications (Hashmi, Carpenter, Khera, Tichelli, & Savani, 2015). Hence, the need for long term follow up (Bhatia et al., 2017). In November (Nov) 2014, a dedicated nurse-led AlloBMT LTFU service was established to provide annual and lifelong physical and psycho-social care to AlloBMT survivors who are two or more years post-transplant and in remission.

Aim: To provide an overview of the number of patients referred and reviewed in a dedicated AlloBMT LTFU clinic over the last seven (7) years.

Method: Using the ethics approved database of an AlloBMT LTFU service, 591 individual patients have been referred to the LTFU clinic from Nov 2014 to April (Apr) 2022. This includes referrals from bone marrow transplant (BMT) centres in Victoria, interstate and overseas BMT centres, and patients transitioning from paediatric care.

Results: 513 patients were from BMT centres in Victoria, 9 from interstate and overseas, and 69 transitioning from paediatric care. Of the 591 individual patients, over 96% (568) attended their first LTFU review, 3% (20) did not attend (DNA) and less than 1% (3) cancelled or re-scheduled their LTFU review. Since its establishment, 1808 AlloBMT survivors living beyond 2 years have been booked in to the LTFU clinic, 1724 (95.4%) attended their reviews, 68 (3.7%) DNA and 16 (<1%) cancelled or re-scheduled (see Table 1 for breakdown). Table 1: Number of LTFU reviews from Nov 2014 to Apr 2022

Month/Year	Patients booked	Attended	DNA	Cancelled or Re-scheduled
Nov 2014 – Oct 2015	168	167	1	0
Nov 2015 – Oct 2016	164	163	1	0
Nov 2016 – Oct 2017	211	208	3	0
Nov 2017 – Oct 2018	302	290	9	3
Nov 2018 – Oct 2019	278	258	12	8
Nov 2019 – Oct 2020	264	244	17	3
Nov 2020 – Oct 2021	278	261	17	0
Nov 2021 – Apr 2022	143	133	8	2

Conclusion: This snapshot shows a steady and growing number of AlloBMT survivors reviewed in the AlloBMT clinic annually. These results provide the next steps to (1) identify patients suitable for nurse-led review, (2) further promote shared care LTFU review with patients' primary care physician, and (3) to design and implement eligibility criteria for frequency of LTFU reviews to reduce overbooking and to accommodate new referrals.

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Identifying sexual health issues experienced by couples post allogeneic (allo) haematopoietic stem cell transplant (HSCT)

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Background: One of the common survivorship issues experienced by an individual or couple, but not often discussed after HSCT is sexual dysfunction (Li, et al., 2015). Sexual health assessment is an essential component in survivorship reviews. Physical problems and treatments (current and previous) can affect sexual function of HSCT survivors and can lead to sexual difficulties (Yi, 2009; Syrjala, et al., 2021) and relationship problems as partners may experience adversities adjusting to role changes (Lupinacci, Lamore, & Seyeux, 2021).

Aim: To describe sexual health issues reported by survivors of allogeneic HSCT and their partners who participated in a recent pilot study from a single centre.

Method: Permission was sought from the Principal Investigator (PI) to present the sexual health and relationship issues experienced by couples who participated in the pilot study evaluating feasibility and acceptability of a psychosexual intervention for couples post allo HSCT. The sexual health assessment tool Permission, Limited Information, Specific Suggestions, Intensive Therapy (PLISSIT) was utilised during the interview.

Results: 212 individuals who are more than three (3) months post allo HSCT have been screened for eligibility. 85 (40%) individuals were eligible for the pilot study and 126 (60%) were not eligible because of death, ongoing issues, and relapse disease. 14 (16.5%) were interested to participate, 46 (54.1%) not interested and 25 (29.4%) did not reply.

The common sexual health issues identified by eight (8) survivors of allo HSCT (four men and four women) who participated in the study include body image disturbance – not feeling attractive, dyspareunia, low libido, and vaginal dryness in women. Men experienced erectile dysfunction and low libido. The common relationship issues identified include communication – not talking about it, feeling alone and lost – did not know who talk to, feeling scared and not feeling confident.

Conclusion: The results show the common sexual health problems experienced by survivors of allo HSCT and how these issues can affect the couples' relationship and quality of life. These findings highlight the importance continuing routine sexual health assessment in post allo HSCT survivors to (a) facilitate early identification of sexual dysfunction (b) provide information, validation and education regarding patient's sexual health issues and (c) facilitate timely specialist referral.

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Syrjala, K. L., Schoemans, H., Yi, J. C., Langer, S. L., Mukherjee, A., & Onstad, L. a. (2021). Sexual functioning in long term survivors of haematopoietic cell transplantation. *Transplantation and Cellular Therapy, 27*(1), 80.e1-80.e12. doi:10.1016/j.bbmt.2020.09.027

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Redesigning outpatient cancer care services to deliver care to COVID-19 positive haematology patients

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Aims: Due to their immunosuppression, haematology patients are at significant risk of morbidity and mortality from COVID-19. Outpatient services were redesigned to ensure continued access to contemporary therapies and optimal clinical management for COVID-19 positive Haematology, Bone Marrow Transplant and CAR-T patients. A secondary aim was to limit COVID-19 exposure to vulnerable patients in the general cancer outpatient setting.

Method: Utilising a multi-disciplinary approach and a high level of coordination, a flexible, specialised cancer care outpatient infusion clinic was established. This was located in the isolated outpatient area of the infectious diseases ward, of a large tertiary hospital. This clinic was staffed by cancer care nurses and adapted to the individual needs of patients. This included outpatient treatment for COVID-19 or maintaining the continuity of their planned cancer care treatment.

Results: From 1st January to 15th May 2022, 49 episodes of care were provided for 34 individual patients. 31 (91%) patients who required care were haematology, BMT or CAR-T patients. 8 patients (24%) required greater than 1 episode of care while COVID-19 positive. All 8 patients were heamatology, BMT or CAR-T. 16 episodes of care provided were for the administration of sotrovimab, a monoclonal antibody used to treat COVID-19. The remaining 33 episodes of care consisted of blood collections, chemotherapy, supportive therapies or admission.

Conclusions: The redesign of cancer care outpatient services was essential to meet the immediate and continued care requirements of complex and vulnerable Haematology, Bone Marrow Transplant and CAR-T patients diagnosed with COVID-19. This avoided dangerous and protracted treatment delays without compromising the safety of the general cancer outpatient clinic. This design provides a foundation for cancer services that is readily adaptive to the rapidly changing healthcare environment, whilst maintaining continuity of care.

To lay flat for one hour or two after a lumbar puncture? That is the question. Preliminary results of a pilot randomised control trial

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Aim: Lumbar punctures (LP) with or without intrathecal chemotherapy can be required for a haematology diagnosis or treatment. A potential side effect of this procedure is a post-dural puncture headache (PDPH), which can be debilitating. It has been hypothesised that the length of time lying flat following an LP may influence the presentation of a PDPH and the severity of symptoms.

Method: A single centre, parallel-group, pragmatic pilot randomised controlled trial (RCT) was conducted. Adult haematology-oncology participants were assigned to lay flat for two hours (control) or one hour (intervention). The primary outcome was feasibility of a powered RCT with pre-established criteria for eligibility, recruitment, protocol adherence and retention. The secondary outcome was PDPH incidence and severity with data collected post-LP and at 48 hours. Descriptive statistics were reported for feasibility and clinical outcomes.

Results: Feasibility outcomes were met, except for recruitment (≥90%). In total, 198 LPs were screened, 192 (97%) were eligible, and of these 100/192 (52%) were randomised; 51 to the control and 49 to the intervention. A quarter (47/192) LPs were missed as the research nurse was not available to recruit. A total of 14 LPs laid flat for <1 hour (3/51; 6% in the control and 11/49; 23% in the intervention). Retention at 48 hours was similar for the control (98%) and intervention (100%) groups.Prevalence of PDPH at 48-hour was higher in the control group (26% versus 10.2%, difference=-15.8%, 95% CI: -28.5 to -3.1%, p=0.015) with a median severity rating of 3/10 (IQR=2-5).

Conclusion: The results suggest that lying flat for one-hour post-LP does not increase PDHP prevalence or severity. Feasibility of conducting a powered RCT was demonstrated.

The Straight & Marrow educational podcast – about all things allogeneic bone marrow transplant

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Aim: Allogeneic stem cell transplantation is an intensive curative treatment for patients with haematological disorders and requires an intensive and protracted commitment from patients and families. Support structures are required to be in place and a variety of roles and responsibilities adapted to, in order to ensure optimal outcomes and superior quality of life. Ongoing education is a key tenet on the preparation and support of patients and carers through allogeneic transplantation and its wide range of potential complications and challenges. The COVID-19 pandemic magnified service inequities in our provision of education to regional, remote and interstate patients, both pre and post alloBMT. Naturally, a pivot to embrace technological advances and allow for increased reachability and scalability of education has enabled us to develop an additional tool to complement traditional resources. The podcast was identified as the ideal format with its engaging, informal style that allows for flexibility, is inexpensive and is increasingly gaining popularity as a pedagogical tool.

Method: The creation of this podcast has been led by nurse consultants and nurse practitioners within our haematology service with support from medical, pharmacy, allied health colleagues and patients and carers. The development of the podcast included inviting guest speakers with a broad range of experience from multiple transplant centers to address patient centred topics for discussion, from fear of relapse to medication management, from survivorship to understanding risk.

Results: This resource has been well received with 2,830 downloads, over 13 episodes throughout 19 different countries. On average each episode receives 140 downloads and the most popular episode is “The nuts and Bolts of a Bone Marrow Transplant” with 350 downloads. Apple music (18%, n=444) and Spotify (23%, n=584) remain the most popular platforms to listen with 18% (n=458) utilizing the website directly. (Straightandmarrow.net.au)

Conclusion: Limitations in this methodology include difficulty gaining granular metrics and that it is only available in the English language. Qualitative methods may allow for a more holistic insight into the overall podcast performance. Future topics for the podcast will be guided by metrics and consumer feedback.

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Experience of implementing a Shared Model of Care (MOC) between haematologists and general practitioners (GP) for patients with low risk haematology conditions.

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Aim: This pilot project aimed to deliver and evaluate a new shared Model of Care (MOC), where monitoring of patients with low risk haematology conditions was shared between the patient's Haematologist and General Practitioner (GP).

Method: Patients with Chronic Lymphocytic Leukaemia (CLL), Myelodysplastic Syndromes (MDS) and Monoclonal Gammopathy of Undetermined Significance (MGUS) in a monitoring phase with a regular GP were invited to enrol to the shared MOC. After patient consent and enrolment by the haematologist, their GP was contacted seeking consent to participate, and provided with a condition specific pathway containing direct contact links, review schedule and clinical indicators for escalation to haematologist. A dedicated shared MOC nurse was recruited for the project, with responsibilities including coordinating patient care, monitoring adherence to planned visit scheduled and ensuring patient safety. The nurse maintained a review schedule with three out of every four review appointments with GP (three monthly), and annual review with their haematologist. Patients and GPs were invited to complete surveys reporting their experience during enrolment in the MOC.

Results: This pilot project was open to recruitment between January 2020 and June 2021. Through this period 49 patients were screened and deemed eligible for enrolment, with 41 patients and their GPs consenting to participate in this MOC. To project end (June 2021),15 patients had completed a 12-month cycle in the MOC and following annual review with their haematologist, 15 patients (100%) consented to re-enrolment to another 12 months. Patient surveys demonstrated patients significantly favoured visits with their GP, as it equated to less waiting time, shorter travel time and reduced costs associated with travel to and from appointments. Approximately 120 haematologist clinic appointments were able to be transferred from haematologist outpatient clinics to GP visits.

Conclusion: Patients recruited to this MOC reported advantages relating to travel time, wait time, out of pocket expenses and ability to address multiple health issues with the GP. This project demonstrates a model that supports improved patient experience whilst alleviating demand for haematologist outpatient clinics

Self-administration of subcutaneous chemotherapy using a knowledge translation framework

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Aim: To develop a new model of care for myeloma patients to self-administer Bortezomib in the home setting using a knowledge translation framework. The model of care aims to reduce hospital visits and improve patient experience.

Method: A Knowledge-to-Action Framework Process (Graham et al, 2006) was adopted to design the new model of care The core elements of this framework include consultation with key stakeholders, appraisal of the evidence, adaptation to local context, identifying barriers and development of the action plan.

Developing the Evidence Informed Action Plan Evidence supporting the practice change for this program was built upon bortezomib extended stability data which can support home administration. Findings from bortezomib home programs overseas provided evidence of patient satisfaction. Data from the self-administration chemotherapy program run at Central Coast Local Health District was reviewed and confirmed the safety of the proposed approach. A feasibility study protocol to pilot the model of care has been developed and has received ethics approval (2021/STE04489).

Pre-implementation : . A comprehensive practice change package was developed and endorsed by the Cancer Executive committee incorporating a standard operating procedure, competency tools, staff education program, patient resources, telehealth assessment tool alongside changes in processes within pharmacy and the oncology management system.

Implementation

The pilot has commenced recruitment (May 2022). Patient experience will be explored through the use of patient reported outcome measures, patient stories, time burden data and a self-injection assessment questionnaire. Safety and efficacy will be collected using pathology results, adverse events reporting and a symptoms/concerns scale. Staff experience will be evaluated through a satisfaction survey. A cost evaluation will compare the average cost of a Bortezomib injection delivered in the day unit and at home.

Conclusion: The use of a knowledge translation approach to the practice change provided a systematic knowledge-to-action framework to support implementation of high quality research findings into practice.

References:

Graham, I.D., Logan, J., Harrison, M.B., Straus,S.E., Tetroe, J., Caswell, W., et al (2006). Lost in translation: Time for a Mmap? The Journal of Continuing Education in the Health Professions, 26, 13-24

Development of a governance framework and training program for Nurse Practitioners to participate in all aspects of paediatric patient blood management (PBM).

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Aim: Nurse Practitioners (NPs) are highly skilled and routinely prescribe medications within their scope of practice. Historically, they have not participated in elements of PBM such as consent, interpretation of laboratory results, the decision to transfuse, prescription of blood products and management of transfusion reactions as blood is a biological substance rather than a medication.

The aim of this project was to scope the possibility of NP's participating in the above PBM activities and develop a governance framework and training programme to facilitate this.

Methods: Scoping included contacting or reviewing documents from; the Victorian Blood Matters program, Australian and New Zealand Society of Blood Transfusion (ANZSBT), Australian Health Practitioner Regulation Agency (AHPRA), the Nursing and Midwifery Board of Australia and internationally from the United Kingdom. Locally, our Blood Management Committee, hospital executive and relevant teams were contacted for interest and support.

At the time of scoping, we were not aware of any Victorian, or other paediatric hospitals, with a dedicated NP PBM governance and training program.

To ensure adequate governance a dedicated procedure was drafted including eligibility, application, roles, responsibilities, training, competency, clinical supervision, assessment, and endorsement. To support NP's education a training portfolio was formulated to document the scope of PBM practice, completion of mandatory training requirements, self-directed learning objectives and practical elements and supervised PBM practice.

Outcome: After two years of extensive consultation, multiple revisions, tabling at multiple committees and a series of executive and legal approvals the Nurse Practitioner and Paediatric Blood Management Procedure and training portfolio has been published on the hospital intranet.

Conclusion: The team has successfully scoped and developed a governance framework including a procedure and training portfolio to enable NPs to participate in PBM.
We envisage these NPs becoming experts in PBM and provide local mentoring, training, and education.

Haematological cancer nursing workforce in Australia: a subanalysis of the Cancer Nurses Society of Australia (CNSA) Cancer Nursing Workforce Mapping survey

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Aim: This study aimed to describe demographics, work conditions and professional concerns of nurses working in haematological cancer care in Australia.

Method: The CNSA, other professional societies, and clinical networks distributed the 60 question Cancer Nursing Workforce Mapping cross-sectional survey between 10 October 2021 and 20 February 2022.

Results: A total of 930 nurses from all Australian jurisdictions participated. Of these, 463 selected haematology as one of the main tumour streams they worked in. The majority (367/463, 79%) were between 30-60 years of age (30's: 28%, 40's: 26%, 50's: 25%), and most worked in Queensland (23%), NSW (17%) or Victoria (31%) – 3% worked in remote areas and 72% in major cities. Most nurses (87%) had obtained their nursing qualification in Australia (UK: 7%, NZ: 3%). The vast majority of respondents were female, 26% had ≥20 years experience in cancer nursing, and 52% had a postgraduate qualification. Over 70% of nurses worked in the public sector, and most had a clinical role (73%, Admin 11%, Education 10%, Research 3%). Of those providing clinical cancer care (409), most provided specialist care in a dedicated cancer service adhering to specialist competency standards (67%). Median hourly pay was $49/hr (IQR: $45-55), and most respondents had permanent positions (82%), with 68% at ≥0.8 FTE. Twenty-nine percent of respondents planned to stay in cancer nursing for ≤5 years, and 41% for between 10 and 20+ years. Current job satisfaction was rated between 70-90% for 49% of respondents, and main challenges reported were high workload (91%) and information overload (53%).

Conclusion: This study provides the first national data on the haematological cancer nursing workforce in Australia, and enables opportunities for advocacy, workforce planning and development. Findings would help to inform future education, recruitment and succession planning, and provide baseline workforce data for this nursing stream.

Drive-thru to SCIg the queue: Drive-thru subcutaneous immunoglobulin (SCIg) as an alternative approach to patients needing immunoglobulin therapy during the COVID-19 pandemic

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Subcutaneous immunoglobulin (SCIg) offers a home-based treatment option to patients with selected conditions requiring immunoglobulin therapy. The cold chain requirement of the plasma-derived product is managed by the hospital's transfusion laboratory and pharmacy prior to dispensing. Patients enrolled in the Royal Melbourne Hospital SCIg Program are reviewed by the SCIg Program nurse consultant on an 8-weekly basis when collecting their supplies.
The COVID-19 pandemic has prompted for an immediate and alternative approach to promote patient safety and the continuity of care. "Drive-Thru SCIg" is then established after advisory consultations with nurses, doctors, patient advocacy group, carpark management, transfusion laboratory, and pharmacy. This multidisciplinary approach endeavours to protect the cold chain and safety requirement of SCIg products, as well as transitioning eligible patients onto SCIg to reduce patients' COVID exposure and associated fear and anxiety with in-hospital visits. Patients are reviewed via telehealth to address health care needs and blood tests are monitored regularly via external pathology. The Program also partners with the SCIg Project Nurse from Blood Matters to facilitate closer-to-home collection from regional pharmacies for relevant patients.
The Drive-Thru SCIg initiative commenced on 23 March 2020 and continued until August 2020. It was further extended to December 2020 due to the evolving pandemic situation and Stage 4 lockdown in Victoria. Number of SCIg patients: Before March 2020 (n=44), Between March 2020 and December 2020 (n=75), In May 2021 (n=67). 210 encounters of Drive-Thru SCIg collections were conducted between March 2020 and December 2020. Cold chain requirements maintained and zero wastage reported. Positive feedback received from patients of the benefits including feeling confident, safe, stress-free, and being supported. The successful Drive-Thru initiative has moved to the sustain phase in early 2021, alternating in-person clinic and drive-thru/telehealth for review and supply collection.

Utilising Family Centred approach to support Bone Marrow Failure Syndromes patient and family via Case Management Conceptional Framework, delivered by Maddie Riewoldt's Vision Telehealth Consultation Service

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Background/ Motivation: Apply family centred model to support anyone who is impacted by bone marrow failure syndromes (BMFS) via telehealth consultation service. In 2018, Maddie Riewoldt's Vision telehealth consultation service was established under a collaborative partnership with a National Patient Pathways pilot program, an initiative funded by the Australian Department of Health, and co-ordinated by the Centre for Community-Driven Research (CCDR).

Objective: The aims of this service are: 1) to understand the needs and to support patient and family by providing up-to-date BMFS research and treatment information. 2) to enable empowerment by self-management care plans; 3) to provide strategic service by navigating available healthcare system/resources through engagement with research and community; 4) to increase the capacity and capability of patient pathway programme and enable to increase the awareness of BMFS.

Approach/ Method: All enrolled patients have been managed under a case management conceptional framework and nurse led clinical interventions; till March 2022, there are in total of 66 clients enrolled in the service. Individual consultation was conducted using a systematic structured evaluation questionnaire. Service Evaluation Report submitted annually to CCDR in 2020 and 2021.

Findings/ Results: Consultation sessions were delivered weekly, fortnightly, or monthly based on patient treatment stages. Formulated questionnaires were used for every client after enrolment. Average initial consultation was 90.62 minutes to 35.03 minutes for the subsequent long term follow up clients.
More than 400 referrals/interventions have been made at an average of 11.24 interventions per client in 2020 & 2021. Satisfaction post individual session is 5/5.

Conclusion: This program has proven to be a significant enabler in providing support to patient and family during their tough time dealing with BMFS and as such has become the vehicle needed for expansion of Maddie's Vision Telehealth Consultation Service Australia wide.

Embracing the impact from the GRIFFIN protocol – experience from a processing laboratory

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Aim: Frontline induction for myeloma patients has changed to VRD (Bortezomib, Lenalidomide & dexamethasone) since it was approved by the PBS in June 2020. As such, stem cell mobilisation with G-CSF + cyclophosphamide in the VCD era has changed to G-CSF only for VRD as per GRIFFIN protocol[1]. We aim to assess how HPC collections from VRD-treated patients have impacted on the resources of our processing laboratory.

Method: Myeloma patients requiring HPC collection at our institution during May 2018 to May 2022 were included: (i) VCD-treated patients, (ii) VRD-treated patients. Data analysed include the number of apheresis required to achieve target stem cell dose, use of pre-emptive Plerixafor (PXF), product freezing volume per patient, DMSO usage, and the impact on cryogenic storage.

Results: The table below summarised the comparison of the two groups of patients.

	VCD	**VRD**	*P value*
No. of patients (collections)	27 (33)	25 (37)	
Patients with >1 apheresis session to achieve target	6/27 (22%)	12/25 (48%)	0.08
Enough stem cells for 2 transplants	25/27 (92.5%)	20/25 (80%)	
Use of PXF	2/33 (6%)	16/37 (43%)	0.004
Median product total nucleated cells (10^8/ml ;range)	330 (103-1032)	530 (294-1216)	0.0006
Median freezing volume per patient (ml; range)	100 (100-320)	200 (100-500)	<0.001
Total no. of bags from each group of patient	80	102	0.0008
Usage of DMSO (vials)	42	68	

Conclusion: Rate of PXF rescue for successful mobilisation in our VRD group is similar to the GRIFFIN protocol. HPC products collected from VRD-treated patients have high nucleated cell contents, requiring larger freezing volume. This leads to a significant increase in the consumption of freezing bags, DMSO, and a higher demand for cryogenic storage. Compared to the VCD mobilisation regimen, more laboratory resources are needed to process HPCs collected from patients mobilised on the GRIFFIN protocol.

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HSANZ Poster Presentations

Acute Leuk (Poster Board Numbers H001 – H024)

Flow Cytometric Detection of Chromosome Abnormalities in Paediatric Acute Lymphoblastic Leukaemia

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Background and Aim: Paediatric acute lymphoblastic leukaemia (ALL) is characterised by chromosomal abnormalities with high hyperdiploidy (including +4) and t(12;21); *ETV6/RUNX1* being the most common as detected by karyotyping and FISH. We aimed to determine whether these genetic changes could be identified by imaging flow cytometric analysis of whole cells and incorporating immunophenotyping a method called “immuno-flowFISH”.

Method: Bone marrow from 27 paediatric ALL patients were incubated with fluorophore-conjugated CD19, CD34, and CD10 antibodies and then hybridised with FISH probes for the centromere of chromosome 4 (CEP4), or locus specific *ETV6* and *RUNX1*. After nuclear counterstaining, cells were acquired on the AMNIS ImageStreamX MkII and analysed for FISH probe signals using the IDEAS software.

Results: The total number of cells analysed ranged from 1,255 – 21,712 with 3-75% of cells having a chromosomal aberration. There were +4 hyperdiplody in 24 cases, with an average copy of 2.68 and two fused signals of *ETV6* and *RUNX1* in 3 cases. When stratified by phenotype, aberrant FISH patterns were only present in the nuclei of CD19/CD10/CD34 positive blasts. Residual normal cells that lacked the leukaemic phenotype exhibited diploid FISH pattern for all probes assessed.

Conclusion: Immuno-flowFISH, a cutting-edge technology that allows the evaluation of thousands of cells to detect aneuploidy, has been successful in detecting numerical and structural chromosomal changes in ALL. The lowest limit of detection was 3% blast cells with +4. The confidence in this result comes from the sensitivity from analysing thousands of cells, and specificity by inclusion of immunophenotyping to identify leukaemic cells. This proof-of-concept will be further explored for additional chromosomal changes in ALL as well as defining the use of immuno-flowFISH for residual disease studies.

A single centre experience with at home, patient delivered, chemotherapy.

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Aim: Administration of chemotherapy agents and immunotherapies is the backbone of the treatment used in the management of haematological malignancies. These treatments are commonly administered in a hospital setting by specialised chemotherapy accredited nursing staff. Some centres offer at home chemotherapy, but this is most often delivered by specialised nurses in an at home setting.

The workload in chemotherapy suites is high as centres struggle with patient numbers. This, along with the COVID pandemic, has driven a move to patient delivered therapies. One example being the move to SCIg allowing patients to manage immunoglobulin replacement at home. Additionally, in regional centres, some patients must travel long distances to receive quickly administered subcutaneous medications.

We present our experience at Coffs Base Hospital of patient delivered, at home, chemotherapy.

Method: 7 patients were assessed to be capable of undertaking self-delivered therapy and were trained in the preparation, administration and disposal of their treatment agents. Patients identified ranged in ages from 61-80-years-old with 5 females and 2 males. They were diagnosed with MDS-EB, AML and MM the agents administered with azacitidine (3), cytarabine (2) and bortezomib (2).

Results: All patients enrolled successfully delivered their therapies. Of those receiving treatment at home 3 patients continue on therapy, 1 completed “induction” and has undergone autologous transplantation, 1 withdrew due to intolerance, 1 ceased due to progression and 1 moved interstate.

Conclusion: In selected patients, at home self-delivered chemotherapy is a viable option. This approach can empower patients and improve patient quality of life. Furthermore, this approach can reduce the burden on chemotherapy suites and of travel for patients. Given our experience with patient delivered therapies, we believe a formal study evaluating patient outcomes with patients receiving at home vs. in hospital therapies is warranted.

Thrombin generation in Haematology Malignancies before and after induction chemotherapeutics

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Introduction: Increased thrombin generation (TG) is reported in cancer patients undergoing chemotherapeutics. Haematological malignancies at diagnosis and during induction treatment are associated with an imbalance of coagulation and fibrinolysis. Thrombin generation studies in this setting are scarce, and conventional coagulation parameters have limited utility in determining the overall haemostatic picture.

Aim: This study aims to explore the changes in thrombin generation potential within subgroups of haematological malignancies at diagnosis and after induction chemotherapy.

Method: 13 patients with newly diagnosed haematological malignancy stratified in disease groups (ALL, AML and lymphoma), were assessed for thrombin generation parameters at diagnosis and after induction treatment. Thrombin generation studies were carried out using a commercially available kinetic fluorogenic substrate method (calibrated automated thrombogram – CAT). Results were expressed in terms of mean +/-SD, and paired *t*-test carried out using GraphPad-Prism Software.

Results: Within the ALL-subgroup, induction significantly increased rate-of-thrombus formation (shortened Lag time p=0.0058** and Time-to-Peak p=0.0274*) and increase trend in ETP and peak height. The AML-subgroup demonstrated mixed picture, observed increase trend in rate-of-thrombus formation but attenuated TG. Within the lymphoma sub-group, treatment marginally increased rate-of-thrombus formation but no significant change in TG observed. Sample size within AML and lymphoma subgroups were small and results did not reach statistical significance.

Conclusion: Our study provides insight into the differences in disease biology and chemotherapeutic regimens used in haematological malignancies and their varying contributions to disrupting the haemostatic balance. Induction in ALL patients appear to increase TG overall, AML induction showed mixed picture and lymphoma patients represent a heterogenous group of disease of which no difference is seen in TG. This study may translate into larger future studies to confirm these qualitative findings with implications on VTE prophylaxis and prevention of bleeding complications.

Next Generation Karyotyping using Optical Genome Scanning: A Comparative study of Genomic changes in Haematolical Malignancies

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Aim: Optical genome mapping (OGM) is a promising alternative to traditional cytogenetic approaches. The technique evaluates ultra-high molecular weight DNA, allowing high resolution and genome wide assessment of structural and copy number variants. Variant concordance with the current standard genomic techniques of FISH, SNP-microarray and G-banded karyotype was evaluated.

Method: OGM (Saphyr, Bionano Genomics) was utilised to analyse 50 patients with a variety of haematological malignancies (AML, B-ALL, MDS/MPN, MM, CML, CMML, T-ALL, PV, MF, CLL, and lymphoma). Concordances between the different techniques were analysed.

Results: Concordance of OGM genomic variation with FISH was 73% overall and 100% for fusions. G-banded karyotype concordance was 92%. Concordance with SNP-microarray was significantly lower (27%). The majority of discordance was due to changes in minor clonal populations or small CNVs not being detected by OGM.

Conclusion: OGM using the Bionano Saphyr system has the capacity to detect structural and copy number variants in one assay. However, the sensitivity of the assay to detect small clones and small CNVs is currently not comparable to standard techniques.

Successful treatment of acute lymphoblastic leukaemia (ALL) during pregnancy using a paediatric-based protocol incorporating pegylated-asparaginase

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Acute leukaemia affects approximately 1/75000 pregnancies. 1/3 of these cases are ALL. Previous reports documenting the treatment of ALL in pregnancy highlight a heterogenous approach with many patients undergoing termination before treatment or significant alterations are made to protocols due to concerns of fetal or maternal toxicity associated with chemotherapy. Asparaginase is incorporated in the treatment of ALL in adolescents and young adults in protocols adapted from the paediatric population. However, toxicities associated with asparaginase, particularly thrombotic complications, leads to caution regarding its use in pregnancy. Pregnancy is usually an exclusion to clinical trial participation, highlighting the importance of case reports in informing clinical practice.

Case Report: A 27 yo female diagnosed with Philadelphia chromosome-negative precursor B-ALL at 27 weeks of pregnancy was managed on the Australasian Leukaemia and Lymphoma Group ALL06 adolescent and young adult ALL trial. ALL06 was based on BFM2000 and used pegylated-asparaginase in induction, reinduction and high-risk blocks. Pegylated-asparaginase dosing was based on actual body weight and no protocol alterations were made for pregnancy. Following steroids for fetal lung maturation, induction of labour was undertaken at 33+4 weeks gestation prior to initiation of consolidation therapy. The patient achieved MRD negativity at day 33 and 79 (sensitivity <0.01%) and remains well and disease-free almost 8 years post-diagnosis. There have been no medical or developmental sequelae of intra-uterine chemotherapy exposure. To our knowledge, this is only the second case reporting the use of pegylated-asparaginase in pregnancy and the only report including long term maternal and fetal follow-up.

Conclusion: The positive outcome in this case provides evidence that pegylated-asparaginase may be used in induction therapy for ALL in the 3rd trimester of pregnancy. Further studies are needed to confirm the safety of pegylated-asparaginase in pregnancy as access to native l-asparaginase is now limited.

ABL2-fusion genes in high-risk Ph-like ALL are not targetable with asciminib.

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Aim: Ph-like ALL is a high-risk subtype of B-ALL, which is characterised by a gene-expression profile similar to that of Philadelphia positive ALL in absence of the hallmark *BCR*::*ABL1* fusion-gene. The different gene-fusions observed, include the *ABL1* and *ABL2* genes, which may be amenable to targeted therapy with asciminib, a highly specific ABL allosteric inhibitor. Elucidating the efficacy of asciminib against the *PAG1::ABL2*, *RCSD1::ABL2* and *ZC3HAV1::ABL2* fusion-genes may expand the treatment regimen of Ph-like ALL patients.

Method: The pRUFiG2-*PAG1::ABL2* and *RCSD1::ABL2* constructs were transduced into the cytokine-dependent Ba/F3 cell line and validated by RT-qPCR and Sanger sequencing. Asciminib efficacy was assessed by Annexin V/7-AAD staining and the $LD_{50}^{asciminib}$ calculated as a measure of asciminib-induced cytotoxicity. P-values were calculated by unpaired student's t-test. The *ZC3HAV1::ABL2* fusion-gene was identified by transcriptomic sequencing performed on patient cells which were treated with asciminib and stained with pCRKL antibody for intracellular flow cytometric analysis.

Results: Ba/F3 cells expressing *PAG1::ABL2* and *RCSD1::ABL2* exhibited a mean LD_{50} of 25.4 µM and 27.2 µM, respectively. The LD_{50} were not significantly different ($p>0.005$) compared to negative control, Ba/F3 cells expressing an empty pRUFiG2 vector ($LD_{50}^{asciminib}$ of 24.8 µM) but were significantly different to positive control Ba/F3 cells expressing *BCR::ABL1*$^{(e1a2)}$ (21.2 nM, $p<0.0001$). This indicates that asciminib is not effective *in vitro* against ABL2 fusion-genes. Additionally, in *ZC3HAV1::ABL2* patient blasts, asciminib did not affect the phosphorylation of the downstream effector protein of *ABL2,* pCRKL, indicating no efficacy of asciminib against the fusion.

Conclusion: Despite hypothetical activity against *ABL1/2* genes, the $LD_{50}^{asciminib}$ exceeded the clinical achievable range, in cells expressing *PAG1::ABL2*, *RCSD1::ABL2* and *ZC3HAV1::ABL2* fusion-genes. These data provide clinically relevant evidence that asciminib appears to not effectively target *ABL2* fusion-genes of Ph-like ALL patients. Overall, this project improved our understanding of the efficacy of asciminib and will be further explored *in vivo.*

Evaluating the machine learning capabilities of a web-based digital microscopy artificial intelligence platform for white blood cell evaluation in abnormal peripheral blood films

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Aim: We have previously reported on the accuracy of peripheral white blood cell (WBC) differential and blast identification by a digital scanner-agnostic web-based artificial intelligence (AI) system. The aim of the current study was to perform a comparison of the AI protocols over time to assess if there was improvement in cell identification.

Method: Digitised images of 124 abnormal adult peripheral blood films (including 68 acute and 22 chronic leukaemias, plus 15 red blood cell abnormalities) were uploaded to the web-based platform (Techcyte©). Using the online AI software, WBC differentials were performed on the same films in 2019 (AI1) and 2021 (AI2). There was no reassignment by a morphologist at any time point. AI results were correlated to the 'gold standard' of manual microscopy for each WBC class, and comparison of Lin's concordance **coefficient**s (LCC) used to determine the superior AI version. Sensitivity and specificity of blast identification were also calculated.

Results: The classification of 'unidentified' was removed from the AI2 software, requiring all cells from the previously 81/124 slides with cells in this AI1 default group to be categorised. Despite this change, the AI2 and AI1 correlations with manual microscopy were similar for most cell types (AI2: r=0.70-0.86, AI1: r=0.68-0.90), with the exception of immature granulocytes (Metamyelocytes+promyelocytes+myelocytes), where AI2 showed a significantly improved concordance with manual microscopy compared to AI1 (LCC=0.64 vs 0.38; p=0.005). Blasts were correctly identified by AI2 for 64/65 slides, demonstrating a 2% improvement to 98% sensitivity. However, specificity of AI2 was reduced to 14% from 25% for AI1.

Conclusion: Techcyte© AI maintains high sensitivity for blast identification in malignant films, which is clinically more desirable than high specificity for reducing false negative results. Despite improvements in the AI platform, manual review of abnormal blood films is still necessary for accurate cell identification.

NGS-based clonality testing is a sensitive and complementary method for the diagnosis and monitoring of lymphoproliferative disorders.

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Aim: Next generation sequencing (NGS) based clonality testing for IgH and TCR gene rearrangements has been increasingly recognised to improve diagnostic accuracy in lymphoid malignancies. NGS based assays allow identification of the full range of clonal populations with underlying DNA sequences, thereby offering improved sensitivity and specific clonal markers for measurable residual disease (MRD) monitoring. This helps to guide management and promote timely intervention in disease progression or relapse. Here, we interrogate the utility and accuracy of NGS in the workup of lymphoid malignancies and MRD monitoring of acute lymphoblastic leukaemia (ALL).

Method: All IGH and TCR rearrangement assays performed since May 2020 were retrospectively examined and correlated with patients' clinicopathologic details. Patients' DNA from blood, bone marrow and tissue samples were analysed on the LymphoTrack® Dx and MRD Assay platform (Invivoscribe, Inc.). Sequencing was completed using Illumina® MiSeq.

Results: In our diagnostic cohort of suspected B and T cell lymphoid disorders, monoclonal populations were identified in 62.1% of cases (36/58); 32.8% of cases were polyclonal (19/58) and 5.2% were indeterminate (3/58). Where a monoclonal population is present, a diagnosis of lymphoproliferative disorder was made in 86.1% of cases together with clinical, histological and immunophenotypic findings (31/36). In ALL patients, NGS identified diagnostic clones in 82.6% of cases (19/23). Of these, a total of 68 samples were analysed for serial MRD and demonstrated 80.9% concordance with flow cytometry (55/68). All discordance was due to NGS detecting disease below the threshold of detection for flow MRD, and is clinically significant as in three patients positive MRD by NGS heralded disease relapse. Data collection is ongoing.

Conclusion: Our study concludes that NGS-based clonality testing is a powerful tool in assessing lymphocyte clonality. In ALL, it is also a more sensitive method in detecting MRD compared with flow cytometry in the majority of cases where a molecular clone is identified. Thus, NGS shows tremendous promise as an integral element in the diagnostic and management algorithms of lymphoid malignancies.

Aggressive NK cell leukemia (ANKL): A rare and lethal entity posing a diagnostic challenge resulting in delayed diagnosis.

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ANKL is a rare neoplasm of mature natural killer cells, with limited overall survival. It is predominantly Epstein Bar Virus (EBV) related, with majority of cases reported in East Asia.[1] We herein report a unique case of a 65-year-old-male with ANKL who presented with an undifferentiated inflammatory syndrome (or reactive haemophagocytic syndrome), with concomitant manifestations of bone marrow failure, liver disease, hyperferritinemia (Ferritin – 32,926 micrograms/L), pulmonary infiltrates, splenic infarcts, and mesenteric panniculitis. In the absence of marrow haemophagocytosis from an initial bone marrow (BM) biopsy to support primary HLH and no lymphadenopathy on CT neck to abdomen, he was initially treated for Adult onset Still's disease with Anakinra (Interleukin-1 inhibitor). Failing treatment with Anakinra, the diagnosis was revisited as the patient became more pancytopenic and a repeat bone marrow biopsy ultimately revealed the diagnosis of ANKL. The BM abnormal mononuclear cells on flow cytometry were confirmed as NK cells and cytogenetics showed multiple abnormalities confirming clonality. Next generation sequencing revealed a TP53 mutation. He was commenced on DDGP (Dexamethasone, Cisplatin, Gemcitabine and Pegaspargase) chemotherapy protocol. Despite best efforts, he unfortunately had disease progression and succumbed to lung fungal infection and passed away post Cycle 1 of DDGP protocol.

Diagnosis of NKL is challenging, as its presentation can mimic inflammatory conditions of more common aetiologies. This, coupled with the lack of a definitive test to prove NK cell clonality can lead to diagnostic delays. Timely diagnosis demands a high index of suspicion, especially for patients without a history of haematological malignancy. Aggressive clinical course, high EBV DNA levels and leukemic presentation, often with associated haemophagocytosis, should raise suspicion of NK/T-cell neoplasm like ANKL. Serial monitoring of EBV DNA levels shows good correlation with disease activity.

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No treatment-related mortality and excellent overall survival, without alloHSCT, in adult ALL patients (aged 17-60 years) receiving FRALLE-93 paediatric protocol (containing L-asparaginase): Long-term follow-up.

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Aim: To review tolerability and OS with long-term follow-up of adult patients up to age of 60 years with ALL undergoing treatment with a paediatric protocol (containing L-asparaginase).

Method: We reviewed outcomes of thirty-five patients, aged 17.1 – 60.6 (13 aged >40 years) with ALL, treated with FRALLE-93 protocol (July 06 - March 22). Medical records were reviewed for pre-morbid conditions, FBE, BMAT, cytogenetics, molecular investigations. Data regarding time to relapse and salvage therapy were recorded. OS was calculated using Kaplan Meier analysis. Adverse events were collected.

Results: Thirty-five patients were diagnosed with ALL between July 06 - March 22. All patients commenced FRALLE-93 protocol. Median age at diagnosis was 30.7 (range 17.1-60.6) years. CR to induction therapy was achieved in all but two (94.3%). One of whom received salvage therapy and alloHSCT and remains in CR 4.4 years from diagnosis, the other is currently receiving salvage therapy. Four others underwent alloHSCT in CR1 (for high-risk disease) - three remained in CR1, and 1 relapsed and died. Of the remaining 29 achieving CR to induction and not receiving alloHSCT in CR1, twenty-four (82.7%) remained in continuous CR1. Of five relapses, all died, three of ALL, two of transplant-related causes in CR2. Median time to relapse was 2.15 (range 1.2-2.6) years. OS was 82.8% with median follow-up of 4.7 (0.2 - 15.4) years. Toxicities were common, particularly liver dysfunction due to L-asparaginase, but no patient ceased the FRALLE-93 protocol, or died, due to toxicity of the protocol.

Conclusion: The paediatric FRALLE-93 protocol for ALL is well tolerated in adults up to, at least, the age of 60 years in our cohort - with no treatment-related mortality, and a CR rate of 94.3% and an OS of 82.8%. And, in standard risk disease, this protocol can avoid the need for alloHSCT in CR1

Real world molecular characterisation and clonal evolution of acute myeloid leukaemia reveals therapeutic opportunities and challenges

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Aim: Acute myeloid leukaemia (AML) is an aggressive haematologic malignancy with poor prognosis. Increasing understanding of the molecular mechanisms driving clonal proliferation has resulted in advancements in classification and available therapeutic targets. Fms-related tyrosine kinase 3 (FLT3) mutations are prognostically important and offer options for targeted inhibition, however they are not stable and can emerge or disappear at relapse.

The aim of this study was to review diagnostic testing of consecutive cases of newly diagnosed and relapsed AML reported across Queensland public hospitals in comparison to available literature.

Method: We conducted a retrospective review of 1531 samples from 1231 patients diagnosed with AML between January 2008 and August 2021 to identify patterns of molecular testing and AML subtypes in our cohort. Outcomes included World Health Organisation (WHO) classification, European LeukaemiaNet (ELN) risk category and rates of missed FLT3 mutation testing. Differences in diagnostic parameters between different molecular subtypes were also investigated.

Results: Patients aged <60 years had significantly more favourable risk AML (48% vs 25%, p<0.01), with favourable risk chromosomal translocations (t(8;21) and inv(16)) being more common. 13 patients (1%) did not have FLT3 mutation testing at diagnosis, with 103 relapse samples (39%) not being tested. 18 patients (10%) had FLT3 mutations lost at relapse, with 5 patients (3%) developing new FLT3 mutations at relapse.

Conclusion:
This study identifies the subtypes and risk stratification of a large cohort of AML patients over an extended period of time. The relatively high rate of absent FLT3 mutation testing at relapse coupled with the frequency of loss or gain of this targetable mutation highlights the potential missed opportunities for salvage treatment strategies.

Discordant Flow Cytometric And Immunohistochemical CD20 Expression In B-cell Acute Lymphoblastic Leukaemia (B-ALL): A Retrospective Single-Centre Audit.

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Aim: With the advent of monoclonal antibody therapies in haematological malignancies, accurate identification of antigen expression is pivotal. This relies predominantly on flow cytometry (FCM) of bone marrow aspirate or peripheral blood whilst immunohistochemistry (IHC) of bone marrow trephine sections is not routinely performed. CD20 expression is observed in 40-50% of adults with B-ALL and is associated with worst outcomes (1-3). Addition of Rituximab to conventional chemotherapy improved EFS among young adults with CD20 positive Philadelphia negative B-ALL (4). Discordance between FCM and IHC detection of B cell antigens has been reported in B-cell malignancies (5-6). We reviewed the incidence of discordant CD20 expression in cases of B-ALL.

Method: Retrospective analysis of consecutive de novo or relapsed B-ALL cases over 4 year period. For FCM, bone marrow aspirate or peripheral blood were analysed using the anti-CD20 monoclonal antibodies 2H7 and B9E9 clones. For IHC, sections of B5-fixed, paraffin embedded bone marrow trephine were stained using anti-CD20 (L26) antibody. In cases where CD20 IHC was not performed, this was added retrospectively. CD20 positivity was defined as positive staining in >20% of leukemic blasts. The correlation between FCM and IHC was calculated using Pearson correlation and Bland Altman analysis.

Results: All 60 cases of B-ALL had FCM for CD20 expression at initial work-up. CD20 IHC was performed in only 36% of cases which were CD20 FCM[-] at initial diagnosis. The rate of CD20 discordance was 7% (n=4). All discordant cases showed the IHC[+]/FMC[-] phenotype. When comparing percentage of CD20 expression by FCM and IHC, correlation analysis showed strong positive correlation with R=0.8819 (95% CI 0.8091 – 0.9280) with Bland Altman plot showing a slight negative bias of 5.250 (SD of bias 19.08; 95% LOA -42.64 – 32.14) toward FCM.

Conclusion: Although CD20 expression by FCM and IHC show strong positive correlation in the majority of cases, when CD20 is negative by FCM, IHC should be performed to identify CD20 discordance in B-ALL patients who would be eligible for addition of Rituximab therapy. Similarly, when assessing eligibility for other targeted therapies (e.g.: anti-CD19 bispecific antibody and CAR-T cell therapy or anti-CD22 antibody-drug conjugate), negative antigen expression should be confirmed using a second method.

No conflict of interest to disclose

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Chromosomal microarray analysis improves molecular characterisation of acute lymphoblastic leukaemia.

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Aim: Acute lymphoblastic leukaemia (ALL) is associated with recurrent numerical and structural chromosomal aberrations detected by conventional karyotype (CGEN) and florescence in-situ hybridisation (FISH) analysis. Chromosomal microarray analysis (CMA) detects net gain or loss of genetic material and copy-neutral loss of heterozygosity (CN-LOH) and provides a high-resolution genome overview. Here we aim to explore the added benefit of CMA in routine diagnostic workup of ALL.

Method: From 01/Jul/21 until 01/Apr/22, we analysed peripheral blood (n=6) and/or bone marrow (n=43) samples from 30 adult and 19 paediatric patients (pts) with new diagnosis ALL (B-(n=37) and T-lineage n=12). All 49 cases were investigated by conventional karyotype analysis, lineage- and age-determined FISH panels and CMA using Illumina Infinium Global Screening Array-24, v3.0. CMA results were interpreted and reported according to genome build GRCh37 and consensus recommendations from the American College of Medical Genetics and Genomics (ACMG).

Results: Karyotypes were available for 47/49 pts with failed cultures in two. Eight were normal, 17 (36.2%) had WHO recognised recurrent genetic abnormalities and 22 (46.8%) had other aberrations. Abnormalities by FISH were seen in 38 (77.6%) pts; the most common *BCR::ABL* (n=7) and *EVT6*::*RUNX1* (n=6) fusions and *KMT2A* rearrangement (n=4). DNA extraction and CMA were universally successful. Normal molecular karyotype was seen in 7 pts (normal by CGEN/FISH (n=4), balanced t(1;19) (n=1), low clone size (n=2)). In 50% (4/8) pts with normal karyotype by CGEN, CMA detected additional aberrations including Tier 1A variants with strong clinical significance (hypodiploid karyotype; n=2) and Tier 2 variants with some clinical significance (e.g., *IKZF1* deletions). CMA identified aberrations in both cases which failed by CGEN. Further detailed data on additional Tier 1 (e.g., *NUP214::ABL1* fusion in Philadelphia-like ALL), Tier 2 (e.g. *PAX5* and *RB1* deletions) and Tier 3 variants and LOH identified up by CMA will be presented.

Conclusion: CMA improves molecular characterisation of genomic complexity in ALL. This study highlights the need for continued efforts to incorporate CMA as part of diagnostic workup of ALL.

High HMGN1 expression predisposes to P2RY8-CRLF2 Down Syndrome acute lymphoblastic leukaemia

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Aim: Children with Down Syndrome (DS) acute lymphoblastic leukaemia (ALL) have increased relapse rates, chemotherapy-related toxicity and poor overall-survival compared to non-DS patients. The *P2RY8-CRLF2* gene fusion has been identified in 60% of DS-ALL patients, yet the genomic basis for the predisposition remains unknown.

We aimed to investigate the role of the high mobility-group nucleosome-binding protein 1 (*HMGN1*), on chromosome 21, in DS-ALL leukemogenesis

Method: mRNA-seq was performed on 76 ALL patient blast samples. Fusion transcripts were identified and mRNA expression data was generated. To understand the role of *HMGN1* in *P2RY8-CRLF2* development, *HMGN1* was overexpressed (1.5-fold; *HMGN1*^{H}) in Jurkat cells to represent a trisomy expression level. CRISPR/Cas9 gRNAs were designed targeting *P2RY8* and *CRLF2* in Jurkat cells±*HMGN1* to create the 320 KB deletion (PAR1) resulting in *P2RY8-CRLF2*. Cells were single-cell sorted for TSLPR (CRLF2/IL-7R□) and phosphorylation of signalling proteins were measured.

Results: Significantly higher *HMGN1* expression was identified in *P2RY8-CRLF2* ALL patients, compared to the control (*BCR-ABL1*+; $p<0.0001$). This was further evaluated in Jurkat cells ±*HMGN1* using an undirected repair CRISPR/Cas9 approach. *HMGN1*^{H} cells generated the *P2RY8-CRLF2* fusion more readily post gene-editing ($p=0.034$), and proliferation ($p=0.005$), *CRLF2* mRNA expression ($p<0.001$), and pSTAT5 ($p<0.001$) were all significantly increased compared to non-*HMGN1*^{H} cells. This suggests higher *HMGN1* expression predisposed to *P2RY8-CRLF2* formation after a double-stranded-DNA break with undirected repair, consistent with high *HMGN1* expression observed in patient cells with *P2RY8-CRLF2*

Conclusion: We demonstrate that *P2RY8-CRLF2* is associated with high expression of *HMGN1* in ALL patient cells. Furthermore, we identify *HMGN1*^{H} cells favour PAR1 deletion and the subsequent formation of the *P2RY8-CRLF2* gene fusion after DSB and increase cell signalling pathways. Understanding the role of *HMGN1* in DS-ALL patients has the potential to lead to novel therapeutic interventions in this high-risk group of patients with poor efficacious therapeutic optio

De novo isolated extramedullary acute myeloid leukaemia (eAML) presenting as an intracranial mass

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Case: A 63-year-old female developed a parietal lesion with dural extension. Pathological examination following surgical resection was in keeping with eAML. Bone marrow biopsy did not show acute leukaemia. Positron emission scan illustrated fluorodeoxyglucose uptake in the vertebral column. Molecular profiling of the intracranial tissue detected somatic mutations in NPM1 (variant allele frequency (VAF) 39%) and FLT3-ITD (allelic ratio 25%) which were also detected in cell-free DNA (cfDNA) (allelic ratio 11% and 12% respectively), whilst copy number analysis (digital karyotyping) from NGS performed on cfDNA identified copy number variation illustrated in Figure 1. Induction chemotherapy combined with midostaurin was administered followed by whole brain radiotherapy, resulting in radiological response and undetectable variants on cfDNA. The patient then underwent allogeneic stem cell transplantation. At present, she remains in remission.

Discussion: Extramedullary AML without bone marrow involvement occurs in < 1% of de novo AML (Begna et al., 2021), usually associated with normal karyotype and RAS pathway mutations (Abbas et al., 2021). The central nervous system is a rare site of isolated eAML, often seen in children, involving variable intracranial sites. Data regarding prognosis is limited, and treatment approach is extrapolated from intramedullary AML. Molecular profiling in AML is traditionally derived from bone marrow sampling, however cfDNA is emerging as a non-invasive source of genetic information. In this case cfDNA detected somatic mutations at a lower VAF to that found in tissue NGS, and was an useful adjunct for disease monitoring. cfDNA has not been evaluated in eAML however in lymphoma, which similarly involves extramedullary sites not amenable to repeated biopsy, deep sequencing techniques allow sensitive detection of somatic mutations, and may be used to detect early refractoriness to therapy (Bohers et al., 2018).

Conclusion: CNS eAML is an uncommon presentation of de novo AML. Molecular profiling of cfDNA may be a non-invasive tool for disease monitoring, but requires further evaluation.

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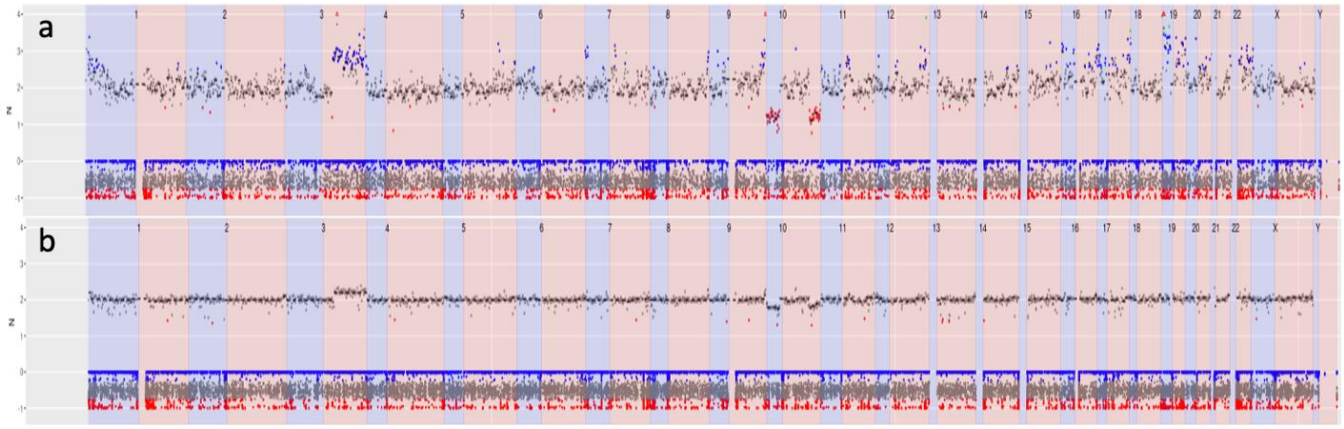

Figure 1. Copy number analysis from NGS at diagnosis illustrating copy number variation in **a)** Left parietal lesion formalin-fix paraffin embedded (FFPE). Gain 3q, del 10p, del 10q, gain 19p. **b)** cfDNA. Gain 3q; del 10p; del 10q.

Next generation sequencing (NGS) in the management of acute myeloid leukaemia (AML): a health economic evaluation

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Aim: NGS provides prognostic information which alters treatment of some AML patients. This testing is not currently reimbursed in Australia which has implications for service development and utilisation. We hypothesise that NGS testing at AML diagnosis will have minimal financial impact from a whole-of-healthcare viewpoint as testing cost will be offset by savings from improved treatment selection.

Method: Our study included 98 bio-banked AML patients treated between 2012 and 2019 in Western Australia. Clinical data and treatment costs were collected. NGS using Sophia Genetics Myeloid Solution was performed on diagnostic samples. Patients were re-risk-stratified according to ELN2017 guidelines. The NGS-directed treatment algorithm is shown below. The anticipated costs of the NGS-directed treatment was calculated using average costs from our dataset. Costs of updated treatment plus NGS costs was compared with actual treatment costs in 2021-equivalent-AUD.

NGS results	NGS-directed treatment algorithm
Favourable risk mutation identified (biallelic CEBPA mutation)	Avoidance of allograft in first complete remission (CR1)
ELN 2017 adverse risk (ASXL1, RUNX1, TP53 in patients with intermediate-risk cytogenetics)	1. Allograft in first complete remission (CR1) for patients 65 yo and minimal co-morbidities • Change of therapy from induction chemotherapy to azacitidine for non-transplant-eligible patients

Results: Amongst intensively-treated patients(n=60), 13 patients(21.7%) were upstaged to adverse risk by ELN-2017. Of these six were 65 years. NGS findings led to two additional allograft recommendations in CR1 as three patients already underwent allograft in CR1 for other clinical reasons and one died after induction. Relapse treatment was salvage chemotherapy (174k for reinduction and 3 consolidation) and azacitidine (59k) respectively. Allograft cost was 166k per patient in our cohort. Seven patients who had induction therapy would be recommended for azacitidine. Assuming unchanged median survival of 12 months and cost/month of 11.5k based on the evaluable azacitidine-treated cohort; treatment cost for these patients would be reduced to 966k from the actual cost of intensive therapy of 1.549 million. NGS inclusive of labour costs for all patients was 91k, leading to potential cost-savings of 390k. Additionally, 28 patients had targetable mutations (*FLT3, IDH1/2 or TP53*).

Conclusion: Upfront NGS is expected to be cost-saving from a whole-of-health perspective, while potentially improving patient outcomes and minimising time in hospital for futile therapy.

High economic burden of AML treatment in Perth, Western Australia (WA)

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Aim: To estimate the total cost of AML therapy in WA.

Method: This study included AML patients bio-banked in Western Australia (WA) who were diagnosed between 2012 to 2019 at Sir Charles Gairdner and Fiona Stanley Hospitals. Detailed clinical data was collected from medical records, treatment costs from diagnosis to death, last follow-up or 30/6/21 was collated from finance department. Costs were converted to 2021-equivalent Australian dollars using 3% annual inflation rate. Cost data was analysed by treatment received; intensive (induction/consolidation +/- allograft), non-intensive (azacitidine or low-dose cytarabine regimens) or supportive care. Continuous variables (Kruskal-Wallis test) and categorical variables (Pearson's chi-squared test) were analysed using STATA/IC v16.1.

Results:

	Intensive	**Non-intensive**	**Supportive Care**	**p-value**
Number of pts	60	15	23	
Age in years [median (range)]	57 (21,76)	78 (70,84)	77 (61,88)	0.001
Alive at last follow-up	25	1	0	
Median survival	21.7 months	8.2 months	2.3 months	0.001
Costs				
Average cost /pt (median)	339.3k (307.0 k)	126.9k (120.0k)	48.2k (26.9k)	<0.001
Range (min, max)	29.9k, 981.0k	39.6k, 253.0k	1.2 k, 212.0k	
Cost / month alive	13.0k	11.5k	12.4k	

Table 1.0 Patient characteristics and actual treatment costs with k representing thousands in AUD (2021)
Average costs was highest amongst intensively treated patients, patients received 1-2 induction cycles (88.2k/cycle) followed by 2-4 consolidation cycles per patient (41.2k/cycle). Induction/consolidation only was curative for 8/60 patients; 6 with core-binding-factor AML. Twenty-three patients underwent allograft, average allograft costs including care for 12 months post-allograft care was 166.4k, 55% costs were incurred during conditioning and engraftment. Thirty-two of sixty patients experienced relapse, twelve were treated with salvage chemotherapy (74k/cycle) with six proceeding to allograft in second remission. Within non-intensive group, costs/cycle was similar at 16.5k (azacitidine) and 15.5k (low-dose cytarabine). Supportive-care patients incurred higher than expected costs. Almost half of the patients (n=10) spent >30% of their days-alive as inpatients. The cost is also under-estimated, as costs of rural patients (n=6) receiving transfusions at their local hospital were not included.

Conclusion: This study highlights the economic burden of current AML treatment. The high costs, significant inpatient stays and poor survival associated with supportive-care only is worthy of consideration when considering treatment decisions.

CPX-351 treatment for acute myeloid leukaemia (AML) in England: real-world outcomes in adults aged <60 years versus ≥60 years

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Aim: CPX-351 (Vyxeos®) is a dual-drug liposomal encapsulation of daunorubicin/cytarabine in a synergistic 1:5 molar ratio. In England, CPX-351 is recommended for adults with newly diagnosed, therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). This retrospective analysis compared the characteristics and overall survival (OS) of adults 18–59 versus ≥60 years with AML treated with CPX-351 in England.

Method: A diagnosis of t-AML or AML-MRC between 01/01/2013 and 31/03/2021 was determined using ICD-O-3 codes or indirectly using nonspecific ICD-O-2, ICD-O-3, or ICD-10 AML codes in combination with prior systemic anticancer therapy or radiotherapy (t-AML) or a prior diagnosis of MDS/CMML (AML-MRC).

Results: Overall, 211 patients with AML received CPX-351; 60 (28%) were aged <60 years, 151 (72%) were ≥60 years, 87 (41%) had secondary AML (t-AML or prior MDS/CMML), 33 (16%) had other AML-MRC, and 91 (43%) had unspecified *de novo* AML. The cut-off date for OS was 31/08/2021, with a median (IQR) follow-up of 11.3 (4.7, 20.1) months. The estimated median OS (95% CI) was 12.9 (10.5, 17.5) months overall, 18.5 (11.0, not estimable) months for adults <60 years, and 11.2 (8.5, 15.9) months for adults ≥60 years, with 2-year survival of 35%, 44%, and 32%, respectively. Early mortality at 30 days was 3% for adults <60 years and 7% for adults ≥60 years. In patients with ≥3 months of follow-up, haematopoietic cell transplantation (HCT) was reported for 29/50 (58%) adults <60 years and 55/115 (48%) adults ≥60 years. When landmarked from the HCT date, median OS was not reached in either age group. The most common salvage therapy across age groups after CPX-351 was FLAG-based chemotherapy.

Conclusion: These results suggest CPX-351 is effective for patients with AML aged <60 and ≥60 years in a real-world setting that bridged many patients to transplantation, with promising post-HCT outcomes.

Rare Case of elderly high risk B-ALL Jehovah Witness attaining morphologic and cytogenetic remission during the Covid-19 pandemic

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Introduction: Jehovah's witnesses (JW) represent a unique patient group whose religious beliefs prohibit receiving blood transfusions. JW patients who develop acute lymphoblastic leukaemia (ALL) represent a challenging population as most chemotherapy regimens require regular transfusion support to prevent life threatening pancytopenia. Furthermore, elderly patients with ALL have poorer survival outcomes and more treatment complications.[1] We report a rare case of a 72-year-old JW patient with high risk complex cytogenetics t-(4:11)-[KMT2A:AFF1 fusion]) B-ALL who attained morphological, cytogenetic remission after 2nd line-treatment with a bispecific agent.

Case Summary: She presented in January 2022 with a peripheral blast count of 550 $x10^9$/L and platelet count of 17$x10^9$/L, requiring emergency leucopheresis for symptomatic hyperleucostasis. First line modified-CALGB-induction regimen commenced with an initial response but progressed after 3-weeks, and proceeded to 2nd-line blinatumomab. *Morphological and cytogenetic remission was achieved after 1-cycle*. A judicious JW-tailored supportive care regimen was instituted throughout her induction with eltrombopag, darbopoeitin, cryoprecipitate and oxygen support. (2) Her induction-course was uneventful despite a haemoglobin trough of 27g/L. Her remission period was complicated by asymptomatic pulmonary emboli and bilateral occlusive leg DVTs detected after noting a significant up-trend D-dimer values, requiring therapeutic enoxaparin. She acquired COVID-19 in the community and her immunosuppressed state led to persistent high viral loads delaying her 2nd-cycle of consolidation blinatuzumab, unfortunately leading to an aggressive relapse with clonally evolved *CD19-negative* B-lymphoblasts necessitating commencement of third line inotuzumab. After an initial response with a peripheral blast count drop from 52$x10^9$/L to 1$x10^9$/L, she progressed over the next few weeks with gram negative sepsis and the consensus was for palliative management. She passed away in May 2022.

Conclusion: This case highlights the complexity and challenges in managing elderly JW patients with B-ALL during the COVID-19 pandemic. Bispecific T-cell engager therapies and aggressive supportive care measures may reduce treatment toxicity and prolong survival.

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Philadelphia positive acute undifferentiated leukaemia - a previously unreported entity

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Aim: Acute undifferentiated leukaemia (AUL, ICD-O 9801/3) is a rare leukaemia that does not express lineage defining markers. A range of molecular and cytogenetic abnormalities have been described (Weinberg, 2019). To our knowledge, Philadelphia chromosome (Ph) has not been reported. Here we report two cases of Ph+ AUL.

Method: Investigations included morphology, flow cytometry, IHC, NGS, Ph FISH and RT-PCR. IHC and flow were used to assign lineage according to WHO 2017 (Swerdlow SH, 2017).

Results: Case 1 received Dasatinib/dexamethasone with clearance of circulating blasts; however, with 45% marrow blasts and BCR-ABL of 39% at d30. Treatment was changed to ponatinib which attained CR1 at 6 months with karyotype 46XX and BCR-ABL 2.45%. She succumbed to Covid-19 at 9 months. Lymphoid features including TCR rearrangement, *EBF1* deletion, STAT5 and Crlk activation were identified. Case 2 was induced with FLAG-IDA-Dasatinib which attained a haematological CR, normal karyotype, BCR-ABL 9% and resolution of mediastinal mass. He received FLAG/Dasatinib consolidation and awaits transplantation.

Conclusion: This report identifies an unreported type of AUL and effective treatment in both fit and frail subjects. We identify shortcomings of conventional methods of lineage assignment and benefits of ancillary molecular techniques to clarify disease lineage.

	Case 1	Case 2
Demographics		
Age	85	26
Sex	Female	Male
Pathologic characteristics		
WBC (x10^9/L)	75.4	17.5
Marrow blasts	87%	38%
LDH (U/L)	634	958
Extramedullary	No	Mediastinal mass
Cytogenetics	t(9;22), del(5)	Complex
BCR-ABL type	p190	p190
TCR/IGH	TCR beta	Not detected
Targeted NGS	No variants identified	TP53, EZH2
Phospho-flow	Stat5, Crkl activation	NA

Case	CD19	CD34	CD3s/c	CD7	Tdt	HLA DR	CD13	CD33	CD117	MPO
1	-	+	-	-	-	+	+	-	-	-
2	-	-	-	+	-	+	-	+	subset	-

Reference:

Cooperative deletions of key lymphoid transcription factors are strongly associated with recurrent genomic lesions in B-cell acute lymphoblastic leukaemia

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Aim: Focal deletions of lymphoid transcription factors and tumour suppressor genes are common in B-cell acute lymphoblastic leukaemia (B-ALL), although cryptic to cytogenetics. We aimed to ascertain the frequency of these deletions in B-ALL subtypes established through transcriptomic sequencing of an Australian cohort.

Method: B-ALL samples negative for aneuploid karyotypes (n=330) were transcriptionally sequenced and subtypes assigned according to identified fusion genes, single nucleotide variants and gene expression profiles. Samples were evenly distributed across all age groups. Gene deletions were detected by multiplex ligation-dependent probe amplification (MLPA).

Results: Focal gene deletions occurred in 78% of samples (257/330) across all subtypes and age groups, with the lowest frequency observed in *KMT2A* rearranged cases (21%, 4/19). *IKZF1* deletions were present in all but the *ETV6-RUNX1* subgroup, occurring with greatest frequency in patients with *BCR-ABL1* (67%, 64/95), ABL-class rearrangements (70%, 7/10) or JAK-STAT alterations (78%, 38/45). A subset of patients from these three subgroups also demonstrated co-occurring deletions of *CDKN2A/B*, *PAX5* or *PAR1* representing the high-risk profile IKZF1^{plus} (42%, 50% and 57% respectively). Deletions of *CDKN2A/B* were common across the cohort but strongly associated with *PAX5* p.P80R (82%, 9/11) or PAX5alt (77%, 10/13). Co-deletion of *PAX5* and *CDKN2A/B* was also more frequent in PAX5 associated subtypes (86%, 18/21). *ERG* deletions predominately occurred in samples classified as *DUX4* rearranged by transcriptomic analysis (37%, 11/30). *ETV6* deletions were most common in *ETV6-RUNX1* (64%, 16/25) and frequently involved whole gene deletion suggesting that bi-allelic alteration of *ETV6* is common in this subgroup. Overall a strong correlation was observed between genomic subtype and the collection of focal gene deletions.

Conclusion: Integrating MLPA data with transcriptomic analysis provides a comprehensive overview of cooperative genomic alterations associated with B-ALL subtypes. Work is on-going to further characterise individual subtypes and identify cooperating mutations that can assist in patient prognostication.

Myelodysplastic syndrome with nucleophosmin (NPM-1): more than just the blast percentage?

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Background: While myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) can generally be distinguished by blast percentage, some cytogenetic or molecular abnormalities are sufficient to confer a diagnosis of AML independently of this. While nucleophosmin (*NPM1*) mutation is considered a founder of and specific to AML, it is not an AML-defining mutation based on current WHO classification. It has been hypothesised that the subgroup of MDS positive for NPM1 mutation may be more akin to AML, regardless of blast percentage, and this has implications for both diagnosis and treatment of this patient population. This case illustrates the hypothesis that NPM1 mutated MDS may be more appropriately treated as AML.

Method: We present a case of a 44 year old female who presented with skin lesions and sepsis secondary to a large vulval abscess, requiring admission to ICU. Histopathologic examination of lesions indicated neutrophilic dermatosis (Sweet's syndrome). A bone marrow biopsy was performed to exclude a haematologic driver of her Sweet's syndrome.

Results: This biopsy was suggestive of a myelodysplastic syndrome (MDS) or a myeloproliferative neoplasm (MPN) with blast percentage <20%. Canonical MPN mutations were negative. Given the likely reactive drivers at the time of her acute presentation, the patient was observed and commenced on steroids for Sweet's syndrome with normalisation of her blood counts. Next generation sequencing results on the bone marrow subsequently returned demonstrating mutation in the nucleophosmin (NPM1) gene. The patient was treated as NPM1 mutated AML. She successfully achieved complete remission (CR) following 2 cycles of daunorubicin-cytarabine (DA 3+8) induction therapy. She remained in CR with undetectable minimal residual disease (MRD) achieved following three cycles of HIDAC consolidation therapy.

Conclusion: Beyond the blast percentage, reconsideration of NPM1 as an AML defining mutation may have significant implications for the treatment and therefore clinical outcomes of affected patients.

Central nervous system involvement in acute myeloid leukaemia – A 6-month single centre experience

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Aim: Central nervous system involvement of acute myeloid leukaemia is thought to be a rare event (6 patients between 1979 and 2009, Maritinez-Cuadron, Haematologica 2022). This, however, has not been analysed by Australian centres.

Method: We examined the presentations, investigations, and clinical outcomes in patients with CNS AML in a 6-month period at St. George Hospital, Sydney.

Results: Three patients are identified, aged 45-74, 2 females and 1 male. All received 7:3 induction. Two had refractory AML - one managed with azacitadine/venetoclax, the other received re-induction and allogenic SCT. Time from initial diagnosis to CNS relapse ranged from 2 to 23 months, all were in morphological remission on bone marrow. Presentation ranged from multi-nerve deficits to status epilepticus. MRI findings include T2 signal changes of parenchyma, pons, spinal cord, and oedema at the cranial nerves. One patient had a neurological PET scan with abnormal FDG uptake. CSF of all patients demonstrated marked leukaemic infiltrates, confirmed by immunophenotyping. One had CSF molecular study, which revealed FLT3 mutation, not previously present. Treatment included intrathecal therapy and WBRT. All progressed rapidly. At time of abstract submission, one patient is alive. Time from presentation of CNS relapse to death was 28 and 57 days for the other two patients.

Conclusion: The report indicates that CNS AML is a more frequent finding than previously thought. Induction regimen is unlikely to affect the risk of CNS relapse. Predicting factors may include genetic markers and hyperleukocytosis at diagnosis. Any neurological symptoms should prompt clinicians to consider CNS disease, regardless of marrow remission status. The prognosis of this disease entity is unacceptably poor. Future research is required to improve risk stratification to direct therapy accordingly.

BMT (Poster Board Numbers H025 – H038)

COVID-19 Infections in Western Australian Haemopoietic Transplant Recipients- Incidence, Outcomes & Management.

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Aim: To review COVID-19 infections in WA transplant patients; COVID-19 infection has had very severe implications in haemopoietic transplant recipients in many overseas centres. With WA's strict border controls and isolation policies, COVID-19 infection is a recent issue. Planning strategies developed to learn from experience interstate and overseas. Fiona Stanley Hospital is the only allogeneic stem cell program in Western Australia, with approximately fifty autologous and fifty allogeneic haemopoietic transplants performed annually.

Method: We reviewed the incidence of COVID-19 in the transplant population at Fiona Stanley Hospital, via a live data bank, which was cross-referenced with Pharmacy and Infectious Diseases Departments. We obtained information regarding the patients infected with COVID-19, including age, sex, date of transplant, underlying disease, immunosuppression, Graft vs Host disease, immunisation status, severity of infection, hospitalisation time, ICU stay, treatments given and outcomes including death in cases up until 13/5/2022.

Results: There were no COVID-19 infections in the haemopoietic transplant population prior to March 2022. Over the subsequent two months, there have been 23 patients identified as infected with COVID-19. Of these, 9 had received autologous transplantation from periods varying from 3 months to six years previously. Most of these patients were managed in the community and did not require admission, with most not receiving specific therapy. None of the autograft recipients have died. There have been 14 allogenic recipients (including one from a haplo-identical donor) infected with COVID-19, at varying times post-transplant, some with GvHD and immunosuppression. Various agents including Paxlovid, Molnopuravir, Sotrofamab, Dexamethasone, Ramdesivir and Evushield have been administered. Two patients have been treated in ICU. One patient with concurrent Gram-negative sepsis died.

Conclusion: There have been limited numbers of COVID-19 infections in Western Australian haemopoietic transplant recipients. Early information indicates more favourable outcomes locally, with beneficial effects of disease control, immunisations, newer strains, novel therapeutic agents and supportive care.

Point-of-care manufacture of CD19 CAR-T cells using the Miltenyi Biotec CliniMACs Prodigy®

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Aim: To manufacture CAR-T cells for use in phase I clinical trials using a semi-automated closed system within a clinical cell processing laboratory.

Method: Mononuclear cells (MNC(A)) were collected by apheresis and processed fresh or following overnight storage at 4°C. A maximum of 3 x10^9 CD3+ T cells were loaded onto the Miltenyi Biotec CliniMACs Prodigy® for immunomagnetic selection of CD4+ and CD8+ T cells. 1 x10^8 CD3+ T cells were activated with TransAct™ and transduced 24h later with the CD19 4-1BB-based CAR lentiviral vector, LTG1563 (Lentigen, USA). Cells were expanded for a further 11 days in TexMACS GMP medium supplemented with IL-7 and IL-15. Quality assurance testing was performed on the MNC(A), CD4+/CD8+ selected MNC(A), in-process samples on days 5, 9 and 12, and the formulated CAR-T cells. CAR-T cells were released and infused without cryopreservation on day 12 of manufacture. The cell doses were 0.5 or 2.0 x 10^6 viable CAR T cells per kg depending on the risk of cytokine release syndrome (CRS). Excess CAR-T cells were cryopreserved.

Results: We have manufactured and infused CD19 CAR-T cells for 6 patients enrolled on a phase I clinical trial. All CD19 CAR-T cells met specification for viability, transduction efficiency, microbial contamination, mycoplasma, endotoxin, and qPCR for replication competent lentivirus (VSVG) and vector integrant copy number. On the day of infusion, the median transduction efficiency was 26.5% and the median number of CAR T cells in the formulated product was 1150 x 10^6 cells. One patient with rapidly progressing mantle cell lymphoma did not meet target cell dose and died at day +23. The remaining 5 patients received target cell doses ranging from 62 to 233 x10^6 with CAR-T cells readily detectable from day 7 onwards.

Patient	**#1**	**#2**	**#3**	**#4**	**#5**	**#6**
CAR+ (%) of CD3+ cells	20.8	27.4	8.7	25.6	34.0	37.0
CAR-T (10^6) manufactured	1146	1154	7	1224	944	1491
CAR-T (10^6) target dose	220	184	37.5	62	214	233
CAR-T (10^6) infused	220	184	7	62	214	233

Conclusion: Point-of-care manufacture of CAR-T cells in a hospital-based cell processing laboratory is feasible and enables a short vein to vein time for the patient of 12-13 days.

Cost-effectiveness of extracorporeal photopheresis for the treatment of chronic graft versus host disease in the Australian setting

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Aim: The objective of this study was to assess the cost-effectiveness of integrated, closed-circuit extracorporeal photopheresis (ECP) with methoxalen compared with standard of care (SoC) therapy for the treatment of cGVHD patients who are refractory to steroid therapy in Australia.

Method: A cost-utility Markov model was developed to compare the costs and quality-adjusted life-years (QALYs) of ECP with current publicly funded SoC second-line therapies (tacrolimus, ciclosporin and mycophenolate mofetil) over a 10-year time horizon. Health states in the model included response to treatment, progressed disease, and death. Transitions between health states were modelled on treatment response data from Australian observational studies and randomised controlled evidence. Patients who responded to treatment continued in the response health state. Patients that were assessed as non-responders, transitioned to the progressed health state. Treatment duration was calculated from the median duration of maintenance therapy in the observational evidence. Disease-specific mortality was calculated separately for treatment response and progressed health states from patient level Australian data. Quality of life utility values were sourced from a published cost-effectiveness analysis of ECP for cGVHD and applied based on treatment response. The model adopted an Australian health care perspective and included costs associated with second-line treatment, healthcare resource use associated with disease progression and subsequent immunosuppression therapy.

Results: Over a 10-year horizon, including ECP as a second-line treatment option for steroid refractory cGVHD dominated (less costly, more effective) over SoC in terms of cost-effectiveness. ECP decreased overall costs by A$24,006, attributed to savings associated with delaying treatment with subsequent therapies, reduced disease management and hospitalisations associated with progressed disease. ECP was associated with an incremental QALY gain of 1.10 due to greater treatment response compared to SoC.

Conclusion: This analysis demonstrates that ECP is a highly cost-effective option for treatment of refractory cGVHD patients in an Australian population compared with SoC the

Refractory myositis-related chronic graft versus host disease

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Aim: To present a case report of refractory myositis-related chronic GVHD (cGVHD) in a 55-year-old woman with acute myelomonocytic leukaemia post allogeneic transplant and review the literature on myositis presentation of cGVHD.

Method: We obtained informed consent to present our case of myositis related cGVHD. A pubmed search was conducted using the terms myositis and chronic GVHD.

Results: A 55 year old Caucasian woman with CMML relapsed following RIC MUD allogeneic SCT (Flu/Mel/ATG conditioning), progressing to acute myelomonocytic leukaemia requiring salvage fludarabine, cytarabine and idarubicin with second RIC MUD allogeneic SCT (Flu/TBI(2Gy) conditioning). She subsequently developed skin, liver, and mouth cGVHD despite cyclosporin and mycophenolate prophylaxis, progressing to limb girdle weakness over 18 months. Investigations demonstrated positive smooth muscle antibody and PL-12, muscle oedema on MRI, chronic partial denervation on electrophysiology studies, and perifascicular atrophy with HLA class I up-regulation on biopsy consistent with cGVHD myositis (Figure 1A-C). Prednisone, cyclosporin and mycophenolate was ineffective, as was subsequent ruxolitinib, rituximab, and extracorporeal photopheresis. Repeat biopsy showed marked atrophy with reduction in perimysial inflammation, consistent with cGVHD (Figure 1D). Sirolimus, aldesleukin (peak Treg cell response 26% of CD4+T cells), methotrexate and IVIg 2g/kg was administered. Despite this, upper limb paralysis remained.

Myositis-related cGVHD is rare (incidence 0.5-3%). Biopsy findings range from mild perimysial lymphocytic infiltrates to extensive endomysial inflammation with necrotic degenerating muscle fibres. CK levels correlate with clinical course or necrotic fibres on biopsy. To our knowledge, our patient is the first case of biopsy confirmed cGVHD myositis with anti-synthetase antibody without raised CK.

Retrospective case series of cGVHD myositis with varying CK levels demonstrated at least partial response to steroids, rituximab, IVIg or tacrolimus, although several required treatment escalation. Response rates are similar to idiopathic polymyositis.

Conclusion: Further research into myositis related cGVHD is needed to elucidate pathogenesis and guide therapy.

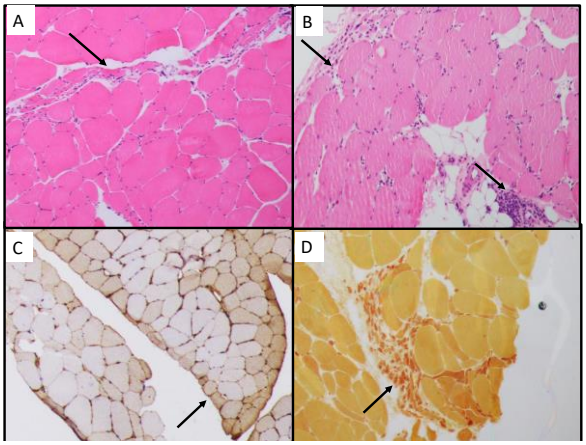

Figure 1. A-C, First muscle biopsy; 100x magnification. A. Myofibre atrophy with perifascicular distribution (H&E stain). B. Perifascicular atrophy and perimysial inflammation (H&E stain). C. HLA class I upregulation, with accentuation of staining in a perifascicular distribution (HLA-1 IHC stain). D, Second muscle biopsy; 100x magnification., Esterase positive denervated atrophic fibres, a finding which can occur in cGVHD (esterase stain).

Viral morbidity in allogeneic stem cell transplant recipients receiving ATG for GvHD

Healthcare utilisation and costs of care of allogeneic BMT in NSW: a State and National data linkage study protocol.

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Introduction: Improvements in survival following allogeneic BMT (allo-BMT) have led to an increasing burden of late effects requiring life-long care. There is limited data on the impact of late effects on healthcare utilisation and costs of care, and no studies which report impact >5 years post-BMT.

Aims: To use cross jurisdictional data linkage to assess health impacts and costs of care associated with survival following allo-BMT in NSW, and identify factors impacting healthcare use.

Methods: Using a retrospective cohort of ~1500 BMT recipients transplanted between January 2006 and December 2016, we will link ABMTRR data to the following NSW administrative datasets: Admitted Patient Data Collection (APDC), Emergency Department Data Collection (EDDC), Registry of Births, Deaths and Marriages (Death Registrations) and Cause of Death (COD), via the Centre for Health Record Linkage (CHeReL). Data will also be linked via the Australian Institute of Health and Welfare (AIHW) to MBS and PBS datasets. All data will be transferred and analysed within a mandated Secure Unified Research Environment.

Analysis and Reporting: Regression models will be used to understand health care-utilisation pathways, costs and variation in care, to investigate the impact of clinical and other patient relevant factors on the costs and use observed. Information on variation will be used to develop a cost-effectiveness analysis to assess the value of the various treatment approaches evident in the data.
Findings will be reported in accordance with the Reporting of studies Conducted using Observational routinely collected health Data (RECORD) statement and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.

Conclusions: We expect this study to provide a model to assess long term treatment burden associated with allo-BMT. This will assist BMT clinicians, administrators, and policymakers to identify areas for improvement in the health service delivery and long-term care of allo-BMT patients.

Weight-based dosing of Ciclosporin A in obese patients undergoing haematopoietic stem cell transplantation: Blood levels and clinical outcomes

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Aim: Cyclosporin A (CSA) is a standard immunosuppressant used in allogeneic haematopoietic stem cell transplantation (HSCT). It is commonly initiated as weight-based doses, followed by dose adjustment according to blood levels. It is not clear what weight should be used in obese patients to calculate initial CSA doses. This study aimed to retrospectively compare CSA blood levels, incidence of acute kidney injury (AKI), and incidence of acute graft-versus-host disease (aGVHD) between obese and non-obese patients after actual weight-based CSA dosing.

Method: Inclusion criteria was adult patients who received matched allogeneic HSCT following Fludarabine - melphalan (FluMel) or Cyclophosphamide - total body irradiation (CyTBI) between 2017 and 2020, who received CSA and methotrexate as standard GVHD prophylaxis, and who were not on a strong CYP3A4 inhibitor or inducer. Included patients were divided into two groups: obese (actual body weight > 120% of ideal body weight) and non-obese. Blood CSA levels from initiation to neutrophil recovery were collected. Incidence of AKI prior to engraftment was determined according to the KDIGO Guidelines. Medical records were reviewed to confirm aGVHD diagnosis.

Results:

In total, 263 (118 obese and 145 non-obese) patients were included. Patient characteristics except weight were similar between two groups. Mean initial CSA levels and mean pre-engraftment CSA levels were significantly higher in obese patients (236.5 vs 187.3 ng/mL and 220 vs 188.9 ng/mL). However there was no significant difference in incidence of AKI between the two groups. Obese patients had higher incidence of aGVHD (all grade 65% vs 50%) despite higher CSA levels, which suggests obesity may be an independent risk factor for aGVHD.

Conclusion:
This study demonstrated that actual body weight based CSA dosing in obese patients is associated with significantly higher initial CSA levels. However, this did not appear to impact clinical outcomes such as AKI and aGVHD.

Bariatric surgery and allogeneic hematopoietic progenitor cell transplantation: a case series

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Aim: The prevalence of bariatric surgery is increasing in the community, and some of these individuals also have haematological malignancy and may become candidates for allogeneic hematopoietic progenitor cell transplantation (HPCT). Caloric and nutritional deficits, which are well established adverse effects of bariatric surgery, may be intensified during HPCT. We investigated morbidity and mortality associated with HPCT among patients with prior bariatric surgery at our centre.

Method: Of 297 patients who had undergone allogeneic HPCT at our centre between February 2015 to February 2022, we identified seven patients with a history of prior bariatric surgery.

Results: Four patients had a history of sleeve gastrectomy and three had undergone prior laparoscopic adjustable gastric banding. Median weight loss over 6 months from date of transplant was 11% (range 3 – 17%). Most patients (5/7) required parenteral nutrition in the peri-transplant period and four patients were re-hospitalised for recurrent gastrointestinal symptoms. The median length of stay of the transplant admission was 45 days (range 29 – 191 days). Five patients (71%) were diagnosed with grade III-IV lower gastrointestinal (GI) GvHD; four of these had simultaneous upper GI acute GVHD. Of the two patients without a diagnosis of acute GVHD, one suffered *Mycobacterium abscessus* infection of the gastric band site prior to transplant and GI chronic GVHD after transplant, while the other had no gut toxicity other than mucositis. After a median follow-up of 5 years, two patients in the bariatric surgery cohort have died, of disease relapse and multiorgan failure, respectively.

Conclusion: This case series highlights a high incidence and severity of acute GI GvHD in bariatric surgery patients undergoing HPCT, in addition to significant weight loss, use of parenteral nutrition and re-hospitalisation due to persisting gastrointestinal symptoms. Larger cohort studies are needed to guide management of this rare but increasingly prevalent population of patients undergoing HPCT.

Real-world outcomes of CD19 CAR-T cell therapy for B-cell malignancies: results from the Queensland state-wide CAR-T program

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Aim: Chimeric antigen receptor T cell (CAR-T) therapies targeting CD19 have transformed treatment of relapsed/refractory large B cell lymphoma and B cell leukaemia. Our institution is the sole provider of CAR-T cell therapy in Queensland. Here, we present clinical outcomes of all patients treated with commercial CAR-T products since the program commenced.

Method: All patients referred to the Royal Brisbane and Women's Hospital commercial CAR-T program between July 2020 to April 2022 were identified. Clinical and laboratory data were obtained by retrospective chart review. The primary outcome was overall response rate (ORR; defined as combined incidence of complete (CR) and partial (PR) responses) at day+30 and day+180 post infusion. Secondary outcomes were mortality and incidence of cytokine release syndrome (CRS) and immune effector cell acute neurotoxicity (ICANS).

Results: Of those infused 27 were evaluable at D+30 and 20 were evaluable at D+180. ORR for the entire cohort was 67% (18/27) at D+30 and 35% (7/20) at D+180. At D+30 and D+180, incidences of CR were 7 (26%) and 7 (35%) respectively. Five patients to date who achieved CR at D+30 remained in CR at D+180. CRS and ICANS occurred in 78% and 22% respectively, with only two episodes of grade >3 ICANS. At census date 27 patients have been infused and 11 have died, with one death attributed to treatment related mortality (due to severe infection). See figure 1 below

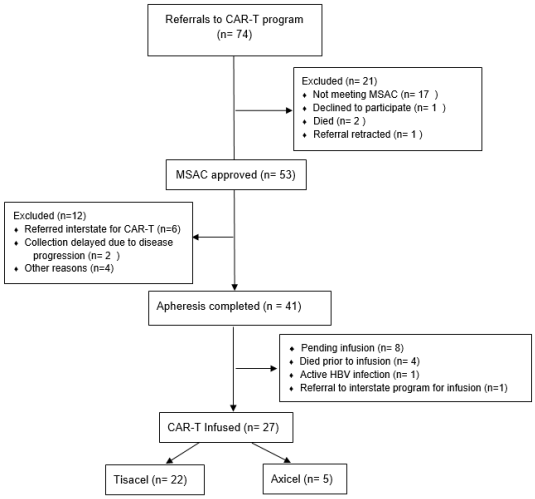

Figure 1. Flow chart of patients submitted for CAR-T approval

Conclusion: The interim results demonstrate that CAR-T is deliverable with response rates similar to other real-world data. As the program continues to grow, ongoing review will aim to improve patient selection and appreciation of determinants for long-term and sustained CAR-T response.

Increasing incidence, validation of risk factors and subsequent outcomes of Poor Graft Function Post Allogeneic Transplantation

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Aim: Poor Graft Function (PGF) is characterised by the presence of multilineage cytopenia in the setting of complete donor chimerism post allogeneic stem cell transplantation (alloSCT).

Objectives:

1. Quantify cumulative incidence (CI) of PGF
    1. Validate risk factors associated with PGF
    2. Describe outcomes following establishment of PGF

Method: This study aimed to validate previously discovered risk factors for PGF in 308 patients transplanted from 2017-2020. In our historical cohort (2000-2016), myeloproliferative neoplasm (MPN), non-matched sibling donor (non-MSD), ICU admission and positive blood cultures within first 30 days, acute graft versus host disease (GVHD), CMV and non-CMV viral reactivation were associated with PGF. Risk factors were applied to the validation cohort utilising binomial regression. PGF was defined as ≥95% donor chimerism, ≥2 lineage cytopenias - thrombocytopenia ≤30x10^9/L from D40-D60 OR ≤50 x10^9/L from D60 +/- neutropenia requiring filgrastim post D40 +/- Hb <80g/L.

Results: 49 patients with PGF were identified from 2017-2020. The CI of PGF was 16% at 24 months post-alloSCT which was significantly higher than 5% compared to the historical cohort (p<0.001). Multivariate analysis confirmed non-CMV viral reactivation, ICU admission, and GVHD was associated with PGF. The median follow-up of the cohort was 27.6 months. The 2- year OS was significantly lower in the PGF group compared to those without PGF (60% versus 75%, p=0.002). Twenty-six patients (53%) did not recover blood counts and had a median survival of 8 months. 97% of PGF patients were transfusion dependent and the median duration of cytopenias in those that did recover was 142 days (51-789).

Conclusion: PGF is an immunologically mediated bone marrow failure syndrome from which patients are at risk of prolonged transfusion dependence and death. The CI of PGF is increasing and factors underlying this trend require further investigatio

Haemorrhagic cystitis post allogeneic stem cell transplant: review of outcomes at a single centre

Dr Portia Smallbone[1,2], Ms Tandy-Sue Copeland[1], Dr Marcus Lombard[1], Dr Julian Cooney[1,2], Dr Matt Wright[1,2,3], Dr Duncan Purtill[1,2,3]

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Aim: Haemorrhagic cystitis (HC) is a significant complication following haemopoietic stem cell transplantation, associated with morbidity, prolonged hospital stay and economic cost. With increasing use of post-transplant cyclophosphamide, regular use of cyclophosphamide conditioning regimens and frequency of mismatched or haploidentical transplantation, incidence is increasing. Imlay et al reports incidence up to 75% in those patients receiving cyclophosphamide conditioning.[1] Regular clinical review of outcomes to assess preventative methods is required.

Method: We retrospectively analyzed 91 consecutive patients aged over 18 years undergoing allogeneic stem cell transplantation between January 2020 and March 2022 at our tertiary institution. All haploidentical transplant recipients were prescribed post-transplant cyclophosphamide during this period.

Results: Baseline characteristics are listed in Table 1. Haemorrhagic cystitis developed in 17/91 (18%) of all patients. The incidence of HC in all haploidentical transplant recipients was 17% (6/35). The majority of HC patients (88%) received cyclophosphamide, either with conditioning or post-transplant. 70% of HC patients developed symptoms more than 7 days post-transplant, with associated BK viruria. 50% of patients required 3-way catheterization. 70% received cidofovir, with majority being intravesical. 64% of patients had complicating renal impairment (defined as abnormal age-adjusted GFR). Refractory cases were treated with hyperbaric oxygen therapy to complete resolution (23%), cystoscopy and diathermy (23%) with other adjunctive therapies including ciprofloxacin and intravenous immunoglobulin, to varying effect. Patients with refractory disease all had concurrent acute GVHD and/or thrombocytopenia (defined as reduction of >20% from baseline). **Conclusion:** Haemorrhagic cystitis causes considerable morbidity in the post-transplant setting, with increased incidence in recipients of high dose cyclophosphamide, particularly after haploidentical transplantation. In our small case series, we observed some patients who appeared to benefit from hyperbaric oxygen therapy and invasive management by cystoscopy. Adherence to preventative methods including hyperhydration, continuous Mesna infusion and forced diuresis may reduce incidence, and additional evidence-based therapies are required.Table 1, Baseline Characteristics

	Baseline Characteristics
Type of HSCT	
Matched unrelated donor (n, %)	47, 52%
Haploidentical (n, %)	35, 38%
Matched related donor (n, %)	17, 19%
Conditioning Regime (n, %)	
Busulfan/cyclophosphamide	5, 29%
Fludarabine/busulfan	6, 35%
Fludarabine/melphalan	2, 12%
Fludarabine/TBI	1, 5%
Cyclophosphamide/TBI	1, 5%
Fludarabine/cyclophosphamide	1, 5%
Cyclophosphamide alone	1, 5%
Post transplant cyclophosphamide	7, 41%
ATG	11, 65%
Median date of onset (days, range)	28 (1-345)
Median duration of symptoms (days, range)	56 (3-168)
Early Disease, <7 days (%)	23%
Late Disease, >7 days (%)	70%

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Ruxolitinib use in chronic graft-versus-host disease affecting the central nervous system: a case report

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Although rare, chronic graft-versus-host disease (cGVHD) affecting the central nervous system is associated with significant morbidity and mortality. To our knowledge, there are 30 cases reported in the literature. Adams et al reports mechanisms behind CNS cGVHD, including upregulation of IFN-y,[1] supporting the attenuation of IFN-y as a therapeutic target in cGVHD of the CNS. Ruxolitinib is an oral selective JAK1/2 inhibitor that crosses the blood brain barrier[2], with inhibition of signalling downstream of IFN-y.[3] We report our experience with ruxolitinib in a 32 year old with imaging and histopathologic evidence of CNS GVHD post haploidentical transplantation with no clinical response.

Our patient presented with painless bilateral central scotomas, 250 days post transplantation for myelodysplastic syndrome associated with GATA2 immunodeficiency. Initial neurological examination revealed lower limb hypertonicity and sustained right ankle clonus, without other abnormality. Brain MRI findings were incongruent with the mild clinical symptoms, revealing extensive lesions within the cerebral hemispheres, brainstem and cervical spinal cord, with patchy T2/FLAIR hyperintensity, some with restricted diffusion and enhancement. Progressive neurologic decline developed including cognitive disturbance (mixing words, impaired memory), unsteadiness, right upper limb weakness, paraesthesia and myoclonic spasms and progressive visual changes.

Biopsy of right temporal lesion revealed changes consistent with lymphocytic vasculitis without evidence of alternate pathology. Despite therapy, there was further clinical progression and the patient passed away two weeks later.
Treatment included high dose intravenous immunoglobulin, high dose pulse methylprednisolone, plasma exchange, 1mg/kg prednisolone, tacrolimus, ruxolitinib and natalizumab, without clinical effect. Ruxolitinib (5mg BD) was commenced as sixth-line therapy for a total duration of approximately four weeks, with treatment interrupted prior to brain biopsy. There was clinical progression despite its use, although short.

Conclusion: CNS GVHD is rarely described in the literature, with limited treatment options. Although preclinical studies offer insight into potential therapeutic targets, response to therapy is poor.

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Nivolumab for relapsed or residual haematological malignancies after allogeneic haematopoietic stem cell transplantation (NIVALLO) – final clinical results.

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Aim: Relapse of haematological malignancies after allogeneic stem cell transplantation (alloSCT) is a major cause of mortality. This was an investigator-initiated phase II clinical trial to evaluate the safety and efficacy of nivolumab to augment the graft-versus-tumour effect after alloSCT.

Method: Patients with relapsed or persistent haematological malignancies following alloSCT were eligible. Patients with current or prior graft-versus-host disease (GVHD). Participants received nivolumab fortnightly for up to 48 weeks.

Results: Fourteen participants received treatment with nivolumab. Primary haematological malignancies relapsing post-alloSCT included Hodgkin lymphoma (3), non-Hodgkin lymphoma (2), CLL (2), AML/MDS (4), ALL (2), myelofibrosis (1). The median time from alloSCT to commencement of nivolumab was 20 months. Six participants commenced treatment at 3mg/kg; of these two developed grade 3 acute GVHD rapidly following the first dose of nivolumab (5 days and 13 days). The remaining 8 participants commenced nivolumab at 1.5mg/kg following a protocol amendment. Of these, 1 participant developed mild chronic GVHD and 2 developed pneumonitis. In total, five (36%) participants developed GVHD or immune related adverse effects (irAE). Of the participants who developed GVHD, the median time from transplant to first dose of nivolumab was 5 months compared to 34 months for those who did not develop GVHD. The overall response rate was 43%; all these six participants achieved complete response (CR). All 3 participants with Hodgkin lymphoma achieved CR. No participant with AML/MDS responded.

Conclusion: Nivolumab induces potent immune stimulation after alloSCT and can result in GVHD particularly if administered within 12 months of transplant. Response to nivolumab for the treatment of relapse of haematological malignancies post-alloSCT is varied, with high rates of response in Hodgkin lymphoma however poor responses in AML and MDS.

Outcomes of HLA-mismatched unrelated donor allo-HCT for AML using thymoglobulin as GVHD prophylaxis – a single centre study

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Aim: To assess outcomes of single-HLA mismatched (MMUD) versus fully matched unrelated donor (MUD) using thymoglobulin as GVHD prophylaxis in allo-HCT for AML.

Method: Retrospective audit of MMUD vs MUD outcomes at our centre using a prospectively maintained departmental database. Thymoglobulin was administered as GVHD prophylaxis in conditioning (total dose 2.5mg/kg) administered from day -2 through day 0. Each cohort were compared for outcomes including engraftment, relapse, TRM, DFS and OS. R Statistical Functions were employed. $P<0.05$ was considered significant.

Results: Since 2011 we identified 59 unrelated allo-HCT that had received thymoglobulin as GVHD prophylaxis at our centre. N=46 received MUD, n=13 received MMUD (11/12, n=6, 9/10, n=6, 7/8, n=1). For the entire cohort, median age 60 (20–73) yrs. 52.5% were male. Median follow up 513 (4-2472) days.

In MUD cohort, median age 61 (17-73) yr, 50% (23/46) were male, 76% (35/46) were de novo AML, 50% (23/46) patients had adverse cytogenetic risk, 80% (37/46) were CR1 at time of allo-HCT and 83% (38/46) patients received RIC conditioning.

For MMUD cohort, median age was 57 (45-70) yr, 61.5% (8/13) were male, 69% (9/13) were de novo AML, 54% (7/13) were adverse cytogenetic risk, 38% (5/13) were CR1 at time of allo-HCT and 92% (12/13) received RIC.

Outcomes were similar between MUD and MMUD – neutrophil (18 vs 18 days, $p=0.408$) and platelet engraftment (p=0.350, 0.258, 0.377), relapse rate (26% vs 31%, p=0.737), TRM (26% vs 38%, p=0.384), and DFS and OS (46% vs 54% cohorts p=0.82 and 41% vs 54% cohorts p=0.88). CMV, EBV reactivation rates and GFRS will be assessed.

Conclusion: In this single centre study, we found similar outcomes between MUD and MMUD when thymoglobulin was used as part of conditioning. Larger studies will be required to assess the impact of various GVHD prophylactic strategies in MMUD.

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CLL (Poster Board No H039 – H053)

First-in-human global study of lisaftoclax (APG-2575), a novel BCL-2 inhibitor (BCL-2i), in patients with relapsed/refractory chronic lymphocytic lymphoma (CLL) and other haematologic malignancies (HMs)

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Aim: Many B-cell malignancies evade apoptosis by overexpressing BCL-2 proteins. Investigational agent lisaftoclax is a novel, potent, selective BCL-2i active against HMs and is under clinical development.

Method: The endpoints of this phase 1 study included safety, pharmacokinetics, pharmacodynamics, efficacy, and maximum tolerated (MTD)/recommended phase 2 dose. Lisaftoclax was orally administered daily in a 28-day cycle. Patients with CLL with intermediate-to-high risk of tumour lysis syndrome (TLS) were initiated on a daily ramp-up schedule until the assigned dose was achieved.

Results: On April 15, 2021, 36 patients had been enrolled and treated with lisaftoclax (doses from 20 to 1,200 mg) and had diagnoses of relapsed/refractory CLL or small lymphocytic lymphoma (SLL; n = 15), multiple myeloma (n = 6), non-Hodgkin lymphoma (n = 12), myeloid (n = 2) and hairy cell lymphoma (n = 1). No dose-limiting toxicity was observed. MTD was not reached, and no laboratory or clinical TLS was reported. Median (range) treatment duration was 6 (1-24) cycles. Any grade treatment-related adverse events (TRAEs) in > 10% of patients included neutropaenia (22%), anaemia (16.7%), fatigue (27.8%), diarrhoea (19.4%), constipation (11.1%), and nausea (11.1%). A total of 12 of 15 evaluable patients with relapsed/refractory CLL/SLL achieved partial response, for an overall response rate (ORR) of 80.0%. Preliminary pharmacokinetic profile showed that exposures increased with doses from 20 to 1,200 mg (average half-life: 4-8 hours). On BH3 profiling, lisaftoclax rapidly triggered changes in the BCL-2 complex in CLL/SLL patient samples.

Conclusion: Based on these data, lisaftoclax offers a potential treatment alternative for patients with relapsed/refractory CLL/SLL and other HMs (Ailawadhi S et al. J Clin Oncol 2021;39: abstract 7502). This includes a potentially advantageous daily ramp-up schedule to prevent TLS and a potentially lower rate of severe neutropenia. Internal study identifier APG-2575-001; clinical trial registration: NCT03537482.

Defining the demographics, clinical presentation, and management of Australian patients with chronic lymphocytic leukaemia (CLL) on the Lymphoma and Related Diseases Registry (LaRDR), 2016 to 2021

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Aim: To describe the diagnostic characteristics and initial management of CLL patients entered on the LaRDR, which now incorporates CLL. A new CLL-specific dataset was introduced to LaRDR in 2019, and patients are entered at diagnosis and followed prospectively.

Method: Data for CLL patients were obtained from the LaRDR from January 1, 2016, to August 30, 2021, including demographics, clinical presentation and stage (i.e., Rai and Binet staging, ECOG and CIRS score), IGHV and TP53 mutation status, diagnostic investigations, first- and second-line treatment. For each treatment line, response rate (RR), progression-free survival (PFS) and overall survival (OS) were calculated.

Results: Of the 285 CLL patients, median age was 68 (range 59.1-74.4) years at diagnosis, with a 2:1 male-to-female ratio. Most patients were Rai stage 0 (42.4%) or Binet stage A (57%) at presentation (Table 1). In keeping with the early stage of presentation, most patients (61%) were managed initially with a watch-and-wait approach. When patients did require treatment, at a median of 29.2 (95% CI: 17.8–34.6) months, the most common regimens were chlorambucil-based (40.9%) or fludarabine-based (33.3%), reflective of the treatment options available at the time (Table 2). Due to small sample size (n=21), results from second-line treatment are limited. The median PFS from time of treatment was 29.3 months (Figure 1). This may be skewed by limited numbers of patients and participating sites for CLL cases, and a bias toward patients treated sooner after diagnosis, requiring further analysis to determine the causes. There was insufficient follow-up to calculate median OS (Figure 2).

Table 1. Baseline presentation and clinical characteristics at diagnosis (N = 285)

Male	177/284 (62.3%)
Age at diagnosis (yrs), median (IQR)	68.5 (59.3, 74.4)
ECOG score ≥ 2	18/223 (8.1%)
CIRS, median (IQR)	2.0 (1.0 - 4.5), N = 15
Rai stage III-IV	19/135 (14.1%)
Binet stage A	72/126 (57.1%)
Binet stage B	34/126 (27.0%)
Binet stage C	20/126 (15.9%)
IGHV mutation	17/34 (50.0%)
TP53 mutation	11/25 (44.0%)

Conclusion: Initial data on Australian CLL patients from LaRDR appear comparable to larger international cohorts. With the availability of novel therapies on the Pharmaceutical Benefits Scheme, which heavily influences prescribing and investigations, understanding patient characteristics and patterns of care is critical for deriving Australian-specific management recommendations and understanding outcomes.

Table 2. First-line treatment, response to treatment and survival analyses

	Chemoimmunotherapy				Targeted therapy	
	Fludarabine-based	Bendamustine-based	Chlorambucil-based	Other	BTKi	BCL-2 inhibitor
N = 89	28 (31.5%)	7 (7.9%)	41 (46.1%)	11 (12.4%)	1 (1.1%)	1 (1.1%)
Age at diagnosis median (IQR)	58.9 (52.8, 65.4), N=28	70.2 (64.1, 75.7), N=7	75.4 (71.2, 81.2), N=41	74.2 (71.0, 78.3), N=11	63.6 (63.6, 63.6), N=1	72.4 (72.4, 72.4), N=1
Male	20/28 (71.4%)	5/7 (71.4%)	30/41 (73.2%)	11/13 (84.6%)	2/3 (66.7%)	0/1 (0.0%)
ECOG ≥ 2	0/24 (0.0%)	1/6 (16.7%)	10/35 (28.6%)	0/7 (0.0%)	0/1 (0.0%)	
CIRS median (IQR)	1.0 (0.0, 2.0), N=3	2.5 (2.0, 3.0), N=2	2.0 (1.0, 3.0), N=9	5.0 (5.0, 5.0), N=1	7.0 (7.0, 7.0), N=1	3.0 (3.0, 3.0), N=1
Rai stage III - IV	4/6 (66.7%)	1/3 (33.3%)	10/22 (45.5%)	1/3 (33.3%)	0/1 (0.0%)	1/1 (100.0%)
IGHV mutation	4/8 (50.0%)		0/1 (0.0%)	1/3 (33.3%)		
TP53 mutation	1/2 (50.0%)		2/3 (66.7%)	1/1 (100.0%)	1/1 (100.0%)	
Response						
CR	15/25 (60.0%)	5/6 (83.3%)	7/29 (24.1%)	4/9 (44.4%)	0/1	
CR (incomplete BM recovery)	1/25 (4.0%)	0/6 (0.0%)	1/29 (3.4%)	0/9 (0.0%)	0/1	
PR	6/25 (24.0%)	0/6 (0.0%)	12/29 (41.4%)	2/9 (22.2%)	0/1	
SD	1/25 (4.0%)	0/6 (0.0%)	7/29 (24.1%)	3/9 (33.3%)	1/1 (100.0%)	
PD	2/25 (8.0%)	1/6 (16.7%)	2/29 (6.9%)	0/9 (0.0%)	0/1	
ORR	22/25 (88.0%)	5/6 (83.3%)	20/29 (69.0%)	6/9 (66.7%)	0/1	
PFS (12m survival)	92% (71-98%)	71% (26-92%)	62% (42-76%)	75% (13%-96%)	NA	NA

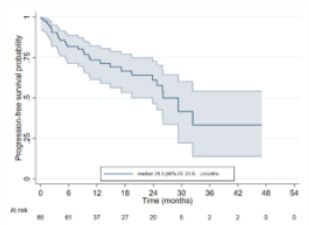

Figure 1. Progression-free survival

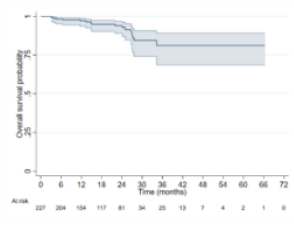

Figure 2. Overall survival

Certainty in uncertainty: determining the rate of reclassification of variants of uncertain significance in haematological malignancy

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Aim: Our aim was to determine the rate of reclassification of variants of uncertain significance (VUS) in patients' with haematological malignancy. We investigated whether re-evaluating VUS in 12-24 months or greater than 24 months post initial classification was significant enough to warrant continuing periodic reviews. The outcome of significance was the re-classification of VUS as benign or malignant.

Method: A retrospective audit of haematological malignancy patients referred to the Molecular Medicine Department at the John Hunter Hospital in Newcastle, Australia between September 2018 and December 2021. Patients' genetic data was analysed for VUS, which were then re-analysed in Agilent Alissa, Mastermind, ClinVar, Varsome and Sophia using current somatic variant guidelines. Proportions of VUS at baseline were compared to post re-analysis.

Results: The most common diagnosis in the patient cohort (n=944) were AML (40%), MDS (25%) and CMML (3%). A total of 210 VUS (153/944 patients) were re-analysed for classification. The most common variants in all patients with VUS were TET2 (20%), RUNX1 (10%) and DNMT3A (9%). One hundred and three were re-analysed at greater than 24 months post initial classification and 107 were re-analysed between 12-24 months post initial classification.

In total, 30 (14%) VUS were re-classified as either benign or malignant, with 18 (17%) re-classified at greater than 24 months and 12 (11%) re-classified at 12-24 months post-initial classification.

The most common variants that were re-classified in both groups were CSF3R (32%), TET2 (29%), ASXL1 (11%) and ZRSR2 (11%). The most common diagnoses in patients with VUS that were re-classified were AML (39%), MDS (29%) and CMML (7%).

Conclusion: This study demonstrates that one in seven VUS were re-classified 12 months post initial classification. This can inform practice guidelines and potentially lead to discoveries related to the prognosis, diagnosis and treatment of haematological malignancy.

The Spectrum of Tonsillar Involvement in Chronic Lymphocytic Leukaemia (CLL)

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The clinical manifestations of CLL; lymphocytosis, adenopathy, hepatosplenomegaly, and bone marrow failure have been recognised for many years. These features were systematised in 1975 and 1985 into the Rai and Binet Staging classifications respectively. Infiltration of other organs is well recognised and can occur in virtually any organ or anatomical site. Tonsillar involvement has only rarely been described as a site of CLL. We believe this is under recognised as a disease site, occasionally complicated by airway obstruction, or as a site of Richters Syndrome.
We report a case series of 13 patients with CLL with recorded tonsillar involvement, illustrating the 4 main clinical presentations for this group of patients:

1. Asymptomatic (relatively) CLL tonsillar enlargement in proportion to other disease sites - the most common manifestation - 6 patients
    1. Symptomatic CLL tonsillar involvement with upper airway obstruction (UAO) – managed with standard CLL therapy required for both UAO and overall CLL disease status - 3 patients
    2. Symptomatic CLL tonsillar involvement with airway obstruction – managed with tonsillectomy when disproportionate to overall CLL disease status - 3 patients
    3. Tonsils as site of Richter's transformation – 1 patient

This case series serves to illustrate the under recognised frequency of tonsillar involvement in CLL. At our institution, these 13 patients with recorded tonsillar involvement over 20 years represents approximately 3% of CLL patients at our institution. Awareness of the spectrum of tonsillar involvement in CLL and associated therapeutic approaches are key to avoid delays in diagnosis and treatment especially with emerging UAO. It also highlights role of tonsillectomy to avoid or delay systemic therapy in patients with predominant, symptomatic tonsillar involvement that is disproportionate to overall disease status.

Severe autoimmune haemolytic anaemia following SARS-CoV-2 vaccination in patients with treatment naïve B-cell neoplasms – a case series.

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Aim: In this case series, we report four patients with pre-existing or new concurrent diagnosis of B-cell neoplasms, presenting with severe autoimmune haemolytic anaemia (AIHA) following SARS-CoV-2 vaccination. We highlight that this population may be an at-risk group for this rare immune complication following SARS-CoV-2 vaccinations, and discuss presentation and management.

Methods: Four patient cases were compiled from three tertiary hospitals. Initial presentation, investigations, management and longer-term follow-up were ascertained from treating clinicians and documentation. A detailed literature review was conducted.

Results: Two patients with pre-existing, stable, early-stage and treatment-naïve chronic lymphocytic leukemia (CLL) as well as two patients who were concurrently diagnosed with indolent B cell malignancies (splenic marginal zone lymphoma (SMZL) and CLL respectively), were diagnosed with AIHA following SARS-CoV-2 vaccination (ChAdOx1nCoV-19 in 3 patients, BNT162b2 in 1 patient). Despite presenting with severe anaemia requiring inpatient admission and initial transfusion support, all patients responded to first-line therapy with prednisolone +/- IVIg.
In the two patients with known CLL, a concurrent exacerbation of peripheral lymphocytosis (6-fold and 2.5-fold respectively) was seen, which resolved over a similar trajectory as their AIHA. Relapses were common, with one patient requiring rituximab and another requiring R-CVP for SMZL.

Conclusion: To our knowledge, this is the first documentation of this complication in patients with B-cell neoplasms, and following the ChAdOx1nCoV-19 vaccine. We have only identified this complication in patients with concurrent or pre-existing B-cell neoplasms, suggesting that this population is at an increased risk of this complication, similarly to those following SARS-CoV-2 disease.
Similar exacerbations of lymphocytosis have also been reported in multiple CLL patients with SARS-CoV-2 infection[1-3]. Distinguishing this 'pseudo-progression' in the setting of SARS-CoV-2 infection and vaccination is important, as it may impact decisions around commencement of CLL therapy.

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Immune restoration and synergistic activity with first-line (1l) ibrutinib plus venetoclax (I+V): translational analyses of the multicenter phase 2 CAPTIVATE study of patients with chronic lymphocytic leukemia (CLL)

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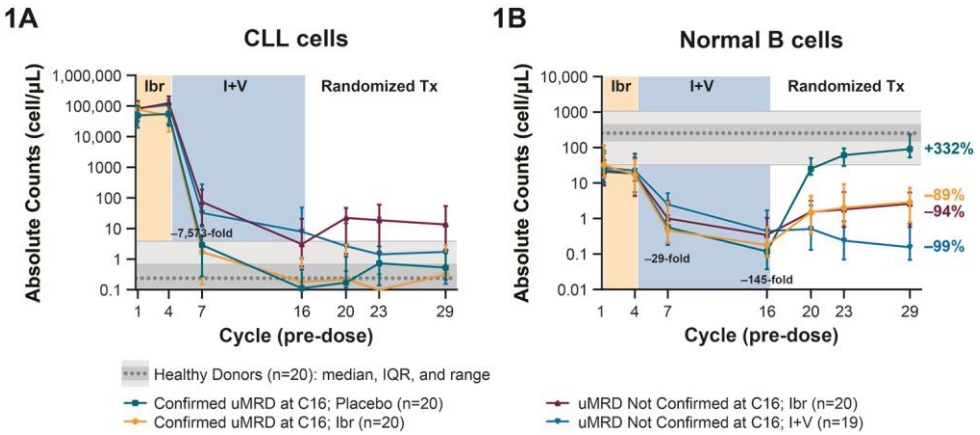
Aim: To confirm the sensitization of BCL-2 by single-agent ibrutinib in CLL cells and assess the cellular immune profile of CAPTIVATE (NCT02910583) patients treated with I+V.

Methods: Ibrutinib effects on anti-apoptotic proteins were evaluated by flow cytometry with samples from 3 previously untreated patients with CLL treated for 1 cycle (28 days). In the CAPTIVATE MRD cohort, patients received 16 cycles of I+V, inclusive of a 3 cycle ibrutinib lead-in; patients with confirmed uMRD were then randomized to placebo or ibrutinib; patients without were randomized to ibrutinib or I+V. Immune restoration was evaluated in 79 patients. Peripheral-blood mononuclear cells at baseline and day 1 of cycles 4, 7, 16, 20, 23, and 29 were analyzed by high-dimensional flow cytometry. Counts of immune cell subsets were compared with those from healthy donors (n=20). Median changes from baseline are reported.

Results: Ibrutinib for one cycle decreased expression of MCL-1, BCL-XL, and BCL-2 in lymph node-emigrant CLL cells by 74%, 95%, and 10%, respectively, confirming BCL-2 inhibitor sensitization. In patients treated with I+V, a significant decrease in circulating CLL cells occurred within 3 cycles of venetoclax initiation (**Fig. 1A;** cycle 7). From cycle 16, patients with Confirmed uMRD, but not those without, attained CLL cell counts similar to healthy donors (≤0.8 CLL cell/mL) (**Fig.1A**). Patients randomized to placebo (fixed duration I+V) attained normal B-cell levels by cycle 29 (**Fig.1B**). Across all arms, counts of T-cells, classical monocytes, and conventional dendritic cells were at healthy-donor levels within the first 6 months of treatment and were maintained thereafter, regardless of randomized treatment.

Conclusion: BCL-2 sensitization by ibrutinib supports the synergy of ibrutinib and venetoclax. Treatment with fixed duration I+V eradicated CLL cells to healthy-donor levels and enabled sustained regeneration of normal B-cells and other immune cells. These data demonstrate evidence of immune restoration with I+V.



Fixed-duration (FD) ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL): 3-year follow-up from the FD cohort of the phase 2 CAPTIVATE study

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Title: Fixed-duration (FD) ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL): 3-year follow-up from the FD cohort of the phase 2 CAPTIVATE study

Aim: To report 3-year follow-up results from the FD cohort of the CAPTIVATE (NCT02910583) phase 2 study investigating first-line ibrutinib + venetoclax in CLL.

Methods: Patients aged ≤70 years with previously untreated CLL received orally 3 cycles of ibrutinib then 12 cycles of ibrutinib + venetoclax (ibrutinib 420 mg/day, venetoclax ramp-up to 400 mg/day). Efficacy outcomes and ibrutinib-related serious AEs (SAEs) >30 days after last dose are reported.

Results: Overall, 159 patients were enrolled (median age: 60 years), including those with high-risk features of del(17p)/*TP53* mutation (17%) and unmutated IGHV (56%). Of those, 147 (92%) and 149 (94%) completed treatment with ibrutinib and venetoclax, respectively. Median time on study was 39 months (range 1-41). ORR was ≥96% and was consistent in patients with high-risk features (Table). Complete response (CR) in patients without del(17p) (n=136) increased nominally from 56% (95% CI, 48-64) to 58% (95% CI, 50-66); and in all patients from 55% (95% CI, 48-63) to 57% (95% CI, 50-65). Overall, 93% of patients with CR had durable responses lasting ≥12 months post-treatment. Of patients with undetectable minimal residual disease (uMRD) in peripheral blood at 3 months post-treatment, 66/85 (78%) evaluable patients maintained uMRD through 12-months post-treatment. At 36 months, PFS and OS were similar between patients with and without high-risk features (Table). All patients have stopped treatment; no new SAEs have occurred since the primary analysis. As of January 2022, 12 patients were retreated with single-agent ibrutinib (duration range: 3-29 months) after disease progression; of evaluated patients, 7/9 had partial responses and 2/9 had stable disease.

Conclusions: Fixed duration ibrutinib + venetoclax continues to provide deep, durable responses and clinically meaningful PFS, including in patients with high-risk features. Safety profile was manageable, without additional OS events or SAEs. To date, successful single-agent ibrutinib retreatment responses have been observed.

Table. Efficacy outcomes in patients treated with FD ibrutinib + venetoclax

Efficacy outcomes	**FD Cohort – All treated population N=159**	**del(17p)/*TP53* n=27**	**Unmutated IGHV n=89**
ORR, n (%)	153 (96)	26 (96)	86 (97)
CR, n (%)[a]	91 (57)	15 (56)	57 (64)
36-mo PFS, % (95% CI)	88 (82–92)	80 (58–91)	86 (77–92)
36-mo OS, % (95% CI)	98 (94–99)	96 (76–99)	97 (90–99)

[a]Included 3 patients with CR with incomplete bone marrow recovery

Australian data on the utilisation and duration on treatment of ibrutinib with a proton pump inhibitor

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Aim: Gastric pH may reduce bioavailability of Bruton tyrosine kinase (BTK) inhibitors which rely on an acidic environment for absorption. Proton pump inhibitors (PPI) are commonly prescribed medications, particularly in older patients with chronic lymphocytic leukaemia (CLL). The aim of this study was to compare outcomes of patients with relapsed/refractory (R/R) CLL treated with ibrutinib and a PPI to those of all R/R CLL patients treated with ibrutinib.

Method: A retrospective cohort analysis was conducted using Pharmaceutical Benefit Scheme (PBS) data, from a randomly selected 10% sample of PBS prescriptions from December 2017 to December 2021. Patients receiving PPI concurrently with ibrutinib were identified. Duration on ibrutinib was defined as continuous script filling of ibrutinib, with less than a 6-month period between drug dispensation. Duration on treatment for the ibrutinib/PPI cohort and comparison to the entire ibrutinib cohort was evaluated using Kaplan-Meier curves and log-rank tests.

Results: 103 of 193 (53.4%) patients had ibrutinib alongside a PPI PBS script. The median age of ibrutinib/PPI cohort was 75 years, 66% male, and 59.2% at first relapse. Median duration on ibrutinib treatment for ibrutinib/PPI cohort was 41 months with 46.8% still on therapy at 48 months. Duration on treatment for ibrutinib/PPI was not significantly different to that of the full R/R CLL population (p =0.778). Sensitivity analysis comparing duration on ibrutinib/PPI treatment to ibrutinib patients not on PPI, further validated the original results.

Conclusion: More than half of ibrutinib patients use PPIs concurrent to their CLL treatment. Persistence on ibrutinib is not affected by concurrent PPI usage. The requirement for continuation of a PPI is important as the impact of high gastric pH on drug absorption may vary across drug

Significant Humoral Immune Deficiency in Monoclonal B-cell Lymphocytosis (MBL)

Dr Yandong Shen[1], Dr Jane Freeman[2], Dr Asha Soosapilla[3], Dr Luke Coyle[1], Dr Ian Kerridge[1], Dr Matthew Greenwood[1], Dr Naomi Mackinlay[1], Dr Christopher Ward[1], Dr William Stevenson[1], Dr Stephen Mulligan[1]

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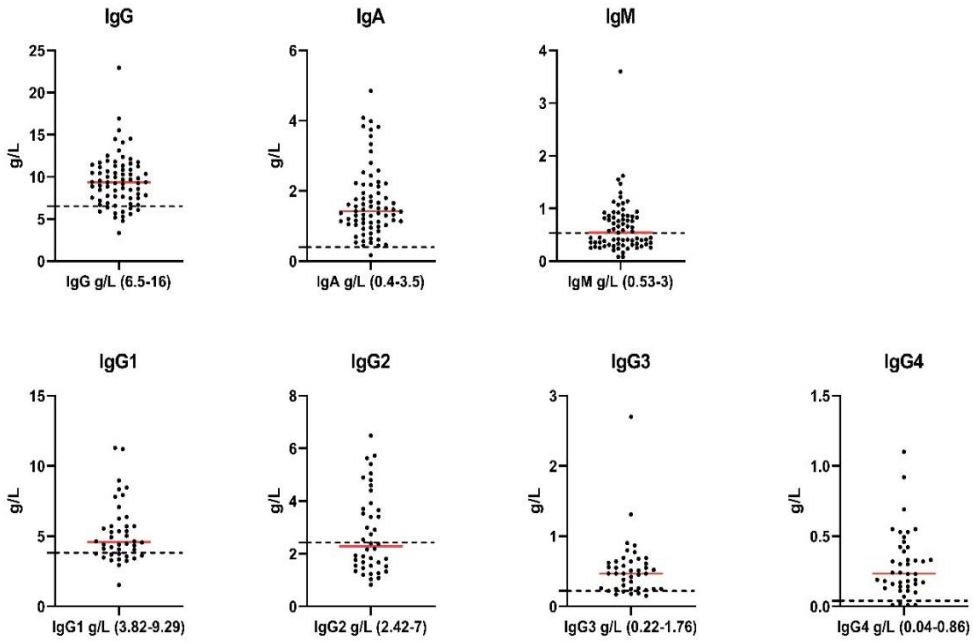
Aim: MBL is asymptomatic, and common, occurring in ~10% of individuals aged >60 years. Progression to chronic lymphocytic leukaemia (CLL) is reported as ~1-2% annually. Immune dysfunction, especially hypogammaglobulinemia is common in CLL; our previous studies demonstrated a significant association between reduced immunoglobulin (Ig), infection and shorter survival (Freeman, BJHaem, 2013; Crassini, Haematologica 2018). We evaluated Ig and immunoglobulin G (IgG) subclasses levels in MBL.

Method: This retrospective study analysed data from patients managed at Royal North Shore Hospital and Sydney Adventist Hospital, Sydney, with informed consent. MBL patients were diagnosed in accordance with WHO guidelines. Ig, IgG subclass and clinical data were collected at latest follow-up or prior to progression to CLL.

Results: There were 81 MBL patients included in the study, of whom 19 (23.5%) progressed to CLL with a median MBL duration of 4 years. The shortest and longest times to CLL progression were 7 months and >7 years respectively, while 62 patients remained MBL, with the longest follow-up time of 23 years. Reduced total IgG was observed in 11/74 (14.9%), and they had a statistically higher risk of infection (OR=5.71, 5.7-30.1, p=0.04) but too few deaths (3) to interpret survival. IgG subclass deficiency was observed with IgG1 in 12/42 (28.6%), IgG2 in 23/42 (54.8%), IgG3 in 5/42 (11.9%) and IgG4 in 4/42 (9.5%). IgM and IgA deficiency was observed in 36/73 (49.3%), and 1/73 (1.4%) respectively.

Conclusion: Immune impairment is very common in MBL with IgM and IgG2 deficiency in half, IgG1 deficiency in a quarter, and reduced total IgG in ~15%, the latter associated with significantly higher infection risk (p=0.04), and also contributes to higher second malignancy (Shen, eJHaem 2021) and impaired COVID-19 vaccination responses (Shen, BJHaem 2022). The MBL risk profile is more substantial than possible CLL progression and results from significant immune failure. line Dotted line indicates the lower cut-off of normal Ig or IgG subclass range.

Figure 1. Ig and IgG subclass levels in patients with MBL. Median is shown by the red line.



SNP Microarray Genomic Evaluation in Chronic Lymphocytic Leukaemia (CLL): Demonstration of Multiple Recurrent Genetic Rearrangements with 6 Year Follow-Up

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Aim
Gold-standard cytogenetic evaluation for CLL is conventional G-banding. Fluorescence in-situ hybridization (FISH) is used but evaluates only 4 targets. Virtually all risk stratification from CLL trials has been with “4-target-FISH”: deletion 17p (TP53), deletion 11q (ATM), deletion 13q and trisomy 12. Transition to Single Nucleotide Polymorphism (SNP) microarray platforms reveals high diversity and complexity in CLL. We sought to identify recurrent SNP array rearrangements in CLL.

Method
We reviewed >2000 chromosomal microarray CLL investigations over a 6-year period and identified key recurrent targets. Cumulative events of chromosomal abnormalities were used for analyses. A subset of 625 microarray investigations performed on 272 patients with full clinical data and follow-up were interrogated for associations with recurrent rearrangements.

Results
Of 272 patients, a “4-target-FISH” lesion was identified in 174/272 (64.0%): 13q- (54.4%); +12 (7.4%), 11q- (10.3%) and 17p- (7.0%). Additional non-FISH detectable lesions were found in 62/174 (35.6%) of these patients. The most common non-FISH detectable lesions were 2q, 4q, 6q, 8p, 12p, 14q.
In patients with no “4-target-FISH” lesion (98, 36.0%), 21/98 (21.4%) had an abnormality identified. The most common abnormalities among those patients include 4q, 6q, 8q, 12p and 14q.

Conclusion
SNP array demonstrates significant genomic complexity in CLL. There are a large number and proportion of recurrent genetic rearrangements, in addition to “4-target-FISH”. Unfortunately, little is known of their impact on prognosis, treatment, and outcome due to systematic exclusion from iwCLL guidelines of SNP array or G-banding karyotyping for clinical trials.

The ClpP activator, TR-57, is highly effective as a single agent and in combination with venetoclax against chronic lymphocytic leukaemia (CLL) cells in vitro.

Dr Yandong Shen[1], Dr Narjis Fatima[3], Dr Kyle Crassini[1], Dr Edwin Iwanowicz[4], Dr Henk Lang[4], Dr Donald Karanewsky[4], Prof Richard Christopherson[3], Prof Stephen Mulligan[1], Dr Giles Best[2]
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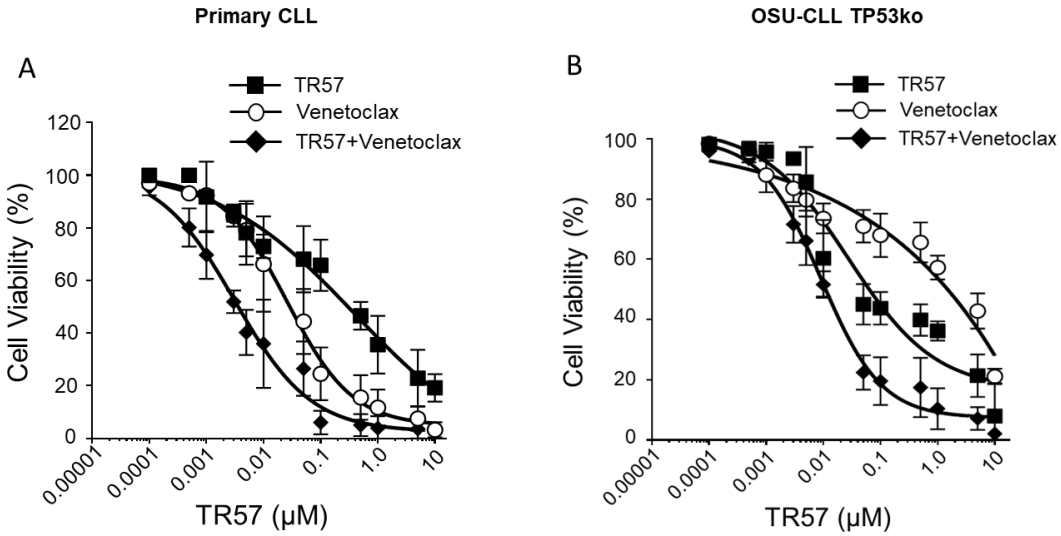
Aim: Treatments of CLL are challenged by relapse with drug-resistant disease. Emerging evidence demonstrate that imipridones are effective against a range of different cancers, including CLL (Fatima, *et al.* 2021), via activation of the mitochondrial protease caseinolytic protease (ClpP), and the unfolded protein response (UPR). Here we evaluated the therapeutic potential of a novel activator of ClpP, TR57 (Madera Therapeutics), as a single agent and in combination with the Bcl-2 inhibitor venetoclax in CLL.

Method: The cytotoxicity and synergy of TR-57 and venetoclax were measured by flow cytometry against primary CLL cells co-cultured with CD40L-expressing fibroblasts to mimic the tumour microenvironment (TME). The effects of the drugs were also assessed against an OSU-CLL TP53 knock-out cell line generated using CRISPr Cas-9. Cell cycle analyses were performed in primary CLL cells stimulated with Dsp30 in combination with IL-2. The migratory capacity of primary CLL cells were assessed using stroma-derived factor 1-α. Mechanism of the synergy was analysed by immunoblotting.

Results: TR-57, has efficacy as a single agent (IC50 287±50.45nM) and is synergistic (combination index 0.13) with venetoclax against CLL cells cultured under *in vitro* conditions that mimic the TME. The cytotoxic effects of TR-57 are independent of poor-risk features in CLL, including TP53 dysfunction. The combination had a greater effect than individual treatments in inducing cell-cycle arrest and attenuating the migratory capacity of CLL cells. The mechanisms of action of TR-57 and its synergy with venetoclax involves activation of the unfolded protein responses (UPR), inhibition of the AKT/ERK pathways and a pro-apoptotic shift of the BCL-2 proteins.
Conclusion: TR-57 is highly synergistic with venetoclax and induces apoptosis and cell cycle arrest of CLL cells under conditions that mimic the TME. This combination may represent an effective treatment option for CLL, including for patients with poor-risk disease primary CLL cells co-cultured with CD40L-expressing fibroblasts and (B) OSU-CLL TP53 knockout cell line.

Figure 1. Dose responses for TR57 and venetoclax, as a single agent and in combination, in (



Analysis of Monoclonal B-Lymphocytosis (MBL) and Chronic Lymphocytic Leukaemia (CLL) Diagnoses in the Flow Cytometry Laboratory.

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Aim: To evaluate the current (2015-2020) incidence and classification of MBL and CLL in a large flow cytometry laboratory

Methods: A retrospective analysis was conducted at Laverty Pathology; a large, non-hospital-based pathology laboratory. The World Health Organisation (WHO) definition of CLL is a clonal B-cell population with a specific phenotype in the peripheral blood 5.0x10^9/L, and MBL a B-cell clone in the peripheral blood <5.0 x 10^9/L. MBL can be subdivided into "low-count" (LC-MBL) and "high-count" MBL (HC-MBL).

Results: Analysis involved all flow cytometry reports on 27,996 individual patients processed between 2015 and 2020 inclusive. There were 3261 (11.6%) identified with a B-cell clone of which 1977 were MBL and 1284 with CLL (Table 1). MBL (60.6%) is more common than CLL (39.4%). The majority of MBL have a typical CLL-like phenotype (63.7%) (Table 2). The age distribution is very similar between MBL and CLL, with a very low incidence <40 years (~1%) and the highest incidence 60-79 years (~57-63%). The male (M) to female (F) ratio is higher in CLL (M:F 1.6:1) than MBL (M:F 1.2:1) Most MBL cases are HC-MBL (~67%) and ~5.5% progressed to CLL (~0.9% per year). LC-MBL were 28% of MBL cases detected with a 'CLL-like' B-cell count below 0.5x10^9/L, with 10.6% having fewer than 0.05x10^9 clonal B-cells/L. Most LC-MBL persisted over long periods without progression; of 654 patients with LC-MBL analysed, 3 progressed to CLL and 1 to MCL (~0.10% per year). More frequent progression to CLL occurs in atypical CLL-like MBL phenotype (3.5%) compared to typical CLL-like MBL phenotype (1.1%).

Conclusion: MBL is more common than CLL in non-hospital referrals, mainly HC-MBL as most are to investigate lymphocytosis. Although uncommon, some LC-MBL (~0.10% per year) do have progression to CLL. More progression is seen in atypical-CLL-like (3.51%) than typical-CLL-like MBL phenotype (1.42%).

Table 1.

		MBL (2015-2020) Clone <5.0x10^9/L	**CLL (2015-2020)** Clone <5.0x10^9/L (with a CLL specific phenotype)
Total		1977	1284
Sex	**Male**	1069 (54%)	781 (61%)
	Female	908 (46%)	503 (39%)
Mean age (range)		71.2 (21-99)	69.0 (18-104)

Table 2.

	Low count MBL (LC-MBL <0.5x10^9/L)	**High Count MBL** (HC-MBL 0.5-5.0x10^9/L)
Typical MBL	353 (28%)	906 (72%)
Atypical MBL	57 (27.1%)	153 (72.9%)
Non-CLL MBL	244 (48%)	264 (52%)
Total	654 (33.1%)	1323 (66.9%)

Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in previously treated CLL/SLL: updated results from the phase 1/2 BRUIN study

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Aim: To evaluate the safety and efficacy of pirtobrutinib in previously treated CLL/SLL.

Method: BRUIN is a phase 1/2 multicenter study (NCT03740529) of oral pirtobrutinib monotherapy in pts with advanced B-cell malignancies who have received >2 prior therapies. Primary objective for phase 1: determine the RP2D. Primary objective of phase 2: ORR. Secondary objectives included DoR, PFS, OS, safety and tolerability and pharmacokinetics.

Results: As of 27 Sept 2020, 323 pts with B-cell malignancies (170 CLL/SLL, 61 MCL, 26 WM, 26 DLBCL, 13 MZL, 12 FL, 9 RT and 6 other) were treated on 7 dose levels (25-300mg QD). Median number of prior lines of therapies=3 (1-11). No DLTs were reported and MTD was not reached (n=323). 200mg QD was selected as RP2D. Fatigue (20%), diarrhea (17%) and contusion (13%) were the most frequent TEAEs regardless of attribution or grade seen in >10% pts. Most common AE of grade ≥3 was neutropenia (10%). 139 CLL/SLL pts were efficacy-evaluable with a median follow up time of 6 months (0.16-17.8+). ORR was 63% (95%CI 55-71) with 69 PRs (50%), 19 PR-Ls (14%), 45 SDs (32%) and 1 PD (1%), and 5 (4%) discontinued prior to first response assessment. Among 121 BTKi pretreated pts, ORR was 62% (95%CI 53-71). Responses deepened over time with an ORR of 86% among pts with >10 months follow-up. ORR was similar in pts who discontinued prior BTKi due to progression (67%), or adverse events or other reasons (52%). Of 88 responding pts, all except 5 remained on therapy.

Conclusion:
Pirtobrutinib demonstrated promising efficacy in heavily pretreated CLL/SLL pts. Pirtobrutinib was well tolerated and exhibited a wide therapeutic index. Updated data, including approximately 100 new pts with CLL and an additional 10 months since the prior data cut will be presented.

Population-wide patterns of care in chronic lymphocytic leukemia (CLL) in Australia: An analysis of the Pharmaceutical Benefits Scheme (PBS) dataset

Prof Constantine Tam[1,2,3,4], Fei-Li Zhao[5], Raj Gauba[5], Keri Yang[6], Shu Chuen Li[7], Boxiong Tang[6]
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Aim: The CLL treatment landscape in Australia is changing with the approvals of Bruton's tyrosine kinase inhibitors (BTKis). To better understand the practice impact of introducing publicly funded novel agents for CLL, this study aimed to describe CLL treatment patterns in Australian patients from 2011-2021 using population-wide prescription records.

Method: Patients who initiated CLL treatment from 01Jan2011-31Jul2021 were extracted from the Services Australia 10% PBS dataset, which includes dispensing records for 10% of the Australian population and captures all publicly funded treatments in Australia. The index date was the commencement of any drug for treatment of CLL. First-line (1L) therapy was considered the first treatment prescribed for CLL. A patient was defined as relapsed/refractory (R/R) if they commenced a drug in a different therapeutic category, or restarted a regimen after a >180-day gap. Descriptive analyses were conducted to examine treatment regimen use for the overall 10-year population by therapy line. Analyses by calendar year were performed to assess changes in treatment patterns.

Results: 803 patients with CLL were identified. The majority were male (65%) and >60 years old (77%; 33% were 70-79 years). Baseline comedications included antihypertensives (47%), antipsychotics/antidepressants (17%), and/or anticoagulants (13%). In the overall population (2011-2021), most patients received fludarabine-cyclophosphamide-rituximab (FCR; 49%), chlorambucil ± CD20 (27%), or CD20 monotherapy (17%) as 1L treatment. The most commonly used R/R regimens included CD20 monotherapy (56%), BTKi (41%), or FCR (33%). A trend in adoption of novel agents was observed in subsequent years following PBS listing. From 2011-2020, 1L FCR use decreased from 78% to 10% and BTKi use for R/R CLL increased from 0% to 62%.

Conclusion: Australian CLL treatment patterns have changed significantly since introduction of BTKis (e.g., ibrutinib, acalabrutinib). Use of FCR as 1L CLL treatment has decreased and BTKi use in R/R patients has increased.

Incidence of Venetoclax induced tumour lysis syndrome (TLS) among Australian Chronic Lymphocytic Leukaemia (CLL) patients - a single centre retrospective analysis

Ashley Whitechurch[1], Dr Rory Bennett[1], Dr Mary Ann Anderson[1,2], Dr Dennis Carney[1,2], Professor John Seymour[1,2], Professor Constantine Tam[3], Dr Sasanka Handunnetti[1,2], Professor Andrew Roberts[1,2]
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Aim:
Venetoclax is a potent BCL2 inhibitor used to treat CLL in both frontline and relapse settings. Induction with this agent is associated with a risk of TLS that can be mitigated by the use of risk stratification (by tumour-burden based on node size and lymphocyte count), step-wise dose ramp-up and protocolised prophylaxis[1,2]. Peter MacCallum Cancer Centre (PMCC) established a nurse consultant-led multidisciplinary approach in 2019 to oversee the venetoclax onboarding process. Rates of TLS outside of clinical trials have been infrequently published. This study aims to describe the incidence, timing & features of TLS in the real world Australian setting.

Method:
A retrospective analysis of PMCC patients treated with standard of care Venetoclax was undertaken from March 2019 to May 2022. TLS was defined using Howard criteria[4], and risk categories as described in the product information[3].

Results:
Thirty three patients were identified including 12 low-, 11 intermediate-, and 10 high-risk for TLS. 42% were treated in combination with obinutuzumab and 58% as monotherapy prior to rituximab. Laboratory TLS occurred in one high risk patient only (3%; 95% CI 0.2 – 16%), without evidence of clinical TLS. Biochemical abnormalities not reaching Howard TLS criteria occurred in a further 12% and were restricted to the intermediate- and high-risk groups. Pre-emptive interventions such as additional intravenous fluids or rasburicase were administered to three (9%) patients (all intermediate-, or high-risk). One patient fulfilled high-risk criteria, but was intentionally managed with the intermediate-risk protocol uneventfully.

Conclusion:
The rate of TLS seen in our setting with specialist nurse-led oversight of venetoclax onboarding replicated the low rate reported in clinical trials. The low rate of TLS with stringent application of prophylaxis & monitoring in this real world study suggests that future studies could safely explore less burdensome approaches to TLS risk management.

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CML (Poster Board No H055)

Dasatinib use and outcomes in real-world patients with chronic myeloid leukaemia (CML)

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Aim: To investigate prescribing patterns, tolerability, and effectiveness of dasatinib in real-world patients with CML, and to explore the impact of clinical trial eligibility criteria on outcomes.

Method: A retrospective cohort study of patients with CML commencing dasatinib (2006 to 2018) was conducted at two Australian hospitals. Comprehensive chart review was performed to collect dasatinib dose variations, response, survival and toxicity. A Fine-Gray subdistribution hazard model was used to assess variables associated with response and adverse drug reactions (ADRs). Patient characteristics were compared with eligibility criteria for DASISION clinical trial and subgroup analysis was performed on patients who would have been ineligible for the trial.

Results: 52 patients receiving dasatinib were identified, 22 treatment-naïve and 32 with ≥1 prior line of therapy. 50% of patients had pre-existing serious or poorly controlled comorbidities. Dasatinib dose reductions or interruptions were frequent (cumulative incidence 51% by 2 years). After 5 years, 47% of patients had discontinued dasatinib, predominantly due to ADRs. The 2-year cumulative incidences of dasatinib-related grade ≥3 ADRs and ADRs requiring hospitalisation were 51% and 38%, respectively. Higher dasatinib starting dose, ECOG and pre-existing poorly controlled hypertension were independently associated with a higher risk of grade ≥ 3 ADR. Cumulative incidence of deep molecular response at 2 years was 73%. Estimated 3-year overall survival was 96% (95%CI, 90-100%). Of the 52 patients, 56% would have been ineligible for the DASISION trial and these patients had a higher risk of ADRs resulting in dasatinib dose change or discontinuation (subdistribution HR [SHR], 3.02; 95%CI, 1.44-6.33) or ADRs resulting in hospitalisation (SHR, 2.65 95%CI, 1.11-6.33).

Conclusion: A large proportion of patients receiving dasatinib had greater medical comorbidities and a higher frequency of grade ≥3 and treatment-limiting ADRs than patients in the original clinical trials. Careful patient selection and monitoring for toxicities when commencing dasatinib are recommended.

Lymphoma (Poster Board No H056 – H082)

Retrospective analysis of patients diagnosed with secondary CNS lymphoma in a 20 year period

Dr Sylvia Ai[1], Dr Shir-Jing Ho[1]
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Aim: Describe the disease characteristics, treatment modalities and outcomes of patients diagnosed with secondary CNS lymphoma (SCNSL) in the South Eastern Sydney Local Health District (SESLHD).

Method: Patients diagnosed with SCNSL were identified by searching pharmacy and radiotherapy records from 2000-2020, and cross referencing with ARIA, the local haematology/oncology database used in the SESLHD. Information was extracted regarding patient characteristics, disease characteristics, treatment course and outcomes. Data was collated and analysed using IBM SPSS version 25. Survival analyses were calculated using the Kaplan-Meier method.

Results: A total of 40 patients were diagnosed with SCNSLs between 2000-2020. Patients were an average of 65.8 +/- 13.6 years old at the time of diagnosis of their CNS lymphoma. 80% of patients were diagnosed with CNS relapse of systemic lymphoma, and the remaining 20% had synchronous CNS disease.

Of those that had a CNS relapse of lymphoma, 17% of patients received CNS prophylaxis.

In the 35 patients who received treatment for their CNS lymphoma, there was no significant difference in the overall survival or progression free survival between the different first line treatment regimens or modalities (systemic chemotherapy vs. radiotherapy alone).

The median overall survival was 14.4 months, with improved overall survival for those who underwent an autologous transplantation (autoHSCT) compared to those who did not (median OS not reached vs. 11.6 months, p=0.021). Overall progression free survival was a median of 11.2 months, with superior progression free survival in those who received an autoHSCT compared to those who did not (median PFS not reached vs. 8.6 months, p=0.033).

Conclusion: The prognosis of SCNSL remains poor. The treatment of SCNSL is an area which requires further prospective studies to determine optimal strategies. Autologous stem cell transplantation appeared to associated with improved outcomes in this retrospective study.

High prevalence of dapsone – induced oxidative haemolysis in patients with haematological malignancy on high dose methotrexate chemotherapy: A retrospective study

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Aim: Adult haematology patients receiving high dose methotrexate (HD-MTX) chemotherapy unable to tolerate trimethoprim-sulfamethoxazole (TMP-SMX) are recommended dapsone for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis. Dapsone can induce haematological toxicities such as oxidative haemolysis (OxHb) and methemoglobinemia (MetHb). This study aims to investigate the prevalence of these adverse events in this patient population.

Method: Patients with haematological malignancy who received HD-MTX chemotherapy and dapsone for PJP prophylaxis from January 2008 to June 2019 were reviewed. The primary endpoints of OxHb and MetHb were determined using peripheral blood film changes and blood gases respectively. Results were presented as raw numbers, percentages and medians for non- parametric data.

Results: Of the 99 patients who met the inclusion criteria, 84 (85%) experienced haematological toxicities. Sixty patients (61%) had OxHb, 2 (2%) MetHb and 22 (22%) experienced both toxicities. Dapsone induced OxHb occurred after a median of 20 days (interquartile range [IQR],15 to 32) post dapsone initiation. Of the 22 patients with both toxicities, 21 continued to receive dapsone after the first event with a median of 10 days (IQR, 3 to 22) between events.

The median decrease in haemoglobin from baseline to nadir was 50g/L (95% confidence interval [CI] of 45 to 55g/L), $p < 0.001$ in patients with OxHb and 50g/L (95% CI, 36 to 62g/L), $p < 0.001$ in patients with both toxicities. The median units of blood transfused was 2 (IQR, 0 to 5) units for OxHb group and 4 (IQR 2 - 5) units in the patients with both toxicities, $p = 0.152$.

Conclusion: Prevalence of dapsone induced OxHb in patients with haematological malignancy on HD-MTX chemotherapy was high. A significant drop in haemoglobin from baseline to nadir was observed. Careful monitoring is imperative to detect events and to facilitate prompt cessation of dapsone therapy.

Changes to platelet quality and function in Waldenström Macroglobulinaemia

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Aim: Platelet glycoprotein (GP) receptors are essential for initiating platelet adhesion, activation and aggregation. Reduced levels can occur when thrombopoiesis or haematopoiesis is disturbed. Both GPVI and GPIbα are metalloproteolytically shed from platelets. Waldenström Macroglobulinaemia (WM) is a B-cell lymphoma with common symptoms including bleeding/bruising and thrombocytopenia. WM is treated with Bruton's tyrosine kinase inhibitors (BTKis) and chemotherapies, which exacerbate bleeding. Platelet function and quality are under-investigated in WM. This project aims to evaluate platelet quality and function, and clotting potential in WM.

Method: Relative platelet receptor levels, reticulation and activation were measured by whole blood or PRP flow cytometry in 16 WM patients compared with 66 healthy donors (HDs), from the Canberra Hospital and JCSMR respectively. Blood was enumerated by automated analyser; metalloproteolytically-shed soluble GPVI was measured by ELISA; whole blood clotting potential was evaluated using ROTEM. P-values were determined by Mann-Whitney t-test.

Results: WM blood displayed significantly reduced (**$p<0.01$) yet enlarged ($p^{**}<0.01$) platelets, bearing less GPVI (**$p<0.01$), GPIbα (*$p<0.05$) and reticulation (*$p<0.05$), and increased tetraspanin CD9 (***$p<0.001$) compared with HDs. Soluble GPVI was within HD ranges. Samples from WM patients displayed normal ROTEM parameters in intrinsic and extrinsic clotting assays, but markedly reduced thrombus size (****$p<0.0001$) compared to HD values in FIBTEM. When recalcified (NATEM), WM patient blood formed thrombi 58% faster (****$p<0.0001$), that were enlarged 22% (****$p<0.0001$) over HDs.

Conclusion: WM patient platelets bore reduced levels of key receptors governing platelet function. Reductions may be due to changes in platelet maturation/production, as GPVI shedding was not evident and reticulation was reduced. Global clotting capacity was normal, however the relative contributions of platelets and plasma components were abnormal, consistent with deranged haemostatic regulatory capacity in WM. Future work will assess the utility of these measurements in stratifying patients for bleeding risk

Patient characteristics and management of aggressive lymphoma in metropolitan and non-metropolitan centres in Australia from the Lymphoma and Related Diseases Registry (LaRDR).

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Aim: To describe baseline characteristics and management for patients with aggressive lymphoma, in metropolitan and non-metropolitan Australian centres participating in LaRDR.

Method: We assessed all patients with diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and classical Hodgkin lymphoma (HL) entered on LaRDR[1]. Patients were stratified according to their location. Baseline demographics, disease characteristics and management including use of ASCT were evaluated Categorical variables were compared using chi-squared test and comparisons between continuous variables were performed using a Wilcoxon rank-sum test'.

Results: 1975 patients aged 18 years and above diagnosed between January 2016 and March 2022 were included in this audit. 89% and 11% of patients received treatment at metropolitan (n=1752) and non-metropolitan (n=223) centres respectively. Baseline demographics and disease incidence were similar with no difference in age, gender, staging or prognostic indices. Fewer non-metropolitan patients had bulky disease (13.6% vs 23%, p=0.002) at diagnosis but more patients demonstrated poor performance status, ECOG 2-4 (21.8% vs 12%, p<0.001). There was no difference between treatment intensity for DLBCL and HL. However, more MCL patients in metropolitan centres received moderate to high intensity treatment (90.5% vs 62.5%, p=0.008). Fewer patients in non-metropolitan centres were treated on a clinical trial (4.4% vs 0.8% DLBCL, 0% vs 9.2% HL and 0% vs 19.2% MCL). Response rates and survival are captured in the registry and will be reported after additional follow-up.

Conclusion: Numbers of patients at non-metropolitan LaRDR sites are growing, and in this 'first look' analysis, fewer non-metropolitan patients were enrolled on clinical trials. Access to clinical trials must be improved as a priority for non-metropolitan, rural and regional patients. Follow-up to understand the implications of differences in patient and disease characteristics and management is ongoing through the registry.

Superiority of axicabtagene ciloleucel (axi-cel) over standard of care (SOC) as second-line therapy for large B-cell lymphoma (LBCL) with poor prognostic factors associated with tumor aggressiveness (ZUMA-7)

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Aim: To compare association of prognostic factors with response to axi-cel versus SOC in second-line treatment of patients with relapsed/refractory LBCL.

Method: In ZUMA-7, eligible patients ≥18 years with LBCL refractory to or relapsed ≤12 months of first-line chemoimmunotherapy were randomized 1:1 to axi-cel (an autologous anti-CD19 chimeric antigen receptor T-cell therapy) or SOC (2-3 cycles of a chemoimmunotherapy regimen followed by high-dose chemotherapy with autologous stem cell transplant [HDT-ASCT] if chemoimmunotherapy-responsive). The primary endpoint was event-free survival (EFS, blinded central review). Exploratory analyses included tumor characteristics (pretreatment tumor burden [TB] and serum lactate dehydrogenase [LDH]). Associations were assessed descriptively.

Results: As of 3/18/21, 359 patients were randomized to axi-cel (N=180) or SOC (N=179). The primary endpoint of EFS was met (HR, 0.398; *P*<.0001; estimated 24-mo EFS rate: 41% axi-cel vs 16% SOC). Axi-cel EFS was superior to SOC for high (>median) and low (≤median) TB (HR, 0.31 and 0.48, respectively; both *P*<.001), and elevated and nonelevated LDH (HR, 0.37 and 0.49, respectively; both *P*<.001). In axi-cel patients, EFS was not significantly different for patients with high versus low TB (*P*=.88) or elevated versus nonelevated LDH (*P*=.33). For SOC patients, a higher risk of EFS events was observed for those with high versus low TB (HR, 1.48; *P*=.03) and elevated versus nonelevated LDH (HR, 1.48; *P*=.02). Non-germinal center B-cell subtype was a poor prognostic factor for SOC EFS (HR, 1.76; *P*=.02) but not for axi-cel. Axi-cel showed superiority in pts with other poor prognostic factors, including primary refractory disease, extranodal disease, and bulky disease.

Conclusion: In patients with relapsed/refractory LBCL, axi-cel was superior to SOC across prognostic groups, including high TB and elevated LDH. The benefit of axi-cel is pronounced in patients with tumor aggressiveness features and should replace chemoimmunotherapy/HDT-ASCT as the second-line SOC for early relapsed/refractory LBCL

Using baseline PET/CT to estimate osteoporosis risk in patients undergoing CHOP-based chemotherapy for lymphoma

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Background / Aim: High fracture rates are reported following CHOP-based chemotherapy, but lymphoma-specific guidelines for osteoporosis (OP) risk management are unavailable. Bone mineral density correlates with CT-measured Hounsfield units using L1 vertebra (L1HU) (Abbouchie, 2022). An L1HU threshold of <180 detected moderate-severe osteopenia/osteoporosis with sensitivity 79%(OR=2.1, p<0.001). L1HU can be obtained using routine PET/CT. We aimed to assess L1HU change in lymphoma patients undergoing CHOP-based chemotherapy, and determine prevalence of risk factors (RF) for fragility fracture.

Method: A single-centre, retrospective audit of OP RF in lymphoma patients undergoing R-CHOP-based chemotherapy (2019–2021). Medical record review elucidated lymphoma, treatment details and OP RFs: hypogonadism, menopause ≤45 years, hormone-deprivation, malabsorption, systemic autoimmune disease, prior corticosteroid, body mass index <18.5, smoking and alcohol excess. L1HU was assessed on baseline PET/CT and following treatment, using mean L1HU of 3 consecutive CT slices. Descriptive statistics were used.

Results: 90 patients were eligible. Median age was 68 years (range 20-93), follow-up 477 days (68-968). Cumulative prednisolone doses totalled 600–4,700mg. 96% had no systematic pre-treatment OP RF documentation, but on detailed review 57(63%) had ≥1 RF. Vitamin D replacement was documented in 19(21%).

24(27%) had reduced BMD (on DXA or clinically) at baseline (OP n=5; osteopenia, n=6; fragility fractures, n=13). 4 were receiving OP therapy. During follow-up, minimal trauma fracture occurred in 3 (not on OP treatment), and 2 had new DXA-identified osteopenia.

Baseline CT L1HU of 80 patients without known osteoporosis identified 62(77%) with L1HU <180, suggesting possible osteoporosis/osteopenia. Following chemotherapy, L1HU decreased by an average 21% (145 to 113). 9 new patients (11%) exhibited L1HU <180.

Conclusion: OP RF burden is significant (63% clinically, 77% by L1HU) but underreported in lymphoma, with no consistent management approach. Development of lymphoma-specific risk management tools is crucial. CT L1HU could improve recognition of high-risk patients, and further assessment is warranted and planned (HREC/79155/Austin-2021).

Outpatient delivery of care in patients treated with commercial tisagenlecleucel (Tisa-cel) for large B-cell lymphoma (LBCL)

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Aim: Tisa-Cel is a CD19-targeting 41BB co-stimulated CAR-T cell product available for Australian patients with R/R LBCL. Many centres admit patients post infusion to monitor for CAR-T associated toxicity. We developed a risk-stratified approach to preserve patient safety while reducing unnecessary admissions. Here we report health-care utilisation, toxicity, and efficacy of an 'outpatient-first' CAR-T service providing Tisa-cel.

Method: We conducted a retrospective review of 51 consecutive patients treated at our centre with Tisa-cel for B-NHL between April 2019 and May 2022. Data were collected on baseline patient and disease characteristics, toxicity (cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and cytopenias) and health-care utilisation (hospital and intensive care unit (ICU) admissions, and length of stay (LOS))
Results: After clinician-determined risk stratification, 39 patients [39/51;76%] were infused with Tisa-cel as outpatients, and 12 patients [12/51;23%] were infused as inpatients. Baseline characteristics, toxicities and D+28 response of the cohorts are shown in Table 1. Common indications for inpatient admission were advanced disease stage [12/12; 100%] and treatment-refractoriness [9/12;75%]. Amongst planned outpatients, 34/39 (87%) of patients required admission within 28 days, occurring at a median of D+3 post-infusion (range 0-8). Planned admissions had longer median LOS than unplanned admissions (10 vs 5 days). ICU admission rates were comparable at 17% [2/12] in the inpatient group versus 10% [4/39] in the outpatient group. Planned inpatients trended towards higher grades of CRS and inferior D+28 response.
Conclusion: In our institutional experience, risk stratification facilitates safe outpatient delivery of Tisa-cel with a reduction in resource utilisation. No adverse events were attributed to delayed identification of toxicities. Validated risk models are needed to objectively and prospectively identify patients at high risk of toxicities to stratify patients to inpatient versus outpatient infusion. Outpatient delivery of CAR T-cell therapy will likely improve cost-effectiveness of this resource-intensive therapy.

Table 1

		Planned inpatients (n=12)	**Planned outpatients (n=39)**
Baseline characteristics	Age (years; median (range))	62 (43 - 73)	66 (44 - 78)
	Stage III-IV disease (n (%))	12 (100)	25 (64)
	LDH ≥ ULN (n (%))	4 (33)	10 (26)
	Refractory to most recent line of therapy (n (%))	9 (75)	19 (49)
Health-care utilisation	Unplanned admissions (n (%))	2 (17)	34 (87)
	ICU admission (n (%))	2 (17)	4 (10)
Toxicity	CRS G□2 (n (%))	6 (50)	9 (23)
	ICANS G□2 (n (%))	1 (8)	0 (0)
D+28 Response	CR (n (%))	4 (33)	24 (62)

The RE-TELL study: A qualitative study of CAR T-cell recipient, support person, co-ordinator and clinician experiences to inform clinical service design

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Aims:
To understand patient, support person, clinician and co-ordinator experiences and perspectives of CAR T-cell therapy, with the goal of informing design of a national chimeric antigen receptor (CAR) T-cell service in Aotearoa New Zealand.

Methods:
Qualitative interviews were undertaken by a health psychologist experienced in qualitative research, with 18 New Zealand participants, comprising: five CAR T-cell recipients, three support people, six clinicians and four co-ordinators (including transplant; travel assistance; and charitable organisations). 4 participants identified as Māori. Interviews focused on themes of: experience through treatment; elements that work well and those that could be improved upon; practical needs; informational needs; emotional experiences; cultural elements; and system flow. Interviews were analysed using thematic analysis to identify key themes.

Results:
Thematic analysis identified 8 'key themes': access and equity, centralised point of information, discuss expectations and possibilities; cultural pathway (building trust); bridging agencies (e.g. cancer charities); ceremony/reverence for cells; inpatient experience of treatment; and supporter/kaitiaki needs. Identified potential improvements included: improved geographical access to CAR T-cell therapy, while also preserving consolidated clinician experience; a 'dashboard' with key information on CAR T-cell treatment, timeframes and manufacture; a "concierge", or health navigator, to guide, support, and signpost care along the journey; respect for indigenous data sovereignty and ownership of cells; outpatient administration and monitoring where possible; and a ceremony for cell infusion, including family involvement and Māori cultural elements.

Conclusion:
The RE-TELL qualitative study identified key themes and areas for attention for national CAR T-cell service design, some of which are unique to Aotearoa New Zealand. These insights will inform the design of CAR T-cell clinical trials in New Zealand, and of future CAR T-cell service delivery.

Characteristics and Outcomes of Elderly Patients with classical Hodgkin Lymphoma (cHL): An Australian Lymphoma Alliance (ALA), and Lymphoma and Related Disease Registry (LaRDR) Study

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Introduction: Elderly cHL patients have inferior outcomes compared to younger patients and many are excluded from clinical trials. This study aimed to provide a snapshot of the presentation and contemporary management of elderly Australian patients with cHL.

Methods: Retrospective review from 7 ALA sites and LaRDR on cHL patients aged ≥61 years diagnosed between 2011-2020. LaRDR and ALA were combined for some analyses due to differences in variables collected. Descriptive statistical and Kaplan-Meier survival analyses were performed on STATA v17.

Results:

Dataset: ALA and LaRDR (N=195)

Median age 72 years (range 61-93); 56.4% male, median baseline ECOG 1, 35.3% stage I-II, bulk present in 9.2%, 33.9% had extra-nodal disease, 48.2% B-symptoms. Median IPS was 4. Histological subtype: nodular-sclerosing 24.6%; mixed-cellularity 17.4%; lymphocyte-rich 9.2%; lymphocyte-deplete 1%; unknown 47.7%.

91.3% commenced chemotherapy, with an anthracycline-based regimen used in 80.5%; of these 86.6% had ABVD-AVD, 5.1% CHOP, 5.1% PVAG, 3.2% other. Median number of cycles for stage I-II was 2 (range 0-6) and stage III-IV was 6 (range 0-8), 26.2% had radiotherapy. Response to front-line chemotherapy was CR 56.4%; PR 7.2%; SD 1.5%; PD 7.2%; unknown 27.7%.

Dataset: ALA (N=123)

Median Charlson Comorbidity Index 6 (range 4-15), 96.8% lived independently, 39.8% required ≥5 medications at diagnosis.

Using GHSG classification, 13.4% had early-stage favourable; 15.2% early-stage unfavourable; 71.4% advanced stage. 10 patients had Richter's transformation. Where data were available, 20/109 patients were CD20 positive, 39/86 were EBERish positive.

During frontline therapy, unplanned hospitalisation occurred in 58/123, 7/123 required ICU. Infection was the most common reason for hospitalisation (41/123). Treatment-related mortality was 6/123.
Median follow-up 2.3 years (range 0.01-9.39). Estimated 2-year PFS 63.7% (95% CI: 53.8-72%), 2-year OS 71.2% (95% CI: 61.6-78.8%). Disease relapse occurred in 24/123. 50 patients died, 21/50 from progressive cHL.

Conclusions: This Australian study highlights the characteristics and challenges of treating cHL in elderly patients.

Investigating Ferroptosis as an Approach to Treating Diffuse Large B Cell Lymphoma

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Aim: The aim of this project is to determine whether ferroptosis could be a valuable therapeutic strategy for diffuse large B cell lymphoma (DLBCL). Ferroptosis is a newly discovered form of iron-dependent regulated cell death, characterised by the accumulation of oxidised membrane polyunsaturated phospholipids to lethal levels [1].

Methods: A range of DLBCL cell lines and the healthy B cell line (FH9) were cultured with the GPX4 inhibitor RSL3 to induce ferroptosis together with ferroptosis substrates ferric ammonium citrate (FAC) or arachidonic acid (AA) for 24 hours. Flow cytometry was used to assess cell viability after annexin-V/propidium iodide staining and oxidised lipids (lipid ROS) using C11-BODIPY. Liproxstatin-1 was used to confirm ferroptosis as the responsible cell death mechanism.

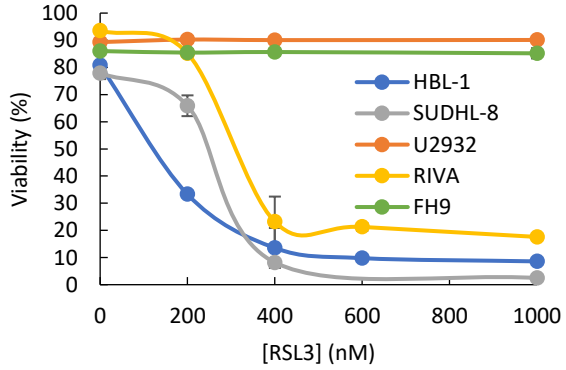

Figure 1. DLBCL cell lines are mostly sensitive to ferroptosis. Cell viability assessed by annexin-V/PI flow cytometry after culturing cells with RSL3 for 24 hours. FH9, healthy B cell line. Mean +/- SEM of duplicate measurements shown.

Results: DLBCL cell lines were mostly sensitive to RSL3, exhibiting IC_{50}s in the range of 150 nM to 300 nM, whereas U2932 and FH9 cells were insensitive. GPX4 inhibition resulted in increased cellular lipid ROS in all cell lines except FH9. The combination of RSL3 and FAC/AA resulted in synergistic cell death in all DLBCL cell lines with sub-100 nM IC_{50}s, while also inducing synergistic lipid ROS accumulation. Cell death was attributed to ferroptosis as it could be prevented by liproxstatin-1. FH9 cells did not exhibit a reduction in cell viability or an increase in lipid ROS, suggesting preferential sensitivity of DLBCL cells to ferroptosis over healthy B lymphocytes.

Conclusion: DLBCL cell lines are generally highly sensitive to ferroptotic cells death. The promising efficacy of inducing ferroptosis in DLBCL cells *in vitro* may allow ferroptosis to be harnessed for the development of novel therapeutic approaches in the future.

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Targeted repeat biopsy of discordantly 18F-Fluorodeoxyglucose (FDG) avid lymph nodes has high PPV for diffuse large B-cell lymphoma (DLBCL) in patients with follicular lymphoma (FL) from an initial biopsy.

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Title: Targeted repeat biopsy of discordantly 18F-Fluorodeoxyglucose (FDG) avid lymph nodes has high PPV for diffuse large B-cell lymphoma (DLBCL) in patients with follicular lymphoma (FL) from an initial biopsy.

Aim: Histologic transformation (HT) is a significant event in patients with FL. Often, the initial diagnosis is from accessible lymph node biopsy prior to PET-CT scan being performed. The PET-CT occasionally shows discordantly FDG avid disease at an alternate site to that biopsied, raising the question about whether repeat biopsy is required to exclude DLBCL. Limited evidence supports repeat biopsy, and there is wide variability in clinical practice. We performed a single centre retrospective study to assess the utility of targeted repeat biopsy; to identify HT in this clinical setting.

Method: We performed a single centre retrospective study, screening patients at Sir Charles Gairdner Hospital. The inclusion criteria were initial histologic diagnosis of FL, baseline PET-CT scan, and repeat biopsy driven by identification of a discordantly FDG avid additional nodal site. Descriptive statistics, sensitivity analysis, and receiver operating characteristic (ROC) curve analysis were used to analyse the predictive power of PET-CT discordance.

Results: Among 515 patients screened, 8 met inclusion criteria and 6/8 repeat biopsies found DLBCL histology; 2 found FL histology. Sensitivity and ROC curve analysis were minimally practicable due to sample size limitations. The positive predictive value (PPV) of repeat biopsy for HT in our series was 75% when driven by PET-CT discordance in conjunction with clinician judgement.

Conclusion: This small study suggests potential utility for a PET-driven repeat biopsy strategy to identify DLBCL in patients with an existing diagnosis of FL who have PET-CT scans showing discordantly FDG avid lesions. Further study of this strategy is warranted.

Utility of a single anti-TRBC1 antibody in the flow cytometric assessment of clonality in mature T-cell lymphoproliferative disorders

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Aim: Unlike B cell lymphomas, the assessment of clonality in T-cell lymphoproliferative disorders (LPDs) is challenging and requires a combination of cyto-morphology, flow cytometry and genomic testing. Flow cytometry is unable to confirm T cell clonality as aberrant antigen expression is frequently seen and some T-cell LPDs have a normal immunophenotype. A new flow cytometry technique has emerged using the binary expression of the constant region of the beta chain in the T-cell receptor (TRBC) to assess clonality T-cell LPDs that have surface expression of CD3 and TCR alpha-beta (CD3+/TCRαβ+). Normal and reactive T cell populations display a mixture of TRBC1 and TRBC2, while clonal populations display TRBC restriction. Using an antibody against TRBC1, recent studies have demonstrated that TRBC1-based flow cytometry has high sensitivity and specificity for demonstrating T cell clonality, with a high degree of agreement with T-cell receptor gene rearrangement PCR. We undertook a validation study of TRBC1 based flow cytometry to assess its sensitivity and specificity.

Method: 20 patients with known or suspected CD3+/TCRαβ+ T-cell LPDs and 24 controls were included. Fresh samples of peripheral blood, bone marrow and nodal tissues were submitted for flow cytometry using a single 10-antibody T-cell tube including TRBC1. TCR gamma polymerase chain reaction (PCR) was available for 15 patients and 10 controls

Results: TRBC1-based flow cytometry demonstrated a 95% sensitivity and 100% specificity for confirming T-cell clonality. There was 100% concordance with TCR gamma PCR for the positive cases. 10% of patients and 20.8% of controls demonstrated small t-cell clones of undetermined significance which were easily identified based on size and immunophenotype.

Conclusion: TRBC1 based flow cytometry is a highly sensitive and specific technique for assessing clonality in mature CD3+/TCRαβ+ T-cell LPDs.

An open-label, phase 1/2 study of favezelimab (MK-4280; anti–LAG-3) and pembrolizumab co-blockade in patients with anti–PD-1–naive relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL)

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Aim: The MK-4280-003 study (NCT03598608) investigated favezelimab plus pembrolizumab in R/R hematologic malignancies. Results for patients with anti–PD-1–naive R/R cHL (cohort 1), are presented.

Method: Eligible patients had R/R cHL after autologous stem cell transplantation (ASCT) or were ineligible for ASCT, with no prior anti–PD-1 therapy. Safety lead-in (part 1; all cohorts) was followed by dose-expansion (part 2). In part 1, patients received pembrolizumab 200 mg + favezelimab 200 mg or 800 mg IV Q3W. Recommended phase 2 dose (RP2D) was established using modified toxicity probability interval design. In part 2, patients received favezelimab + pembrolizumab at RP2D for ≤35 cycles. Primary end point: safety. Secondary end point: objective response rate (ORR). Exploratory end points: duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Results: In part 1, 1 dose-limiting toxicity (DLT) (grade 4 autoimmune hepatitis) occurred with favezelimab 200 mg; no DLTs occurred at 800 mg. RP2D was established as favezelimab 800 mg + pembrolizumab 200 mg. Cohort 1 included 30 patients. Median follow-up at database cutoff (March 21, 2022) was 14.1 months. Treatment-related adverse events (TRAE) occurred in 26 patients (87%); most commonly (≥20%) hypothyroidism (27%), infusion-related reactions (23%), and fatigue (20%). Grade 3/4 TRAEs occurred in 7 patients (23%); 4 (13%) discontinued due to TRAEs. No grade 5 TRAEs occurred. ORR was 73% (95% CI, 54-88; 8 complete responses; 14 partial responses). Median DOR was not reached ([NR]; 95% CI, 2.6-25.9+ months); 7 (55%) had a response ≥12 months. Median PFS was 19.4 months (95% CI, 8.5-NR); 12-month PFS was 62%. Median OS was NR (95% CI, NR-NR); 12-month OS was 96%.

Conclusion: Favezelimab 800 mg + pembrolizumab 200 mg Q3W had acceptable safety and demonstrated antitumor activity in anti–PD-1–naive R/R cHL. Studies comparing the combination with pembrolizumab are warranted.

Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in previously treated mantle cell lymphoma: updated results from the phase 1/2 BRUIN study

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Aim: To evaluate the safety and efficacy of pirtobrutinib in previously treated patients (pts) with MCL.

Method: BRUIN is a multicenter phase 1/2 study (NCT03740529) of oral pirtobrutinib monotherapy in pts with advanced B-cell malignancies who have received >2 prior therapies. The primary objective for phase 1 was to determine the RP2D. The primary objective of phase 2 was ORR. Secondary objectives included DoR, PFS, OS, safety and tolerability, and pharmacokinetics.

Results: As of 27 Sept 2020, 323 pts (170 CLL/SLL, 61 MCL, 26 WM, 26 DLBCL, 13 MZL, 12 FL, 9 RT and 6 other NHL) were treated on 7 dose levels (25-300mg QD). Among the 61 MCL pt, median number of prior lines of therapy was 3 (1-8).No DLTs were reported and MTD was not reached (n=323). 200mg QD was selected as the RP2D. Fatigue (20%), diarrhea (17%) and contusion (13%) were the most frequent TEAEs regardless of attribution or grade seen in >10% pts. The most common AE of grade ≥3 was neutropenia (10%). Treatment-related hemorrhage/hypertension occurred in 5 (2%)/4 (1%) pts. 5 (1%) pts discontinued due to TEAEs. 52 prior BTKi treated MCL pts were efficacy evaluable with an ORR of 52% (95%CI 38-66; 13 CR (25%), 14 PR (27%), 9 SD (17%), 11 PD (21%) and 5 (10%) discontinued prior to first response assessment). Median follow up was 6 months (0.7-18.3+). Responses were observed in 9/14 pts (64%) with prior autologous or allogeneic stem cell transplant, and 2 of 2 with prior CAR-T cell therapy.

Conclusion: Pirtobrutinib demonstrated promising efficacy in heavily pretreated, poor-prognosis MCL following multiple prior lines of therapy. Pirtobrutinib was well tolerated and exhibited a wide therapeutic index. Updated data, including approximately 60 new pts with MCL and an additional 10 months since the prior data cut will be presented.

What is the utility of clinical follow-up in detecting the relapse of diffuse large B cell lymphoma in remission? A decade long experience in the New Zealand Midland region.

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Aim: Diffuse large B cell lymphoma (DLBCL) treated with intensive immunochemotherapy has excellent survival outcome. Post remission surveillance strives to detect early relapse to enable second line treatment prior to significant host compromise. International guidelines recommend a schedule of clinical reviews with tapered frequency as the risk of relapse diminishes. This recommendation is based on expert consensus and non-comparative studies, resulting in large appointment and investigation burdens for both patients and the healthcare sector. This study describes the relapse pattern of those with treated DLBCL in first remission and determines the efficacy of the current pre-scheduled surveillance strategy compared with patient-initiated healthcare visits.

Method: We performed a multicentre retrospective analysis of all DLBCL diagnosed and treated in the Midland Cancer Region of New Zealand between 2010-2019. Histological diagnosis, treatment intent, chemotherapy regimen, response, surveillance strategies and relapse data were recorded through to May 2022. Cases of de novo DLBCL treated with curative intent regimens who attained partial or complete remission entered final analysis. Kaplan-Meier survival analyses were performed. Relapses were categorised according to detection by routine surveillance or unplanned healthcare interaction.

Results: 324 patients met criteria for analysis with a median follow-up of 69.6 months. 63 (19.4%) cases relapsed before the study end point. The two-year progression free and overall survivals were 85.5% and 91.8%. 47 (74.6%) relapses presented with symptomatic disease outside of routine review. Of relapses detected at routine review, 10 were symptomatic, while only 6 had asymptomatic relapse detected through pre-scheduled surveillance investigations.

Conclusion: Majority of relapses present with symptomatic disease outside of scheduled appointments. Only a small proportion of relapses were asymptomatic and detected by routine surveillance. The current data suggests the "number needed to follow" to detect an asymptomatic relapse is 54. New strategies are necessary to design surveillance programmes that provide high-value care.

ASPEN: Long-term follow-up results of a phase 3 randomized trial of zanubrutinib vs ibrutinib in patients with Waldenström macroglobulinemia (WM)

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Aim: ASPEN is a randomized, open-label, phase 3 study comparing zanubrutinib, a potent and selective Bruton tyrosine kinase inhibitor (BTKi), with the first-generation BTKi, ibrutinib, in WM. Data with a median follow-up of 43 months are presented.

Method: In cohort 1, patients with *MYD88* mutations were randomized 1:1 to receive zanubrutinib 160mg twice daily or ibrutinib 420mg once daily; stratifications were *CXCR4* mutations and prior lines of therapy. In cohort 2, patients without *MYD88* mutations received zanubrutinib 160mg twice daily. The primary endpoint was the proportion of patients with complete response/very good partial response (CR+VGPR).

Results: In cohorts 1 and 2, 201 (zanubrutinib=102; ibrutinib=99) and 28 patients were enrolled, respectively. More cohort 1 patients in the zanubrutinib vs ibrutinib arm had *CXCR4* mutations (32% [33/98] vs 20% [20/92] with next-generation sequencing data) and were aged >75 years (33% vs 22%). With median treatment durations of 42 (zanubrutinib) and 41 (ibrutinib) months, 67% and 58% remain on treatment, respectively. Investigator-assessed CR+VGPR rate was 36% vs 22% (zanubrutinib vs ibrutinib; P=0.02) and 31% in cohort 2 (1 CR). CR+VGPR rates for wild-type *CXCR4* were 45% vs 28% (zanubrutinib vs ibrutinib; P=0.04) and were 21% vs 5% (P=0.15) for mutated *CXCR4*. Median progression-free survival and overall survival were not yet reached. Rates of atrial fibrillation, diarrhoea, hypertension, localized infection, haemorrhage, muscle spasms, pneumonia, grade ≥3 infection, and adverse events leading to discontinuation/death were lower for zanubrutinib vs ibrutinib as were exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension (0.2 vs 0.8 and 0.5 vs 1.0 persons/100 person-months; P<0.05); neutropenia rate was higher. Zanubrutinib safety outcomes were similar between cohorts.

Conclusion: ASPEN is the largest phase 3 WM trial with head-to-head BTKi comparison. At a median follow-up of 43 months, zanubrutinib had higher CR+VGPR rates and clinically meaningful advantages in long-term safety/tolerability vs ibruti

Real World duration on treatment for Ibrutinib in relapsed/refractory Mantle Cell Lymphoma in Australia

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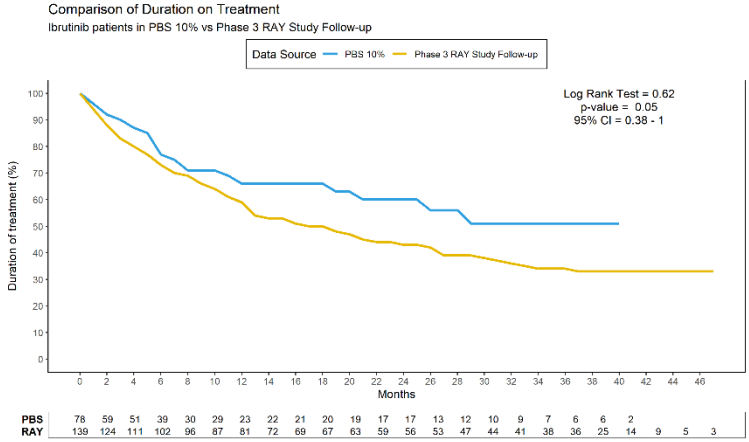
Aim: Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin's lymphoma characterised by an aggressive clinical course and a tendency for relapse [1]. In the Phase 3 RAY clinical trial, ibrutinib demonstrated significant improvement in progression-free survival versus temsirolimus in patients with relapsed or refractory (R/R) MCL [2]. A 3-year follow-up of study [3] supported these results [2]. Clinical trial populations are often highly selected and may not reflect "real-world" clinical practice. There are limited data available on the use of ibrutinib in the Australian general community [4]. The primary aim of this study was to describe duration on treatment (DoT) with ibrutinib in R/R MCL patients in Australia and to compare this to DoT from the 3-year follow-up of the Phase 3 RAY clinical trial.

Method: A retrospective cohort analysis was conducted using baseline patient characteristics. Patient DoT was estimated using the Kaplan-Meier (KM) methodology for both the RAY clinical trial (n=139) and the Pharmaceutical Benefit Scheme (PBS) 10% datasets. Differences in DoT between the PBS dataset and data from the RAY clinical trial were compared using log-rank tests.

Results: Between August 2018 and December 2021, 78 R/R MCL patients in the PBS dataset received treatment with ibrutinib. The median age was 77 years (range: 33-91) with 81% of the cohort being male. The median ibrutinib DoT in the PBS dataset has not been reached, while 12-month persistence was 66% compared to 59% in the RAY dataset. KM curves for DoT for the RAY ibrutinib population versus the PBS population were not statistically different (p = 0.05, HR: 0.62, 95% CI: 0.38-1), however, there was a tendency toward longer DoT in the PBS cohort compared to RAY follow-up study.

Conclusion: These results suggest that DoT with ibrutinib in R/R MCL observed in the RAY study are reproducible in real-world Australian clinical practice.



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Patterns of BTK inhibitor therapy for mantle cell lymphoma in an Australian and UK cohort

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Aim: BTK inhibitors represented a paradigm shift in the treatment of relapsed MCL, providing long periods of disease control compared to cytotoxic therapies. However, with increasing utilisation in combination and in the upfront setting, their optimal use is yet to be defined. We aim to describe the patterns of BTKi use and outcomes.

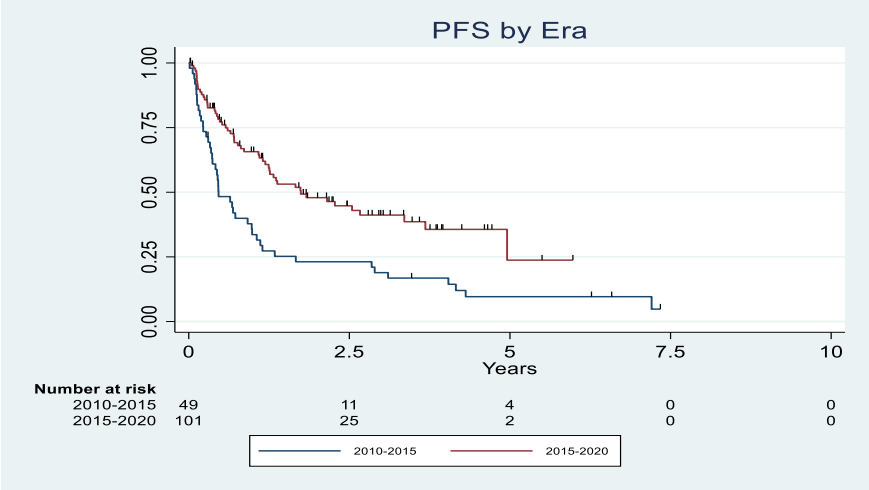
Method: 389 consecutive adult patients with mantle cell lymphoma diagnosed between 1st January 2010 and 1st January 2020 were included from 12 centres in Australia and the UK.

Results: 23 of 362 treated patients (6.4%) received frontline BTKi treatment, all without ASCT consolidation. Frontline BTKi therapy consisted of monotherapy (n=8), or combination with chemoimmunotherapy (bendamustine-rituximab, n=8), monoclonal antibody (rituximab, n=6) or targeted therapy (venetoclax, n=1). Frontline BTKi resulted in median PFS of 2.6 years (95%CI 0.74-NR) and median OS was not reached (95% CI 2.03-NR) at median follow up of 3.9y.

170 frontline treated patients experienced relapse, with 150 (88%) receiving a subsequent line. Second-line treatment consisted of a BTKi containing regimen in 95 patients (63% of treated patients); 70 as monotherapy and 25 in combination. Combination treatments consisted of venetoclax n=18, chemotherapy n=6, and durvalumab n=1. BTKi therapy in the second line demonstrated median PFS of 1.36y (95%CI 1.0-2.7) and OS of 2.5y, largely consistent with other real-world cohorts. BTKi use in second-line was infrequent prior to 2016 (15/50 treated patients (30%)) while forming the majority of second-line therapy after 2016 (75/100 treated patient (78%)). PFS was significantly longer in patients treated in the later era (median 1.74y (95%CI 1.2-3.4) v. 0.46y (95%CI 0.4-1.0); p<0.001) (Figure 1). 12 patients received a BTKi in third or subsequent line.

Conclusion: This large Australian and UK cohort demonstrates significant uptake of BTK inhibitors, predominantly in the second line. Increasing use was associated with significant improvement in PFS. Further analyses, including multivariate comparisons, will be presented.

Figure 1.



CLIPPERS, HLH and lymphoma: fortuitous relationship or unrecognised association?

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Aim: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a rare and poorly understood neuroinflammatory condition. Whilst originally thought to be a benign entity, more recent case reports have suggested CLIPPERS may represent a pre-malignant state, a paraneoplastic syndrome or an inflammatory condition secondary to an immunological trigger, alike haemophagocytic lymphohistiocytosis (HLH). In addition to its association with a variety of non-haematologic conditions, CLIPPERS has been described as preceding diagnoses of cerebral lymphomatoid granulomatosis, systemic lymphoma and primary central nervous system lymphoma.

We report the first case of CLIPPERS, haemophagocytic lymphohistiocytosis and Hodgkin lymphoma all occurring in the same patient.

Results: A 56-year old woman presented with six weeks of progressive neurological symptoms. Following extensive radiological, serological and cerebrospinal fluid investigations a clinicoradiological diagnosis of CLIPPERS was confirmed in the absence of cerebral biopsy due to disease location in the brainstem. A characteristic clinical and radiological response to high-dose corticosteroids further reinforced the diagnosis although disease relapse eventually necessitated steroid sparing immunosuppression.

Twenty-five months following the diagnosis of CLIPPERS our patient presented with high-grade fevers and pancytopenia, with bone marrow examination and biochemistry consistent with HLH (HScore 279, >99% probability HLH). Sacral biopsy of an FDG-PET avid lesion led to a histologically challenging diagnosis of stage IVB classical Hodgkin lymphoma.

The patient had a partial response to two cycles of ABVD chemotherapy and progressive disease following her fifth cycle. The HLH resolved following commencement of chemotherapy but CLIPPERS symptoms progressed concurrently with her lymphoma. The patient suffered an unexpected and fatal intracerebral haemorrhage during her first cycle of salvage chemotherapy.

Conclusion: The relationship between CLIPPERS, HLH and haematologic malignancy remains unclear but there is increasing evidence that these entities co-exist and may be biologically related. Our case supports the hypothesis that CLIPPERS represents a form of CNS immune dysregulation, most likely an HLH-like syndrome in response to an underling immunologic trigger of which lymphoma can be a precipitant.

The integration of Biobanking as standard practice across a range of haematological malignancies in the Australian private healthcare setting

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Aim: Biobanks are essential tools for researching risk factors that underlie complex diseases, including cancer. The Molecular Oncology and Cancer Immunology (MOCI) Biobank Study at Epworth HealthCare is a repository of biospecimens and clinical information of participants from a variety of clinical backgrounds. As such, the primary aim of this study is to maintain a resource to facilitate ethically approved research studies to discover new ways to treat, monitor and prevent diseases with the overarching goal of developing a foundation for improved personalised medicine.

Method: This is a single site, multi-centre study across Epworth HealthCare's 11 sites in Victoria. Once a patient is referred by a clinician, a clinical research coordinator obtains informed consent and collects biospecimens and clinical information. Samples are then processed within two hours of collection and stored onsite, data is securely entered and maintained online. Ethically approved project proposals are submitted to Epworth MOCI to recall biospecimens and/or data for future research.

Results: To date, 368 participants have consented and donated biospecimens to the MOCI Biobank Study. The Biobank currently holds over 6,000 aliquots from both haematological (95%) and solid organ (5%) malignancies. Notably, a wide array of haematological malignancies are represented, from B- and T-cell lymphoproliferative disorders (42%) to plasma cell dyscrasias (23%) and myeloid disorders (35%). Biospecimen types collected thus far include whole blood, plasma, serum, buffy coat, PBMCs, bone marrow and tumour tissue.

Conclusion: Epworth MOCI has successfully established and maintained a substantial Biobank containing samples and clinical information from a range of patients across numerous haematological malignancies, which are readily available for future collaboration with both internal and external researchers. Such collaboration will add value to the investigation of haematological malignancies and promote the pursuit of personalised medicine.

Impact of BTKi use in haematologic malignancies on inflammatory response signatures

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Aim: Bruton's tyrosine kinase inhibitors (BTKi) used in the treatment of lymphoid malignancies affect immune pathways, including immune cell activation, differentiation, and survival. This research aims to understand changes in the haematological landscape caused by BTKi therapy by characterising inflammatory signatures of BTKi-treated oncohaematological patients, which may reveal potentially targetable pathways for infections.

Method: Pre- and post-BTKi treatment plasma from 20 diffuse large B-cell lymphoma (DLBCL) patients from the ALLG NHL29 trial and 20 chronic lymphocytic leukaemia (CLL) non-trial patients from Canberra and Melbourne were obtained along with 10 healthy controls. Immune markers were analysed using a human 48-multiplex kit. Statistical analysis included non-parametric comparisons between cases and controls, pre- and post-treatment, and between lymphoma subtypes.

Results: Using a 95% confidence level, sCD40L, EGF, fractalkine, G-CSF, IFNy, IL-1a, IL-4, IL-7, IL-12p70, IL-13, IL-17F, MCP-3, PDGF-AB/BB, TGFa, lymphotoxin-alpha, and VEGF-A were lower in the BTKi cohort at baseline compared to controls. IL-10, IL-18, IL-27, IP-10, MIG, MIP-1b, and PDGF-AA were higher in BTKi-treated patients at baseline compared to controls. BTKi treatment affected inflammatory signatures, with IL-10, MDC, and MIP-1b higher during treatment than at baseline. In contrast, IL-27, MIG, and PDGF-AB/BB were higher at baseline than on-treatment. At end-of-treatment, IL-10 and MIP-1b were reduced compared to baseline. Stratification by pre- and post-treatment survival revealed G-CSF, IL-4, PDGF-AA, and PDGF-AB/BB as markers of significance.

Response to BTKi therapy was associated with higher baseline M-CSF and MIP-1b compared to patients with no response. Compared to all others, patients with complete response to treatment displayed lower on-treatment IFNa2, IL-8, IL-27, and MDC.

Conclusion: These results contribute to our understanding of the inflammatory landscape in lymphoma with potential impacts on development of therapeutic targets, and reveal the effects of BTKi on inflammatory signatures. The significant post-BTKi reductions in IL-10 and MIP-1b need confirmation in larger studies.

Haemophagocytic lymphohistiocytosis and subcutaneous panniculitis-like T cell lymphoma unmasked by mRNA COVID-19 vaccination

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Aim: Haemophagocytic lymphohistiocytosis (HLH) is an inflammatory disorder with immune dysregulation and cytokine release, described in a number of inherited and acquired conditions. Diagnostic challenges remain due to disease rarity, severity, multiorgan involvement and variety of triggers. There are emerging reports of COVID-19 vaccination triggering HLH, and awareness of this condition is important to improve patient outcomes.

Case Report: A 34 year Samoan man had multiple admissions with fevers and rigors, night sweats, myalgia, and fatigue following the second dose of the BNT162b2 COVID-19 vaccination. Infectious screen was non-revealing. He was diagnosed with vaccine-related myocarditis. CT showed abdominal wall and mesenteric fat stranding and subcutaneous tissue infiltration, although initial investigations were non-diagnostic for HLH or lymphoma. He underwent further investigations, including PET imaging, bone marrow biopsy, and multiple tissue biopsies without a definitive diagnosis. He developed progressive cytopenias, coagulopathy, and deranged biochemistry, with an eventual diagnosis of HLH made based on fever, splenomegaly, hypertriglyceridaemia / hypofibrinogenaemia, hyperferritinaemia, and haemophagocytosis on repeat marrow biopsy, with confirmation from markedly elevated sCD25 level. Due to his deteriorating condition, HLH-specific treatment was initiated prior to diagnosis of lymphoma. The diagnosis of subcutaneous panniculitis-like T cell lymphoma (SPTCL) was protracted due to inadequate biopsies which lacked subcutaneous tissue, and polyclonal T cell receptor gene rearrangement and without clonality, with the need to demonstrate *HAVCR2* germline mutation.

Conclusion: The development of HLH in this patient appears to be temporally related to COVID-19 vaccination, and associated with cutaneous T cell lymphoma (SPTCL). A causal link between vaccination, HLH, and SPTCL has not been defined, but the latter two entities are linked with accelerated inflammation. Identification of the mechanisms of inflammation may lead to potential treatment strategies in the future. This case also illustrates the challenges with timely diagnosis of HLH and cutaneous T cell lymphoma.

A case of Extra Nodal NK/T Cell Lymphoma, Nasal Type

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Aim: The aim is to demonstrate the diagnosis and clinical sequelae of a rare, aggressive lymphoma

Method: A retrospective review of the diagnostic process and clinical management of a case of extranodal NK/ T cell lymphoma, nasal type. Information was obtained from the medical record.

Results: A 24 year old male presented with bulky cervical lymphadenopathy and haemophagocytic lymphohistiocytosis (HLH). A CT/ PET scan demonstrated stage 4 disease with extensive lymphadenopathy above and below the diaphragm, SUV max up to 24.9, and extranodal involvement of the left nasal and paranasal sinuses, spleen, lung, adrenal glands, kidney and liver. A core biopsy of a left cervical lymph node demonstrated a diffuse infiltrate of large cells with nuclear enlargement and areas of necrosis and apoptotic debris. These cells were positive for CD3, CD30, EBER ISH, Granzyme B and TIA1 and weak for CD56. Ki67 approached 100%. This was consistent with a diagnosis of Extranodal NK/T cell lymphoma, nasal type. Flow cytometry of the lymph node biopsy demonstrated a population in the monocyte region that expressed CD2+/ CD7+ / CD16+ and CD56+ and was negative for CD3 and CD5. CSF and the Bone Marrow aspirate and trephine were not involved at diagnosis. The patient was started on Brentuximab, Doxorubicin, Vincristine, Etoposide, Cyclophosphamide and Prednisolone (BV-CHEOP) and had progressive disease after two cycles with increasing lymphadenopathy and recurrence of HLH. For second line therapy he was commenced on Cisplatin, Dexamethasone, Gemcitabine and Pegaspargase (DDGP). After two cycles, he demonstrated progressive disease with clinical features of cerebellar dysfunction, auditory hallucinations and status epilepticus. Repeat CSF demonstrated lymphoma involvement and circulating lymphoma cells were seen on the peripheral blood film.

Conclusion: This case demonstrates the clinical and pathological features of a rare, aggressive lymphoma.

Population-wide patterns of care in mantle cell lymphoma (MCL) in Australia: An analysis of the Pharmaceutical Benefits Scheme (PBS) dataset

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Aim: The MCL treatment landscape in Australia is changing with the introduction of Bruton's tyrosine kinase inhibitors (BTKis) and bendamustine. This study analyzed the practice impact of introducing publicly funded novel agents for MCL by evaluating MCL treatment patterns in Australian patients from 2011-2021 using population-wide prescription records.

Method: Patients who initiated MCL treatment from 01Jan2011-31Jul2021 were extracted from the Services Australia 10% PBS dataset, which includes dispensing records for 10% of the Australian population and captures all publicly funded treatments in Australia. The index date was the commencement of any drug for MCL. First-line (1L) therapy was the first prescribed MCL treatment. A patient was defined as relapsed/refractory (R/R) if they commenced a drug in a different therapeutic category, or restarted a regimen after a >180-day gap. Descriptive analyses were conducted to examine treatment use for the overall 10-year population by therapy line. Analyses by calendar year were performed to assess treatment pattern changes.

Results: 241 patients with MCL were identified; majority were male (68.4%) and > 60 years (84.9%; 70-79 years=42.1%). Baseline comedications included antihypertensives (44.1%), anticoagulants (14.5%), and/or antipsychotics/antidepressants (12.5%). In the overall population (2011-2021), most 1L treatments were bendamustine-rituximab (BR, 53.9%), rituximab+other regimens (27.6%), or rituximab monotherapy (11.2%). The most common regimens for R/R patients included BTKis (66.3%), rituximab monotherapy (52.8%), or rituximab+other regimens (31.5%). A trend in adoption of novel agents was observed throughout the years following PBS listing. From 2011-2020, 1L BR use increased from 0% to 50% while 1L use of all other rituximab-containing regimens decreased from 100% to 16.7%; BTKi use in R/R patients increased from 0% to 74.7%.

Conclusion: Australian MCL treatment patterns have changed significantly since the introduction of BTKis and bendamustine-containing regimens. Use of 1L rituximab-containing regimens except BR has decreased and BTKi use in R/R patients has increased.

BRAF-V600E inhibition with low dose vemurafenib in an elderly patient with relapsed/ refractory (R/R) hairy cell leukaemia (HCL): a case report

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Aim: Classical HCL is a rare indolent mature B-cell malignancy with the molecular signature of BRAF-V600E mutation. In the setting of R/R disease, combination therapy with oral BRAF-V600E kinase inhibitors and rituximab has been an appealing chemotherapy-free approach. We report the case of a patient with R/R HCL and prior life-threatening infections treated with third line low dose vemurafenib monotherapy during the coronavirus (COVID-19) pandemic.

Method: An 88-year-old male with prior R/R HCL complicated by severe infections presented with progressive cytopenias suggestive of relapse. He had constitutional symptoms and delayed wound healing for a total hip replacement that was otherwise successful. ECOG 0. He was the primary carer for his cognitively impaired wife. Imaging confirmed recurrent splenomegaly.

This occurred on a background of cryptococcal meningitis leading to his diagnosis and treatment of classical HCL in 2010 with cladribine, and life-threatening invasive aspergillosis after reinduction cladribine following relapse in 2016.

Peripheral blood film revealed atypical lymphocytes with cytoplasmic projections and immunophenotyping confirmed relapsed HCL with a small B-cell population co-expressing CD11c/CD25/CD103/CD123. BRAF-V600E mutation was confirmed using digital droplet PCR (ddPCR).

The patient commenced low-dose vemurafenib monotherapy (240mg twice daily) without rituximab after considering his advanced age, prior infections, heavy purine-analog pre-treatment, location in regional NSW, the evolving COVID-19 pandemic and his role in his family.

Results: The patient achieved haematological CR within three months of therapy which he still maintains at last follow-up (7 months) with minimal toxicity.

Conclusion: Low dose oral vemurafenib has been successful in our elderly, pre-treated, immunocompromised patient with R/R HCL. Further clinical trial evaluation is required.

Pralatrexate and total skin electron beam therapy as bridging agents to allogeneic stem cell transplantation for refractory Sézary syndrome

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Aim: Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma (CTCL), characterised by the accumulation of malignant CD4+ T-lymphocytes in skin. Sézary syndrome (SS) is the leukaemic variant of MF, constituting 5% of CTCL cases, with patients typically presenting with peripheral blood involvement of Sézary cells, lymphadenopathy, and erythroderma. Management of advanced-stage MF and SS remains challenging and requires systemic treatment, with current therapies often lacking durable response.

Method: N/A

Results: We describe a gentleman in his 40's with heavily pre-treated relapsed/refractory Sézary Syndrome that achieved disease control with bridging pralatrexate prior to allogeneic stem cell transplantation.

Conclusion: In suitable candidates, pralatrexate in combination with skin-directed therapies may be an option to bridge treatment refractory patients over to alloSCT.

Cellular and cell-free genomic analysis of hairy cell leukaemia

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Aim: The genomic landscape of hairy cell leukaemia (HCL) beyond the *BRAF* Val600Glu mutation has only been explored in a limited number of studies. We sought to further understand the molecular pathogenesis of HCL and to assess the utility of plasma cell free DNA (cfDNA) for HCL disease monitoring.

Method: Sequence variants, whole genome copy number variation and structural variants were assessed in 9 diagnostic and 2 relapsed HCL samples using a custom Agilent SureSelect panel targeting 365 genes recurrently mutated in haematological malignancy. NGS IGHV mutational analysis was performed on 9/11 samples. Sensitive *BRAF* Val600Glu ddPCR was performed on 26 paired peripheral blood and cfDNA samples.

Results: A *BRAF* Val600Glu mutation was identified in 9/11 patients. One patient with relapsed HCL harboured a non-canonical *BRAF* mutation (Asn486_Pro490del) and no detectable *BRAF* Val600Glu mutation. Mutated genes in addition to *BRAF* included *DIS3*, *EGR1*, *IGLL5*, and *LTB*. Copy number analysis demonstrated gain of 3q and loss of 21q in one patient and structural variant analysis identified a novel IGH translocation t(2;14) potentially targeting *TRIB2,* a gene associated with the MAPK pathway. The majority of patients (6/8) were classified as IGHV-mutated status. Analysis of *BRAF* Val600Glu mutation by ddPCR identified four cases where the mutation was detectable in the cellular blood sample but not in the corresponding paired cfDNA sample. Three paired samples had *BRAF* Val600Glu mutations detectable in both cellular blood and cfDNA. There were no cases where *BRAF* Val600Glu mutations were only detectable in cfDNA and not in the cellular blood sample.

Conclusion: We have identified novel genomic aberrations in a cohort of patients with HCL through comprehensive genomic profiling, further contributing to the understanding of this disease. Our data suggests that HCL is not highly represented in the cfDNA compartment, which has implications for disease monitoring using this approach.

MDS (Poster Board No H083 – H085)

10-year multi-centre review of real-world myelodysplastic syndrome outcomes from Victorian hospitals in the Azacitidine-only era

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Aim: Standard of care for Australians diagnosed with myelodysplastic syndrome(MDS) in the last decade has been limited to azacitidine for PBS-eligible patients. Promising preliminary results from novel agents such as venetoclax, magrolimab and sabatolimab have brought new hope, with randomised trial outcomes awaited. However, these trials represent a highly selected cohort. We aim to study real-world practice and outcomes of adults with MDS across transplant/tertiary(H-City) and non-transplant/outer-suburban(H-Sub) hospitals, and identify barriers impacting outcomes.

Method: Retrospective review of adult patients with newly-diagnosed MDS at the Northern(H-Sub), Western(H-Sub) and Alfred(H-City) Hospitals in Victoria between 2010-2021.

Results: 384 patients(222;58% H-Sub) were identified. Median follow-up was 50months(mo). Median age was 75years(22-101). Overall survival(OS) based on IPSS was 56, 41, 19 and 14mo for low, intermediate-1, intermediate-2, high risk, respectively. Key predictors of OS were age, Charlson Comorbidity Index(CCI), IPSS, performance status, allograft and hospital. Only age, CCI, IPSS retained statistical significance on multivariate analysis. Most frequent causes of death included infections(29%), acute leukaemia(24%) and cytopenia-related complications(16%). There was significant healthcare utilisation with 49% of patients transfusion-dependent, 76% with □1 hospital admission(median 3 admissions, median 27 total admission days).

OS was inferior for H-Sub compared to H-City(p=0.05). Notably, H-Sub patients were older (median age 77vs72), had higher proportions of overseas-born(59%vs46%), non-English-speaking(30%vs14%) patients, higher comorbidity burden(p<0.001) and worse performance status(p<0.001). CCI significantly impacted on outcome: median OS was 53mo, 36mo and 14mo for scores 0-3, 4-7 and ≥8 respectively(p<0.005).

Of 148 patients eligible for PBS-Azacitidine, 108(73%) received treatment: allograft(12; 9 from H-City), azacitidine(53), clinical trial(30) and lenalidomide(8). Trial participants were more likely from H-City(26%vs10%, p<0.05) and English-speaking(p=0.05).

Conclusion: Our real-world analysis highlights an older and more comorbid population in outer-suburban hospitals, which may have impacted on eligibility/access to transplant/trial and poorer outcomes. This review provides a retrospective benchmark that may be used for future evaluations of MDS therapies in Australia.

Morphological descriptions of dysplasia used in bone marrow biopsy reports for classification of myelodysplastic syndrome (MDS): Report from the Australian MDSLink registry

Dr Marsali Maclean[1], Dr Linda Saravanan[1]
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Title: Morphological descriptions of dysplasia used in bone marrow biopsy reports for classification of myelodysplastic syndrome (MDS): Report from the Australian MDSLink registry

Aim: Myelodysplastic syndromes (MDS) are heterogeneous disorders which require accurate description of bone marrow morphology for diagnosis and classification. Standardised classification is also important for research purposes, including registry analysis. Morphological reporting is subject to significant inter-observer variation. This audit aimed to identify the most common descriptors of dysplasia used within bone marrow biopsy reports of MDS patients entered into the MDS*Link* registry[1] and to evaluate adherence to WHO criteria.[2]

Method: Qualitative and quantitative audit performed on 60 bone marrow biopsy reports entered into the MDS*Link* Registry RedCap platform.[1]

Results: Dyserythropoiesis was described only within the aspirate, with the most common terms being 'abnormal or patchy haemoglobinisation' (n=36), 'nuclear-cytoplasmic asynchrony' (n=31) and 'multinuclearity' (n=24). The two most commonly used terms are not included in WHO criteria[2]. Dysmegakaryopoiesis was most frequently described as 'nuclear hypolobation' (n=33 in aspirates; n=41 in trephines), a standardised WHO description; however 'small' (n=22 in aspirates; n=25 in trephines) and 'nuclear dispersion' (n=25 in aspirates; n=18 in trephines) were frequently used and are not standardised WHO descriptions[2]. In contrast, descriptions of dysgranulopoiesis within the aspirate were almost entirely in keeping with WHO, with the most common features described being 'hypogranularity' (n=40) and 'nuclear hyposegmentation' (n=25).[2] However trephine descriptions frequently employed the non-standardised term of 'abnormal localisation of immature precursors (ALIPs)' (n=15).

Conclusion: This audit confirms common use of descriptive terms of dysplasia that are not strictly recognised in standardised WHO criteria. This was observed most frequently in the erythroid lineage, in keeping with previously published literature.[3] This audit comprised a small sample size from just two sites, limiting the number of reports and pathologists audited. However, these data should encourage haematopathologists to ensure adherence to published guidelines to enable objective, accurate and reproducible bone marrow assessment.

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VEXAS syndrome- a recent retrospective diagnosis with challenges in treatment- a case report

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VEXAS syndrome is a newly discovered adult onset syndrome that link haematological and autoimmune symptoms. The first description of VEXAS was published in NEJM in December 2020. VEXAS- Vacules, E1 enzyme, X-linked, autonflammatory, somatic

Case: We report a case of a 69 year old man, who was known to our institution's Rheumatology department since 2019 for relapsing polychrondritis. He also had a diagnosis in 2016 of Interstitial lung disease known to the Respiratory team. He was on immunosuppression including prednisolone, methotrexate and colchicine when he developed macrocytic anaemia and mild thrombocytopenia.

A bone marrow biopsy performed in June 2020 revealed evidence of dysplasia deemed not sufficient to diagnose MDS especially in the setting of methotrexate use.

Following the discovery of VEXAS syndrome, in July 2021 in the setting of difficult to control polychronditis and worsening cytopenia the bone marrow biopsy was repeated and the morphology was suggestive of VEXAS with myeloid vacuolization. (figure 1).

This was then confirmed on molecular testing with somatic mutation in UBA1 gene.

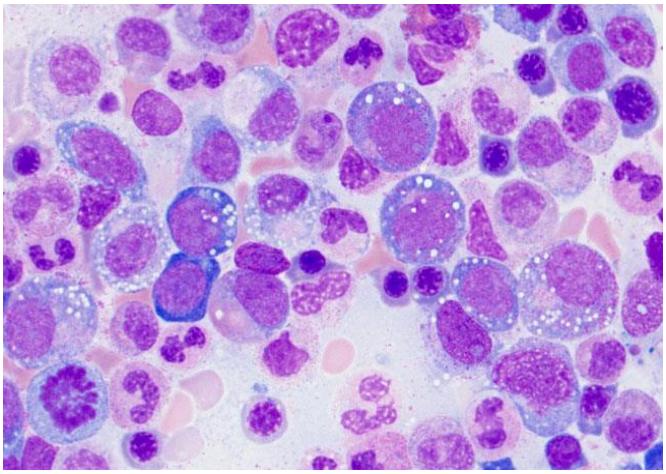
He was treated with prednisolone and tocilizumab and continued to have aggressive flares of his autoimmune condition including vasculitis involving the skin. Steroid withdrawal was challenging and lead to significant myopathy and infections.

In an attempt to reduce steroid dependence 1 cycle of azacytidine was delivered. However there was no clinical improvement the patient died to infection and complications related to staphylococcus aureus bacteraemia 12 months following the diagnosis of VEXAS syndrome.

Discussion: This case highlights the importance of having an awareness for VEXAS and working in collaboration with our Rheumatology colleagues to identify , test and treat VEXAS syndrome. It is too early to determine the actual prevalence of this syndrome.

Patients often have symptoms for several years prior to the diagnosis and the long term prognosis appears poor, such as in this case.

Figure 1: Bone marrow aspirate x60 objecti



MPD (Poster Board No H086 – H093)

Loss of TCF3 regulation is associated with bone marrow fibrosis in myeloproliferative neoplasms.

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Aim: Progression to myelofibrosis (MF) in myeloproliferative neoplasms (MPN) is characterised by morphological and genetic abnormalities in megakaryocytes. Megakaryocytic dysregulation of transcription has been identified as a high-risk molecular trait in patients that progress to MF. We aimed to assess genomic and proteomic changes in DNA transcription regulator *TCF3,* in both megakaryocytes and platelets, from MPN patients.

Method: Megakaryocyte mutations from 41 MPN patients (essential thrombocythemia (ET)/polycythemia vera (PV)=30, MF=11) were analysed using a targeted 120-gene myeloid panel and prioritised for non-synonymous variants predicted to change protein function. Platelet mRNA expression was quantified from 55 MPN patients (ET/PV=43, MF=12) and nine controls, using transcriptomic next-generation sequencing. Platelet proteomic quantification of 31 MPN patients (ET/PV=22, MF=6) and three controls was obtained using data-independent acquisition method SWATH-MS (Sequential windowed acquisition of all theoretical fragment ion-mass spectra). To verify subsequent findings, we performed immunohistochemistry on megakaryocyte *in-situ* sections, totalling 69 MPN (ET=25, PV=15, MF=18) patients and six controls.

Results: An odds-ratio analysis of the megakaryocyte gene variants in MF compared to ET/PV revealed *TCF3* to have the highest odds-ratio, with mutations in *TCF3* being associated with 10.9-times increased likelihood of MF (95% C.I. 0.99-199.2). Upon further analysis, four *TCF3* variants (MF=3, PV=1), were assessed to have pathogenic potential according to the MutationTaster2 mutation prediction software.1 Ingenuity pathway analysis using platelet gene (z=-1.163, padj=2.09×10-7) and protein (z=-2.236, padj=1.20×10-3) expression data predicted *TCF3* to be inhibited in MF (but not ET/PV), in concordance with the megakaryocyte mutation data. Further, downstream prognostic genes that regulate cell-cycle progression (*AURKA, CCND1* and *MYC*) are upregulated as a result. Immunohistochemical analysis found elevated TCF3 megakaryocyte positivity in MF (padj=0.003), ET (padj=0.032) and PV (padj=0.046) respectively, compared to controls.

Conclusion: DNA mutation, dysregulated platelet gene and protein expression analyses suggest *TCF3* has a central role in transcriptional dysregulation of megakaryocytes associated with MF progression.

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Ruxolitinib for the treatment of polycythemia vera (PV) in patients resistant to or intolerant of hydroxyurea: a retrospective non-interventional study using the US Optum electronic health record data source

Ms Amy Gye[1], Mr Rudolf Schrover[2], Dr Asif Siddiqui[3], Dr Christina Gkitzia[3], Dr Lucy Connolly[4]
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Aim: Treatment of patients with PV is focused on reducing the risk of thrombotic events (TEs) and minimising the risk of transformation to myelofibrosis or acute myeloid leukaemia. Ruxolitinib (RUX) is an inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 indicated for adult patients with PV resistant to or intolerant of hydroxyurea (HU). In the RESPONSE and REPONSE-2 trials, treatment with RUX significantly reduced elevated haematocrit (HCT) versus best available therapy (BAT), however, the effect of RUX on improving longer-term outcomes, including risk of TEs has not been demonstrated. The objective of this analysis was to identify a sub-group of patients at higher risk of TEs and estimate the benefit of RUX in reducing risk of TEs in this population.

Method: Patients with PV in the US Optum Electronic Health Record between April 2007 and June 2019 resistant to or intolerant of HU, according to modified European Leukemia Net criteria (HCT ≥ 45% with phlebotomy, or platelet count > 400 x 109/L and presence of palpable splenomegaly) were included. Patients were risk stratified using classification and regression tree (CART) analysis. Crude incidence rates (IR) for RUX were compared to BAT for the outcome of TEs.

Results: A total of 1,576 patients met the eligibility criteria (BAT, N=1,367; RUX, N= 209). Patients with lymphocyte counts ≥ 7.85 and HCT ≥ 51.55% were at higher risk of experiencing a TE (≥ 1 per year; Figure 1). In this higher-risk subgroup, the IR of TEs was significantly lower in the RUX group (165.26) versus BAT group (304.08) during the study period.

Conclusion: In patients with PV who are resistant to or intolerant of HU, risk stratification can identify patients at higher risk of TE. The analysis showed that in this higher-risk population, patients treated with RUX experienced fewer TEs versus BAT.

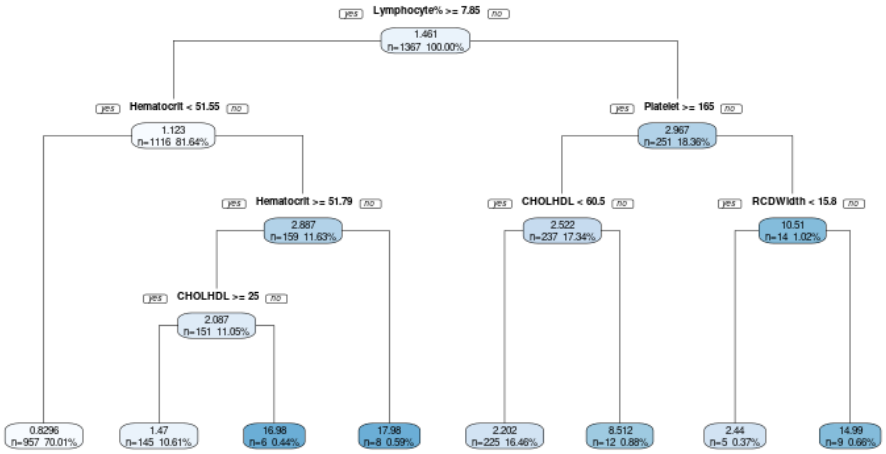

Figure 2 Classification and regression tree (CART) model using thromboembolic event codes consistent with RESPONSE for the best available therapy (BAT) group

Biomarker analysis in patients with steroid-refractory/dependent chronic graft-vs-host disease treated with ruxolitinib or best available therapy in the randomized phase 3 REACH3 study

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Aim: To assess whether baseline levels of proinflammatory cytokines, chronic graft-vs-host disease (GVHD) biomarkers, and immune cell subsets were predictive of response to treatment in the exploratory analysis of REACH3.

Method: Patients aged ≥12 years with moderate or severe steroid-refractory/dependent chronic GVHD were randomized 1:1 to receive ruxolitinib 10 mg twice daily (n=165) or investigator-selected BAT (n=164). A total of 316 patients had valid biomarker levels at baseline.
Blood samples were collected at baseline, cycle 1 day 1 [C1D1], C1D8, C1D15, C2D1, and C7D1.
Biomarkers assessed are summarized in **Table 1**.
Patients were stratified by response (complete response [CR], partial response [PR], no response [NR]) to ruxolitinib or BAT at C7D1; biomarker levels were assessed by disease severity and key patient characteristics, including organ involvement at screening and history of acute GVHD.
Changes in biomarker levels over time were analyzed using ANOVA methods.

Results: In patients with steroid-refractory/dependent chronic GVHD, baseline levels of proinflammatory cytokines, chronic GVHD disease markers, and immune cell markers did not predict overall and organ-specific responses, regardless of disease severity. Given the heterogeneity of chronic GVHD, the predictive value of these biomarkers was assessed while accounting for the impact of patient baseline characteristics on biomarker expression. Most findings were consistent with the prior analysis; however, among patients with baseline gastrointestinal involvement, those with lower baseline levels of Reg3A, a marker indicative of gastrointestinal involvement in acute GVHD, were more likely to respond to ruxolitinib treatment than patients with higher baseline Reg3A levels (**Figure 1**). No substantial changes in most biomarker levels were observed over time in either treatment arm.

Conclusion: This analysis underscores the heterogeneity and complexity of chronic GVHD and suggests that, although known blood biomarkers are of limited value for predicting treatment response, patients might derive benefit from ruxolitinib treatment regardless of their baseline inflammatory biomarker level

Ruxolitinib demonstrates a greater corticosteroid-sparing effect than best available therapy in patients with corticosteroid-refractory/dependent chronic graft-vs-host disease

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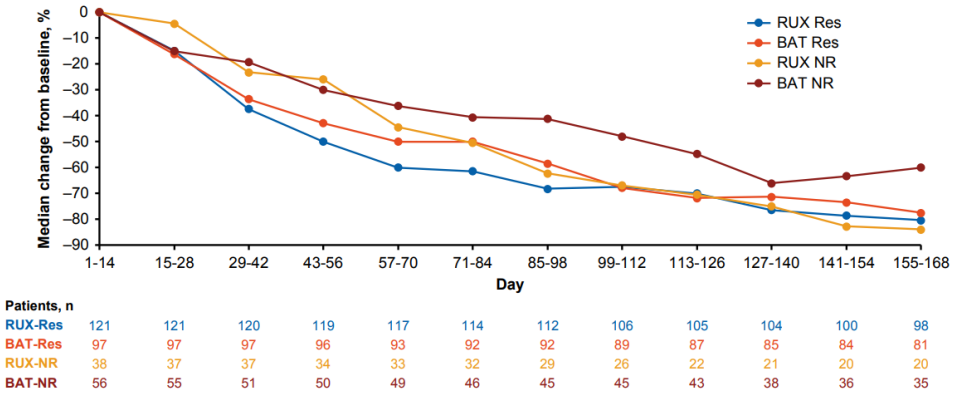
Method: Patients aged ≥12 years with moderate/severe SR/D cGVHD were randomized 1:1 to receive either ruxolitinib 10 mg twice daily (n=165) or investigator-selected BAT (n=164) along with corticosteroid (prednisone or equivalent) ± calcineurin inhibitor for 24 weeks. In this post hoc, descriptive analysis, changes in corticosteroid use over time (baseline–week 24) were analyzed by treatment and best overall response (BOR; responders vs nonresponders).

Results: Baseline characteristics, including BMI and corticosteroid dose, were generally balanced between groups. Median corticosteroid dose decreased over time in both treatment groups but a trend towards a greater decrease in the median percentage decrease from baseline in corticosteroid dose over time was observed in the ruxolitinib group, particularly in ruxolitinib-responders (Figure).
A similar proportion of ruxolitinib-treated and BAT-treated patients achieved a ≥50% reduction from baseline in corticosteroid dose at any time (81.2% [134/165] vs 79.9% [131/164]); this proportion was similar between responders (Table). The median (95% CI) time to ≥50% reduction in corticosteroid dose was1.9 months (1.4-1.9 months) in ruxolitinib-treated patients vs 2.4 months (1.9-2.8 months) in BAT-treated patients.
The proportion of patients who achieved a corticosteroid dose of ≤7.5 mg/day at any time was higher with ruxolitinib vs BAT (71.5% [118/165] vs 61.6% [101/164]). Corticosteroid discontinuation rates were higher with ruxolitinib vs BAT (48.5% [80/165] vs 35.4% [58/164]).

Conclusion: Ruxolitinib led to a larger reduction in corticosteroid dose vs BAT, with a greater proportion of ruxolitinib-treated patients discontinuing corticosteroids. Median decreases in corticosteroid dose were similar among ruxolitinib-treated patients, regardless of response. Future studies, with specific endpoints that measure corticosteroid-free remission, are warranted.

Figure. Median Percentage Change From BL in CS Dose by BOR



Patients, n												
RUX-Res	121	121	120	119	117	114	112	106	105	104	100	98
BAT-Res	97	97	97	96	93	92	92	89	87	85	84	81
RUX-NR	38	37	37	34	33	32	29	26	22	21	20	20
BAT-NR	56	55	51	50	49	46	45	45	43	38	36	35

BAT, best available therapy; BL, baseline; BOR, best overall response; CS, corticosteroid; NR, nonresponder; Res, responder; RUX, ruxolitinib.

Table. Changes in CS at any time, by BOR

	RUX Res (N=126)	NR (N=39)	BAT Res (N=99)	NR (N=65)
≥50% reduction from baseline in CS dose, %	81.7	79.5	86.9	69.2
CS dose of ≤7.5 mg/day, %	69.8	76.9	71.7	46.2
CS discontinuation, %	42.9	66.7	33.3	38.5

BAT, best available therapy; CS, corticosteroids; NR, nonresponder; Res, responder; RUX, ruxolitinib

Patient-reported outcomes (PROs) among patients with steroid-refractory or dependent chronic graft-vs-host disease randomized to ruxolitinib vs best available therapy (an in-depth analysis of REACH3)

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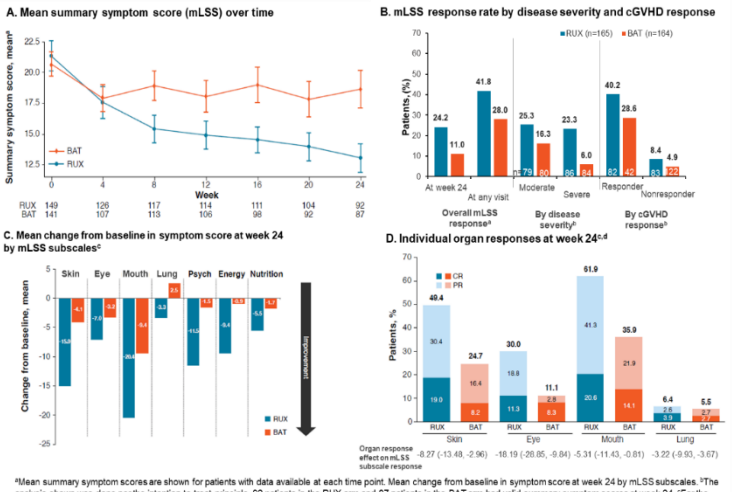
Aim: Ruxolitinib, a selective Janus Associated Kinases 1 and 2 inhibitor, has been approved for the treatment of patients aged ≥12 years with chronic graft-vs-host disease (cGVHD) who have inadequate response to corticosteroids in the US and Europe. In the phase 3 REACH3 (NCT03112603) study, ruxolitinib has demonstrated superior efficacy and improved symptoms vs best available therapy (BAT) at week 24. This analysis assessed the impact of ruxolitinib vs BAT on various PROs in REACH3 (data cutoff: May 8, 2020).

Method: 329 patients aged ≥12 years with moderate-or-severe steroid-refractory or -dependent cGVHD were randomized 1:1 to receive ruxolitinib 10 mg twice daily (n=165) or investigator-selected BAT (n=164) for 24 weeks. Endpoints included the mean cGVHD-specific modified Lee Symptom Scale (mLSS) score, mLSS response (≥7-point reduction from baseline), mLSS response stratified by disease severity and overall disease response, and mLSS subset analysis (including seven subscales: skin, mouth, eye, lung, energy, nutrition, and psychological).

Results: Ruxolitinib led to a rapid and continued reduction in mean mLSS score, whereas only an initial reduction at week 4 was seen with BAT (Figure A). A greater mLSS response rate with ruxolitinib was observed at week 24 (regardless of cGVHD severity) and at any visit up to week 24 (Figure B). Among patients achieving a complete or partial cGVHD response, those receiving ruxolitinib were more likely to have an mLSS response vs BAT (40.2% vs 28.6%, respectively). Greater mean reductions in mLSS were achieved with ruxolitinib vs BAT across all organ subscales (Figure C). Greater improvements in organ-specific subscales corresponded with higher objective cGVHD responses in the respective organ in both arms (Figure D).

Conclusion: In REACH3, ruxolitinib treatment led to greater reductions in symptom burden (mLSS) vs BAT, regardless of disease severity. An organ cGVHD response at week 24 was predictive of mLSS subscale response.



[a]Mean summary symptom scores are shown for patients with data available at each time point. Mean change from baseline in symptom score at week 24 by mLSS subscales. [b]The analysis shown was done per the intention-to-treat principle. 92 patients in the RUX arm and 87 patients in the BAT arm had valid summary symptom scores at week 24. [c]For the analysis pertaining to organs, patients were included if they had both organ response and mLSS data for the specified organ at week 24 and met ≥1 of the inclusion criteria. Skin (RUX n=79; BAT n=73); eye (n=80; n=72); mouth (n=63; n=64); lung (n=78; n=73). For the psychological, energy and nutrition mLSS subscales, change from baseline was calculated for all patients with available data at baseline and week 24 (RUX, n=85; BAT, n=81). [d]Organ response of complete or partial response as documented by investigator at week 24.

A retrospective review of chronic myelogenous leukaemia (CML) treatment and outcomes over a 6-year period at the Peter MacCallum Cancer Centre (PMCC) and Royal Melbourne Hospital (RMH) Clinical Haematology Service

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Aim: to characterise the RMH/PMCC CML cohort outcomes in the era of tyrosine kinase inhibitors where achieving durable deep molecular responses (DMR) and attempting treatment-free-remission (TFR) are key treatment objectives.

Method: Adult patients receiving TKI prescriptions were identified from hospital dispensing records between 2013-2018. Baseline characteristics, treatment details and disease response (ELN criteria) were recorded.

Results: Of 91 patients, 75 had serial BCR::ABL1^{IS} results for response assessment. Patient characteristics are shown in *Table 1*.
1st-treatment: Patients in CP-CML received: IM^ (69.2%), DAS (14.2%), NIL (3.3%), PON (1.1%), HU (2.1%), IFN (2.1%). All AP$^{\#}$ patients received IM. All BP$^{\#}$ patients received IC^ and IM. IM scripts fell 23%, DAS increased 17%, NIL increased 1.6% after October 2011*. 60% achieved major molecular response (MMR) or better (16% MMR, 13.3% MR4, 30.7% MR4.5). 1st TKI median duration: 11.3 months [0.7-151]. *Tables 2-3* show molecular responses(MR).
Changing to 2nd-TKI and 3rd-TKI: 35 patients (47%) changed to 2nd-TKI, n=16 (45.7%) for inadequate MR. 4/14 (28.5%) had kinase domain (KD) mutations. Major AEs causing TKI change: fatigue/myalgias (31%), gastrointestinal(GI, 24%), haematological(16%). 24 patients (32%) changed to 3rd-TKI, 11(45.8%) for inadequate MR/progressive disease. 3/7 patients (42.8%) had KD mutations.
TFR attempts (n=8 of 36 eligible): Median 1st TKI duration 6.6 [3-8] years - IM(4), DAS(2), NIL(2). Median MR4/MR4.5 duration pre-TFR: 59.4 months [36.1-103.4]. 5 were successful. 3 relapsed after a median of 121 days [96-189]. All regained DMR within 6months after restarting same TKI. Survival: Median follow-up duration: 7.7 years [0.83-23.3]. Estimated OS: 87% at 5 yrs, 80% at 10 yrs (all cohort).

Conclusion: This cohort review demonstrates prescribing patterns and clinical outcomes in CML with DAS preferred over NIL for 2nd gen TKI 1st-line treatment. Over a third of patients required TKI change with 46% due to poor efficacy. TFR attempts were infrequent and this requires exploration.

Table 1. Baseline characteristics (n=91)		n (%)
Sex	Male | Female	47 (51.6) | 44 (48.4)
Median age at diagnosis [range], years		54.8 [19.7-89.1]
Disease phase at presentation	Chronic phase (CP) Accelerated phase (AP) Blast phase (BP)	85 (93.4) 2 (2.2) 4 (4.4)
Cytogenetics	t(9:22) alone With additional changes Not available	71 (78.0) 14 (15.4) 6 (6.6)
BCR::ABL1 transcript	b2a2/b3a2 other Not available	79 (86.8) 1 (1.1) 11 (12)
Sokal score	Low (<0.8) Intermediate (0.8-1.2) High (>1.2) Not available	14 (15.4) 30 (32.9) 20 (22) 27 (29.6)
EUTOS	Low (≤ 87) High (>87) Not available	65 (71.4) 9 (9.9) 17 (18.7)
Median number of treatments [range]		2 [1-6]
Comorbidities at time of diagnosis (Note: some patients had ≥ 2 comorbidities)	Cardiovascular Respiratory Endocrine Neurological Renal Active malignancy	32 (34.8) 18 (19.6) 14(15.2) 6 (6.5) 5 (5.4) 4 (4.3)

	Hepatic None	2 (2.2) 15 (16.3)

Table 2: Best molecular response to first treatment according to TKI						
	MMR only	**MR4 only**	**MR4.5**	**Time to MMR**	**Time to MR4**	**Time to MR4.5**
	n (%)			**Median months [range]**		
IM (n=61)	9 (14.6)	6 (9.8)	16 (26.2)	7.1 (2-27)	8.8 [2-53]	17.1 [2-90]
DAS (n=10)	2 (20)	3 (30)	5 (50)	5.3 (2-8)	10.5 [5-16]	13 [5-27]
NIL (n=3)	1 (33.3)	0 (0)	2 (66.7)	3.6 (3-7)	11.5 [5-18]	13.5 [9-18]
PON (n=1)	0 (0)	1(100)	0 (0)	N/A	N/A	N/A

Table 3: Best molecular response for first treatment according to disease phase						
	CP (n=69) (n(%))			**AP/BP (n=6) (n(%))**		
	MMR	**MR4**	**MR4.5**	**MMR**	**MR4**	**MR4.5**
IM	7 (13)	6 (11)	13 (24)	2(33.3)	0 (0)	3 (50)
DAS	2 (20)	3 (30)	5 (50)	-	-	-
NIL	1 (33.3)	0 (0)	2 (66.7)	-	-	-
PON	0(0)	1 (100)	0 (0)	-	-	-
Time to MR months [range]	5 [2-27]	10.8 [2-51]	16 [2-53]	5.5 [3-22]	9.8 [3-15]	10 [5-15]

Footnotes and references:
*2nd generation TKIs for 1st line treatment were listed on the PBS in October 2011
#CP – chronic phase, AP – accelerated phase, BP – blast phase
^ IM – imatinib, DAS- dasatinib, NIL – nilotinib, PON- ponatinib, IFN – interferon, HU – hydroxyurea, IC – induction chemotherapy
+ PBS: Pharmaceutical Benefits Scheme (Australia)
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Application of massively parallel sequencing in B and T cell clonality analysis and minimal residual disease detection

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Aim: Clonality analysis of immunoglobulin and T-cell receptor genes have until recently been predominantly been performed with fragment analysis with limited sensitivity. Massively parallel sequencing (MPS) has afforded improved resolution and depth of information to aid patient management in this testing.

Method: Specimens were analysed for rearranged immunoglobulin heavy chain and T-cell receptor gene by end-point PCR-capillary gel electrophoresis and MPS in parallel. Sequences were analysed with LymphoTrack (InvivoScribe Inc.) reagents on the MiSeq (Illumina) platform. Sequence analyses were performed using LymphoTrack Dx MiSeq Data Analysis Software v2.4.3, LymphoTrack MRD Software v2.0.2, IMGT/V-QUEST v3.5.28 and ARResT/AssignSubsets v10.11.19

Results: MPS clarified ambiguous results obtained from gel electrophoresis with clonal results reclassified as non-clonal. In addition, minimal residual disease detection based on clonal sequence information is now possible. Moreover, chronic lymphocytic leukaemia (CLL) specimens harbouring double clones can be separately analysed, improving prognostication of this patient population.

Conclusion: In summary, MPS is a powerful tool in analysing B and T cell gene rearrangements as part of the diagnostic work up in diseases where neoplastic B or T cells are implicated, prognostication of CLL with double clones and minimal residual disease detection such as post bone marrow transplantation.

Cytogenetic findings in Myeloproliferative Neoplasms (MPN): 2 year data from the Victorian Cancer Cytogenetic Service (VCCS)

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Aim: MPNs including primary myelofibrosis (PMF), polycythaemia vera (PV) and essential thrombocythaemia (ET) are diagnosed by a combination of full blood examination, bone marrow morphology and evidence of clonality in known driver gene(s). Chromosome analysis is integral in prognosticating PMF yet plays a minor role in the diagnosis or prognosis of PV and ET. Here we review the cytogenetic aberrations detected in a cohort of confirmed or suspected MPN.

Method: From 01/Aug/2019 until 31/Jul/2021, the VCCS processed 1171 BM samples; 628 confirmed MPN (161 ET, 144 PV, 208 PMF, 115 post-ET/PV MF), 155 MPN-unclassifiable, 266 with insufficient features for an MPN diagnosis and 122 with persisting eosinophilia. G-banded chromosome analysis on overnight or synchronised cultures and interphase FISH were performed as indicated.

Results: Karyotype analysis was successful in 87.6% of cases. Abnormal karyotype was identified in 20.2% of confirmed MPN cases [8.1% of ET (age-related -Y seen in 38%), 18.1% of PV (trisomy 9 23.1%, del(20q) 19.2%, gain 1q 11.5%), 25% of PMF (trisomy 8 19.6%, del(20q) 19.6%, +9 19.6%), 32.2% of post-ET/PV MF (del(20q) 32.4%, gain 1q 18.9%, del(13q) 16.2%]. Complex karyotype was identified in 9.8% of PMF cases and 16.2% post-ET/PV MF with evidence of clonal evolution in 18.9% of secondary cases. Abnormal karyotype rate in MPN-unclassifiable was 18.0% with non-specific –Y (41.7%) and del(20q) (25%) most common. Abnormality rate was lower in cases with suspected than confirmed MPN cases (6.0% vs. 20.2%; $p<0.0001$). Aberrations were largely non-specific with recurrent myeloid-associated changes seen in 3 cases (1.1%). Clonal changes were identified in 3.3% karyotypes investigating eosinophilia while interphase FISH for rearrangement of *PDGFRA/B* or *FGFR1* was negative in all cases assessed.

Conclusion: Cytogenetic aberrations identified in MPNs are non-specific for a MPN subtype and while vital in PMF prognosis, careful considerations should be made when utilising this limited resource investigating PV, ET and suspected MPNs where molecular markers of clonality may be more informative.

Myeloma (Poster Board No H095 – H125)

Targeting microenvironmental Gremlin1 to prevent multiple myeloma development

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Aim: Multiple myeloma (MM) is a fatal haematological malignancy characterised by clonal proliferation of neoplastic plasma cells (PCs) within a pro-tumoural bone marrow (BM) microenvironment (ME). Our published findings propose a supportive role for BM-ME derived Gremlin1 (Grem1) in MM, as antibody mediated Grem1 neutralisation reduced tumour burden by 81.2% *in vivo*. Grem1 protein staining colocalises with M2 polarised macrophages in crescentic glomerulonephritis; however, it is unknown if Grem1 prevents cancer immunosurveillance. M2-like tumour associated macrophages (TAMs) are abundant within the BM-ME, where they stimulate MM-PC proliferation, chemotherapy resistance and immune evasion. We therefore hypothesise that Grem1 contributes to MM pathogenesis by favouring M2-like TAM polarisation.

Method: To generate macrophages with conditional *Grem1* knockout, BM from n=6 UBC-CreER^{T2};Gremlin1$^{fl/fl}$ mice was cultured with 25ng/mL macrophage colony stimulating factor for 6-days and 2ng/mL 4-hydroxytamoxifen for 24-hours. Differentiated macrophages were stimulated for 24-hours with 20ng/mL interferon-γ and 100ng/mL lipopolysaccharide, or 20ng/mL interleukin (IL)-4 and 20ng/mL IL-13, to generate M1 and M2 phenotypes, respectively, before qPCR analysis. To develop a conditional *Grem1* knockout murine model, C57BL/6J (n=11), UBC-CreER^{T2} (n=9) and Gremlin1$^{fl/fl}$ (n=8) mice received intravenous injection of 5x10^5 Vk*MYC MM-PCs and tumour burden was monitored by weekly paraprotein quantification.

Results: A significant reduction in *Grem1* expression was accompanied by a decrease in *Arg1* and *Fizz1* expression, and an increase in *Nos2* expression, by M2 and M1 macrophages, respectively ($p<0.05$, paired t-tests). 100% of C57BL/6J (11/11) and UBC-CreER^{T2} mice (9/9), compared to 25% of Gremlin1$^{fl/fl}$ mice (2/8), had detectable paraprotein at endpoint ($p<0.001$, Fisher's exact tests).

Conclusion: This research proposes Grem1 as a novel mediator of *ex vivo* macrophage polarisation and future studies will investigate whether *Grem1* knockout repolarises MM-PC educated M2-like TAMs towards a tumouricidal phenotype. Vk*MYC penetrance must be increased in Gremlin1$^{fl/fl}$ mice before the consequences of *Grem1* knockout on TAM function can be investigated *in vivo*

A novel massively parallel sequencing panel for the assessment of prognosis and genetic evolution in patients with plasma cell myeloma.

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Aim: Despite new therapeutic options in multiple myeloma (MM), relapse is inevitable and it remains an incurable haematological malignancy. The increased availability of high throughput sequencing has enabled detailed analysis of the MM genome. These identified recurrent mutations in the MAPK[1] and NFkB[2] pathways and confirmed TP53 as prognostically significant[3]. Additionally, a new poor prognostic entity has been defined, the molecular "triple hit myeloma", a disease harbouring a CKS1B and TP53 mutation in conjunction with t(4;14) or t(14;16)[4].

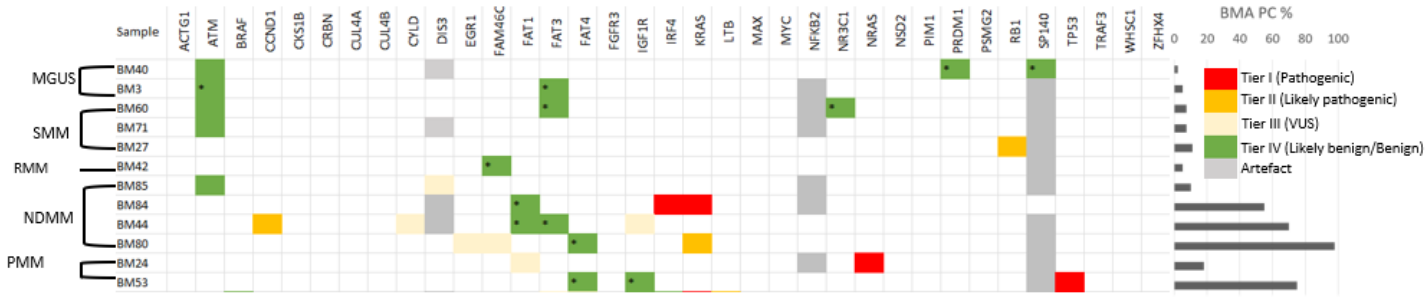
We aimed to (1) develop a novel massively parallel sequencing (MPS) panel incorporating frequent and clinically significant mutations (e.g. CKS1B[4], CYLD[5], EGR1[6]), including those most recently detected by whole genome and exome sequencing, and (2) establish its ability to identify poor prognostic markers compared to standard FISH and cytogenetic analysis.

Method: A novel 34 gene MPS panel was developed to assess genetic aberrations in primary MM cells. 12 samples with plasma cell involvement between 5-100% were assessed. DNA was extracted from stored buffy coat of bone marrow samples using the Maxwell16. 130ng DNA from each sample was used for library generation. These were processed using the standard Archer VariantPlex protocol, sequenced on MiSeq and analysed using Archer's platform.

Results: Variants were identified on all samples (Fig 1) with Tier I to III variants identified in 7 samples. RAS pathway gene variants were seen in our cohort, consistent with previous reports. Tier I and II variants identified include TP53, CCD1, IRF4 and RB1. The frequencies of Tier I-III variants were 0 (MGUS), 0.3 (SMM), 2.25 (MM), 0 (RMM), 1.5 (PMM).

Conclusion:A novel MPS panel was successfully designed and implemented in a pilot study to assess for genomic variants at different disease stages. These results lay groundwork for an expansion study to compare standard and MPS risk assessment, and to explore clonal evolution in progressive MM.

Figure 1. Summary of variants identified in pilot study of 12 patients sequenced using this novel MM MPS panel. Variants were detected in ATM, FAM46C, FAT1, FAT3, FAT4, IGF1R, NR3C1, PRDM1, SP140 at allele frequencies of ~50% in some patients, and therefore may represent constitutional variants (marked *). Abbreviations: monoclonal gammopathy of unclear significance (MGUS), smouldering MM (SMM), treated MM with biochemical response (RMM), newly diagnosed MM (NDMM), progressive MM (PMM).



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Single-cell analysis reveals disease induced perturbations of CD8+T-cell subsets in the bone marrow (BM) and peripheral blood (PB) of newly diagnosed multiple myeloma (MM) patients.

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Aim: $CD8^+$T-cells have a well-established role in myeloma control. We examined the impact of MM on $CD8^+$T-cells within BM compared to PB, using age-matched individuals without MM as controls.

Method: Purified $CD8^+$T-cells were isolated from BM and PB mononuclear cells (MNC) from NDMM patients (n=4) and subjected to single-cell RNA sequencing (scRNA-seq). BM and PB-MNC from MM, MGUS and age-matched controls (n=6 each cohort) were assessed by cytometry. Analysis was performed using custom bioinformatics pipelines and FlowJo. Statistical analysis was undertaken using the non-parametric Mann-Whitney, Kruskal-Wallis and Wilcoxon Rank Sum tests.

Results: Unsupervised clustering revealed effector memory (T_{EM}) cells as the dominant subset in BM. BM-T_{EM} from MM patients reflected the transcriptional profile of TCR activated cells from age-matched controls, demonstrating significant ($p<0.0001$) enrichment in several AP-1 associated genes (e.g., *FOS*, *JUN* and *JUNB*) and other markers of activation. Differences between BM and PB were apparent by cluster restricted expression of *GZMB* and *GZMK*, with the latter predominantly evident within the BM, and largely co-expressed *CD69,* reflecting activation and/or BM-retention. Further analysis revealed CD69 expression was restricted to the BM and delineated two independent $CD8^+$T-cell subsets. Although there were no differences in the proportion of $CD8^+$T-cells expressing CD69 in any cohort, NDMM patients demonstrated significantly greater expression levels of CD38 and CD69 ($p<0.01$) within the $CD69^+$ subset and marked differences in Granzyme expression patterns in the $CD69^-$ subset compared to age-matched controls.

Conclusion: While BM-$CD8^+CD69^-$ T-cells cells appear phenotypically diverse and demonstrate markedly higher levels of Granzyme B expression in MM compared to age-matched controls, BM-$CD8^+CD69^+$ T-cells demonstrate relative homogeneity, with MM-associated changes largely restricted to enhanced levels of CD38 and CD69 and increased transcriptional activity of early effector genes, suggestive of chronic activation of these cells in myeloma.

A bioinformatics approach to identifying CD8+T-cell specificity and transcriptomic states in multiple myeloma (MM).

Mr James Favaloro[1,2,3], Dr Christian Bryant[1,4], Dr Edward Abadir[1,4], Dr Shihong Yang[1], Mr Samuel Gardiner[5], Dr Najah Nassif[3], Dr Lisa Sedger[3], Prof Douglas Joshua[1,4], Prof Phoebe Joy Ho[1,4]
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Aim: The anti-tumour activity of $CD8^+$T-cells in multiple myeloma (MM) is well documented. We examined the possibility of naturally occurring anti-myeloma $CD8^+$T-cells in newly diagnosed (ND)MM patients and the impact of the MM micro-environment on these cells.

Method: Purified $CD8^+$T-cells were isolated from BM and PB mononuclear cells of four NDMM patients and subjected to single-cell RNA sequencing, inclusive of paired TCR sequencing. Analysis of TCR specificity was performed by means of sequence similarity using TCRMatch in conjunction with established databases and the deep-learning tool, pEptide tcR matchinG prediction (ERGO-II) in conjunction with a previously published analysis of the ligandome in MM.[1] Data was then linked back to the transcriptional profile of cells using a custom bioinformatics pipeline.

Results: Analysis of the top 10 dominant clonotypes within each sample by TCRMatch revealed potential matches to 56 of 80 assessed sequences, with the majority suggesting specificity to peptides from CMV, EBV or Influenza A, present in both BM and PB. ERGO-II analysis against clones expanded to ≥0.1% of a sample's repertoire revealed 16 clonotypes potentially reactivity to 104 peptides, predominantly observed in BM. Peptides from the proteins PDIA4, MOGS and CMTR1 were unevenly represented, with multiple individuals demonstrating potential reactivity against common peptides, suggesting immunodominance of these peptides. Identified clones demonstrated restricted gene usage, possibly suggestive of public clonotypes, rendering them of immunotherapeutic interest. Transcriptional analysis revealed more transcriptional heterogeneity within the PB than the BM, however, dominant clonotypes did not appear to exhibit micro-environmental induced differences in gene expression, suggesting these cells retain functional capacity to induce cell death.

Conclusion: Analysis of clonotypic data reveals potential targets for functional studies and may suggest cross-reactivity between viral specific $CD8^+$T-cells and malignant plasma cells as a means of disease control in MM.

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First results from CC-92480-MM-002: a phase 1/2 study of the novel CELMoD agent CC-92480, in combination with dexamethasone (DEX) and bortezomib (BORT) in patients (pts) with relapsed/refractory multiple myeloma (RRMM)

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Introduction/Aim: CC-92480, a potent cereblon E3 ligase modulator (CELMoD®) agent, has shown marked synergy with proteasome inhibitors, DEX, and CD38 mAbs in myeloma cells. We report preliminary results from the CC-92480+BORT+DEX cohort of the CC-92480-MM-002 study (NCT03989414).

Methods: Eligible pts had: RRMM; 2–4 prior regimens; progressive disease during or after last therapy. Over a 21-day cycle (C), CC-92480 was given at 0.3, 0.6, or 1.0mg on days (D)1–14 with BORT on D1, 4, 8, and 11 of C1–8 and D1 and 8 of >C8. DEX was given on D1, 2, 4, 5, 8, 9, 11, and 12 of C1–8 and D1, 2, 8, and 9 of >C8. Primary objectives: evaluate safety and preliminary efficacy; determine MTD/RP2D. Immune pharmacodynamics and Ikaros/Aiolos levels were assessed.

Results: As of 26May2021, 19 pts received CC-92480+BORT+DEX. Median number of prior regimens: 3; prior therapies included BORT, lenalidomide, pomalidomide, and CD38 mAbs; 4 pts were triple-class refractory. Median follow-up: 8mo; median number of cycles received: 10, with 9 pts continuing treatment and 5 pts discontinuing due to progressive disease. All pts had ≥1 TEAE. Eighteen pts had grade (Gr)3/4 TEAEs including neutropenia, thrombocytopenia, and anemia. One pt had Gr3/4 infection; 2 pts discontinued because of TEAEs. CC-92480, BORT, and DEX dose reductions occurred in 5, 7, and 8 pts, respectively. MTD was not reached; no pt had a DLT; 2 deaths occurred. ORR across all doses: 73.7%; responses were observed at all dose levels. Median time to first response: 0.95mo; median DoR: 10.4mo. Pharmacodynamic studies showed potent degradation of Ikaros/Aiolos 3–6 h post-treatment and reduced mature B cells levels. CC-92480 at 1.0mg was selected as the RP2D.

Conclusions: In pts with RRMM, CC-92480+BORT+DEX appears to be safe and well tolerated with encouraging preliminary efficacy. The CC-92480-MM-002 study is ongoing

Outcomes of autologous stem cell transplantation (ASCT) for systemic immunoglobulin light chain (AL) amyloidosis in the Victorian amyloidosis referral centre.

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Aim: To review the outcomes of patients treated with ASCT for AL amyloidosis.

Method: We identified 25 AL amyloidosis patients treated with ASCT at the Victorian and Tasmanian Amyloidosis Service (VTAS) from 2014 onwards using our electronic medical records (EMR). Patient characteristics and outcomes were reviewed.

Results: Between September 2014 - March 2022, 25 patients received an ASCT at VTAS. Our cohort comprised 84% males with median age of 64 years at transplantation & median ECOG performance status of 1. Patients had a median Revised Mayo Stage of 2 (range: 1 – 4) with a median of 1 organ system involved (range 1 – 4); 15 patients had cardiac, 12 renal, 5 peripheral nerve and 4 gastrointestinal involvement.

Patients predominantly received VCD (bortezomib, cyclophosphamide & dexamethasone) induction for AL amyloidosis. Patients received split-dose melphalan conditioning; most patients (88%) received a total of 200mg/m^2 and the remainder 140mg/m^2. Patients' neutrophils and platelets engrafted at a median of 12 days (range 11-20 & 9-25 respectively) and six patients (24%) required ICU admission.

Median follow up duration was 24.8 months (range 1.3 – 73.7). We saw very good partial or complete haematological responses in 88% of patients with an overall 12-month progression-free survival rate of 79%. Four patients died: one patient from transplant-related complications (*Campylobacter* septic shock), one from disease progression & two from non-transplant/amyloidosis causes (complicated abdominal aortic aneurysm repair & intracranial haemorrhage). Median overall survival has not been reached.

Conclusion: Our patients achieved high response rates following ASCT as seen in reports by other centres. In the absence of head-to-head trials comparing novel targeted therapies (eg. daratumumab, venetoclax) to ASCT, this report further reinforces the role of ASCT in suitable patients for the treatment of AL amyloidosis

Update of the MM24 ALLG/IFM Phase 2 single-arm study evaluating the efficacy of isatuximab, pomalidomide and dexamethasone, in patients with AL amyloidosis not in VGPR or better after previous therapy.

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Background: Systemic AL amyloidosis (AL) is caused by misfolded monoclonal immunoglobulin light chains (sFLC) deposition in organs, leading to impairment or failure if untreated. Very good partial responses (VGPR) or greater from chemotherapy targeting sFLC is associated with improved organ function and survival (OS). Daratumumab (DARA) is an antiCD38 monoclonal antibody (mAb) that improves ≥VGPR rates when added to CyBorD for newly diagnosed AL. DARA and pomalidomide (POM) are effective therapies in relapsed/refractory (RR) disease but have never been studied together as therapy.[1] Isatuximab (ISA) is an alternative antiCD38 mAb.

Objective: To evaluate the efficacy and safety of ISA and POM in AL patients not achieving ≥VGPR and/or who have relapsed.

Material & Methods: We plan to enroll 46 patients in this multicenter Australian and French, single-arm, phase 2 study. Main inclusion/exclusion criteria: ≥1 therapy without VGPR/CR; dFLC >50 mg/L; amyloidotic organ involvement; no overt MM; no cardiac stage IIIb patients; ECOG<3; no previous antiCD38 or POM. Eligible patients receive 28-day cycles of ISA (10mg/kg, IV, weekly for 1 cycle then fortnightly), POM 4mg (days 1-21) and dexamethasone (10-20mg, weekly). Treatment is for 12 months, unless CR after 9 cycles, disease progression or unacceptable toxicity occurs. The primary endpoint is ≥VGPR after 6 cycles. Secondary endpoints include: HR rates at various time points; progression-free survival; organ responses at 1 year; OS; time to HR and organ responses; safety and tolerability; and quality of life (EQ-5D-3L). Exploratory endpoints include: impact of t(11.14) on responses; minimal residual disease by NGS and mass spectrometry.

Results: As of May 25th, two patients are enrolled, two are in screening with one screen failure. No unexpected toxicities have been observed.

Conclusion: This is the first prospective study of ISA treatment with POM and dexamethasone in AL. Preliminary results and safety data will be reported during the Congress.

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Cardiac Amyloid Reaching for Extended Survival (CARES): Two Placebo-Controlled, Double-Blind, Randomised, International Phase 3 Trials Assessing CAEL-101 in Patients with Mayo Stage IIIa or Stage IIIb AL Amyloidosis

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Background: Immunoglobulin light-chain amyloidosis (ALA) is characterized by production of amyloidogenic monoclonal light chains that form amyloid fibrils depositing in tissues causing organ damage. The major determinant for prognosis is cardiac involvement. Mayo Stage IIIa and IIIb[1,2] patients have a median overall survival of 24 and 4 months, respectively.[3] Treatment has focused on therapies that halt production of light chains. However, no therapies are approved to remove deposited fibrils from organs.

CAEL-101 is a monoclonal antibody that binds to misfolded light chains. In Phase 1 and 2 trials, with or without concurrent standard of care (SOC) for the underling plasma cell dyscrasia (PCD)[4], CAEL-101 was generally well tolerated and improvement of cardiac and renal biomarkers were observed in some patients (NCT04304144)[5].

Aim: These current studies hope to evaluate the efficacy and safety of CAEL-101 versus placebo with SOC anti-PCD therapy in treatment-naïve patients with cardiac ALA, Mayo Stages IIIb (NCT04504825) or IIIa (NCT04512235).

Method: These international, multicenter, double-blind, randomised, phase 3 trials, are enrolling newly diagnosed adults with ALA Mayo Stage IIIa or IIIb and histopathological diagnosis of amyloidosis with cardiac involvement. Patients cannot have any other form of amyloidosis, symptomatic orthostatic hypotension, or supine systolic blood pressure <90 mmHg.

Results: These studies are recruiting at five hospitals in Australia: Princess Alexandra, Brisbane (n=5); Fiona Stanley, Perth (n=1); Eastern Health, Melbourne (n=1); Royal Adelaide, Adelaide (n=0); and Westmead, Sydney (n=1).

Conclusion: CARES is evaluating efficacy, through survival, and safety of CAEL-101 in ALA patients with a dismal prognosis. Despite a huge unmet need, such patients are often excluded from trials. Given the paucity of data in this rare disease, we encourage referral of suitable patients to these studies. Contact details can be found at: www.aan.org.au and www.clinicaltrials.gov.

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Lenalidomide, bortezomib, dexamethasone (RVd) therapy in transplant ineligible patients with newly diagnosed multiple myeloma (NDMM): an update of the NSW RVd Harmonisation study

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Aim : We proposed the implementation of two dose attenuated RVd protocols (modified SWOG or modified RVd-lite, Table 1) in transplant ineligible NDMM patients across 9 NSW sites. We aim to evaluate the toxicity, dose modification patterns, treatment response and the impact of patient frailty on treatment decisions in this population.

Method: All transplant ineligible NDMM across 9 NSW sites were prospectively registered. Data was collected including demographics, disease characteristics, documented frailty scores and choice of induction therapy. Treatment response and disease status was collected at 6 monthly follow up intervals.

Results: At time of abstract, 53 patients have been registered. 36 patients were male with a median age of 75 (66-86). Of the total, 44 patients had a calculated R-ISS score (I in 10, II in 29, III in 5). Modified SWOG was given to 24 patients and modified RVd-lite to 28. 31 patients had a calculated frailty score (20 Mayo [median 1], 11 IMWG [median 1]). 34 patients have completed induction to date. Treatment was prematurely ceased in 12 patients, secondary to treatment toxicity in 8 cases. Dose reduction/cessation was seen with lenalidomide (14/34), bortezomib (4/34) and dexamethasone (17/34). Peripheral sensory neuropathy was observed in 13 patients (10 Grade 1; 1 Grade 2; 2 Grade 3). Hospitalisation during induction was seen in 15 patients. At post induction follow up, 20 patients had a □ VGPR, 10 PR and 2 PD.

Conclusion: Harmonised treatment protocols continues to be deliverable across NSW sites. Treatment cessation and dose modifications were frequently observed, particularly with dexamethasone and lenalidomide. Further data is required to assess toxicity with current protocols and the influence of frailty on choice of treatment and treatment response.

Table 1

	Bortezomib	Lenalidomide	Dexamethasone
Modified SWOG Regimen (28 day cycle)			
Induction	1.3mg/m^2 SC Day 1, 8, 15, 22	25mg daily Day 1-14	20mg Day 1, 2, 8, 9, 15, 16, 22 and 23* *Consider dose reduction to weekly if >/= 75
Post-Induction		10-25mg daily Day 1-21	20mg Day 1, 18, 15, 22* *Consider dose reduction or possible omission of dexamethasone depending on patient characteristics and toxicity
Modified RVD-Lite Regimen (35 day cycle)			
Induction 1-6	1.3mg/m^2 SC Day 1, 8, 15, 22	15mg daily Day 1-21	20mg Day 1, 2, 8, 9, 15, 16, 22, 23* *Dexamethasone 20mg days 1, 8, 15 and 22 in patients aged > 75 years
Induction 7-8	1.3mg/m^2 SC Day 1, 8, 15, 22		20mg Day 1, 2, 8, 9, 15, 16, 22, 23* *Dexamethasone 20mg days 1, 8, 15 and 22 in patients aged > 75 years
Maintenance		10-25mg daily Day 1-21	20mg PO Day 1, 8, 15, 22* * Consider dose reduction or possible omission of dexamethasone depending on patient characteristics and toxicity

Epidemiological Modelling of Australian Patients with Myeloma

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Aim: New treatments have improved outcomes for patients with multiple myeloma, an incurable cancer, but at significant cost. Furthermore, survival achieved with newer agents in randomised controlled trials (RCTs) is not always replicated in routine clinical care. The Epidemiological Modelling of Australian Patients with Myeloma (EpiMAP Myeloma) project aims to address critical knowledge gaps in myeloma care to inform policy and funding decisions of emerging and high-cost therapeutics in myeloma.

Method: We developed a microsimulation model to map out complex treatment pathways for myeloma patients based on the Australian and New Zealand Myeloma and Related Diseases Registry and administrative data. The model predicts a patient's treatment pathway through sequential lines of therapy until death. Treatment pathways comprise induction chemotherapy, followed by autologous stem cell transplantation (ASCT) in eligible patients, and subsequent multi-line chemotherapy. Modelled outcomes include survival, quality of life, and costs.

Results: The EpiMAP Myeloma model has been developed to query the impact of changes to the complex treatment pathway. Through simulation, these modelled analyses extrapolate the MRDR data and facilitate a quantitative assessment of previously infeasible research questions. Example modelled analyses include the impact of the government decision to limited access to new therapies for relapsed and refractory myeloma patients only, or the impact of providing ASCT to older patients. The model can also quantify changes in outcomes related to differences in population such as that between myeloma patient populations included in RCTs to those in the 'real world' MRDR.

Conclusion: Treatment complexity will continue to escalate as the armamentarium of myeloma therapies expands and are implemented into routine practice. The EpiMAP Myeloma project will provide decision-makers with evidence of the impacts of policy and funding decisions on myeloma care and build Australian capacity in epidemiological modelling in blood cancers.

Real-world experience of patients receiving daratumumab in Australia

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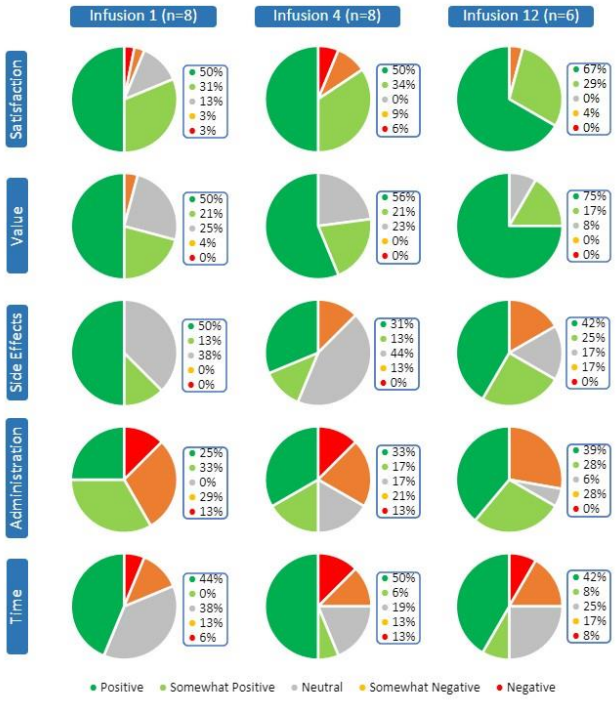
Aim: The intravenous (IV) formulation of daratumumab requires relatively long median infusion times at the first (7h), second (4h) and subsequent infusions (3h) which may adversely impact patient experience. Our aim was to describe the real-world patient experience and how it changes over time.

Method: This was a small (N=8), prospective, observational study in which patients receiving daratumumab IV for the treatment of relapsed/refractory multiple myeloma in Australia completed a survey via computer-assisted telephone interviews. Responses were collected within 72h of their first (week 1), fourth (week 4) and 12th (week 15) daratumumab IV infusions. Patients were enrolled between December 2020 and August 2021 (before daratumumab SC became available).

Results: Responses were summarised into 5 themes associated with satisfaction, value, side effects, administration, and time. At infusion 1, positive ratings (4 and 5) were 81%, 71%, 63%, 58% and 44%, respectively. There was a trend across most themes towards a more positive experience throughout the treatment; by infusion 12, 96% and 92% of the responses associated with satisfaction and value had positive ratings, respectively, and 83% of patients indicated that they would “definitely recommend” the treatment to another patient, compared with 38% at the first infusion. Initial issues with the administration improved over the treatment course with 73% of patients responding neutrally/positively by infusion 12, compared to 58% after the first infusion. After the 12th infusion, 75% patients had switched their preference and responded that the daratumumab IV infusion became equal/better compared to previous treatments.

Figure 1. Summary of patient responses related to daratumumab IV infusions



Conclusion: Although small numbers, these results suggest that the patient experience improves further over the course of treatment with daratumumab IV, as administration duration shortens and time between treatments lengthens. Future studies need to assess whether the SC formulation improves the patient experience further in the real-world, given its shorter 3 to 5-minute administration time

Clinical administration characteristics of subcutaneous and intravenous administration of Daratumumab in Multiple Myeloma patients at Mayo clinic

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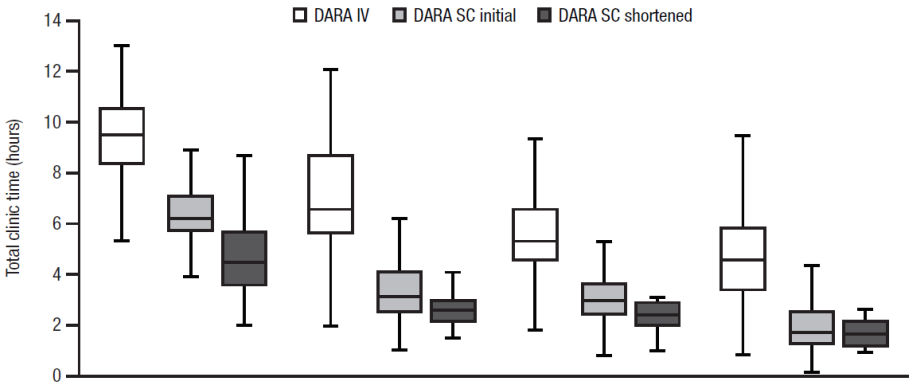
Aim: To describe updated clinical administration characteristics for subcutaneous daratumumab (DARA-SC) at Mayo-Clinic infusion centers before and after reduction in procedure-mandated observation time, versus intravenous DARA (DARA-IV), using novel empirical data extraction approach from Electronic Health Records (EHR).

Methods: Adult multiple myeloma (MM) patients with ICD-9/10 and first DARA-treatment between 05-April-2017 and 22-June-2021 were identified in Mayo-Clinic's EHR database. On 03-May-2021, Mayo treatment plan was amended to shorten mandated post-administration observation time for DARA-SC Dose-1 from 4- to 2-hours and from 1-hour to 30-minutes for Doses-2&3, with no observation time for Doses-4+. Data were captured for patients initiating DARA-IV throughout defined treatment window, while for patients on DARA-SC, data are from before (DARA-SC initial) and after shortening the post-administration observation time (DARA-SC shortened). Time-based measures included: total clinic, total chair, and observation time. Medication administration time documented for DARA-SC was 0 minutes due to default duration for SC injections in EHR.

Results: Total, 755 MM patients (DARA-IV, n=586; DARA-SC[initial, n=145; shortened, n=24]) received DARA-treatment. Median total clinic time was 2.9-hours shorter for DARA-SC (2-hours[initial]) versus DARA-IV (4.9-hours). Median total clinic time for DARA-SC and DARA-IV was highest at Dose-1 and lower for subsequent doses (Figure). Similarly, median total chair time was 2.7-hours shorter for DARA-SC versus DARA-IV for all doses combined. Median total chair time for DARA-SC and DARA-IV was highest at Dose-1 and lower for subsequent doses.

Conclusion: Marked reductions in time spent in clinic and in chair were observed with DARA-SC versus DARA-IV, with additional time savings observed following the Mayo procedure change to reduce the DARA SC mandated observation time, further indicating a reduction in the burden on both clinical resources and patients in Mayo-Clinic infusion centers. These results add to the growing evidence supporting DARA-SC use as an efficient and convenient treatment option for MM patients.

Figure. Median total clinic time[a] for patients receiving DARA IV or DARA SC[b].



	Dose 1			Dose 2			Dose 3			Doses 4+		
	DARA IV	DARA SC		DARA IV	DARA SC		DARA IV	DARA SC		DARA IV	DARA SC	
	All	Initial	Shortened	All	Initial	Shortened	All	Initial	Shortened	All	Initial	Shortened
Patients, n	369	145	21	366	138	19	348	138	12	403	135	9
Clinic visits, n	369	145	21	366	138	19	348	138	12	6125	1453	20
Median (hrs)	9.5	6.1	4.4	6.6	3.1	2.6	5.3	2.9	2.4	4.6	1.7	1.6

DARA, daratumumab; IV, intravenous; SC, subcutaneous.
[a]Total clinic time was defined as the duration from check-in time through patient check-out, including total chair time (time from infusion room entry to infusion room exit or check-out time, including order review, pharmacy preparation time, and post-administration observation time)
[b]Data for DARA SC patients were captured before (DARA SC initial) and after (DARA SC shortened) adoption of the update to the Mayo treatment plan on May 3, 2021, which reduced the mandated post-administration observation time for DARA SC.

First-line use of Daratumumab, Lenalidomide, and Dexamethasone (D-Rd) confers survival benefit compared with second-line Daratumumab-based regimens in transplant-ineligible (TIE) patients with multiple myeloma (MM): Analysis of different clinical scenarios

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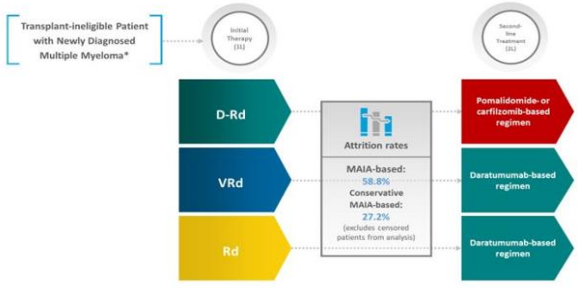
Aim: Real-world(RW) data showed that while most patients(pts) with newly diagnosed MM(NDMM) receive first-line(1L) treatment(tx), attrition rates are high in later line of therapy(LOT). In MAIA study, D-Rd demonstrated significant progression-free survival(PFS) and overall survival(OS)-benefit vs Rd. Subgroup analysis (≥65years) in SWOG S0777 showed bortezomib(V)-Rd had no significant OS-benefit vs Rd. In the absence of head-to-head studies comparing different tx sequences, we examined different clinical scenarios to explore the clinical value of using daratumumab(DARA) first vs saving it until a later LOT.

Method: We examined 3 potential clinical tx sequences using a lifetime three-health state clinical simulation (1L[time on tx+any subsequent tx-free interval]; 2L[time on 2L+any subsequent LOT]; death) to estimate survival outcomes (median OS, 5-/10-year survival rates) in TIE-NDMM pts as per clinical guidelines (**Figure**). Time spent in 1L-health state based on time to next tx/death(TTNT) curves was derived from MAIA for D-Rd and Rd and PFS HRs estimate from PEGASUS for VRd. Time spent in 2L-health state with DARA-based/ pomalidomide[POM] or carfilzomib[CAR]-based regimens was based on RW data from Flatiron Health database.

Results: Using D-Rd in 1L improved median OS (2.5/3.5years) compared with delaying DARA-based regimens until 2L after VRd/Rd. The probability of being alive at 5 and 10 years was higher with D-Rd than VRd/Rd as initial therapy (**Table**). The absolute difference in median OS was preserved with an incremental OS-benefit consistently >2years.

Conclusion: Our approach shows that achieving the longest possible PFS in 1L drives OS outcomes. Saving agents until later LOT does not take into account attrition rates in MM. In TIE NDMM, starting with D-Rd may provide up to 3.5 years of additional OS gain with the currently available 2L-tx, reinforcing the importance of using the best agents first, to increase the probability of pts benefitting from tx currently in development.

Figure Treatment sequences analyzed



*Average age: 74.1 years. D-Rd, daratumumab, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.

Table Survival rates

	Base Case (58.8% attrition rate)			Sensitivity Analysis (27.2% attrition rate)		
	D-Rd in 1L, POM-/CAR- in 2L	VRd in 1L, DARA- in 2L	Rd in 1L, DARA- in 2L	D-Rd in 1L, POM-/CAR- in 2L	VRd in 1L, DARA- in 2L	Rd in 1L, DARA- in 2L
OS, years	7.6 (6.75–8.83)	5.1 (4.42–6.33)	4.1 (3.33–5.33)	9.1 (8.00–10.50)	6.7 (5.92–7.92)	5.7 (4.83–7.00)
Incremental (D-Rd vs VRd or Rd), years	--	2.5 (1.00–3.75)	3.5 (1.92–4.92)	--	2.4 (0.75–4.00)	3.4 (1.67–5.08)
5-year survival rate, %	62.6 (56.7–73.3)	51.0 (47.3–60.2)	44.1 (40.1–53.2)	69.9 (62.8–80.1)	60.7 (55.5–70.3)	54.9 (49.4–65.3)
10-year survival rate, %	41.8 (39.8–45.0)	29.6 (27.3–33.0)	22.8 (20.5–26.2)	46.7 (43.1–52.3)	35.4 (31.5–40.6)	28.6 (24.4–34.1)

All results are reported in point estimate (95% CI). 95% CIs are based on 1000 simulations. 1L, first line; 2L, second line; CAR, carfilzomib; DARA, daratumumab; D-Rd, daratumumab, lenalidomide, and dexamethasone; OS, overall survival; POM, pomalidomide; Rd, lenalidomide and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.

Partial 5'IGH deletion as a sole IGH abnormality by fluorescence in situ hybridization (FISH) is a recurrent finding in myeloma.

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Aim: The Victorian Cancer Cytogenetics Service (VCCS) provides a two-tiered fluorescence in situ hybridization (FISH) panel for patients with newly diagnosed myeloma. Along with probes for detection of 1q gain and 1p and 17p deletions the Metasystems *IGH* break-apart (*IGH BA*) probe is used to detect *IGH* gene rearrangements including the 4;14, 11;14, 14;16 and 14;20 translocations that are common findings in myeloma.

We review VCCS FISH results with the *IGH BA* probe, in particular the partial deletion of *5'IGH* that includes the IGH variable region (*IGHV*).

Method: FISH studies were carried out following enrichment for CD138+ plasma cells using EasySep manual cell isolation and cytogenetic harvest. FISH results from 1227 myeloma bone marrow samples received at the VCCS between June 2020 and January 2022 were assessed. *IGH BA* was run on 1018 (83%) samples with rearrangements and partial *5'IGH* or 3'*IGH* deletions further investigated to identify t(4;14), t(11;14), t(14;16) and t(14;20) fusions.

Results: No *IGH BA* rearrangement was identified in 439 (43.1%) samples, rearranged *IGH BA* with *IGH::FGFR3, IGH::CCND1, IGH::MAF* or *IGH::MAFB* fusions was detected in 335 (32.9%) samples and rearranged *IGH BA* with no fusion partner identified was seen in 128 (12.6%) samples.

Two *IGH BA* fusions (no rearrangement) with either a partially deleted 3' (proximal) or 5' (distal) signal were seen in 6 (0.6%) and 120 (11.8%) of samples respectively with no fusion partner identified.

Conclusion: Complex rearrangement and deletions within the *IGH* gene and in particular the 5'*IGHV* region are well described in myeloma. Our FISH results support this finding, with partial *5'IGH* deletion as the sole *IGH* abnormality detected in 120 (11.8%) samples. Partial *5'IGH* deletion may also result from an unbalanced translocation with an unknown partner gene however, in over 1000 samples we have seen no evidence of *IGH::FGFR3, IGH::CCND1, IGH::MAF* or *IGH::MAFB* fusions. Whether cascade testing of fusion probes following detection of this *IGH BA* signal pattern will continue at the VCCS is still to be determined.

Cytogenetic Analysis of Circulating Tumour Plasma Cells in Multiple Myeloma

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Aim: The aim of this feasibility study was to determine whether del(17p), one of the most significant chromosomal abnormalities in myeloma, could be identified in CTPC identified by their phenotype by immuno-flowFISH.

Method: Blood samples were obtained from 12 myeloma patients. After red cell lysis, cells were incubated with monoclonal antibodies (CD38-BV605, CD138-BV480) to identify plasma cells. Following fixation, cell membranes were permeabilised and DNA denatured. FISH was performed by hybridisation of fluorophore-conjugated probes to the chromosome 17 centromere (C17) and a locus specific 17p13 region. Nuclei were stained with SYTOX AADvanced and cells acquired on the Amnis ImageStream®X MkII imaging flow cytometer. Digital images captured at x60 magnification and quantitative data were used to assess FISH signals overlying nuclei of CD38/CD138-positive plasma cells.

Results: 10,000-428,000 (mean 188,500) cells were acquired and CD38/CD138-dual positive CTPC could be identified in all samples (0.0025-90.65% of cells). FISH probe binding for both C17 and 17p region was evident by fluorescing “spots” overlying the nucleus. In two cases there was only one FISH signal with the 17p13 probe but diploid centromeric FISH spots, indicating del(17p); the lowest number of CTPC with del(17p) detected was 0.0075 x 10^9/L. Another case had a single FISH spot for 17p13 and centromeric probes indicating loss of the entire chromosome 17 (i.e. monosomy 17; in 0.009 x 10^9/L CTPC. In 9/12 samples there were 2 FISH signals for both C7 and 17p13, a normal pattern.

Conclusion: Chromosome 17 abnormalities, both loss of the 17p13 region and monosomy 17, are detectable in CTPC in myeloma using the immuno-flowFISH method. This provides a novel approach for assessing chromosome 17 aberrations in myeloma in blood, something currently unachievable with standard FISH. This technique has potential as a highly sensitive non-invasive blood-based tool for assessing the most significant chromosomal abnormalities in myeloma.

The development of a pre-clinical model of bortezomib induced peripheral neuropathy

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Aim: Peripheral neuropathy (PN) is a major dose-limiting toxicity of the standard-of-care myeloma therapy bortezomib (VELCADE®). Bortezomib-induced PN (BIPN) is characterised by pain and sensory loss in hands and feet, altered proprioception and, in some cases muscle weakness. There is, therefore, an urgent need for effective strategies to reduce BIPN while maintaining optimal tumour treatment. The aim of this study was to develop a clinically relevant mouse model of BIPN that can be used to investigate novel strategies to manage this condition.

Methods: To establish a therapeutic bortezomib dosing regimen, C57BL/KaLwRij mice bearing orthotopic 5TGM1 cell tumours (two weeks after i.v. injection of $5x10^5$ 5TGM1-Luc cells (expressing luciferase and GFP) were treated i.v. with high-dose (1mg/kg) or low-dose (0.5mg/kg) bortezomib, or vehicle alone, twice weekly for two weeks. Tumour burden was assessed using bioluminescence imaging and flow cytometric detection of GFP-positive tumour cells in the bone marrow. To assess BIPN, C57BL/6 mice (treated twice weekly with high-dose or low-dose bortezomib, or vehicle alone, for two weeks) underwent a general assessment of spontaneous behaviour (behavioural spectrometry) and specific sensory nerve (von Frey filament) and motor function (rotarod) assessments. Histopathological analysis was also performed on nerves tissues.

Results: High-dose and low-dose bortezomib-treated mice displayed 100-fold and 9-fold reductions in tumour burden, respectively, compared with vehicle alone (P<0.001). In addition, high-dose bortezomib-treated mice displayed reduced exploratory activity and increased fine grooming activity, specifically, of paws (P<0.001) (Fig 1). Moreover, high-dose bortezomib-treated mice displayed sensory loss on von Frey filament mechanical testing (P<0.0001). Motor function assessments and histopathological analyses on nerve tissues are ongoing.

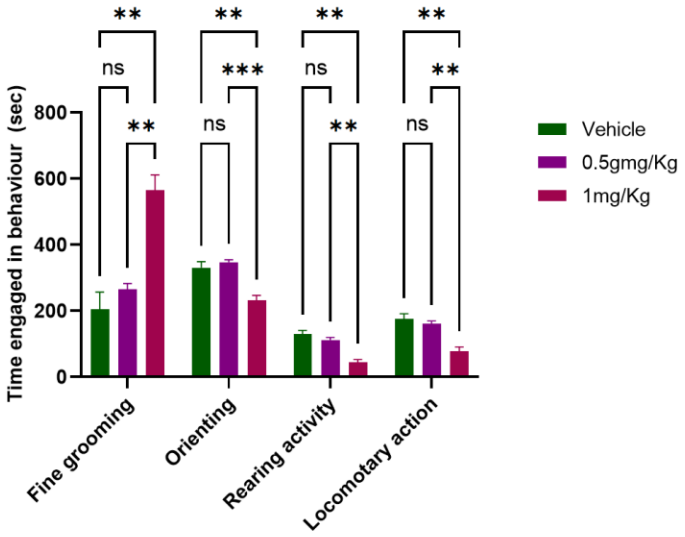

Fig 1: Assessment of behavioural changes in C57Bl/6 mice (n=10/group) treated with 0.5 or 1mg/kg bortezomib or vehicle. Data represents mean ± SEM (two-way ANOVA with Tukey's multiple comparison test).

Conclusion:
We have developed a clinically relevant mouse model of BIPN. This model will be used to investigate novel strategies to reduce the incidence and severity of BIPN, in order to improve quality of life and survivorship in patients with myeloma.

Multiple myeloma cells can be sensitised to a new form of regulated cell death termed ferroptosis.

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Aim: The aim of this study is to assess the sensitivity of multiple myeloma (MM) cells to ferroptosis. Ferroptosis is a newly-discovered form of iron-dependent regulated cell death characterised by the accumulation of oxidised membrane polyunsaturated phospholipids to lethal levels [1].

Methods: MM cell lines (KMS-11, KMS-18, LP-1 and OPM2) were cultured with the GPX4 inhibitor RSL3 +/- arachidonic acid (AA) or ferric ammonium citrate (FAC). After 24 hours, flow cytometry was used to measure cell viability (annexin-V/propidium iodide) and lipid peroxidation (C11-BODIPY). Liproxstatin-1 was used to confirm the involvement of ferroptosis. The expression of proteins associated with ferroptosis was assessed by Western blot.

Results: MM cell lines are considered resistant to ferroptosis compared to some other cancers (e.g. lymphoma) [1]. Three of the four MM cell lines were more resistant to GPX4-induced ferroptosis (cell death IC_{50}s over 1 µM RSL3) compared to OPM2 (IC_{50} below 75 nM). Both AA and FAC increased the cytotoxic effects of RSL3 in KMS-18, OPM2 and LP-1 cells, and to a lesser extent in KMS-11. This decrease in cell viability was associated with an increase in lipid peroxidation, both of which could be prevented with liproxstatin-1. Proteins associated with ferroptosis (ACSL4, FTH1 and HO-1) were upregulated in the sensitive OPM2 cell line compared to KMS-11. However, the target protein of RSL3 and ferroptosis regulator, GPX4, did not differ at baseline between the two cell lines. Importantly, ferroptosis suppressor protein-1 (FSP1), which has been shown to inhibit ferroptosis, was absent in OPM2 and expressed in KMS-11.

Conclusion: These data suggest MM cells can be sensitised to ferroptosis by providing relevant substrates that may be lacking in this cancer, such as polyunsaturated phospholipids and iron. Moreover, variation in ferroptosis sensitivity may be due in part to FSP1. Thus, ferroptosis may represent a novel approach for treating MM.

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"Lumpy legs" – a tale of 3 patients with Nodular Cutaneous Amyloid Deposits (NCAD) but with differing autoimmune disorders.

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NCAD are rare, typically localised and found unexpectedly on biopsy. We report 3 cases associated with differing autoimmune conditions.

Case 1 A 61-year-old female with chronic hepatitis B presented with bilateral cutaneous leg lesions (maximum 5cm diameter), growing slowly over 10 years. Biopsies revealed amyloid, staining positive for Congo red and kappa with green birefringence under polarised light; negative for lambda, TTR and AA. Cyclophosphamide, dexamethasone and doxycycline was trialled for 12 weeks, but ceased due to side-effects. Autoimmune hepatitis is associated with NCAD. The patient was observed for two years with no discernible progression.

Case 2 A 64-year-old female with Sjogren's syndrome presented with a breast lesion detected on mammogram and 10 years of bilateral subcutaneous thigh lesions. Biopsies of the breast and leg lesions demonstrated amyloid with positive Congo red and kappa staining. FDG-PET identified a 7mm pulmonary nodule possibly representing amyloid. Sjogren's syndrome is associated with localised breast and nodular pulmonary amyloid[1]. The patient was observed for two years with no progression.

Case 3 A 45-year-old man with Type 1 diabetes and Addison's disease presented with bilateral 1cm nodules of the deltoids. Biopsy confirmed amyloid with non-specific kappa and lambda staining but strong insulin staining. He had injected synthetic insulin into his deltoids for >30 years. Localised insulin amyloid deposits are a well-recognised complication of long-term insulin injections. Treatment is avoidance of nodular areas and rotation of injection sites.
NCAD is associated with autoimmune conditions, such as Sjogren's syndrome, diabetes & inflammatory hepatic disorders. Treatment is observation or local surgical measures[2] once systemic disease is excluded. None of our cases had a plasma cell dyscrasia or systemic amyloidosis on blood/urine testing +/- echocardiography, bone scintigraphy and/or bone marrow biopsy. Prognosis is excellent. There is no role for radiotherapy or chemotherapy in the routine management of such patients.

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A zebra amongst horses – a case report of IgM multiple myeloma with cytogenetically cryptic IgH gene rearrangement and review of the literature

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Background: IgM multiple myeloma is a rare entity, accounting for <1% of new myeloma diagnoses [1]. These cases typically harbour a t(11;14) translocation with cyclin D1 overexpression [2]. This case report outlines an uncommon case of a patient presenting with an IgM paraprotein found to have multiple myeloma with a cryptic IgH rearrangement.

Case presentation: We report a case of a 65 year old man referred with an IgM lambda paraprotein (30g/L) and raised lambda serum free light chains (2500, K/L ratio <0.01) for investigation. Blood tests showed normocytic anaemia, hypercalcaemia and mild renal impairment. PET scan showed multiple intense FDG-avid skeletal lytic lesions, with no FDG-avid lymphadenopathy or hepatosplenomegaly.

The patient underwent bone marrow aspirate and trephine with 36% typical plasma cells on aspirate, with a minority having plasmablastic morphology. Trephine showed heavy interstitial involvement with plasma cells on CD138 immunohistochemistry (IHC). These plasma cells were CD20 negative and PAX5 positive, with a subset positive for cyclin D1.

FISH testing using IgH breakapart probes showed an IgH gene rearrangement with an unknown partner gene. Further FISH testing using available probes for IgH including t(11;14), t(4;14), t(6;14), t(14;16) and t(14;20) were negative. Karyotype was normal (46,XY) with mosaic duplication of chromosome 7q on microarray. Molecular testing for MYD88 was negative.

The patient started weekly bortezomib, lenalidomide and dexamethasone achieving a partial response after 2 cycles.

Conclusion: This case highlights a rare presentation of multiple myeloma with typical clinical and pathological features however an IgM paraprotein, cyclin D1 expression and IgH gene rearrangement without identifiable partner gene despite extensive investigation. This serves as a timely reminder to consider plasma cell neoplasms in the workup of IgM gammopathy.

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Real world experience of induction therapy for treatment of newly diagnosed multiple myeloma: an analysis from the Australian and New Zealand, and the Asia-Pacific Myeloma and Related Diseases Registries (MRDR).

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Aim: To review RWE of three induction regimens for NDMM patients.

Method: We analysed all patients aged ≥18 years with NDMM, commencing induction therapy between Jan 2016 and Dec 2021 with either bortezomib, cyclophosphamide and dexamethasone (VCd), bortezomib, thalidomide and dexamethasone (VTd) or bortezomib, lenalidomide and dexamethasone (VRd), using data from the ANZ, and the APAC MRDR. Progression free survival (PFS), overall survival (OS), overall response rate (ORR, ≥ partial response) were assessed. PFS and OS were estimated using Kaplan-Meier methods.

Results: 2939 patients were included. Median age of VCd patients was 65.3 years; VTd: 60.8 years, VRd: 64.9 years (p-value < 0.001). 91% of VTd patients were treated in Korea and 84% of VRd patients in Australia. 11.5% of VCd patients had high risk disease (International Myeloma Working Group criteria); VTd: 25.6%, VRd: 17.4% (p-value < 0.001). 56.4% of VCd patients received an autologous stem cell transplant (ASCT); VTd: 75.1%, VRd: 58.3% (p-value < 0.001). In the ASCT group, ORR for VCd patients was 85.8%, VTd: 98.1%, VRd: 94.7% (p-value < 0.001). Kaplan-Meier survival curves showed a statistically significant difference between treatments in PFS (figure 1), but not OS. PFS advantage for VRd in ASCT patients remained when adjusted for country - hazard ratio (95% CI) with VCd as reference: VTd 1.46 (0.64-3.37) p = 0.37, VRd 0.61 (0.37-0.99) p = 0.044. In patients who did not have an ASCT, ORR for those on VCd was 83.3%, VTd: 87.8%, VRd: 92.9% (p-value 0.049). No difference was seen on Kaplan-Meier survival curves for PFS and OS between treatments.

Conclusion: For ASCT patients, VRd confers longer PFS than VCd or VTd, but not in OS. In patients not receiving an ASCT, there was no difference in PFS or OS between therapies. Short follow-up time, and different database and patient management between countries may confound results.

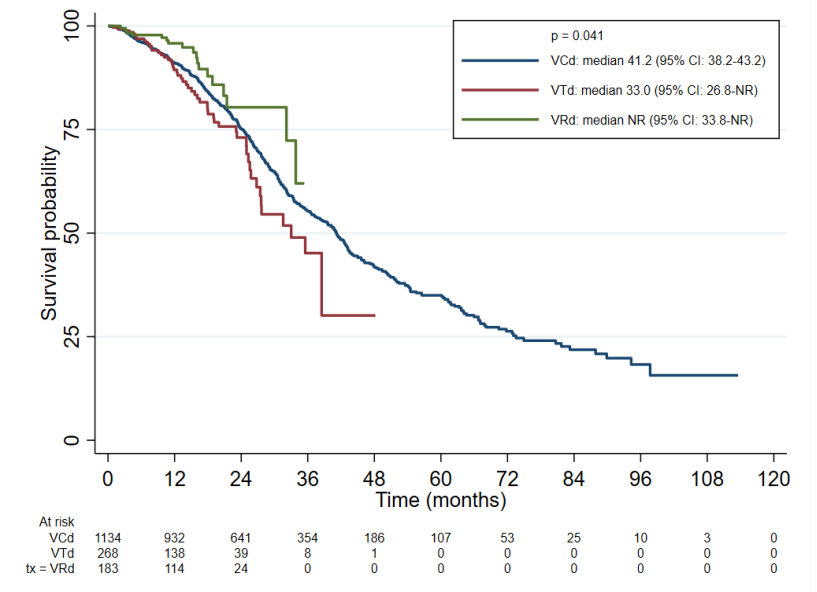

Figure 1: Progression-free survival of patients receiving A

Efficacy of daratumumab, lenalidomide, and dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma and impaired renal function from phase 3 MAIA study based on lenalidomide starting dose

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Aim: In phase 3 MAIA study daratumumab (D), lenalidomide and dexamethasone (Rd) prolonged progression-free survival (PFS) and overall survival (OS) vs Rd alone in transplant-ineligible newly diagnosed multiple myeloma (NDMM) patients. Results from MAIA for D-Rd vs Rd in patients with impaired renal function based on lenalidomide starting dose at a median follow-up of 56.2 months reported here.

Method: NDMM patients ineligible for high-dose chemotherapy and autologous stem-cell transplantation were randomized 1:1 to D-Rd/Rd. Patients in both arms received 28-day cycles of oral Rd (R: 25mg [10mg: for creatinine clearance (CrCl): 30-50 mL/min], days 1-21; d: 40mg [20mg: aged >75 years or body-mass index<18.5 kg/m^2: days 1, 8, 15, 22). D-Rd arm patients also received intravenous D (16mg/kg once weekly: Cycles 1-2, once 2-weekly: Cycles 3-6, and once 4-weekly thereafter). Primary endpoint: PFS, secondary endpoint: OS.

Results: Of 737 patients (D-Rd, n=368; Rd, n=369); 162 (44%) patients in D-Rd arm and 142(38%) patients in Rd arm had renal impairment (RI). RI patients receiving lenalidomide starting dose of 25mg D-Rd showed PFS and OS advantage over Rd while patients receiving lenalidomide starting dose of <25mg D-Rd prolonged median PFS and OS vs Rd (*Table*). In 25mg subgroup, death due to disease progression was noted in 6/12 (50%) patients in D-Rd arm and 10/29 (34%) patients in Rd arm, while in <25mg subgroup, it was noted in 16/44 (36%) patients in D-Rd arm and 11/37 (30%) patients in Rd arm.

Conclusion: After ~5 years of follow-up, D-Rd showed a PFS improvement vs Rd in transplant-ineligible NDMM and RI patients, regardless of lenalidomide starting dose. An OS advantage for D-Rd vs Rd was observed in patients with RI receiving lenalidomide starting dose of 25mg. Our results support the frontline use of D-Rd to provide prolonged disease control in transplant-ineligible NDMM and RI patients.

Table. **PFS and OS in pts with renal impairment (CrCl ≤60 mL/min) based on lenalidomide starting dose (25mg/<25mg)**

	D-Rd	Rd	HR (95% CI)	*P* value
25 mg subgroup	n=60	n=62		
PFS				
Median PFS, months	NR	35.4	0.42 (0.24-0.72)	0.0012
5-year PFS rate, %	63.1	33.3	–	–
OS				
Median OS, months	NR	NR	0.37 (0.19-0.73)	0.0028
5-year OS rate, %	79.0	50.9	–	–
<25 mg subgroup	n=98	n=75		
PFS				
Median PFS, months	49.1	24.9	0.56 (0.38-0.83)	0.0029
5-year PFS rate, %	40.3	18.6	–	–
OS				
Median OS, months	62.8	54.8	0.81 (0.52-1.26)	0.3468
5-year OS rate, %	54.0	44.1	–	–

PFS, progression-free survival; OS, overall survival; CrCl, creatinine clearance; D-Rd, daratumumab/ lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; NR, not reache

CAMMA 3: A multicentre Phase Ib trial evaluating the safety, pharmacokinetics, and activity of subcutaneous cevostamab monotherapy in patients with relapsed or refractory multiple myeloma (RRMM)

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Aim: Cevostamab is an FcRH5xCD3 bispecific antibody that facilitates T cell-directed killing of myeloma cells. Cevostamab has demonstrated promising activity and manageable safety when administered intravenously in patients with heavily pre-treated RRMM (Trudel et al. ASH 2021). Subcutaneous administration of therapeutic antibodies has been shown to be effective and well tolerated in patients with haematological malignancies, and offers several advantages over intravenous dosing, including improved patient convenience and reduced healthcare utilization. The slower absorption rate associated with subcutaneous dosing relative to intravenous dosing may also provide an additional mechanism for the mitigation of cytokine release syndrome, an established complication of T-cell-engaging immunotherapy. CAMMA 3 (ISRCTN26168155) is an ongoing open-label, multicentre Phase Ib study of subcutaneous cevostamab in patients with RRMM. We describe the study and conduct.

Method: For inclusion, patients must be aged ≥18 years and have RRMM for which no established therapy is available or appropriate. Cevostamab is administered by subcutaneous injection in 28-day cycles, with step-up dosing in Cycle 1, Q2W dosing in Cycles 2–6, and Q4W dosing in Cycles 7–13. Patients may receive up to 13 cycles, unless disease progression or unacceptable toxicity occurs. Patients who respond to cevostamab but develop recurrent or progressive disease after 13 cycles may be eligible for re-treatment.
Primary objectives are to evaluate the safety and tolerability (including the maximum tolerated dose and dose-limiting toxicities) of subcutaneous cevostamab and to identify a recommended Phase II dose (RP2D). Secondary objectives include assessment of pharmacokinetics, activity, and immunogenicity, and identification of biomarkers associated with response and resistance.

Results: CAMMA 3 is an ongoing study that aims to enrol ~60 patients in 6–15 sites globally.

Conclusion: CAMMA 3 will establish the safety and tolerability of subcutaneous cevostamab in patients with RRMM and will identify a RP2D for evaluation in future studies.

Sustained improvement in HRQoL in transplant-ineligible patients with newly diagnosed multiple myeloma treated with daratumumab, lenalidomide and dexamethasone versus lenalidomide, and dexamethasone: update of the phase-3 MAIA trial.

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Aim: Phase-3 MAIA trial compared daratumumab+lenalidomide+dexamethasone (D-Rd) vs lenalidomide+dexamethasone (Rd) in transplant ineligible (TIE) patients with newly diagnosed multiple myeloma (NDMM). At a median follow-up of 28 months and longer, D-Rd significantly prolonged progression-free survival (PFS), improvements in PROs and benefits in overall survival (OS) compared to Rd. Here we present 56.2 months follow-up update.

Method: In the phase-3, randomized and open-label MAIA trial (NCT02252172), TIE patients with NDMM were randomly assigned 1:1 to receive D-Rd or Rd until disease progression (PD) or unacceptable toxicity. PROs were recorded using the EORTC Quality of Life Questionnaire Core 30-item and the EQ-5D-5L visual analog scale. Questionnaires were completed at baseline, on day 1 of cycles 3/6/9/12 for year 1, and Q6W thereafter until PD. Analyses were conducted on all patients with a baseline and ≥1 post-baseline PRO assessment. Thresholds for meaningful improvement and worsening were defined a priori based on published literature. Treatment effect was analyzed using a mixed-effects model for repeated measurements.

Results: At a median follow-up of 56.2 months, discontinuation rates were lower with D-Rd than Rd (56.8% vs 80.8%). Numerically greater proportion of patients achieved meaningful improvement with D-Rd vs Rd for physical functioning/fatigue and dyspnea (Table 1). The median time-to-improvement was numerically shorter with D-Rd vs Rd for physical functioning and pain. The median time-to-worsening was significantly longer with D-Rd than Rd for physical functioning/pain and dyspnea (Table 2). Between-group differences for LS mean change from baseline for PROs favored D-Rd vs Rd at all assessment time points except cycle 3 for physical functioning and cycle 6 for fatigue; differences were significant at ≥1 timepoint for each scale.

Conclusion: Sustained and clinically meaningful-improvements in HRQoL with D-Rd vs Rd with almost 5-years of follow-up were observed and, supports the use of D-Rd in older patients.

Table 1. Proportion of patients with meaningful improvement and worsening at any time on-treatment for select PROs

	Patients with Improvement, %[a]			Patients with Worsening, %[a]		
	D-Rd (N=368)	Rd (N=369)	OR (95% CI)	D-Rd (N=368)	Rd (N=369)	OR (95% CI)
GHS	57.3	51.8	1.25 (0.94, 1.67)	49.5	45.3	1.18 (0.89, 1.58)
Physical functioning	**51.6**	**41.7**	**1.49 (1.11, 1.99)***	44.0	44.7	0.97 (0.73, 1.30)
Fatigue	**65.8**	**55.6**	**1.54 (1.14, 2.07)***	64.4	61.0	1.16 (0.86, 1.56)
Pain	66.3	60.2	1.30 (0.97, 1.76)	44.6	45.5	0.96 (0.72, 1.29)
Dyspnea	**40.5**	**32.2**	**1.43 (1.06, 1.93)***	50.3	48.0	1.10 (0.82, 1.46)

[a]≥10-point change from baseline. *Significant results shown in **bold**.

CI, confidence interval; D-Rd, daratumumab, lenalidomide, and dexamethasone; GHS, global health status; OR, odds ratio; Rd, lenalidomide and dexamethasone.

Table 2. Median time to meaningful improvement and worsening for select PROs

	Median time to improvement, mo[a]			Median time to worsening, mo[a]		
	D-Rd (N=368)	Rd (N=369)	HR (95% CI)	D-Rd (N=368)	Rd (N=369)	HR (95% CI)
GHS	8.15	7.46	0.94 (0.77, 1.15)	26.78	21.26	0.87 (0.71, 1.08)
Physical functioning	10.41	15.61	1.13 (0.91, 1.40)	**45.47**	**21.52**	**0.77 (0.62, 0.96)***
Fatigue	7.39	5.59	1.01 (0.83, 1.21)	4.86	4.80	0.85 (0.71, 1.02)
Pain	2.46	4.57	1.01 (0.84, 1.21)	**39.43**	**17.97**	**0.69 (0.55, 0.86)***
Dyspnea	NE	54.60	1.13 (0.88, 1.44)	**29.01**	**15.74**	**0.78 (0.63, 0.96)***

[a]Kaplan-Meier estimate. *Significant results shown in **bold**.

CI, confidence interval; D-Rd, daratumumab, lenalidomide, and dexamethasone; GHS, global health status. HR, hazard ratio; mo, months; NE, not evaluable; Rd, lenalidomide and dexamethasone.

Clinical outcomes in patients (pts) with dose reduction of selinexor in combination with bortezomib, and dexamethasone (XVd) in previously treated Multiple Myeloma from the BOSTON study

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Aim: Most anti-cancer regimens require dose modifications to optimise the therapeutic window. Appropriate dose modifications improve tolerability while maintaining anti-cancer activity. The combination of once weekly selinexor, bortezomib, and dexamethasone (XVd) is TGA approved for previously treated multiple myeloma (MM). In the BOSTON study, compared to standard twice weekly bortezomib plus dexamethasone (Vd), XVd demonstrated significantly prolonged median PFS and TTNT, increased ORR, reduced rates of peripheral neuropathy, and a trend towards improved OS. Here, we analysed efficacy and AEs in pts whose dose was reduced compared to those where it was not.

Method: BOSTON consisted of two arms: pts treated with selinexor QW (100mg), bortezomib QW (1.3mg/m2) and dexamethasone BIW (20 mg) (n=195 in the ITT population) compared to standard BIW Vd.

Results: Of the XVd treated pts 126 had a dose reduction of selinexor and 69 did not. Median PFS in dose reduced pts was 16.6 months and was 9.2 months in pts who did not. The ORR in the dose reduced group was 81.7% compared to 66.7% in pts who did not. DOR was NR in the dose reduced group and was 12.0 months in the group without reduction. TTNT was 22.6 months in the dose reduced group and 10.5 months in pts with no dose reductions. The most common AEs (dose reduction and without dose reduction) of any grade were thrombocytopenia (69.8% and 42.0%), nausea (55.6% and 40.6%), and fatigue (49.2% and 29.0%). The rate of treatment discontinuation was 24.6% vs 14.5%.

Conclusion: While all pts on XVd initiated therapy at 100mg selinexor QW, appropriate dose reductions were associated with a longer PFS, DOR, and TTNT, and significantly reduced AE with improved tolerability, highlighting dose reductions as an important tool to optimise the therapeutic window for pts with RRMM.

Effects of cytogenetic risk on outcomes in multiple myeloma treated with selinexor, bortezomib, and dexamethasone (XVd)

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Aim: In contrast to multiple myeloma (MM) with standard-risk cytogenetics (SR), high-risk cytogenetics (HR) in MM can result in shorter PFS and OS with less durable responses. Therefore, treatment regimens that can overcome the negative effect of HR are required. The combination of once weekly selinexor, bortezomib, and dexamethasone (XVd) is TGA approved for previously treated MM. In the BOSTON study, XVd significantly prolonged median PFS and improved ORR, with a trend towards prolonged OS amongst all patients and those with HR. We performed a post hoc analysis on patients from the XVd arm of the Phase 1b/2 STOMP and BOSTON studies to determine the effects of cytogenetics on outcomes.

Method: The HR group included patients with ≥1 of the following at initial diagnosis or screening: del(17p), t(4;14), t(14;16), or gain(1q) (≥3 copies).

Results: 106 patients with HR and 131 patients with SR were identified. In the XVd arm, the median PFS for HR was 12.9 months and 16.6 months for SR patients. The median PFS on the BOSTON Vd control arm were 8.6 and 9.5 months with HR and SR, respectively. In the XVd arm, the median PFS was 13.2 and 13.9 months for t(4;14) and gain1q subgroups, respectively. The ORR was 76.4% for HR patients with following ORR for subgroups: del(17p) (72.0%), t(4;14) (88.0%), and gain1q (73.8%). The ORR of the SR group was 69.5%. The ORRs on the BOSTON Vd control arm were 57.7% and 64.7% for HR and SR, respectively. The rates of the most common TEAEs of any grade were similar across HR and SR.

Conclusion: HR MM patients treated with XVd demonstrated a comparable ORR and PFS, with a manageable safety profile compared to SR patients, supporting the use of XVd in patients with any cytogenetic profile and the use of the selinexor in earlier lines of therapy.

To marrow or not to marrow, that is the question: predicting significant bone marrow plasmacytosis in patients with monoclonal gammopathy

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Aim: Monoclonal gammopathy of undetermined significance (MGUS) is commonly encountered in haematology practice. Selection criteria for bone marrow aspiration and trephine (BMAT) varies between clinicians. This retrospective study seeks to identify patients who may benefit from BMAT, specifically those with bone marrow plasmacytosis > 60% (BM60), where treatment is indicated in the absence of other CRAB criteria.

Method: We identified BMATs performed at our institution between 2018-2022 for patients with MGUS or myeloma. We excluded cases with IgM paraprotein, light chain only disease, non-secretory myeloma, and previous myeloma therapy.

Using a quasi-random algorithm, 100 samples were selected for inclusion. 62% were male, with median age 72 years (46 – 92 years), 67% IgG paraprotein, 33% non-IgG paraprotein, 26% had a diagnosis of MGUS, 74% plasma cell myeloma, and mean bone marrow plasmacytosis was 33.6% (2.5% – 100%).

Data was analysed using Stata v17. A multivariate logistic regression model was developed to identify predictors of BM60. Subgroups were compared using Student's t-test.

Results: Only paraprotein size > 10g/L (p=0.04) and abnormal free light chain (FLC) ratio (p=0.03) were predictive of BM60. Paraprotein type (IgG or non-IgG) was not predictive of BM60 (p=0.90).

For patients with abnormal FLC ratio and paraprotein of at least 10g/L, 15g/L, and 20g/L the rates of BM60 were 39.7%, 48.9%, and 56.8% respectively. For patients with abnormal FLC ratio and paraprotein less than 10g/L, 15g/L, 20g/L, and 30g/L the rates of BM60 were 7.1%, 7.4%, 8.6%, and 15.2% respectively. For samples with normal FLC ratio and paraprotein less than 30g/L (n=27/100), we did not identify any patients with BM60.

Conclusion: Patients with paraprotein < 20g/L, even with abnormal FLC ratio, are low risk for BM60 and consideration may be given to delaying BMAT until CRAB features are evident. Patients with normal FLC ratio and paraprotein < 30g/L are very low risk for BM60 and appear unlikely to benefit from BMAT in the absence of CRAB features

Daratumumab in combination with bortezomib plus dexamethasone (D-Vd) or lenalidomide plus dexamethasone (D-Rd) in relapsed/refractory multiple myeloma (RRMM): CASTOR/POLLUX subgroup analysis in patients with early/late relapse after initial therapy

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Aim: In phase 3 CASTOR and POLLUX studies, D-Vd and D-Rd significantly improved progression-free survival (PFS), regardless of cytogenetic-risk, and achieved higher rates of complete-response or better (□CR) and minimal residual disease (MRD)-negativity vs Vd/Rd alone in patients with RRMM. Post-hoc analyses of these studies evaluated D-Vd vs Vd and D-Rd vs Rd in patient subgroups with 1 prior line of therapy (LOT) based on timing of relapse (early/late).

Method: In CASTOR and POLLUX, patients with RRMM and □1 prior LOT were randomized to D-Vd/Vd or D-Rd/Rd, respectively. The primary endpoint was PFS. The early relapse (ER) subgroup included patients with 1 prior LOT who relapsed <18 months (m) after initiating their first LOT; patients with 1 prior LOT who relapsed □18m after initiating their first LOT were included in the late relapse (LR) subgroup.

Results: 49 and 186 patients from CASTOR and 99 and 196 patients from POLLUX were included in the ER and LR subgroups, respectively. Median follow-up was 72.6m (CASTOR) and 79.7m (POLLUX). PFS consistently favored the DARA-containing regimens across subgroups (**Table**). In CASTOR, □CR rates were higher with D-Vd vs Vd in ER (21% vs 17%; *P*=0.7360) and LR (51% vs 14%; *P*<0.0001) subgroups. In POLLUX, □CR rates were higher with D-Rd vs Rd in ER (53% vs 12%; *P*<0.0001) and LR (62% vs 38%; *P*=0.0012) subgroups. MRD-negativity rates (10^{-5}) were higher with D-Vd/D-Rd vs Vd/Rd regardless of relapse timing (CASTOR: early, 13% vs 0%; *P*=0.1476; late, 23% vs 3%; *P*<0.0001; POLLUX: early, 30% vs 4%; *P*=0.0006; late, 34% vs 14%; *P*=0.0009).

Conclusion: Post-hoc analyses of CASTOR and POLLUX showed PFS and depth-of-response benefits of DARA-containing regimens in patients with 1 prior LOT, regardless of relapse timing (early/late). Our results support use of D-Vd and D-Rd in RRMM, and in patients with functional high-risk.

Median PFS, months	**D-Vd**	**Vd**	**HR (95% CI); *P* value**	**D-Rd**	**Rd**	**HR (95% CI); *P* value**
Early relapse	15.4	9.0	0.51 (0.26-1.00); *P* = 0.0488	36.9	11.7	0.41 (0.26-0.65); *P* = 0.0002
Late relapse	27.7	7.9	0.20 (0.14-0.29); *P* <0.0001	69.3	29.7	0.53 (0.37-0.77); *P* = 0.0007

Validation of the second revision of the International Staging System in a real-world myeloma population: A Myeloma and Related Diseases Registry Study.

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Aim: The R2-ISS risk algorithm is a revision to the R-ISS scoring system to improve myeloma risk stratificatio. However, the R2-ISS was conceived based on a clinical trial myeloma population(1). Our study aimed to:

1. Validate the prognostic value of the R2-ISS in an Australian "real-world" population, according to progression free survival (PFS) and overall survival (OS),
   - Examine the R-ISS II PFS and OS according to R2-ISS recategorization.

Method: R2ISS scoring was retrospectively applied to 1,013 newly diagnosed multiple myeloma patients in the Myeloma Related Diseases Registry (MRDR) diagnosed between January 2012 and February 2022. The Kaplan-Meier method was used to calculate PFS and OS, with groups compared using the log-rank test.

Results: Median follow-up was 33 months. R2-ISS score-stratified PFS and OS are shown in Figure 1a-b. There was a significant difference in OS between R2-ISS I versus III (HR3.7 (95%CI 2.1-6.4), p<0.001) and I versus IV (HR5.7 (95%CI 2.8-11.5), p<0.001), but not group I versus II (HR1.6 (95%CI 0.88-2.92), p=0.121). Similarly, there was a significant difference in PFS between R2-ISS I versus III (HR2.11 (95%CI 1.5-2.9), p<0.001) and R2-ISS I versus IV (HR3.93 (95%CI 2.52-6.11), p<0.001), but not I versus II (HR1.17 (95%CI 0.82-1.66), p=0.394).
R-ISS II patients were distributed across all four R2-ISS risk groups when re-categorise, highlighting the heterogenous nature of the R-ISS II patient group. There were statistically significant differences in PFS and OS between R2-ISS II versus III (PFS HR1.66 (95%CI 1.29-2.13), p<0.001; OS HR1.88 (95%CI 1.30-2.72), p=0.001) and the II versus IV (PFS HR2.59 (95%CI 1.45-4.62), p=0.001; OS HR3.02 (95%CI 1.36-6.71), p=0.007; Figure 1c-d).

Conclusion: The R2-ISS was largely able to risk stratify our real-world patient cohort but with no clear distinction between R2-ISS groups I and II in this population. The R2-ISS would provide a robust framework for high-risk-stratified front-line clinical trials.

Reference:

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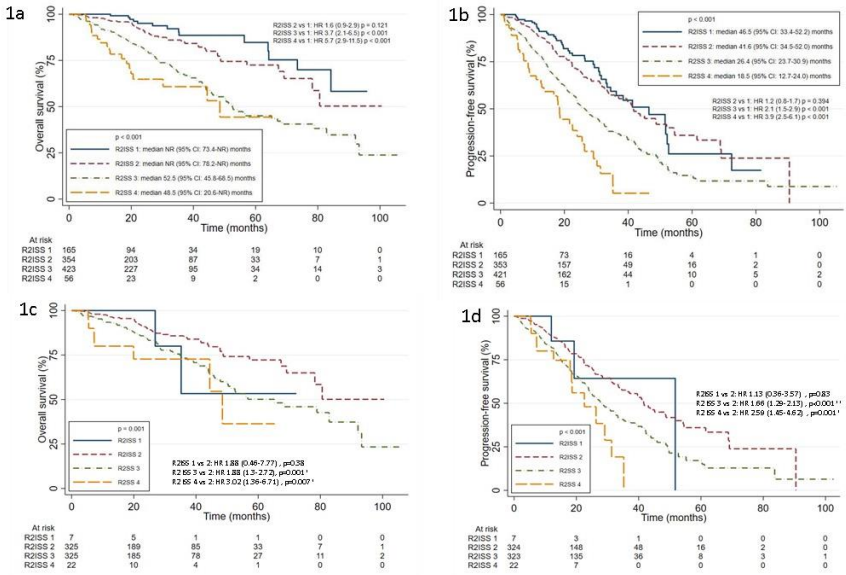

Figure 1a-d: OS (1a) and PFS (1b) for all patients according to R2-ISS categorisation. OS (1c) and PFS (1d) for patients previously categorized as R-ISS II according to R2-ISS recategorisation.

Case highlighting the diagnostic and therapeutic challenges between plasmablastic lymphoma and plasmablastic myeloma.

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Plasmablastic lymphoma (PBL) and plasmablastic myeloma are distinct disease processes with very different treatment strategies and prognosis. However, their similar clinical, morphological and phenotypic features poses a diagnostic challenge. We present an unusual case of a previously well 38-year-old male, who presented with a destructive T12 mass with associated cord compression, large right soft tissue scapular lesion, right axillary lymphadenopathy and extensive lytic lesions. He underwent emergency epidural debulking and decompression surgery. Histopathology demonstrated features of "*high grade plasmablastic neoplasm*" with high Ki67 80%, the differentials included plasmablastic lymphoma versus plasmablastic myeloma. PET imaging showed extensive uptake throughout the skeleton most intense in the right axillary nodes of SUV 31.5 max. CT skeletal survey confirms extensive lytic lesions throughout. Serology demonstrated pan-hypogammaglobulinemia with a kappa light chain burden of 828mg/L. Bone marrow biopsy showed heavy infiltrate of a large immature population of plasmacytoid cells with plasmacytic immunophenotype. Cytogenetic studies showed hypodiploidy and a complex high risk karyotype including 17p deletion and complex abnormalities in chromosomes 1 and 8. Myeloma based therapy with VRd (velcade, lenalidomide and dexamethasone) induction was promptly commenced with an initial clinical and serological response, however progression was soon evident on imaging and serology, necessitating a change in treatment strategy to involve more intensive salvage chemotherapy options, early consideration for novel agents and long term curative options such as allogeneic stem cell transplantation. This case highlights the diagnostic and therapeutic challenges between these two disease processes. Distinct molecular signatures may be helpful, however, timely definitive diagnosis remains a challenge, as well as a need for targeted treatment options to improve prognosis.

Characterising bone marrow adipocytes in MGUS and multiple myeloma

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Aim: Multiple myeloma is a haematological malignancy, preceded by monoclonal gammopathy of undetermined significance (MGUS). The bone marrow microenvironment promotes myeloma plasma cell proliferation and survival. The role of bone marrow adipocytes (BMADs) in myeloma progression remains unclear; however, co-culture of BMADs with myeloma cell lines increases their proliferation and protects from chemotherapy *in vitro*. This study aimed to investigate the differences in BMAD phenotype and mesenchymal stromal cells (MSCs) adipocyte differentiation between MGUS and myeloma patients, and healthy controls.

Method: BMAD quantitation was conducted on CD138-stained trephines from age-matched controls (n=4), MGUS (n=9), and myeloma (n=14) patients using Osteomeasure and NDP.view2. MSCs from age-matched controls (n=7), MGUS (n=14), and myeloma (n=14) were cultured in 100nM dexamethasone and 60µM indomethacin for 21 days and adipocyte-differentiation was assessed via Nile Red/DAPI and Oil-Red O staining. ImageJ quantitated adipocyte number, size and lipid droplet number/adipocyte. Statistical analyses included Kruskal-Wallis and log-rank tests.

Results: In trephines, BMAD number and size did not significantly differ between MGUS and myeloma, or controls; however, myeloma patients with larger mean BMAD size (>2100um^2) had significantly poorer overall survival, compared with patients with smaller BMADs (median survival: 113.3 and 231.1 weeks, respectively; p=0.045, log-rank test). There was no difference in BMAD size in regions of high tumour compared with low tumour. The adipocyte-differentiation capacity and phenotype was similar in myeloma and age-matched control MSCs; however, there was a 2-fold increase in adipocyte numbers and increase in lipid droplets/adipocyte in MGUS-derived MSCs (p=0.0048), compared with myeloma.

Conclusion: Differences in adipocyte-differentiation capacity were observed in MGUS patients suggesting there may be early microenvironmental changes preceding progression. Larger BMADs in trephine biopsies of this myeloma cohort were associated with poorer overall survival; future studies will investigate if altered adipokine profiles are involved in myeloma cell proliferation and resistance to therapy.

Effect of lenalidomide on stem cell mobilisation in newly diagnosed multiple myeloma patients

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Aim: To study the effect of lenalidomide on stem cell mobilisation prior to autologous stem cell transplantation in newly diagnosed multiple myeloma patients.

Method: This is a retrospective review of patients receiving induction therapy with bortezomib, lenalidomide and dexamethasone (VRd) or bortezomib, cyclophosphamide and dexamethasone (VCd) prior to autologous stem cell transplant at a single tertiary centre. Ordinal data were analysed using Fisher's exact and Mann-Whitney-U tests, continuous data were analysed using t-tests and Wilcoxon Rank-Sum.

Results: Fifty-three patients were included, 27 receiving VRd and 26 VCd. Overall response rate was similar between groups (100% VRd vs 92% VCd, p=0.226). Plerixafor was more commonly used for mobilisation in the VRd group (29.6% VRd vs 3.8% VCd, p=0.024). Mean peripheral blood CD34 count was significantly lower in the VRd group (54.12×10^6/L VRd vs 79.49×10^6/L VCd, p=0.024) and there was a trend towards fewer CD34 cells collected in the VRd group (6.29×10^6/kg VRd vs 7.52×10^6/kg VCd, p=0.088). Time to neutrophil and platelet engraftment was similar between groups (neutrophils for both groups median 12 days, p=0.32; platelets 18 days for VRd vs 18.5 days for VCd, p=0.81). When aiming for sufficient CD34 cells for one transplant, there was no difference between groups. However, when aiming for >1 transplant, this target was met less often when VRd was the induction regimen, compared to VCd.

Conclusion: In newly diagnosed multiple myeloma patients, VRd induction resulted in fewer peripheral blood CD34 cells and increased use of plerixafor for mobilisation compared to VCd induction therapy, without affecting engraftment. The effect of lenalidomide on stem cell harvest was more notable when aiming to collect cells for more than one transplant.

Non-malig (Poster Board No H126 – H146)

Change in iron overload status after transitioning from deferasirox dispersible tablet (Exjade) to film coated tablet (Jadenu) in patients with transfusion dependent thalassaemia.

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Aim: Iron overload is an significant comorbidity in patients with transfusion dependent thalassaemia (TDT). Oral deferasirox is one of three iron chelators available for clinical use in chronic iron overload[1]. It was initially available as a dispersible tablet (Exjade), but in 2019 a film coated tablet (Jadenu) became available. It has been shown that Jadenu has a similar safety profile to Exjade, but with increased compliance given less gastrointestinal side effects[2,3]. However, its long term effects on iron overload status have not been reported. The aim of this study was to determine whether switching from Exjade to Jadenu had any effect on iron overload status.

Method: A retrospective observational audit was performed involving TDT patients treated at a haematology unit in Brisbane. Patients were included if they had previously been treated with Exjade as a single iron chelator, and were then transitioned to Jadenu as a single iron chelator. Iron overload status was measured by monitoring serum ferritin levels, as these have been accepted to be a surrogate for measuring trend in total body iron stores[1]. Serum ferritin values were recorded for the first 24 months on Jadenu treatment, as well as for the preceding 24 months on Exjade treatment. The mean serum ferritin levels were then analysed with a paired T-test.

Results: 7 TDT patients were analysed. Of these, 5 patients experienced a decrease in their mean serum ferritin levels following transition to Jadenu. As was hypothesised, there was a non-significant decrease in serum ferritin levels on Jadenu treatment ($p = 0.058$), as compared to previous treatment with Exjade.

Conclusion:
It can be concluded that there is potential decrease in iron overload once TDT patients are transitioned to Jadenu, which lends support to its continued long term use. However, further studies on a larger scale are required to confirm significance of these results.

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Comparison of EQA variation between two Sysmex instruments over a four-year period.

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Aim: To determine the cause of the variation of White Cell Count (WCC) results returned for Sysmex XN and Sysmex XN-L instruments enrolled in the RCPAQAP Full Blood Count Program.

Method: The RCPAQAP FBC program consists of 12 surveys per year with two samples per survey. From 2018 a dual population together with an increased CV was noted in the Sysmex XN-L group. For this study WCC results from survey samples between 2018-2021 were reviewed to assess variance on the CVs and Medians between Sysmex XN-L and Sysmex XN instruments. RCPAQAP inhouse software was used to calculate the median, mean, SD, and CV. The sample results were assessed at three levels, ('Low', 'Medium' and 'High') using t-test on the CVs and Medians.

Results: The comparison of the two instruments at all three levels indicated that there was less variance in the XN group results compared to the XN-L group over the four-year period. As shown in table 1, the CVs for the XN-L group was on average 1.9, 1.8 and 2.1% higher for the low medium and high groups, respectively. This difference was found to be statistically significant with a p-value of <0.01 for all groups. Although, the difference in medians obtained from the two instrument groups was found to be statistically significant, the average difference was small in magnitude.

Conclusion: The two instruments assessed in this study showed a significant difference in reporting for WCC although the medians obtained did not differ in a clinically significant manner, the CVs showed a higher variation in results from the XN-L instrument group. This could be due to several sample processing difference between the instruments including the presence of a secondary QC mode on the XN-L instrument.

Tables and Figures:

	Average Difference	
	Median (x10^9/L)	**CV (%)**
Low	-0.03*	1.9**
Medium	-0.04*	1.8**
High	-0.19*	2.1**

Table 1. Average difference in results between the XN-L and XN instruments **p-value <0.01, *p-value <0.05.

L-selectin and P-selectin glycoprotein ligand-1 are expressed on erythroid precursors.

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Aim: *Erythropoiesis is governed by a close relationship between erythroid precursors and central macrophages, in multicellular clusters termed erythroblastic islands (EBIs), found in the foetal liver, bone marrow and spleen. These important cellular interactions occur via adhesion molecules and their cognate ligands. Here we aim to identify unreported receptor/ligand pairs that may facilitate such interactions within EBIs. To do so, we employed an unbiased transcriptomics approach comparing splenic erythroblast gene expression during homeostasis and chemically-induced anaemia.*

Method: Transcriptomics was performed on FACS-sorted splenic erythroblasts from control and phenylhydrazine-treated outbred QS mice. Flow cytometry was performed on erythroid populations during embryonic and foetal development, in adult bone marrow and spleen during homeostasis, in chemically induced anaemia, as well as in pregnancy.

Results: Transcriptome analysis revealed unexpected expression of L-selectin and P-selectin glycoprotein ligand-1 (PSGL-1) mRNA in splenic erythroblasts. A significant downregulation of L-selectin and PSGL-1 mRNA was observed in splenic erythroblasts during stress erythropoiesis. Immunophenotyping demonstrated that L-selectin and PSGL-1 were expressed on both adult bone marrow and spleen erythroid precursors. Intriguingly, there was a significant depletion in L-selectin and PSGL-1 positive erythroid precursors in the spleen, but not the bone marrow, during pregnancy- and phenylhydrazine-induced stress erythropoiesis. L-selectin was not expressed on primitive erythroid or foetal liver erythroid precursors. Neither E- nor P-selectin were detected at the protein or mRNA level during erythropoiesis.

Conclusion: Here we demonstrate for the first time that the leukocyte adhesion molecules, L-selectin and PSGL-1, are expressed on steady state adult mouse erythroid precursors. L-selectin/PSGL-1 may facilitate cell-cell interactions during erythropoiesis, such as those seen in EBIs. L-selectin/PSGL-1 erythroid expression is diminished during anaemia-induced stress erythropoiesis, and hints at possible shared mechanisms between pre-natal and stress erythropoiesis. Future studies will evaluate expression of L-selectin/PSGL-1 in healthy humans and erythroid diseases, such as sickle cell anaemia, beta-thalassaemia and pure erythroid leukaemia.

Real life clinical outcomes of splenectomised patients with Transfusion Dependent Thalassaemia at a large haemoglobinopathy centre, including infections and vaccination rates.

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Aim: There is well documented increased morbidity and mortality associated with splenectomy. Splenectomy has been utilised in transfusion-dependent thalassaemia (TDT) to decrease anaemia, transfusion requirements, hypersplenism and symptomatic splenomegaly. The aim of this study was to determine morbidity and mortality associated with splenectomy in TDT, including infection outcomes (including COVID-19), thrombotic events and vaccination compliance.

Method: A retrospective audit was performed of vaccination compliance, rates of infections including COVID-19, and thrombo-embolic events (arterial and venous from 1 January 2011 at a large haemoglobinopathy centre in TDT patients who have undergone splenectomy. Vaccination compliance is according to Spleen Australia recommendations. NB. NSW patients are unable to be registered with Spleen Australia.

Results: Thirty patients were identified. Vaccination rates have increased over the last 3 years with implementation of a database to document each vaccination and a targeted campaign. Most do not administer prophylactic penicillin. There was one unexpected death at another hospital with renal, liver and cardiac failure possibly attributed to bacterial sepsis. There were no further documented infections requiring hospitalisation, despite many Covid-19 infections. There were no identified arterial or venous events. Data will be presented in more detail.

Conclusion:
Review of our 'real-life data' demonstrated that admission due to infection, including Covid-19, in splenectomised TDT patients is rare despite poor penicillin prophylaxis, however complacency cannot be afforded. Vaccination compliance is an important part of holistic care. Establishment of a haemoglobinopathy database in 2020 increased ability to be able to identify those not compliant and encourage vaccination, and this resulted in improved compliance. Education of patients and medical teams is ongoing.

Life threatening complications of iron chelation therapy – A reminder of the dangers thal shall face

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Aim: To describe and raise awareness of a case of acute liver failure, coagulopathy and acute renal failure in the setting of iron chelation therapy, deferasirox, leading to tuberculosis reactivation. Deferasirox-induced renal tubular dysfunction has been documented as a rare but serious adverse event and this case highlights the importance of early recognition.

Case summary: A 24-year-old Australian-born male with transfusion-dependent thalassaemia major on deferasirox 720mg daily, had multiple ward and intensive care admissions at another hospital due to abdominal pain and weight loss with no clear cause identified. Subsequently, he was identified to have a non-anion gap metabolic acidosis with associated renal impairment, liver dysfunction and coagulopathy. After withholding deferasirox the acidosis resolved and the renal function improved. As he recovered, fevers developed and further investigations identified tuberculosis reactivation. There have been 57 individual cases described in the literature of renal dysfunction in the setting of deferasirox.

Conclusion: This complex case highlights the rare but serious adverse event of renal tubular acidosis secondary to deferasirox that both patients and prescribers must be vigilant for. It was not initially recognised that this condition could be related to chelation therapy in a centre not familiar with management of thalassaemia patients. This identifies the complexity of managing rare diseases with clinical unfamiliarity and raises the importance of early subspecialised team involvement. Finally, tuberculosis infections continue to be diagnosed following severe illnesses and clinicians should consider a broad differential in the undifferentiated patient.

Analytical principle vs measurement system to assess Haemoglobinopathy EQA results

Mrs Gail Earl[1]

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Aim: To evaluate the preferred category with which to analyse the Haemoglobin A2, Haemoglobin F and variant haemoglobin results submitted by participants in the RCPAQAP Hemoglobinopathy program.

Method: A retrospective analysis of five years' data representing twenty data sets of Hb A2, Hb F and Hb variant (if present in the sample) were categorised and assessed according to the analytical principles i.e. high performance liquid chromatography (HPLC) and capillary electrophoresis (CE) as well as the measurement systems (instruments). The mean, standard deviations (SD) and coefficients of variation (CV) were compared in order to ascertain the preferred category for evaluating the results, and hence the performance of the laboratories enrolled in our program.

Results: The comparison of the statistics for the analytical principles vs measurement system showed there was no significant difference between the mean, SDs and CVs of Hb A2 and Hb F if no haemoglobin variant was present. The presence of certain variants e.g. Hb E does, however, cause instrument bias within the HPLC group due to co-elution of the variant haemoglobin with Hb A2.

Conclusion: With the emergence of new instruments into the Haemoglobinopathy program and a minimum of 6 instruments required for peer group comparison, result comparison within the instrument category has been shown to be more accurate. This strategy would eliminate any biases produced by instruments within a HPLC or CE category, particularly when a haemoglobin variant is present.
The RCPAQAP will continue to assess results according to the specific instrument, as well as provide the statistics for the HPLC and CE groups as a source of additional information.

Corticosteroid use and complications in Immune thrombocytopenia (ITP)

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Background: High-dose corticosteroids form the mainstay of treatment of ITP due to their low cost and efficacy at restoring platelet count. However, such regimens are associated with substantial morbidity, which must be weighed against the risk of bleeding. Recent guidelines encourage corticosteroids to be tapered and ceased within 6 weeks. This study aims to evaluate corticosteroid prescribing at our institution, identify factors associated with longer treatment and provide data on corticosteroid complications.

Method: A retrospective audit was conducted using medical records of 41 ITP patients admitted to The Northern Hospital from 2010-2020. Data comprised: patient characteristics, treatment selection, treatment outcomes, and severity-stratified bleeding and corticosteroid complications. Intervals of <6 weeks, 6-12 weeks, 3-12 months and >12 months corticosteroid duration were used to compare differences between groups. Mann-Whitney U, Kruskal-Wallis, Chi-squared and Fisher-Freeman-Halton Exact tests were used to determine significance.

Results: 88% of patients received a prolonged course of steroids (>6 weeks). Mean duration of treatment was 135 days (range:19-1033). 68% achieved platelet response in <6 weeks, and half (49%) achieved complete response (CR) in <6 weeks. Mean time on corticosteroids after achieving response and CR was 128 and 109 days, respectively. No clinically relevant relationship was determined between frequency of steroid complications and duration of steroid treatment, age ≥60, or pre-existing DM. Significantly higher platelet counts were demonstrated from weeks 2-6 for patients who achieved CR within 6 weeks, compared with groups with delayed or absent CR ($p<0.001$-0.004).

Conclusion: Our results suggest that corticosteroids are being tapered too slowly, with patients remaining on corticosteroids beyond achieving favourable platelet outcomes. No significant relationship between corticosteroid duration and complication rate was established, however the study highlighted a need to improve surveillance and reporting of complications. Further research is needed to characterise the utility of early platelet response in predicting disease course.

Recovery of haematological parameters and thrombosis rates in non-thrombocytopenic thrombotic purpura (TTP) thrombotic microangiopathies (TMAs) in moderate ADAMTS13 activity deficiency

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Aim: Moderate deficiency of ADAMTS13 activity (10-40%) is seen in other TMAs. We compared recovery of haematological parameters and thrombosis rates of patients with a moderate deficiency of ADAMTS13 activity compared to those who were diagnosed with TTP (less than 10%) and those who did not have ADAMTS13 activity deficiency (more than 40%).

Method: Participants were retrospectively identified from those who have undergone ADAMTS13 testing in Monash Health from January 2016 to June 2021. These patients must have demonstrated a platelet count below 150 x 10^9/L and schistocytes on a peripheral blood film, or have histological confirmation of a TMA, and have no prior diagnosis of a TMA.

Results: 78 patients met inclusion criteria. Those with moderate deficiency of ADAMTS13 activity levels had a significantly delayed platelet count recovery compared to those with severe deficiency and no deficiency (p=0.016), with a median of 43 days, compared to 6 days and 8 days respectively. The rate of thromboses in those with TMA was noteworthy, with an overall thrombosis rate of 25.6% up to 6 months post the testing of ADAMTS13 activity. Those with moderate deficiency of ADAMTS13 activity demonstrated a numerically higher proportion of overall thrombosis incidence but the difference was not significant. Regression analyses demonstrated that the Charlson Comorbidity Index was the only evaluated factor that independently impacted the incidence of platelet recovery and overall thrombosis.

Conclusion: A moderate ADAMTS13 activity level of 10.1-40% may be useful in identifying a cohort of patients who are associated with poorer survival, prolonged platelet count recovery, thrombosis rates that are higher than the background population despite a lower platelet count. This correlation however appears to be linked with a higher rate of intercurrent severe illness and more severe co-morbidities.

Agreement of IntraOsseous aspirate and Peripheral Blood samples for predetermined haematological and biochemical tests on automated laboratory analysers and point-of-care devices – a prospective observational study (IOPB study).

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Aim: In the resuscitation and critical illness settings, when timely peripheral or central venous access is not obtained, the intraosseous (IO) route allows indirect access to the venous circulation, facilitating the administration of intravenous fluid and medications. Upon IO cannulation, an aspirate sample is typically collected to confirm placement. The IOPB study examined the agreement of iliac crest and proximal tibia IO aspirate to paired peripheral venous blood (PVB) for measurement of various parameters on automated laboratory analysers (ALA) and point-of-care (POC) devices.

Method: A single centre prospective observational study was performed. Near-simultaneous IO aspirate specimens, along with paired PVB samples, were collected from haemodynamically stable participants. Agreement was assessed through Bland-Altman limits of agreement method (LoA). Measurement differences were compared against the RCPAQAP analytical performance specifications (APS). Given the limitations of using RCPAQAP APS with IO aspirate specimens, agreement was also assessed through clinical judgement of the authors.

Results: 180 individuals (age range 21-87 years) had PVB and iliac crest IO aspirate collected, with 65 also having proximal tibia IO aspirate obtained. Excluding specimens with macroscopic clots, an analyser result was provided in ≥97% of instances for most parameters. When using RCPAQAP APS, strict agreement was apparent for MCV and haematocrit; however, many parameters had their mean differences within these APS criteria and were ultimately deemed to have adequate agreement based on clinical judgement. The measurement differences of certain parameters such as potassium, platelet count, leukocyte count and differentials were deemed excessive.

Conclusion: The IOPB study confirmed the feasibility of analysing IO aspirate on ALA and POC devices. Many parameters were deemed to have adequate agreement for use in the resuscitation setting. Because agreement based on clinical judgement is subjective, clinicians requesting laboratory testing of IO aspirate specimens must appreciate the degree of measurement inaccuracy compared to PVB.

A ten-year Australian experience of splanchnic vein thrombosis

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Aim: There is lack of consensus in the management of splanchnic vein thrombosis (SVT), due to its rarity and heterogeneity. We aim to evaluate the risk factors, management, and complications of SVT.

Method: A ten-year retrospective audit of consecutive SVT presentations at Northern Health, Victoria, Australia, from January 2011 to December 2020 was conducted, and compared to our DVT/PE database of the same period. The mean follow-up was 19 months.

Results: 98 patients (64 males; mean age 64 years) presented with 99 episodes of SVT. 94% were symptomatic with the main portal vein most commonly involved (n=61). SVT cases were more likely provoked compared to DVT/PE (85% vs 61%, p<0.001). Thirty-four patients had cirrhosis (presenting with 35 cases). SVT patients were more likely male (65% vs 47%, p<0.001) and had active malignancy (32% vs 17%, p<0.001). Other common risk factors for SVT include intra-abdominal infection (41%) and recent surgery (13%). Three of thirty-one patients screened for JAK2V617F mutation (including 1 cirrhotic patient) were positive. Cirrhotic patients were less likely to receive anticoagulation than non-cirrhotic patients (66% vs 81%, p=0.08). Eighteen patients (including 5 cirrhotic patients) with SVT received direct oral anticoagulant without known bleeding or thrombotic complications. Cirrhotic patients reported more recurrent thrombotic events (2 SVT and 2 DVT/PE) and/or clot progression (n=2) compared to non-cirrhotic patients with two recurrent thrombotic events (1 SVT and 1 DVT) and one clot progression (15.6 vs 3.9 events/100-person-years; HR 7.0 (95%CI 1.3-36.6), p=0.022). The rate of clinically significant bleeding on anticoagulation was comparable across groups.

Conclusion: SVT are more likely to be provoked compared to DVT/PE, with cirrhosis, intraabdominal infection and malignancy as common causes. Cirrhotic patients have a higher rate of thrombotic complications compared to non-cirrhotic patients (HR 7.0, 95% CI 1.3-36.6) suggesting a careful assessment of individualised anticoagulation decision is needed.

Isolated extracranial stenosis in Sickle cell disease: A paediatric case report

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Background: Stroke is a well-recognised and potentially devasting complication of Sickle Cell Disease (SCD) in children. The existing literature is discrepant in its description of extracranial stenosis in SCD. Some authors believe extracranial stenosis can occur in isolation and is strongly associated with stroke risk[1], whereas others suggest extracranial stenosis always occurs with intracranial stenosis.[2] This case provides a rare example of a paediatric patient with isolated extracranial stenosis, with significant clinical sequalae.

Case description: An 8 year old boy with SCD (Hb SS) developed left sided weakness, consistent with acute stroke. MRI brain demonstrated no intracranial disease, with complete occlusion of the distal right internal carotid artery (ICA) and multifocal infarcts in the frontal watershed regions. Repeat imaging 12 months later demonstrated progressive vasculopathy, with time-of-flight MRA identifying near occlusion of the terminal right ICA. Disease progression occurred despite twelve months of red cell exchange (RCE), with target pre-exchange HbS <30%. Given his significant risk of further vascular events, he is awaiting haploidentical bone marrow transplant (BMT).

Discussion: Current guidelines recommend annual TCD screening (ages 2-16 years) in children with HbSS or HbSB°, however they do not specify any requirements for extracranial imaging. In our centre, extracranial carotid arteries are routinely scanned, in addition to screening as per the STOP criteria. Where TCD is not able to adequately visualise the extracranial vessels, or in cases where stroke is unexplained by standard radiological approaches, we suggest further assessment via MRI/MRA brain and MRA neck to delineate both intracranial and extracranial disease.

Conclusion: Sickle cerebral vasculopathy can be severe and devastating. Clinicians should consider extended screening for extracranial disease, particularly where silent ischaemia or stroke is unexplained. There is growing recognition that transfusion / RCE may not halt the progression of cerebral vasculopathy, and alternative treatments such as BMT may need to be considered.[3]

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Clinical utility of reticulocyte haemoglobin in the assessment of iron deficiency and severe iron deficiency in the paediatric population.

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Aim: To verify reticulocyte haemoglobin (Ret-He) in the Queensland Children's hospital (QCH) laboratory and assess it's clinical utility in the assessment of iron deficiency (ID) and severe ID in paediatric patients.

Method: Samples, from patients <18 years, sent to the QCH laboratory with paired FBC and serum for IS were included in this study. A minimum of 30 samples per age interval were used to confirm previously published age-related biological reference intervals. Eligible samples had Ret-He performed within 72 hours of collection. Sensitivity was determined by comparative verification between ferritin as the reference method and Ret-He as the new method.

Results: Biological reference intervals were confirmed against previous published normal ranges (Table 1, Figure 1). Ret-He is non-inferior to ferritin with good sensitivity and specificity (86% and 92%) when ferritin <10µg/L and Ret-He <29 pg. Ret-He is a stable parameter and can be tested up to 72hours after FBC collection. Ret-He requires less total blood volume for testing and is cheaper than FBC and iron studies.

Conclusion: ID and severe-ID are common in paediatrics. In straightforward ID the diagnosis can be made with a FBC and IS, however there are many situations where, with these tests alone diagnostic uncertainty remains. Ret-He below the reference interval for age is sensitive and specific for the diagnosis of ID and severe-ID and can be used in non-thalassaemic patients with acute or chronic inflammation. Ret-He is equivalent to IS and although it will not completely replace standard testing it can provide clarity to the diagnosis of ID and severe-ID in some clinical situations. Ret-He is stable allowing for centralised testing which improves cost-benefit margin for this test.

A rare case of Haemophagocytic lymphohistocytosis (HLH) with predominant neurological presentation supported by increased histiocytes in cerebrospinal fluid

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Haemophagocytic lymphohistocytosis(HLH) is a syndrome of excess immune activation that has a high mortality. There are also diagnostic challenges that can lead to delays in prompt treatment.

Case: We describe a case of a 69-year-old man who presented to our institution's emergency department with a five-day history of fevers and confusion. He had no pre-existing health issues and was not on any regular medications. He was admitted to the ICU due to haemodynamic instability and had empirical treatment for meningitis. He had seizures in ICU then became obtunded with GCS3, requiring intubation. He had significant new renal and hepatic impairment.

Baseline investigations:

Haemoglobin 193g/L, neutrophils 6.9/nL, platelets 28/nL, creatinine 245 umol/L, albumin 29g/L, ALP 186 IU/L, ALT 185 IU/L, AST 264 IU/L, GGT 332 IU/L and bilirubin 47 umol/L. Ferritin 7750 ug/L, fibrinogen 1.71 g/L, APTT 38 sec, PT 14.2 secs, D-dimer >20 mg/L, lactate 3.0 mmol/L, soluble CD25 10644 pg/ml (high)

CT brain and MRI brain was unremarkable and extensive work up for infections and cultures did not reveal an infectious cause. A PET scan was negative for features of lymphoma.

Cerebrospinal fluid: glucose 7.0 mmol/L (high) and protein 4.62 g/L(high). CSF cytospin revealed numerous histiocytes (Figure 1 and 2)

Bone marrow biopsy, day 8 from presentation revealed features consistent with haemophagocytic lymphohistiocytosis.
A diagnosis of HLH was made and he commenced treatment day 10 of presentation with weekly etoposide and high dose steroids in combination with intrathecal methotrexate and hydrocortisone, based on the HLH-2004 protocol.
Initial clinical improvement was noted; however, he then had an acute deterioration with bacteraemia and cerebral septic emboli and died shortly after.
Discussion: This case highlights the importance of recognising CNS symptoms and signs as a presenting feature of HLH. Although this is not part of the 9 diagnostic features, the literature suggests the neurological ab
normalities are observed in one third of of patients with HLH and that abnormalities in CSF have an increased risk of mortality and neurological sequelae. [1]

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I'm blushing and I'm flushing: a case report of Congenital Erythrocytosis in an adolescent

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Rationale and Objectives: This reports a case of Congenital Erythrocytosis, a rare condition accounting for 0.01% of all polycythemic patients. Awareness of this very rare condition in childhood anticipates elucidation and education to patients, caregivers and hematologists alike. Through this case presentation, it may pave way for the development of tests that may screen/detect and even development of disease specific laboratory ancillaries for Congenital Erythrocytosis. Further studies and observations through case reports with similar disease and clinical profile may follow and further research on prognosis and optimal treatment of the disease.

Case Report: We report a rare case of a 15-year-old female who presented with an elevated hemoglobin level of 209 g/L and hematocrit of 62 vol%, and 2-week history of intermittent body pains. She showed plethora and multiple small folliculocentric keratotic papules on the arms. Pulse oximetry studies showed adequate oxygenation, without nocturnal desaturation. Arterial blood gas and oxygen dissociation curve showed normoxemia and normal p50. Hydration did not improve her polycythemic state. Abdominal ultrasound did not show any mass on the kidneys, liver, gallbladder, bile ducts, pancreas and spleen. Hemoglobin electrophoresis was normal and Epo level was high. JAK2 mutation as negative. She underwent initial and subsequent regular phlebotomy for persistent polycythemia. Body pains and plethora resolved with the intervention.

Discussion and Summary: Establishing the cause must be sought for appropriate management. A case of an adolescent with erythrocytosis worked up was described. Our patient was negative for JAK2 mutation and Erythropoietin was high, making the diagnosis of Polycythemia Vera unlikely. Acquired causes of erythrocytosis were ruled out from the unremarkable history and imaging tests. A normal p50 distinguished her from secondary congenital causes. A normal p50 with high Erythropoietin makes our case more likely of a VHL mutation, a primary congenital erythrocytosis.

Safety and tolerability of nipocalimab administered at different rates of intravenous infusion in healthy adult volunteers: a phase 1 placebo-controlled single-dose study

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Aim: Warm autoimmune hemolytic anemia (wAIHA) is a rare, life-threatening disorder characterized by the destruction of red blood cells by pathogenic IgG autoantibodies. Nipocalimab, which is in clinical development for wAIHA, targets the IgG binding site on neonatal Fc receptor (FcRn) to reduce serum levels of total and pathogenic IgG. The objective of this study was to assess the safety and tolerability of single doses of nipocalimab administered at different IV infusion rates in healthy adults to support the potential use of shortened infusions in future studies.

Method: The trial was a single dose, sequential, randomized, double-blind, placebo-controlled, escalating dose and infusion rate study, in healthy adults. Participants were randomized to 1 of 5 cohorts (n=8 per cohort [6 nipocalimab, 2 placebo]) to receive nipocalimab 30 mg/kg IV infused over 60, 30, 15 or 7.5 min (0.5, 1, 2, or 4 mg/kg/min), nipocalimab 60 mg/kg IV infused over 15 min (4 mg/kg/min) or matching placebo.

Results: A total of 40 participants received study drug and were included in the safety analysis. 40% of patients experienced TEAEs across all nipocalimab dosing cohorts. The most frequently reported TEAE was headache. None of the TEAEs were severe, and no participants discontinued treatment due to TEAEs; there were no serious adverse events or deaths. Lower rates of nipocalimab infusion were associated with fewer TEAEs, while participants receiving 4 mg/kg/min (as either 30 mg/kg infused over 7.5 min or 60 mg/kg infused over 15 min) reported more TEAEs (**Table**).

Conclusion: Single doses of nipocalimab, when administered at doses up to 60 mg/kg and infusion rates up to 4 mg/kg/min were safe and well-tolerated in healthy adults. The frequency of reported TEAEs was lower in participants receiving IV nipocalimab at rates of 1 or 2 mg/kg/min, providing a target infusion rate for current and future studies.

Table. TEAEs by dosing cohort (safety population)

	Nipocalimab						
TEAEs, n (%)	30 mg/kg (60 min; 0.5 mg/kg/min)	30 mg/kg (30 min; 1 mg/kg/min)	30 mg/kg (15 min; 2 mg/kg/min)	30 mg/kg (7.5 min; 4 mg/kg/min)	60 mg/kg (15 min; 4 mg/kg/min)	Total	Placebo
Participants dosed	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	30 (100)	10 (100)
Participants with TEAEs	3 (50)	1 (17)	2 (33)	3 (50)	3 (50)	12 (40)	1 (10)
Most frequent TEAEs							
Headache	1 (17)	1 (17)	0	2 (33)	2 (33)	6 (20)	1 (10)
Nausea	0	0	0	1 (17)	2 (33)	3 (10)	0
Vomiting	0	0	0	0	2 (33)	2 (7)	0
Back pain	0	0	1 (17)	0	1 (17)	2 (7)	0
Nasal congestion	0	0	0	2 (33)	0	2 (7)	0
Rhinorrhea	0	0	0	2 (33)	0	2 (7)	0
Pruritis	0	0	0	1 (17)	1 (17)	2 (7)	0
Rash	0	0	0	1 (17)	1 (17)	2 (7)	0

TEAE, treatment-emergent adverse event.

Selective Targeting of FcRn and IgG Clearance by Nipocalimab Preserves Key Immune Functions

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Aim: Warm autoimmune hemolytic anemia (wAIHA) is a rare, life-threatening autoimmune disorder caused by autoantibodies that attach to and prematurely destroy red blood cells. Nipocalimab is a novel high-affinity, fully human, aglycosylated, and effectorless monoclonal antibody that targets the neonatal Fc receptor (FcRn) in order to reduce levels of circulating IgG antibodies, including pathogenic antibodies. Nipocalimab is in clinical development for the treatment of multiple IgG-mediated disease, including wAIHA. Previously, rapid, sustained lowering of IgG was observed with nipocalimab in the phase 2 VIVACITY study in generalized myasthenia gravis and in phase 1 healthy volunteers. The objective if this research was to characterize the effect of nipocalimab on immune function.

Method: Nipocalimab was evaluated extensively *in vitro* and in nonhuman primate-based chronic toxicology studies to evaluate selectivity, tolerability, safety and immunopharmacology.

Results: Nipocalimab binds specifically *in vitro* to FcRn without activation of effector function or inhibition of antigen presentation. In nonhuman primates administered up to 300 mg/kg nipocalimab QW for up to 6 months, sustained lowering of IgG was observed without adverse effects. Immunotoxicology identified no effect on immune cell phenotypes; CD8 T cell, NK or innate cell functions; T-dependent neoantigen IgM responses. Neoantigen IgG production was observed, but with lowered peak IgG titers consistent with the anticipated increase in IgG clearance with nipocalimab.

Conclusion: These data suggest that nipocalimab can selectively lower IgG and IgG autoantibodies while preserving cellular immunity, complete IgM response and IgG production after neoantigen challenge. Overall, nipocalimab's selective effect on IgG recycling provides a mechanistic rationale for potentially decreased infection risk despite substantial IgG lowering.

Haemophagocytic lymphohistiocytosis and Mycobacterium tuberculosis: a case of the missing granuloma

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Background: Haemophagocytic lymphohistiocytosis (HLH), a rare syndrome of aggressive immune over-activation, often poses a diagnostic challenge.[1,2] Precipitated usually by malignancy, infection or autoimmune disease, it leads to over-activation of macrophages, cytotoxic T cells and natural killer cells, resulting in excess cytokine release and potentially fulminant multi-organ impairment.[1,2] Prompt recognition and treatment is crucial.[1-3]

Here we present a 45-year-old male, having recently immigrated from Vanuatu, with pyrexia of unknown origin, sweats and weight loss. Bloods revealed a severe anaemia (haemoglobin 64g/L), hyperferritinaemia (50200ug/L), hypertriglyceridaemia (4.5mmol/L) and severe liver function derangement (bilirubin 626umol/L). Bone marrow examination showed prominent haemophagocytosis and one necrotising granuloma (acid fast bacilli microscopy negative). Due to concern over malignancy, PET imaging was performed and demonstrated splenomegaly, with moderate liver uptake. A subsequent liver biopsy surprisingly showed numerous granulomas with 1 acid fast bacillus, in keeping with mycobacterial infection.

Our case met five of the eight criteria for HLH.[2] For this, he received dexamethasone as per the HLH-94 protocol. Etoposide was withheld due to severe liver derangement. Due to minimal improvement, Anakinra was added. With AFB seen in liver biopsy, empirical antituberculous treatment was commenced with Moxifloxacin, Ethambutol, Amikacin and Linezolid, in an altered regime due to liver impairment. There was no growth from bone marrow aspirate or liver biopsy, but MycoFLytic blood cultures drawn 5 days after dexamethasone was commenced and before anakinra was introduced, grew *Mycobacterium tuberculosis*. Following marked clinical and biochemical improvement, steroids and Anakinra were weaned, and he was discharged for outpatient antituberculous treatment, which he continues day 42 from presentation.

Conclusion: Mycobacterium tuberculosis is a rarely described precipitant of HLH and should be considered in patients from countries where it is endemic.[3] A modified HLH-94 treatment approach is sometimes required due to severe organ dysfunction, but can be successful.

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Long-term complement inhibition and survival outcomes in patients with paroxysmal nocturnal haemoglobinuria: an interim analysis of the ravulizumab clinical trials

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Aim: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare haematologic disorder causing significant morbidity and mortality. Therapy involves the complement component 5 (C5) inhibitors, eculizumab and recently ravulizumab, which provides complete complement C5 inhibition throughout the 8-week (q8w) dosing interval. We analysed long-term survival data from the global ravulizumab clinical trial program.

Method: Pooled data were analysed from the phase 1b, 2 and 3 trials (NCT02598583, NCT02605993, NCT02946463, NCT03056040) and up to 4 years of open-label extension. Eculizumab or ravulizumab dose varied during the initial studies, with weight-based ravulizumab q8w dosing in the extension phase. Death, patient survival and adverse events causing death, particularly death due to infection or sepsis, were analysed.

Results: We report 1479.0 patient-years of follow-up in 475 patients with ravulizumab-treated PNH. Twelve (2.5%) patients died during the initial and extension studies with an overall incidence of 0.8 deaths per 100 patient-years. Nine deaths occurred within the first 3 years of treatment. Six deaths were due to infection or sepsis. These six patients were predominantly male (83.3%), and white or Asian (50.0%, respectively). Median (range) age was 61 (43–75) years. Two had aplastic anaemia and one had pancytopenia. Most (83.3%) were hospitalised due to onset of infection; however, one patient (white male; 43 years; ravulizumab to ravulizumab) was hospitalized due to worsening aplastic anaemia. He was consequently diagnosed with acute respiratory infection and died from sepsis. Another patient (Asian male; 62 years; ravulizumab to ravulizumab) died from meningococcal sepsis (strain unknown). He was vaccinated against meningococcal groups A, C, Y and W-135, but had not received prophylactic antibiotics. Other causes of death included cardiac disorders (n=1), neoplasms (n=4) and respiratory disorders (n=1).

Conclusion: Long-term ravulizumab treatment was associated with a low incidence of death and few patients died from infection, supporting long-term use of ravulizumab for PNH.

Method comparison between Roche Coaguchek and Abbott I-STAT systems for Point-of-Care INR using a 5-year cumulative review from RCPAQAP EQA datasets.

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Aim: A 5-year cumulative review of INR EQA results is performed where a bias is present between instruments from participants enrolled in RCPAQAP Point of Care INR program.

Method: Yearly RCPAQAP Point of Care INR programs consist of 6 surveys with 2 samples per survey. Analysis was performed on data from surveys conducted from January 2017 to November 2021. Medians and coefficient of variations (CV) were evaluated between Roche CoaguChek XS strips, Roche CoaguChek Pro 2 and Abbott i-STAT INR cartridge participants. Outlier results defined by more than >3SD of the median were excluded from the dataset. Assessment of medians is made against target INRs defined by consensus INR medians across all measurement systems.

Results: A median difference was noted between the Roche and i-STAT devices. I-STAT medians were significantly lower than Roche XS strips at higher INR levels ($p<0.05$). This is also present between the Coaguchek Pro 2 and i-STAT ($p<0.05$). The two Roche systems had no demonstrated significant differences in medians at higher INR levels ($p>0.05$). The mean CVs of the i-STAT were found to be significantly higher than the Roche systems ($p <0.05$).

Conclusion: There is an indication of a bias between the Roche and Abbott systems, with i-STATS reporting significantly lower INR's compared to both Coaguchek systems at INR ratios >3. A difference in precision is also observed as demonstrated by the varying CVs. It is recommended that laboratories with oversight of these devices perform patient correlation with their mainframe analysers to determine if their patient results are suitably correlated.

Paroxysmal nocturnal haemoglobinuria (PNH) screening: indications and incidence of abnormal results

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Aim: Paroxysmal nocturnal haemoglobinuria (PNH) is a rare non-malignant clonal haematopoietic stem cell disorder with variable clinical manifestations, including haemolytic anaemia, thromboses and cytopenias. Modern flow cytometry-based PNH screening has high sensitivity and specificity. The aim of this study was to describe the most common medical indications for laboratory PNH testing and the incidence of abnormal results based on the different indications.

Method: We conducted a retrospective analysis of 605 peripheral blood specimens submitted to our laboratory for testing over a 12-month period. Clinical details collected included age, gender, PNH test result, size of PNH clone, indication for testing, requesting clinician specialty, full blood count parameters, haemolysis parameters, and location of thrombosis where relevant.

Results: Following exclusion of patients with known PNH clones and duplicate testing, there were 537 new patients screened. PNH clones were detected in 9 patients (1.7%). The most common indications for testing were thrombosis (52.3%), unexplained cytopenias (26.6%), haemolytic anaemia (7.6%) and aplastic anaemia (4.3%). The incidence of a detectable clone was highest for patients with aplastic anaemia (20%), followed by haemolytic anaemia (4.8%) and a small number of patients with cytopenias (1.4%). No patients screened for thrombosis tested positive. Approximately 50% of PNH clones were <10% in size, with larger clones found in those with haemolytic anaemia.

Conclusion: Our findings show that PNH testing is most effective in patients with defined haematological abnormalities and that screening performed for thrombosis is of very low yield.

Supptve Care (Poster Board No H148 – H157)

Exploring COVID-19 vaccination status and vaccine concerns in people with haematological malignancies.

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Aim: People with haematological malignancies in Australia were prioritised for COVID-19 vaccination from March 2021 due to their increased risk of severe COVID-19 complications. However, it is unclear whether earlier access to vaccination resulted in high uptake. This study explored COVID-19 vaccine uptake and attitudes towards COVID-19 vaccines in people with haematological malignancies.

Method: Between June and October 2021, an online survey was distributed to people with haematological malignancies at nine health services (Victoria, New South Wales, Queensland, and Tasmania). The survey collected sociodemographic and clinical characteristics, and attitudes towards COVID-19 and COVID-19 vaccination using validated scales including the Oxford COVID-19 Vaccine Hesitancy Scale and the Oxford COVID-19 Vaccine Confidence and Complacency Scale. Regression analyses were used to examine relationships.

Results: Of the 869 survey participants (mean age 64.2 years, 43.6% female), 741 (85.3%) received ≥1 COVID-19 vaccine dose. Of the 127 unvaccinated participants, 72 (56.7%) would definitely/probably have a vaccine if offered. Vaccinated status was associated with increasing age (OR 1.05, 95% CI 1.03-1.06), English as first language (OR 3.48, 95% 95% CI 1.90-6.38) and haematological malignancy diagnosis duration ≥5 years (reference: <6 months; OR 4.22, 95% CI 2.23-8.02). Negative attitudes around the speed of COVID-19 vaccine development were greater in those with university education (reference: no formal/primary/secondary education; B 0.75[SE 0.19]) and >$150,000 annual household income (reference: <$50,000; B 0.97[SE 0.26]), all p<0.001.

Conclusion: The uptake of COVID-19 vaccination was high in people with haematological malignancies. However, it appears to be lower in those who are younger, from culturally and linguistically diverse backgrounds, and recently diagnosed. Concerns about the speed of COVID-19 vaccine development differed between education and household income levels. Clinicians are well-positioned to address their patients' specific vaccine concerns and support the decision-making process, particularly with the need for COVID-19 vaccine boosters.

Infection patterns and outcomes in patients with newly diagnosed MM – preliminary results from the Immunoglobulins in Myeloma Patients: Research into Outcomes, Variation in practice and Epidemiology (IMPROVE) cohort study

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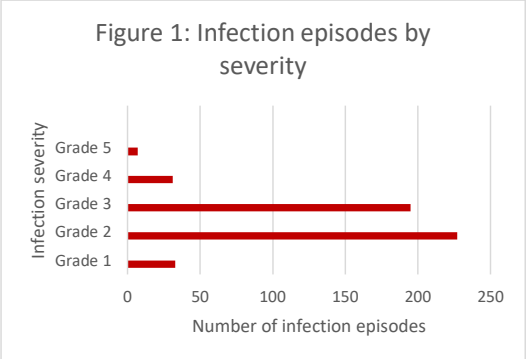
Aim/Method: Interim descriptive analysis of baseline characteristics, infection prophylaxis (including immunoglobulin use), infection patterns and outcomes in patients with newly diagnosed myeloma (NDMM) in the IMPROVE substudy of the Myeloma and Related Diseases Registry (MRDR).

Results: 327 NDMM patients have been enrolled into IMPROVE from 11 Australian and 1 New Zealand sites. Median age at diagnosis is 67.8 years (IQR 59.8-73.9). 62.4% of patients are male and 33.7% are high-risk (ISS-3). A high proportion of participants had multiple co-morbidities: moderate-severe cardiac or respiratory disease were seen in 16.8% and 8.3% patients respectively, and 14.1% had diabetes. Of 201 patients with baseline immunoglobulin levels available, 131 (65.2%) had hypogammaglobulinaemia (IgG<7g/L) and 67 (33.3%) had severe hypogammaglobulinaemia (IgG<4g/L). Most patients (92.7%) received induction chemotherapy, most commonly bortezomib-based (77.4%) and most containing dexamethasone (92.7%). 49.5% of patients underwent ASCT. 495 infection episodes have been detected in 224 patients over 5031m (1.2 per patient-year). Most episodes were classified as grade (G) 2 (requiring oral antimicrobials) (45.9%), or G3 (requiring intravenous antimicrobials, 39.4%); 7 infections (1.4%) were reported to be fatal. 135 (41.2%) patients had ≥1 G3/higher infection (requiring IV antimicrobial therapy, urgent intervention or resulting in death). The most common infection sites were respiratory (31.9%) or urogenital (10.1%). No organisms were identified in the majority of episodes. Of 150 infections with organisms identified, 68.7% were bacterial, 26% viral (none with SARS-CoV-2), 1.3% fungal. Immunoglobulin prophylaxis was reported to be administered to 32 patients (9.8%).

Conclusion: Infections are frequent in Australian and NZ NDMM patients and improved prevention and surveillance strategies are urgently required to improve infection outcomes. Further analysis of IMPROVE will follow, and a parallel study in NHL is underway (ICAN).

Table 1: Baseline patient characteristics

Patient characteristics	Number (%)
Age in years, median (IQR)	67.8 years (IQR 59.8-73.9)
Male sex	204/327 (62.4%)
ISS3	82/243 (33.7%)
ECOG2-4	62/242 (25.6%)
Comorbidities: Cardiac disease	55/327 (16.8%)
Comorbidities: Pulmonary disease	27/327 (8.3%)
Comorbidities: Diabetes requiring medication	46/327 (14.1%)
Induction therapy: Bortezomib-based	253/327 (77.4%)
Induction therapy: Lenalidomide-based	40/327 (12.2%)
Induction therapy: Daratumumab-based	13/327 (4.0%)
Induction therapy: Includes dexamethasone	303/327 (92.7%)
ASCT	162/327 (49.5%)
Hypogammaglobulinaemia	131/201 (65.2%)
Severe hypogammaglobulinaemia	67/201 (33.3%)
Deaths	82/327 (25.1%)



Enabling acutely unwell haematology patients to join and sustain participation in a study of cognitive function: Lessons learnt from a longitudinal study.

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Aim: Cancer-related cognitive impairment (CRCI) is a recognised adverse consequence of cancer and its treatment. This qualitative study was undertaken within a larger prospective project to assess the feasibility of collecting longitudinal data on cognition in patients with newly diagnosed aggressive lymphoma. Participants completed comprehensive assessments pre-chemotherapy, mid-chemotherapy, and six-to-eight weeks post-chemotherapy. Assessments included neuropsychological tests, self-report measures, blood-cell inflammatory markers, and neuroimaging. Our qualitative study aimed to explore reasons people participated in a study of cognitive function at a time of heightened stress related to a new diagnosis of aggressive lymphoma.

Method: We used qualitative descriptive methods with semi-structured interviews. Participants were approached to take part in one audio-recorded interview one week after their final study assessment. Interviews were transcribed verbatim, and a thematic descriptive approach used to analyse the data. Two members of the team co-coded the interviews to establish inter-rater agreement and consistency in coding.

Results: Thirty of 33 eligible patients were recruited to the longitudinal study; 27 participated in a semi-structured interview. Four themes described participants' motivation and ability to sustain participation in the longitudinal study. Themes included: ease of participation; personal values; self-help; and, valued additional support. Participants noted the importance of understanding study requirements, embedding data collection into existing hospital visits and the importance of contributing to a study that may help others. Although reported as challenging, participants stated cognitive testing provided feedback on current cognitive functioning and was described as a welcome distraction and enjoyable. Finally, interaction with the study-nurse was valued as an additional source of oversight and support

Conclusion: This study identified important enablers to study participation for acutely unwell haematology patients, even when study requirements are challenging and occur over a prolonged period. These insights will inform future study design to maximise recruitment and retention to supportive care studies.

Rates of menstruation history taking and counselling before, during and after anticancer treatments are low: women deserve gender specific cancer care.

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Aim: The purpose of this study was to explore the incidence of menstrual history documentation and counselling before, during and after cancer treatment.

Method: The medical charts of 143 consecutive women aged 18-49 receiving anticancer treatment at a major tertiary metropolitan hospital between 2017-2020 were included in this study. Data collected included primary diagnosis, stage of cancer, treatment(s) received, rates of remission or progression, documentation of involvement of a specialist gynaecologist, reproductive history, menstrual disturbances, menstruation counselling or intervention offered, and diagnosis of early ovarian failure. Descriptive statistics were used to summarise results.

Results: Only 15.4% had their menstrual history documented at the initial consult, and 47% had their menstrual history documented at a subsequent consult with their treating oncologist or haematologist. The majority (82.5%) of patients with a menstrual history documented experienced menstrual disturbance post treatment, most commonly amenorrhoea (48.5%), followed by irregular menstrual bleeding (22.3%), menorrhagia (12.6%), menopause (10.7%), dysmenorrhoea (4.9%) and iron deficiency from bleeding (1.9%). Dysmenorrhoea and iron deficiency were more likely to be treated than other disturbances.

Conclusion: Menstruation disturbance is common in women receiving treatment for cancer. This is important to know because chemotherapy predisposes women to abnormal uterine bleeding, including potentially life threatening menorrhagia and irregular menses, potentially leading to premature ovarian failure and infertility. Menstrual care should be integral to cancer care for women, and higher engagement could be achieved through education of medical and allied health staff, information technology systems automating prompts and referral pathways, regular audits to ensure compliance, better alliances between cancer and fertility specialists, and the creation of accessible patient information to promote awareness and facilitate discussion

Rate of sexual history taking and sexual dysfunction counselling before, during and after anticancer treatment

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Aim: To investigate the incidence of sexual history and counselling documentation before, during and after cancer treatment.

Method: Our group conducted a retrospective chart review at a major Australian cancer centre of premenopausal females aged 18-49 years diagnosed with cancer between 2017 and 2020. 143 participants met inclusion criteria. Data collected included primary diagnosis, stage of cancer, treatment(s) received, rates of remission or progression, involvement of a specialist gynaecologist, details of any sexual function/dysfunction discussions, and what treatment was offered. Descriptive statistics were used to summarise results.

Results: Only 9.8% had their sexual history documented by their haematologist or oncologist, and 4.2% had their sexual histories documented by a gynaecologist. 40 patients had documented sexual dysfunction, most commonly vaginal dryness (55%), dyspareunia (28%), body image concerns (28%), bacterial vaginosis (20%), decreased libido (18%), vaginal GVHD (3%), and muscle spasms affecting coitus (3%). When these issues were discussed, they were often addressed by requesting gynaecologist, sexual health specialist and/or psychologist reviews, or by prescribing ointments, antifungals, antidepressants, lubricants, laser treatments, insertion of an intrauterine device, dilators, vaginal moisturisers, topical oestradiol or inserts.

Conclusion: This rate of sexual history documentation is exceptionally low. This needs to be improved as cancer treatment can significantly affect patient sexual function, through physical alterations and psychosocial impacts. Women's sexual function concerns are infrequently raised by physicians or volunteered by patients. To overcome existing barriers, some potential solutions could include improving education of physicians on sexual dysfunction, implementation of technology systems to facilitate sexual history taking and gynaecology referrals, and the provision of patient information sheets to facilitate education and discussion.

Rates of contraceptive uptake and documentation of discussions before, during and after anticancer therapy

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Aim: To investigate the documented rates of contraception counselling and uptake in women of childbearing age at a major Sydney tertiary hospital.

Method: Our group conducted a retrospective chart review at a major Australian cancer centre of premenopausal females aged 18-49 years diagnosed with cancer between 2017 and 2020 (n = 143). Data collected included primary diagnosis, stage of cancer, treatment(s) received, complications, reproductive history, documentation of contraceptive use, and involvement of gynaecologists. Descriptive statistics were used to summarise results.

Results: At the time of diagnosis the following was documented: 8.4% of patients were taking the combined oral contraceptive pill (COCP), 4.9% had an intrauterine device, 0.7% were taking the progesterone only pill, and 0.7% had a contraceptive implant. Of those with an oral contraceptive agent documented, 15.4% had a thromboembolic complication post cancer diagnosis. Only 23.1% were documented to have received contraception advice from a physician or a pharmacist, including avoiding pregnancy during treatment (33.3%), recommending barrier contraception (24.2%), ceasing the COCP (15.2%), IUD removal (12.1%), and IUD insertion (3%).

Conclusion: All women with a cancer diagnosis should be counselled on contraception. Evidence suggests many women with cancer avoid contraception due to fear of worsening disease prognosis. Contraception choice should take into considerations tumour type, thrombotic factors, patient immunosuppression, haematological disorders, bone density, drug interactions, and metabolic or cardiovascular effects. Abstinence should not be assumed or recommended. To better facilitate contraception discussions, cancer specialists could receive education sessions on contraception, have centre-facilitated gynaecology referrals, implement technology systems to better assist history taking and improve compliance, and provide patients with written information to educate and facilitate conversations. Further studies should be conducted the success rates of these approaches.

Rates of fertility discussions and counselling before, during and after anticancer treatments

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Aim: To examine the incidence of fertility counselling documentation in women of childbearing age receiving chemoimmunotherapy.

Method: Our group conducted a retrospective chart review at a major Australian cancer centre of premenopausal females aged 18-49 years diagnosed with cancer between 2017 and 2020 (n=143). Data collected included demographics, cancer diagnosis, treatment(s) received, fertility history, timing and documentation of fertility discussions, referrals to specialist gynaecologists, and fertility outcomes. Descriptive statistics were used to summarise results.

Results: Only 12.6% had a reproductive health history documented at the initial consult, and just over half (58%) had a fertility preservation discussion documented at some point with their primary cancer specialist. A quarter (25.9%) saw a specialist gynaecologist to discuss fertility preservation options, and 11.2% had documented that a referral was declined. Of those with fertility-related outcomes documented, 21.0% had return of menses, 15.4% had >1 oocyte cryopreserved, 9.1% had already completed their families, 9.1% did not want children, 7.7% experienced premature menopause, 2.1% managed a successful pregnancy and birth, 1.4% had embryos cryopreserved, and 1.4% unsuccessfully attempted in vitro fertilisation.

Conclusion: In an Australian major cancer centre only a quarter of women of reproductive age with cancer saw a fertility preservation specialist. The rate of fertility discussions and referrals needs to improve as cancer treatment can significantly reduce reproductive potential in female patients. Promoting and facilitating reproductive counselling documentation could be addressed by promoting relationships between fertility gynaecologists and oncologists/haematologists, the implementation of technology systems ensuring fertility preservation discussions, and improved staff education

The effect of exercise on physical function in adults diagnosed with haematological cancer: A systematic review and meta-analysis

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Background: Individuals diagnosed with a haematological malignancy (HM) experience significant declines in physical function as a direct result of the biological nature of the malignancy and chemotherapeutic agents. With promising evidence supporting the efficacy of exercise performed throughout the cancer treatment trajectory for solid tumours, application for HM is not yet clear.

Aim: To evaluate the efficacy of exercise to improve physical function in HM adult patients throughout the treatment trajectory.

Method: A systematic review with multilevel meta-analysis was conducted. Four electronic medical databases were searched; MEDLINE (EBSCOhost), CINAHL, Scopus and CENTRAL for randomised control trials (RCT) of exercise interventions implemented during or after treatment for adults diagnosed with a HM subtype of Leukaemia, Lymphoma or Multiple Myeloma with an outcome measure of physical function.

Results: Twelve studies with a total of 812 participants were included in our systematic review. Analysis of 36 dependent effect sizes from nine studies revealed participation in a structured exercise program improved physical function (SMD = 0.39; 95%CI 0.21 to 0.57) compared to usual care or an active control. Exercise prescription that included a multimodal design consisting of aerobic and resistance exercise had a significant effect on physical function ($p < 0.001$), while exercise intensity had a significant effect when prescribed at a moderate ($p = 0.003$) and vigorous ($p < 0.001$) intensity.

Conclusion: This meta-analysis provides initial evidence for clinicians to recommend supervised moderate-vigorous intensity exercise with a multimodal design to improve physical function in adults diagnosed with HM. Future research should aim to identify optimal prescription guidelines throughout the treatment trajectory.

COVID-19 vaccination rate in patients with haematological malignancies

Dr Cecily Forsyth[1], **Ms Louisa Morand**, Dr Clare Rogers, Ms Amy Steigler, Ms Elly Henner-Cwin, Ms Madeleine Rogers, Ms Jacqueline Jagger, Dr Richard Blennerhassett
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Aim: We performed a retrospective single-centre cohort study to evaluate vaccination rates amongst patients with haematological malignancies being cared for by practitioners who actively promote vaccination at all consultations and via social media (website and Facebook).

Method: All patients with a haematological malignancy reviewed at least once by a practitioner at our centre between 1 January 2021 and 29 January 2022 were evaluated. COVID-19 vaccination status was determined by reviewing the electronic medical record, the Australian Immunisation Register or via an SMS to the patient. Patients were categorised by disease subtype, age (<60 years or ≥60 years), and treatment with disease-modifying therapy within the prior 12 months (active) or not (inactive).

Results: On 29 January 2022 897 patients were assessed, 726 patients (80.9%) had received 3 doses of a COVID-19 vaccine, 136 patients (15.1%) had received 2 doses and 35 (3.9%) were unvaccinated. Of 762 patients ≥60 years of age 640 (84%) had received 3 doses and 2.7% were unvaccinated. For patients <60 years the unvaccinated rate was 10.4%.
Of 346 active patients 84.1% had received 3 doses compared to 78.8% of 551 inactive patients.
The lowest rates of vaccination were seen in patients with Hodgkin lymphoma (HL) where 18 of 34 patients (52.9%) had received 3 doses; 5 patients (14.7%) were unvaccinated. For patients <60 years the unvaccinated rate was 20%.
The highest rates of vaccination were in patients with multiple myeloma where 66 of the 73 patients (90.4%) had received 3 vaccine doses, 3 patients (4.1%) were unvaccinated.
On 29 January 2022 the NSW-wide rate of 3rd doses in people >16 years of age was 37.5%.

Conclusion: Over 80% of patients with haematological malignancies in our centre had received 3 COVID-19 vaccine doses by late January 2022, twice the rate of the NSW population. Although immunocompromised patients may be more motivated to proceed with vaccination we believe that the active, haematologist-driven promotion of COVID-19 vaccination has contributed to the high vaccination rates at our centre.

ANZSBT Poster Presentations (Poster Board No A002 – A063)

Transfusion considerations in sickle cell disease: alloantibodies and hyperhaemolysis

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A 37-year-old man with sickle cell disease developed a chest crisis following withdrawal of hydroxycarbomide therapy for fertility treatment. Clinically, the patient required a red cell exchange but was known to have a historical anti-C, anti-Doa, anti-Jkb and anti-Fya. Anti-Fy3 had been suspected but was excluded as genotyping revealed a Duffy silencing mutation. There was also another suspected alloantibody that remained unidentified despite reference laboratory investigation.
On this occasion, testing of the patient's plasma revealed pan-agglutination on a 3-cell screen and 11-cell antibody identification panel. Extensive investigation by tube, CAT, IAGT, enzyme and referral of fresh sample to reference laboratory failed to identify specificity of antibodies present. Due to clinical deterioration, the patient proceeded to red cell exchange using eight genotype-matched, but crossmatch incompatible red cell units, by IAGT. Units selected for transfusion were A- or O-positive, C-negative, K-negative, Fya-negative, Jkb-negative, and S-negative. Doa-negative units were not available.
The patient re-presented 8-days later with symptomatic anaemia and biochemical evidence of haemolysis. His haemoglobin fell from 103g/L on discharge to 41g/L. A delayed transfusion reaction with hyperhaemolysis was suspected and he was pulsed with methylprednisone. Privagen (2x 65g) was administered. Patient blood management principles were enacted including prescription of erythropoietin and folate. However, given the risk of developing a second crisis due to severe anaemia and reports of exertional angina, the decision was made to transfuse with one unit of the least incompatible red cells. The patient's haemoglobin incremented to 73g/L following a second unit. He was discharged without evidence of further haemolysis.
This case highlights the importance of involving haematology in all aspects of sickle cell patient care, the investigative pathway for complex alloantibody cases and above all, the importance of patient blood management in high-risk haemoglobinopathy patients.

Unexplained long persistent allo-antibody to RhC in a patient with warm autoimmune haemolytic anaemia

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Aim: To present a case with exceptionally long persistence of a red blood cell (RBC) allo-antibody, and to consider factors that may explain it.

Method: Case report and literature review.

Results: An 89 years old female with warm autoimmune haemolytic anaemia (WAIHA) was found to have an allo-anti-C after allo-adsorption of native plasma. This was consistent with her Rh phenotyping which showed that she was C-. We believe the initial stimulus for this allo-anti-C occurred was a pregnancy at least 57 years prior. Her son, 57 years old, was found to be C+, and moreover had suffered with neonatal jaundice. We also confirmed - from records, and from the patient directly - that there had been no subsequent allo-immunising events.

Treatment with phenotype-matched RBC transfusions and steroids was successful. To consider further the long-persistent allo-anti-C, we examined her HLA class II phenotype. This was DRB1*07:01:01, DRB1*15:01:01, HLA DQB1*02:02:01, *06:02:01 and HLA DQA1*01:02:01,*02:01:01.

Incidentally, 44 years is the longest recorded persistence of an anti-Rh allo-antibody (anti-D and anti-C) we found in the literature. HLA-DRB1*15, and HLA-DQB1*06 are associated with development of multiple RBC allo-antibodies. Interestingly, HLA-DQ6 has been reported as protective against WAIHA. We considered other explanations for the persistent allo-anti-C including molecular mimicry, and WAIHA itself,

Conclusion: We report a very persistent, not-fully-explained, allo-anti-C in a patient with WAIHA. The association of HLA DRB1*07:01:01, DRB1*15:01:01, HLA DQB1*02:02:01 with not merely alloimmunization to RhC, but the long persistence of allo-anti-C needs to be examined. Patients with long-persistent antibodies pose clinical challenges, and there is insufficient information on the risk factors for this. A reliable, clear, and comprehensive history of prior immunizing events is important to understand and resolve RBC antibody issues.

Delivering virtual education, the silver lining to our COVID cloud

Ms Kaylene Bastin[1], Ms Linley Bielby[1], Ms Christine Akers[1], Ms Bridget Glazebrook[1], Dr James Daly[2]
[1]Blood Matters, West Melbourne, Australia, [2]Australian Red Cross Lifeblood, Brisbane, Australia

Background: One aspect of the Blood Matters Program is providing education to clinical staff throughout Victoria. In March 2020, the ability to deliver in-person education ceased due to COVID-19 pandemic lockdowns. Accordingly, the Blood Matters blood management/transfusion education went virtual.

Aim: To provide safe and easily accessible high quality blood education throughout Victoria to meet the clinical need.

Method: A user-friendly virtual education platform was used to deliver blood management/transfusion education. Each session was delivered live and recorded. Attendance and registration data captured. Recorded events distributed to all registrants, including those not able to attend. Events were evaluated. The virtual education attendance and time were compared to similar in-person education conducted in 2018-19.

Results

2020-2021 virtual	No. events	Average attendance/event	Total	Time (hrs)/ event	Total hrs
5 topics in 5 days series	3	95	285	5	15
EN series	3	15	44	4	12
Private health series	2	26	52	4	8
5 topics in 5 days for midwives	1	47	47	5	5
Other	5	122	608	1	5
Total	**14**	**74**	**1,036**	**20**	**45**

Event recordings have been sent to >1,500 registrants, with many intending to share with colleagues. Over 90% found the platform easy to use and would recommend the education to others.

2018-2019 in-person	No. events	Average attendance/event	Total	Average time (hrs)/ event	Total hrs
Regional days	12	21	252	6	72
EN days	2	24	48	7	14
Short sessions	21	17	362	2.5	53.5
Total	**35**	**19**	**662**	**15.5**	**139.5**

Conclusion: In the last two years Blood Matters have provided time effective education beyond Victoria, with participants across Australia; resulting in education reaching a greater audience in less time. Virtual education reaching 23 persons versus 4.7 in-person for each hour. Attendance and the feedback support our COVID silver lining of virtual education, and it will continue

Is the introduction of an electronic medical record (EMR) meeting pretransfusion sample collection safety requirements?

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Aim: To identify the number of health services using EMR for pretransfusion sample collection.

Method: 131 health services from 4 Australian jurisdictions were invited to participate in an EMR survey. Multidisciplinary experiential and objective data were sought.

Results

1. 111 individual responses from 59 health services
   - 51 from 20 health services (34%) reported using an EMR
   - 34 from 11 health services (55%) reported using an EMR for pretransfusion sample collection

Specific aspects of pretransfusion sample collection pertinent to patient safety were analysed as reported below.

	Number health services
EMR test request with an EMR generated paper request form	10
EMR test request only	1
Paper only	2
EMR generated labels	7
Handwritten labels	4
Unique staff identifier entered	1
Signing a printed form	10
Scanning the patient ID pre-sample collection	7
Post collection scanning of sample labels	4
Safety data	
Increase in sample errors	2
Increase in WBIT	2
Decrease in sample error	2 sustained
Decrease in WBIT	2 (1 sustained)

[The pretransfusion test request method varied between departments within 2 health services.]
One health service uses an electronic signature or equivalent to confirm correct patient identification and sample labelling process. All others use a printed form signed by the collector.

Conclusion: Pretransfusion sample collection is used by 55% of health services with EMR. Many have a hybrid system, with handwritten blood sample labels and printed request forms with the collector's declaration, which may negate some the safety benefits of an EMR. Patient ID band scanning with post sample collection tube scanning, which can help with matching the sample to the patient, is performed by a minority of health services.
The variation in responses for sample error and WBIT rates may relate to system differences and respondent roles. Understanding the experience of those with an EMR, can improve system and patient safety.

Stop the bloody waste

Mrs Karen Beattie[1]
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Aim: Blood is a precious, generously donated product that costs $399 per unit. Emergency O negative red blood cell (RBC) wastage in a small rural facility blood fridge was 38%. The aim of this project was to reduce emergency red blood cell wastage from a satellite blood fridge in a small NSW rural hospital to 6% by April 2021.

Method: RBC's are transported to facilities, with no transfusion laboratories, in blood shippers and stored in satellite blood fridges. An improvement science framework was employed for this project to understand the causes of RBC wastage and implement change ideas. Pre-implementation and post implementation waste data and staff knowledge surveys were collected. Pre-implementation, 60% of total RBC wastage was attributed to clinician error. Simulated blood shipper deliveries from a transfusion laboratory were employed to test solutions and implement sustainable practice changes.

Results: This project led to a 47% reduction in emergency RBC wastage. The aim of 6% wastage was not achieved, however wastage was trending down at completion of the project. The project demonstrated a 16-32% improvement in clinician familiarity with blood fridge procedures. On completion, a statistically significant number of surveyed participants did not require additional education regarding the blood fridge (12% pre-implementation verse 73% post-implementation).

Conclusion: Pre-implementation, pathology services and health professionals operated in silos, with poorly defined roles and responsibilities. Engagement with key stakeholders and the formation of collaborative partnerships was necessary to ensure project success. Incorporating existing procedures from NSW Health Pathology into the Western NSW Local Health District project solutions was essential for sustainability and overall governance. Simulated blood shipper deliveries proved an excellent tool to test solutions and improve clinician familiarity with mandated procedures and reduce emergency RBC wastage.

A case of allo anti-D in a pregnant woman with the RHD*0.1N.25 variant allele

Miss Emily Black[1]
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Initial Results: A sample from a 36 year old woman, 20 weeks gestation, was referred to the Australian Red Cross Lifeblood for Non-Invasive Prenatal Assessment (NIPA) for fetal RHD. The referring laboratory indicated the patient was A RhD negative and had allo anti-D with a titre of 128. NIPA testing was inconclusive as results suggested a maternal RHD variant was present. RHD genotyping from maternal genomic DNA was a possible D positive, with a low signal at c.340 C>T by a commercial RHD genotyping kit.

Next Steps: Phenotyping was performed by the Red Cell Reference laboratory as A C+E-c+e+ K-Fy(a+b+) Jk(a+b-) M+ N+ S+ s+ Rh33+ Rh43+. RHCE genotyping was performed to eliminate possible RHCE variants, and none were detected. Antibody identification confirmed the presence of anti-D and titre of 128. An adsorption/elution with anti-D using the acid glycine method was performed. Anti-D wasn't eluted. The sample was referred for RHD sequencing with results indicating a heterozygous nucleotide substitution (c.336-1G>A), leading to a splice site change at the intron 2/exon 3 boundary of RHD. This variant defines the RHD*0.1N.25 allele and a RhD negative phenotype expression.

Patient Management and Clinical Outcome: A sample from the patient's partner was referred for RHD Zygosity testing. The partner was confirmed as homozygous for RHD, indicating the fetus would be RHD positive. Prior to delivery, the patient's anti-D quantitation rose to 12.4 IU/mL with the titre rising to 1028. During delivery she had a 1st degree tear with an estimated 800mL blood loss. The newborn required phototherapy due to mild jaundice, with bilirubin levels peaking at 153µmol/L.

Conclusion: This is the first reported case of allo anti-D in a patient with the RHD*0.11/.25 variant allele. Laboratories performing NIPT for RHD should consider the impact of RHD variants on the interpretation of their results.

WA Antibody Register replacement

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[1]Australian Red Cross Lifeblood, Perth, Australia, [2]Australian Red Cross Lifeblood, Brisbane, Australia, [3]Australian Red Cross Lifeblood, Melbourne, Australia

Aim: To replace the historical Western Australian Antibody Register (ABR) with a new cloud hosted system and migrate the historical data, ensure that the system complies with modern security and privacy requirements, and can easily be accessed by Approved Health Provider's (AHPs).

Method: Replacing the ABR was a Lifeblood agile project. Microsoft Azure DevOps was used to capture project requirements in the form of epics, features and user stories. Each functional user story delivered was tested prior to being marked as complete. Throughout the project, stakeholders and users of the system were showcased the working functional software, to seek and incorporate feedback into the project build.

The ABR was constructed within the Lifeblood landing zone of Amazon Web Services (AWS). It utilises best practice cloud security features, including but not limited to; authentication solutions, firewalls, network restrictions and permissions matrixes.

Following consultation with Legal representatives and consultants, the new ABR was built around an opt-in patient consent management process.

Results: The new cloud hosted ABR was built in-house by Lifeblood who is also responsible for ongoing maintenance and support. 36,601 records were successfully migrated. Lifeblood works collaboratively with AHP's to ensure the data added to the register is current and only people who have provided their consent for inclusion in the register can be searched and viewed. The personal data is secure and can only be accessed by individual authorised users of the system.

Conclusion: The replacement ABR was successfully launched in March 2022 and all Western Australian AHPs were provided access to the system in April 2022. The system gives pathology laboratories timely access to the critical information they need to support patients who require specialised blood components. This information:

1. assists with red cell antibody identification

    - enables the provision of appropriate blood
    - reduces the risk of delay in supply
    - reduces the risk of haemolytic transfusion reactio

Anti-Cra case study; difficulties in donations from a rare phenotype

Mr Bryan Bourke[1], Ms Amy Tearle[1], Mr Brett Wilson[1]
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Aim: Identification of a rare Cromer blood group antibody in a Zambian patient and the appropriate transfusion management, including autologous blood donation.

Method: Whole blood samples were analysed by various serological techniques to identify any antibodies present. Phenotyping was performed using a combination of commercial and rare antisera. Antibody activity was inhibited using recombinant Decay Accelerating Factor (srDAF). Genotyping was completed using Immucor BioArray HEA Precise BeadChip and TruSight One sequencing panel.

Results: The plasma was reactive with all cells tested by column agglutination technology (CAT) and tube indirect antiglobulin test (IAT) methods, however the antibody was non-reactive by NEO solid-phase method. DAF protein inhibition indicated the presence of a Cromer system antibody. Cr(a-) phenotype was confirmed serologically. The patient's cells showed variable reactions with M and S antisera.

HEA BeadChip analysis was unsuccessful.

CD55 gene variation in the Cromer system was detected by sequencing, with homozygosity for the nucleotide substitution c.679G>C, which is responsible for the Cr(a-) phenotype. An MNS system variant was also detected resulting in the GP.He hybrid glycophorin.

Conclusion: Difficulties in relation to blood transfusion arise when confronted with anti-Cr^a antibodies. This case was further complicated by the presence of other inconsistent phenotyping results attributed to a variant glycophorin present. Nucleotide polymorphisms giving rise to this variant glycophorin may be responsible for an unsuccessful HEA BeadChip read.

Although our patient's haemoglobin levels returned to normal, ambiguity surrounds the suitability of autologous donations due to our patient possessing sickle cell trait. Processing of such a donated unit may encounter problems at the leucocyte filtration step, along with possible haemolysis associated with freezing and thawing of donations due to red cell fragility.

As Cromer system antibodies are seldom responsible for HTRs, antigen negative blood is not usually required for transfusion and least incompatible crossmatched blood is generally suggested, with Cr(a-) units potentially being sourced for strong examples of anti-Cr^a.

Twenty years of being BloodSafe in South Australia

Mrs Amanda Catherwood[1], Dr Kathryn Robinson[2], Mr Russell Hunt[3], Mrs Jodie Grech[4], Mrs Joanne Goodwin[5]
[1]Bloodsafe, Adelaide, Australia, [2]BloodSafe, Adelaide, Australia, [3]BloodSafe, Adelaide, Australia, [4]BloodSafe, Adelaide, Australia, [5]BloodSafe, Adelaide, Australia

Aim: Celebrating the 20-year anniversary of South Australia's BloodSafe Program.

Method: In September 2002 at HAA Adelaide (now Blood), a team of enthusiastic, dedicated, and innovative individuals came together to pilot a quality assurance program for blood products in South Australian Hospitals.

It was a collaborative project between the Department of Human Services (now Department of Health and Wellbeing), Australian Red Cross Blood Service (now Lifeblood), Institute of Medical and Veterinary Science (now SA Pathology) and the Metropolitan and Country Clinical Sub Committees of the SA Hospital Safety and Quality Council (now Rural Support Services).
The names may have all changed but the collaboration is still strong 20 years later with many of the founding members/contributors still actively involved.

Results: The pilot has become part of the suite of programs within the Department of Health and Wellbeing's division of Blood Organ and Tissue Programs directed by Susan Ireland. The BloodSafe mission to coordinate a safety and quality framework for all steps of blood transfusion practice to improve patient outcomes and ensure sufficiency of blood supply by supporting and using patient blood management principles continues.

The Clinical Medical Lead Dr Kathryn Robinson (OA) has led the team since 2002. There is currently a BloodSafe Nurse in each metropolitan health network (Southern, Central, Northern, Women's & Children's) along with a private hospital and a regional support nurse.

A few BloodSafe highlights include:

1. Collaboration with Australian and international transfusion groups
    - Flippin' Blood
    - the first prototype of an eLearning, to eventually become BloodSafe eLearning Australia
    - Iron prescribing resources
    - Patient information resources (translated into 18 languages)
    - Initiation of a Private Nurse role
    - Blood Link Nurse framework development

Conclusion: BloodSafe looks forward to the continued collaboration with our dedicated and innovative colleagues across Australia and the world

The double independent bedside check – Development of a how-to video for a healthcare service implementing electronic medical records

Mrs Amanda Catherwood[1], Mrs Joanne Goodwin[2]
[1]*BloodSafe, Adelaide, Australia,* [2]*BloodSafe, Adelaide, Australia*

Aim: The final 'bedside' check of pack and patient details is vital to ensure the *right* blood is given to the *right* patient[1]. In 2019, ANZSBT provided clarification, the transfusion double independent (DI) check is 2 professionals *independently* carrying out and taking responsibility for the procedure[1] rather than the historical process of a shared check between 2 staff.

Our health service commenced staged implementation of a state-wide electronic medical record (EMR) resulting in significant changes to transfusion workflows. The final hospital went 'live' in March 2020; a week into Australia's COVID-19 pandemic lockdown.

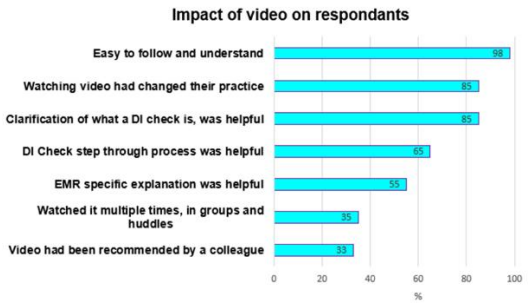
The combined effect of changed workflows and timing, led to unsafe workarounds for critical processes. A hospital bedside check audit confirmed this.

BloodSafe aimed to develop a resource which was accessible, consistent, repeatable, and engaging which could reach large groups quickly to improve patient safety during uncertain times.

Method: BloodSafe produced a 5-minute video, simulating a patient focused, safe process of a DI check using EMR, to ensure risk mitigation in a timely manner. The video was promoted via the BloodSafe intranet page, education portal and organisational wide communications.

A follow up audit of bedside practice will occur when pandemic and hospital acuity permits. In the interim, a survey was conducted to gain insight into the impact the video had for clinicians and their practice.

Results: As of April 2022, the video gained over 4,500 impressions and 604 views. 40 staff responded via Survey Monkey: Of note 85% confirmed watching the video had changed their practice.



Conclusion: Utilising methods such as video demonstrations provides a platform for quick delivery of accessible, consistent, repeatable, concise, and impactful resources to large groups.
The video is now a state-wide resource for Sunrise EMR training and can serve as a 'template' for health services using other EMRs to develop their own resource.

Reference 1. ANZSBT Guidelines for the Administration of Blood Products, 3rd Edition, 2019, Australian & New Zealand Society of Blood Transfusion

Variation in use of immunoglobulin (Ig) and impact on survival in multiple myeloma: A report from the Australia/New Zealand (ANZ) and Asia-Pacific (APAC) Myeloma and Related Diseases Registries (MRDR)

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Aim: To evaluate Ig use in patients with MM in the “real-world” setting, identify variation in practice and predictors of use, and describe association with survival.

Method: Retrospective review of patients with a diagnosis of MM/plasma cell leukaemia registered on the ANZ and APAC MRDR from sites with complete Ig data. Survival and cause of death (COD) was augmented via linkage with death registries for ANZ patients. Patient/disease characteristics, therapy and survival were compared between patients who received Ig by 24 months (m) of diagnosis or did not, using chi-square tests for categorical variables and rank sum tests for continuous variables. Kaplan-Meier survival analysis was used to estimate duration of Ig use. Time-dependent Cox analysis was used to compare survival for patients whilst on and off Ig. Statistical analysis performed using STATAv16.1.

Results: 2445 patients from 19 sites in four countries (Australia, Korea, NZ, Singapore) with a median follow-up of 30m were included. Of patients reaching 24m follow-up, 7.0% received Ig (0-17% between countries). 69% of these Ig-users were estimated to receive >24m duration of Ig. Patients who received Ig by 24m of MM-diagnosis were younger, had lower baseline IgG levels, more likely to have abnormal FISH, receive first-line IMiDs, anti-CD38 and ASCT *(Table 1).* Ig use was not associated with OS (HR=0.72, 0.46-1.14, p=0.16). At last follow-up, there were 623 deaths (25.4%). COD was available for 175 deaths - 65 deaths (37.1%) had infection as primary/secondary COD. 64 infection-related deaths occurred in patients who did not receive Ig. In patients who received Ig, 12.5% had infection-related COD, compared to 38.5% in non-recipients (p=0.14).

Conclusion: Ig use varied between countries and was associated with first-line IMiD/anti-CD38/ASCT. There is a clear need for contemporary studies to better inform patient selection, especially with rising use of Ig, targeted anti-myeloma therapies and high burden of infection-related mortality.

Table 1: Patient demographics, disease characteristics and upfront treatment, by Ig use at 24 months

Characteristics: median (IQR) or percentage (%)	**No Ig within 24 months (1031 patients)**	**Ig within 24 months (209 patients)**	**p-value**
Age at diagnosis	65.3 (58.0, 72.6)	62.6 (55.6, 69.5)	0.01
Female gender	411/1031 (39.9%)	86/209 (41.1%)	0.73
ECOG 2-4	102/674 (15.1%)	20/159 (12.6%)	0.41
Abnormal FISH results	399/610 (65.4%)	96/121 (79.3%)	0.003
ISS-3	230/802 (28.7%)	45/172 (26.2%)	0.51
Serum Ig levels (excluding paraprotein) (g/L)	23.0 (19.0, 40.0)	20.4 (16.6, 24.6)	0.006
Serum IgA levels (excluding paraprotein) (g/L)	0.5 (0.28, 1.1)	0.41 (0.2, 1.1)	0.42
Serum IgM levels (excluding paraprotein) (g/L)	0.2 (0.2, 0.4)	0.20 (0.1, 0.4)	0.11
Serum IgG levels (excluding paraprotein) (g/L)	6.0 (4.0, 10.3)	5.20 (3.3, 7.2)	0.002
First-line treatment with ASCT	550/1031 (53.3%)	124/182 (68.1%)	<0.001
First-line treatment with Proteosome inhibitor	883/1016 (86.9%)	187/206 (90.8%)	0.13
First-line treatment with IMiDs	196/1016 (19.3%)	92/206 (44.7%)	<0.001
First-line treatment with Anti-CD38 therapy	17/1016 (1.7%)	8/206 (3.9%)	0.041
First-line regimen containing Dexamethasone	952/1016 (93.7%)	197/206 (95.6%)	0.29

Retrospective analysis comparing clinical features and outcomes of patients who received out-of-hospital red cell concentrates to untransfused patients en route to The Royal Melbourne Hospital.

Dr Edward Chew[1], Dr Christopher Hogan[1], Dr Victor Lin[1], Professor Karen Smith[2,3], Mr Dilshan Udayasiri[1], Associate Professor Zoe McQuilten[3], **Mr Michael Haeusler[1]**, Mr David Read[1,4]
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Aim: Out-of-hospital transfusion of red cell concentrates (RCCs) has been safely implemented with zero wastage by The Royal Melbourne Hospital (RMH) and Ambulance Victoria since 2011. This retrospective audit aimed to compare the clinical characteristics and outcomes of major trauma patients who received RCC en route to RMH to patients who were untransfused.

Method: Adult patients with major trauma who received out-of-hospital RCCs were identified through chart review of RMH Transfusion Laboratory records. Clinical information of RMH patients with major trauma were obtained from medical records and Victorian State Trauma Outcomes Registry (VSTORM). Qualitative statistics was performed with Microsoft Excel.

Results: From April 2011 to December 2019, 8296 adults with major trauma presented to RMH. Eighty patients (52 males, 28 females) with a median age of 41.5 years (range 18 to 89 years) had out-of-hospital RCC transfusions. A median of 3 RCCs (range 1 to 8 units) were transfused with 30 patients receiving 4 RCCs and 11 patients receiving 3 RCCs.

When patients who received RCCs were compared to untransfused patients, they were more likely to be transferred from regional Victoria (44/80 or 55% versus 2208/7955 or 28%) and involved in motor vehicle accidents (71/80 or 89% versus 4061/8216 or 49%).

Twenty-five patients who received out-of-hospital RCCs died in hospital. The study was not powered to identify any differences in injury severity score or co-morbidities contributing to outcomes within the transfused subgroup.

Conclusion: Patients with major trauma due to motor vehicle accidents in regional Victoria were more likely to be transfused with RCCs en route to RMH. Further analysis with larger case numbers are required to identify factors contributing to transfusion requirements and clinical outcomes in major trauma.

Interleukin-10 and DNase treatment both mitigate endothelial cytotoxicity in a two-hit model of soluble CD40 ligand mediated TRALI

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Aim: Despite the introduction of risk reduction strategies, transfusion-related acute lung injury (TRALI) remains a significant cause of transfusion-related morbidity and mortality. In the absence of specific treatments for TRALI, patients are supported with supplemental oxygen and in some cases mechanical ventilation. Potential specific treatments, including interleukin (IL) 10 and DNase, have successfully prevented or treated experimental TRALI in mouse models; however, their potential to treat clinical TRALI in humans is unknown. We aimed to use an established human in vitro model to assess whether either IL-10 or DNase could mitigate soluble CD40 ligand (sCD40L)-mediated TRALI

Method: Human microvascular lung endothelial cells (HLMVECs) were cultured ± 2 µg/mL E. coli lipopolysaccharide (LPS) for 6 hours. Isolated neutrophils were added to appropriate wells (1:10 neutrophil:HLMVEC ratio). HLMVECs ± neutrophils were either left untreated or treated with sCD40L (10 ng/mL) for 30 minutes ± interventions (IL-10 (10 ng/mL) or DNase (1U/mL)). After trypan blue staining, 3-5 fields per well were acquired and viable HLMVECs were identified by ImageJ analysis. Data were analyzed with repeated measures one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. $P<0.05$ was considered significant.

Results: Both LPS and neutrophils were required for sCD40L-mediated HLMVEC cytotoxicity (LPS-control: 81.96 ± 2.65% viability and LPS+sCD40L: 52.68 ± 6.39% viability, P=0.005), confirming the two-hit neutrophil activation pathway. HLMVEC cytotoxicity was reduced by the addition of either IL-10 or DNase (LPS+sCD40L+IL-10: 73.91 ± 4.87% viability, P=0.003 vs LPS+sCD40L and P=0.34 vs LPS-control; LPS+sCD40L+DNase: 73.11 ± 5.64% viability, P=0.314 vs LPS-control; P=0.0003 vs LPS+sCD40L).

Conclusion: In this human in vitro model, sCD40L induced HLMVEC cytotoxicity via a two-hit neutrophil activation pathway of TRALI. Both IL-10 and DNase treatment mitigated the sCD40L-mediated HLMVEC cytotoxicity, confirming the importance of further research into their potential as specific treatments for clinical TRALI.

Evaluation of packed and washed RBC for immunomodulatory potential

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Aim: Our understanding of transfusion-related immunomodulation (TRIM) and its possible association with higher rates of poor patient outcomes after transfusion remain limited. We previously demonstrated that mediators in packed red blood cells (PRBC) augmented lipopolysaccharide (LPS)-induced interleukin (IL)-1β inflammation in monocytes[1]; however, the contribution of all leucocytes remains unknown. We assessed the effect of PRBC, PRBC-derived mediators and washed (w)RBC on caspase-1/IL-1β inflammation.

Method : PRBC (n=12) were sampled on day (D)2, D21 and D42, with samples centrifuged to prepare supernatant (SN) and washed as per Lifeblood guidelines to produce wRBC. Whole blood from healthy volunteers (n=6) was incubated with PRBC, PRBC-SN or wRBC (2 units each) ± LPS (bacterial infection model; 37ºC, 4h). Culture SN were collected and caspase-1 (ELISA) and IL-1β (cytometric bead array) quantified. Results were analysed by 2-way ANOVA ($P<0.05$ was significant).

Results: PRBC, PRBC-SN and wRBC alone did not modulate caspase-1 and IL-1β production compared to the no transfusion control. Interestingly, LPS-mediated caspase-1 production was reduced by co-culture with D21 or D42 PRBC (D21: P=0.007; D42: P=0.04) or PRBC-SN (D21: P=0.039; D42: P=0.011). Similarly, LPS-mediated IL-1β production was reduced by co-culture with D21 or D42 PRBC-SN (D21: P=0.008; D42: P=0.005). In contrast, LPS-mediated IL-1β production was augmented with the addition of D42 wRBC (P=0.0362).

Conclusions: PRBC and PRBC-SN decreased LPS-induced caspase-1 and IL-1β production while wRBC augmented the levels. Mediators that accumulate in PRBC during storage may inhibit IL-1β driven inflammation. Washing of RBC may remove the inhibitors. The results highlight the complexity of TRIM and the importance of further studies into how TRIM develops.

[1]Chong et al, 2022, Soluble mediators in packed red blood cells augment lipopolysaccharide-induced monocyte interleukin-1β production, Vox Sanguinis, 115:562-569

Guideline for the Prophylactic use of Rh D immunoglobulin in pregnancy care

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Aim: Review and update the 2003 *Guidelines on the Prophylactic Use of Rh D Immunoglobulin (Anti-D) in Obstetrics*.

Method: A multidisciplinary Expert Reference Group (ERG) was established to oversee the Guideline update. A comprehensive search of the literature was conducted in July 2018 by independent commissioned systematic review. An additional search of the literature was conducted in September 2021 to capture any additional research published since the searches in 2018.

The ERG utilised Grading of Recommendations, Assessment, Development and Evaluation (GRADE)2 to determine the certainty of the evidence and the strength and direction of each recommendation. Public consultation was conducted between 20 September and 8 November 2019.

Results: The update resulted in 12 clinical recommendations and 12 consensus-based expert opinion points across four clinical questions:

1. non-invasive prenatal testing (NIPT)
   - dosage regimen for antenatal prophylaxis
   - use of Rh D immunoglobulin in pregnant women with a Body Mass Index (BMI) ≥ 30
   - use of GRADE methodology

Standalone flow charts to demonstrate the care pathway for the prophylactic use of Rh D immunoglobulin in pregnancy care with and without NIPT, and resources on the use and timing of pathology testing and the indications and timing for administration of Rh D immunoglobulin were developed.

The Guideline update was published in May 2021 on the NBA website. The updated literature search in September 2021 did not identify any new studies that could change the direction or strength of the recommendations.

Conclusion: The Guideline for the Prophylactic use of Rh D immunoglobulin in pregnancy care provides clinical advice for the health professionals caring for Rh D negative pregnant women. The guideline includes recommendations on routine antenatal Rh D immunoprophylaxis, sensitising events immunoprophylaxis and immunoprophylaxis regarding BMI.

The Guideline will be republished in MAGICapp to facilitate efficient updating of recommendations when indicated.

[2] GRADE handbook. (2022). Retrieved 20 April 2022, from https://gdt.gradepro.org/app/handbook/handbook.html

Blood Usage, Clinical and Laboratory Systems at Three Different Australian Hospital Sites

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Aim: To review and compare Transfusion Medicine systems, clinical and laboratory services at three different Australian hospital sites: Mildura Hospital in rural Victoria, Peel Health Campus in Western Australia- on the border of rural and metropolitan areas, and Fiona Stanley Hospital, WA's largest teaching hospital.

Method: In collaboration with laboratory and clinical staff at each site, current practices were discussed and reviewed. Product availability and requirements at each site, including management of major haemorrhage, surgical, oncological and obstetric activity was recorded. Local protocols and practises as well as national guidelines were viewed and compared. Blood Component Fate from ARCBS/LifeBlood in 2021 was reviewed.

Results: All sites are compliant with the National Blood Authority Standard 7 and Patient Blood Management guidelines. Regular Transfusion Committee Meetings and close liaison with LifeBlood regarding activity and requirements in the different settings are noted. Mildura Base Hospital being a fairly remove 165 bed teaching hospital requires platelets on site, and adequate supplies of emergency O-Group red cells. The major teaching hospital at Fiona Stanley Hospital has extensive laboratory services and blood products including monoclonal and platelet derived specialised clotting factors. Peel Health Campus is a privately operated 206 bed general hospital one hour south of Perth; platelets are not routinely on site. Blood products are rotated in the network to reduce wastage, which is low. Mildura Hospital expired rate of platelets was 32.8% and RBCs 7.1%, both higher that the national average, unlike the FFP discards of 9.5%.

Conclusion: Robust Transfusion Medicine systems are in place at all three sites. Standards from the National Blood Authority, with supply and guidance from LifeBlood and involvement by Transfusion Committees are instituted at all three sites, including management of major haemorrhage and patients on anticoagulants. Individual factors and requirements related to location and size result in certain local practises, with greater discards at the rural site.

Understanding the Pathophysiology of the Monocyte Monolayer Assay (MMA): Characterizing the Inflammatory Response to Clinically Significant anti-RBC Antibodies.

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Background and Aim: The MMA is a functional in-vitro assay that uses a combination of cell isolation techniques and microscopy to predict whether an anti-RBC antibody present in a patient would result in a transfusion reaction. Whether an anti-RBC antibody results in a clinically significant reaction is not correlated with anti-RBC titre, a specific IgG subtype or the capacity of an antibody to fix complement. Improvements in utilising the MMA to predict transfusion reactions is limited by our understanding of the biology underpinning the assay. We investigated the role of inflammation and cytokine driven cell communication in the pathophysiology of the MMA.

Methods: Supernatants derived from previously performed MMA at Lifeblood were selected based on their monocyte index (MI%) in the MMA (≥5% considered clinically significant). Fourteen clinically significant (anti-D, anti-Jka), 25 non-clinically significant (anti-C, anti-E, anti-Ge, anti-K, anti-M, anti-P1, anti-Yta) and 22 matched saline controls were chosen for assessment of cytokine production using quantitative multiplexed cytometric bead array (IL-6, IL-12, IL-1α, IL-1β, TNF-α, IFN-α, IFN-γ, IL-4, IL-10, IL-8, MIP-1α, MCP-1, IP-10, ICAM-1). One-way ANOVA with Dunnet's post-test was used to compare cytokine production.

Results: Supernatants derived from MMA performed with clinically significant antibodies had significantly increased levels of MIP-1α ($P<0.001$), IL-8 ($P<0.05$), MCP-1 ($P<0.05$) and TNF-α ($P<0.001$), that was not evident when the MMA was performed with antibodies that were deemed non clinically significant. These results suggest exposure to clinically significant antibodies results in monocyte activation and a chemokine driven inflammatory response which recruit additional phagocytic cells to the area facilitating increased RBC clearance.

Conclusions: Our study demonstrated proof-of-principle that monocytes exposed to RBC opsonized with clinically significant anti-RBC antibodies in the MMA produced a heightened inflammatory response. We plan to broaden the panel of anti-RBC antibodies included in the study in order to identify a signature cytokine signal to improve prediction of transfusion reactions and improve patient safety

The importance of transfusion laboratory participation in electronic medical record (EMR) implementation

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Aim: To identify transfusion laboratories input during the various phases of EMR implementation and impact on workflow.

Method: A comprehensive survey about EMR development and implementation was sent to 131 health services in 4 Australian jurisdictions. Perspectives from a variety of craft groups involved in blood management/transfusion was sought, including laboratory scientists. Respondents were asked to record their own experience and observations.

Results:

1. 111 responses from 59 health services, 20 using an EMR
   - 11 health services used the EMR for blood management
   - 7 scientists responded from 7/20 health services with an EMR, 6 were present at go-live
   - 5 of 6 (83%) scientists were involved in EMR implementation
   - 4 (67%) felt their input was valued
   - 2 (33%) felt their input was acted upon
   - 9 of 11 (82%) health services with blood management in their EMR stated laboratory subject matter experts provided direct influence in crucial safety processes and compliance with National Pathology Accreditation Advisory Council requirements.

Respondents reported the EMR resulted in many positive workflow changes, along with some negative aspects.

Positives	**Negatives**
Increased visibility of: • specimen requests/collections (n=5, 71%) • number of outstanding requests (n=4, 57%) • clinical details (n=5, 71%) • contact details (n=4, 57%) • if blood transfused (n=3, 43%)	Decreased ability to • pre-emptively crossmatch prior to order (n=3, 43%) • view when blood was ready for collection (n=2, 29%) Change in terminology (n=4, 57%)

There were mixed reports of impact on overall productivity/workflow management (1 decreased, 2 increased).

Conclusion: Scientists' participation in EMR development is vital to ensure transparent, streamlined, safe and efficient practice is maintained and integrated into the EMR. Scientists and their laboratory processes were not fully considered into EMR development and implementation, and this may have negative impact on the perceived and actual workflow changes resulting from the EMR.

Production of anti-SARS-CoV-2 hyperimmune globulin from COVID-19 convalescent plasma by novel tangential flow electrophoresis-based plasma fractionation technology.

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Aim: Fractionation methods to purify plasma proteins have produced lifesaving immunoglobulin (Ig) and other plasma derived medicinal products for decades. Known limitations associated with conventional fractionation techniques, including the Cohn-Oncley method, have presented challenges relating to yield, purity and preservation of labile plasma proteins, a finite resource[ii],[iii]. An innovative tangential flow electrophoresis-based plasma fractionation technology, HaemaFrac®, isolates plasma proteins in one capture step, without use of ethanol or sub-zero temperatures[iv]. Here, IgG was purified from pooled convalescent plasma (CP) producing anti-SARS-CoV-2 hyperimmune immunoglobulin (hIVIg) to provide passive immunity in the COVID-19 pandemic.

Method: Pooled CP was fractionated (Aegros Ltd, Sydney) using the novel HaemaFrac® process to produce hIVIg complying with European Pharmacopoeia (EP) for human normal Ig for intravenous administration. Samples were independently analysed. Additional analyses of the pooled CP and hIVIG included total anti-SARS-CoV-2 Spike and Nucleocapsid IgG using the Abbott AdviseDx SARS CoV-2 IgG II and Abbott ARCHITECT SARS CoV-2 IgG assay respectively.

Results: HaemaFrac® produced a highly purified and concentrated anti-SARS-CoV-2 hIVIg meeting EP standards which closely reflected source plasma IgG subclass proportions; IgG_1: 58.9% (59.3%), IgG_2: 33.2% (30.1%), IgG_3: 5.6% (5.7%) and IgG_4: 2.2% (4.9%) (Graph 1). Anti-SARS-CoV-2 spike IgG levels were 21,704 AU/mL and positive for anti-SARS-CoV-2 nucleocapsid with a quantitative index value of 7.36.

Conclusion: Manufacturing hIVIg using the HaemaFrac® technology is feasible and effective, producing a highly purified and potent anti-SARS-CoV-2 hIVIg. Maintenance of physiologic levels of IgG_3 in the hIVIg from CP are encouraging given the important anti-viral effector functions of this IgG subclass[v],[vi]. Viral neutralisation activity is yet to be determined. hIVIg may provide therapeutic advantages over CP and monoclonal antibodies[vii]. The clinical utility of an anti-SARS-CoV-2 hIVIg as a passive immunity modality is currently being evaluated in a phase 1/2 clinical trial[viii].

Development of an educational package specific to ordering and labelling pathology samples when using Sunrise electronic medical record

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Aim: The rollout of Sunrise electronic medical record (EMR) across several SA Health networks along with the integration of a new state-wide laboratory information system upgrade resulted in significant changes to clinical workflows for the process of ordering, collecting and labelling blood samples.

The interface resulted in greater visibility of sample labelling errors, including wrong blood in tube and mismatched sample versus request form which raised patient safety concerns. It indicated staff were omitting critical steps, such as confirming patient identity and not labelling samples at the bedside. Staff stated they were unaware of new workflows and lacked understanding of the associated risks.
The primary aim was to create an educational package, consisting of a stand-alone animation explaining the steps in an accessible concise platform, plus a more in-depth course containing instructional videos, assessment, and certificate.

Method: A 5-minute animation was created using Powtoon, to step through ordering, confirming patient identity and bedside sample labelling when using Sunrise EMR. The animation complements EMR training and will be accessible across the SA Health network.

The course encapsulates risks associated with sample labelling errors, correct workflows, supporting instructional videos and assessment for anyone working with or learning Sunrise EMR.

Results: The course and videos will be finalised and displayed on SA Health Learning platforms by the end of June 2022. A survey will be circulated to assess uptake, learning value and feedback from July.

Conclusion:
As more South Australian hospitals go live with Sunrise EMR, this course and instructional videos will be valuable to all new and existing staff and students within SA Health to ensure they understand the importance of confirming patient ID, labelling samples at the patient's side, and preventing incorrect blood products transfused due to wrong blood in tube.

Developing a State-wide Blood Supply Contingency Plan in South Australia

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Aim: To develop and document a State-wide Blood Supply Contingency plan (SWBSCP) that aligns with the National Blood Supply Contingency Plan (NBSCP) and local Emergency Blood Management Plans (EBMP) to ensure a co-ordinated and appropriate response in South Australia to blood or blood product supply emergencies and disruptions.

Method: In South Australia (SA), each Local Health Network (LHN) has its own EBMP which outlines their roles and responsibilities if the NBSCP were to be activated. We assessed all local EBMPs for currency and alignment with the national plan, as well as for consistency between each other. The NBSCP and local plans were reviewed and evaluated to define the roles and responsibilities of key parties during local or national blood or blood product supply shortages or demand surges. Relevant stakeholders were consulted throughout the development of the plan and include Blood, Organ and Tissue Programs, Department for Health and Wellbeing/Disaster Management Branch, SA Blood Management Council, National Blood Authority, Lifeblood, BloodSafe nurses, hospitals, the state-wide pre-hospital retrieval service, and pathology providers.

Results: A state-wide plan has been documented and finalised. The SWBSCP outlines the governance, different phases and responses to local inventory restrictions placed on ordering capacity, detailed action tables outlining the minimum required actions by stakeholders at each alert level of the NBSCP and the communication workflows and pathways.

The plan recommends that all LHNs update their current EBMPs to align with the National and state-wide plan and that pathology providers also develop their own EBMP to ensure consistency of responses across South Australia.

Conclusion: The state-wide plan provides defined information about the roles, responsibilities and communication channels and has been discussed by all key stakeholders. The state-wide plan ensures a consistent and appropriate response by South Australia to blood or blood product supply emergencies and disruptions.

Victorian Subcutaneous Immunoglobulin (SCIg) use in haematology, five years after the introduction of the SCIg Access Program

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Background: The SCIg Access Program was launched by the Victorian Department of Health in February 2017 following approval of SCIg as a treatment for patients with immunodeficiencies in 2013. Blood Matters subsequently employed a project nurse to support the SCIg Access Program in November 2017.

Benefits of SCIg therapy include stable immunoglobulin (Ig) levels and patient-reported improved quality of life. Eligible patients can choose to self-administer smaller more frequent infusions at home, as opposed to day admissions for intravenous immunoglobulin (IVIg).

Aim: To promote SCIg as a treatment option and choice for all eligible Victorian patients.

Method: The project nurse supports health services to implement and develop SCIg programs and to promote the benefits of SCIg. Assistance is provided to overcome implementation barriers, identifying eligible patients, along with product dispensing logistics. Training, enhanced by tools and resources available on the Blood Matters website, is delivered to patient educators.

Results: The figure below demonstrates the number of dispenses for SCIg eligible patients

Patients transitioning to SCIg across haematology and immunology have increased, however the main area of use continues to be in immunology. Data highlights the percentage of SCIg uptake from eligible patients in haematology has been lower each year than that of immunology.

Conclusion: While SCIg patient numbers are increasing, further work is required to ensure haematology patients with secondary immunodeficiencies are aware of and have access to this treatment choice.

Modelling the outcomes of different red blood cell transfusion strategies for the treatment of traumatic haemorrhage in the prehospital setting in the UK.

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Background and objectives: The limited supply and increasing demand of group O RhD-negative red blood cells (RBCs) have resulted in other transfusion strategies being explored by blood services internationally for transfusion in emergency setting.

Materials and Methods: The impact of three prehospital transfusion strategies (RhD-negative RBC, RhD-positive RBC, and no transfusion) on quality-adjusted-life-years (QALYs) of all UK trauma patients in a given year, and the subset of patients considered most at risk (RhD-negative females <50 years old), was modelled.

Results: For the entire cohort and the subset of patients, transfusing RhD-negative RBCs in the prehospital setting generated the most QALYs (141,899 and 2,977, respectively), followed by RhD-positive RBCs (141,879.8 and 2,958.8 respectively), and no prehospital RBCs (119,285 and 2,503 respectively). The QALY difference between RhD-negative and RhD-positive policies was smaller (19.2, both cohorts) than the RhD-positive and no RBCs policies in QALYs term (22,600 all cohort and 470 for the subset), indicating that harms from transfusing RhD-positive RBCs are lower (harms for 0.5 patients and ~0.3 babies, corresponding to 19 fewer QALYs), than harms associated with not transfusing any RBCs (600 additional deaths, ~20,000 fewer QALYs). The number of QALYs lost due to death from hemolytic disease of the fetus/newborn was ~12.4 (both groups).

Conclusion: While the use of RhD-positive RBCs carries risks, the benefits measured in QALYs are substantially higher than if no prehospital transfusions are administered, even for women of childbearing potential. Group O RhD-positive RBCs could be considered when there is a national shortage of RhD-negative RBC.

The output of quality control of blood components preparation

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Aim: To analyze the results of the quality control of blood components Central Blood Transfusion Service–Indonesian Red Cross

Method: An Observational cross–sectional study was conducted from January to December 2021. A total of 192 units of each blood components were chosen during the study,Packed Red Cell (PRC) from 350 ml 4 units per month were evaluated for volume (Vol),hematocrit (HCT), hemoglobin (HB) and Hemolysis.Platelet Concentrate (PC) from 350 ml 4 units per month were evaluated for Vol,platelet count,leucocyte content and pH. Fresh Frozen Plasma (FFP) from 350 ml 4 unit per month and from 450 ml 4 unit per month were evaluated for Vol and Factor VIII (FVIII) then take the test results to analyze statistical values with the criteria of National guideline and standard on blood services in Indonesia.

Results: A total of 192 units were tested for quality control. The mean of Vol, HCT, HB and Hemolysis of PRC 350 mL 48 units was 224±10.61 ml, 67±2.89%, 49±4.09 gr/dl and 0,3±0.17%, respectiely, the result met the standard 100%. The Mean of Vol, platelet count, leucocyte content and pH of PC 48 units was 61±8.34 ml, 55±7.09 x 10^9/unit, 0.005±0.01 x 10^9/unit and 7.2±0.26, the result meet the standard 100%, 98%, 100% and 100%, respectively. The Mean of Vol and FVIII of FFP 350 ml 48 units 189±17.57 ml and 1.1±0.31 IU/ml. The Mean of Vol and FVIII of FFP 450 ml 48 units 229±31 ml and 1.1±0.3 IU/ml, which met the standard 100% both Vol and FVIII.

Conclusion: From the results, it can be concluded that the quality pf blood components; PRC, PC, and FFP being prepared meets the criteria of National guideline and standard on blood services in Indonesia.

Description of characteristics of blood transfusion patients with incompatible crossmatching test results in bekasi regency blood center of indonesian red cross

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Aim: This study aimed to describe the characteristics of blood transfusion patients with incompatible

crossmatching Test results in Bekasi Regency Blood Center of Indonesian Red Cross periode January – May 2021.

Method: This study was carried out collecting data from January – May 2021. Data were collected retrospectively from crossmatching testing form of Bekasi Regency Blood Center of Indonesian Red Cross

Results: From the results of data collection carried out at Bekasi Regency Blood Center of Indonesian Red Cross as many 168 samples of patients who carried out a crossmatching test with incompatibility results in January – May 2021 the most results based on the type of incompatibility were major negative and autocontrol positive as many as 101 samples (60%), autocontrol positive and major positive as many as 37 samples (22%), autocontrol positive as many as 22 samples (13%) , autocontrol positive and major negative as many as 8 samples (5%). Based on gender there were female as many as 94 samples (56%) and male as many as 74 samples (44%). Based on blood type there were blood type O as many as 59 samples (35%), blood type B as many as 49 samples (29%), blood type A as many as 46 samples (27%) and blood type AB as many as 14 samples (8%).

Conclusion: This study is based on incompatible crossmatching test results in Bekasi Regency Blood Center of Indonesian Red Cross periode January – May 2021 with the highest number of incompatibilty types is major negative and autocontrol positive, female gender and blood type O.

Seroprevalence of HBV, HCV, HIV and syphilis in blood donors during 2017–2020 at blood center indonesian red cross

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Aim: This study aimed to determine the seroprevalence of HBV, HCV, HIV and syphilis infections among blood donors from 2017 to 2020 at National Blood Center Indonesian Red Cross

Method: A retrospective study was designed to analyse data collected from the all laboratory blood center in indonesia during 2017-2020.

Results: The total number of 3.200.276 units from blood donating in 2017 prevalence of all infectious markers were 32.260 units (1.01%). HBV 15.383 units was analysed 0.48%. Syphilis 8.509 units was analysed 0.27%. HCV 5.231 units was analysed 0.16%. HIV 3.137 units was analysed 0.10%. The total number of 3.410.880 units from blood donating in 2018 prevalence of all infectious markers were 34.459 units (1.01%). HBV 14.974 units was analysed 0.44%. Syphilis 8.655 units was analysed 0.25%. HCV 6.230 units was analysed 0.18%. HIV 4.600 units was analysed 0.13%. The total number of 3.523.982 units from blood donating in 2019 prevalence of all infectious markers were 32.849 units (0.93%). HBV 14.443 units was analysed 0.41%. Syphilis 8.071 units was analysed 0.23%. HCV 5.782 units was analysed 0.16%. HIV 4.553 units was analysed 0.13%. The total number of 2.990.252 units from blood donating in 2020 prevalence of all infectious markers were 29.974 units (1.00%). HBV 12.954 units was analysed 0.43%. Syphilis 7.491 units was analysed 0.25%. HCV 5.361 units was analysed 0.18%. HIV 4.168 units was analysed 0.14%.

Conclusion: This study shows that the highest seroprevalence of HBV infections, the second highest seroprevalence of Syphilis infections, the third highest seroprevalence of HCV infections and lowest seroprevalence of HIV infections in all Blood Center Indonesian Red Cross.

Neonatal Alloimmune Thrombocytopenia (NAIT) is uncommon, but still important: patient characteristics, management and outcomes from the Australian NAIT Registry

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Aim: NAIT is an uncommon but important cause of profound thrombocytopenia leading to severe haemorrhage in the fetus/neonate. We analysed data from the Australian NAIT registry to describe current treatment and outcomes for NAIT.

Method: All cases registered from 2009 to 2021 were included, defined as:

Pregnant women treated antenatally for NAIT, regardless of laboratory results

Fetus/newborn with thrombocytopenia, bleeding and maternal HPA antibodies.

Results: Case analysis at 27 of 30 Australian sites identified 117 mothers with 134 pregnancies and 139 babies (5 sets of twins). 21% were first time mothers with a median age of 30.5 years.

NAIT was not anticipated in 62% of pregnancies. These neonates had lower platelet counts, required more platelet transfusions, and greater incidence of bleeding (petechiae, purpura, GI, pulmonary, intracranial (ICH) or other) than in anticipated cases. 12 ICHs were reported (8.6% of babies), and 7 neonates made a complete recovery.

	Not anticipated	**Anticipated**
Pregnancies	82	51
Neonates	84	55
Maternal antenatal IVIg	0/82	43/48 (3 cases no data)
Neonatal Platelet Counts (x 10^9/L) (median, IQR)		
First	21 [10, 38]	142 [72, 229]
Lowest	16 [7, 29]	110 [38, 200]
Neonatal Platelet transfusion	59/79 (75%)	12/46 (26%)

Maternal antibodies were identified in 86% of cases, 18% of which were HLA only. Of the HPA antibodies, 66% were anti-HPA-1a, 8% anti-HPA-5b. 90% of anticipated cases were treated with antenatal IVIg, with a total of 47,325g transfused.
68 neonates received 151 platelet transfusions; of these 24% were HPA matched. Median [IQR] pre-transfusion platelet count where bleeding recorded (N = 59) was 13 x10^9/L [6, 21] and 17 x10^9/L [7, 36] in cases where no bleeding recorded (N = 14). Pre-transfusion platelet count was >25 x10^9/L in 36% (5/14) of platelet transfusions in neonates with no bleeding and 14% (8/57) in neonates with bleeding.

Conclusion: The majority of NAIT cases are unexpected, with higher rate of bleeding complications and requirements for neonatal treatment. Platelet transfusion thresholds varied, which likely reflects the lack of data to inform practice in this patient population. Future research should focus on long-term outcomes as well as costs, to inform policy and practice.

Using Point-of-care Devices for Identifying Sickle Cell Trait (HbAS) in Blood Donors Whose Donations Result in Recurrent Leucodepletion Failure During Red Blood Cell Manufacture.

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Aim: Recurrent leucodepletion failure can occur during red blood cell (RBC) manufacture. Failure of leucodepletion impacts RBC quality and usually results in product discard. The authors have previously demonstrated that 40% of Australian donors with recurrent leucodepletion failure have Sickle Cell trait (HbAS). HbAS donors have been detected using variable methods internationally. In Australia, the Sentrix® BeadChip genotyping system has been formally validated however, it is costly to perform. More recently, a lateral flow-based point-of-care assay (Sickle SCAN®) has been developed and validated for the detection of HbS, HbC and HbA. It is also validated for samples collected and stored in EDTA. Our study aimed to analyse the use of Sickle SCAN® in supporting the management of donors with recurrent leucodepletion filter blockage after whole blood donation.

Method: Between 29 May 2021 to 3 May 2022, donations where the filter block processing code was used were identified in the National Blood Management System managed by Australian Red Cross Lifeblood. Residual samples from the EDTA mandatory testing tubes from these donations were obtained and tested on the Sickle SCAN® test as per manufacturer's instructions. Samples were also tested via Haemoglobin electrophoresis (Hb EPG) and HPLC for confirmation.

Results: Twenty-nine donations from blood donors with at least 2 recurrent filter blocking instances were analysed. It was found that 11 (38%) were HbAS donors and 17 (59%) were HbA and one donor needed further investigation. All Sickle SCAN® results were confirmed by Hb EPG and HPLC.

Conclusion: The Sickle SCAN® test could be used to support the management of donors with recurrent RBC leucodepletion filter blockage after whole blood donation. The test may assist to screen donors whose RBCs are used in high risk settings such as intrauterine transfusion or after a single episode of leucodepletion failure to prevent repeated processing issues.

The Prevalence of Transfusion-Associated Microchimerism in 45 and Up Study Participants

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Aim: Since the introduction of leucocyte filtration in the processing of Australian red blood cell (RBC) units, there has been a reduction of transfusion-related reactions in patients. However, transfusion-associated microchimerism (TAM) is still found to occur in 10% of multiply transfused trauma patients. TAM is a condition where genetically distinct donor leucocytes remain in the transfused patient. Its prevalence across all transfusion recipients and whether older patients are more susceptible is uncertain. What remains unknown, is whether TAM has any long-term health consequences.

Participants in the Sax Institute's 45 and Up Study are part of a longitudinal study who answer health and lifestyle questions and have consented to linkages with other routinely collected health administrative data and registries. There are over 267,000 participants across New South Wales (NSW), which provides a unique opportunity to measure the prevalence of TAM in those who have had a RBC transfusion to potentially understand longer-term health consequences.

Method: 45 and Up Study participants who have been transfused with at least one RBC unit were identified from the linked hospitalisation database. Potential participants (n=350) were approached by posted invitational letters. EDTA blood samples for analysis were collected from participants *via* commercial pathology centres and sent to Lifeblood. genomic DNA (gDNA) was extracted from the buffy coat and typing for a series of insertion/deletion (InDel) polymorphisms will be conducted for TAM detection.

Results: This project has been delayed because of COVID-19 restrictions and the 2022 NSW flooding emergency in March 2022. To date 100 participants have been approached. Of those, 25 individuals (25%) provided blood samples for analysis. The remaining 250 participants are being approached in late May.

Conclusion: Study uptake to date was extremely good from the participants of the 45 and Up Study. Sample analysis paired with long-term health data is unique to this cohort and will allow more understanding of transfusion-related patient outcomes.

How Accurate Information on National ABO Prevalence Can Assist the Health Sector

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Aim: During the COVID-19 pandemic it was hypothesised that individuals with certain ABO groups were more susceptible to SARS-CoV-2 infection. Separately, prior to 2020, national data on the ABO Rh(D) prevalence had never been collected despite 30% of Australian residents being born overseas. Having accurate national data to understand ABO Rh(D) prevalence enables supply forecasting for blood and blood products but also assists with emergency health planning, including determining whether there is any correlation between blood group and COVID-19 incidence and severity.

Method: To obtain data from Australian patients across the country, 41 pathology agencies representing 324 approved health providers (AHPs) were approached. Blood donor data was extracted from Australian Red Cross Lifeblood's National Blood Management System. ABO Rh(D) data on blood donors enrolled in the COVID-19 convalescent plasma (CP) program in 2020 was also analysed.

Results: Twenty-eight pathology agencies representing 245 AHPs provided information from 1,318,751 patients. This data indicated blood group prevalence was as follows; O+ 38.4%, O- 6.5%, A+ 32.0%, A- 5.6%, B+ 11.8%, B- 1.5%, AB+ 3.7% and AB- 0.5%.

A total of 490,491 individual blood donors which included 103,798 (21.2%) first-time blood donors were also analysed. The prevalence of each blood group in first-time blood donors was similar to that found in patients. When compared with data from 1993-94, the number of Rh(D)+ Australians has increased by 4.9% in patients and by 2.8% in first-time blood donors.

The distribution of ABO group in CP donors compared to the total donor panel was not significantly different (p = 0.177).

Conclusion: The proportion of Rh(D)+ individuals in Australia has increased over the past 25 years and there was no ABO association in CP donors compared to the blood donor panel. This first national dataset provides contemporary community-wide data for health planning and evaluation of blood holdings. It also highlights the challenge of meeting the demand for Rh(D)- red blood cells.

Building a national transfusion dataset for Australia

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Aim: To establish an integrated National Transfusion Dataset (NTD) with links to clinical outcome data.

Method: The NTD builds on the work of the Australian and New Zealand Massive Transfusion Registry (ANZ-MTR) and the pilot Transfusion Database (TD). Data are obtained from prehospital services and participating hospitals for all blood products transfused to patients ≥18 years, not just massive transfusions. Data items include: demographics, clinical coding (diagnosis, hospital admission), laboratory, transfusion data, and patient outcomes (mortality, clinical response, quality of life).

Where possible, specific patient cohort data (e.g. ICU admission for blood diseases) will be linked with national clinical datasets including:

1. ANZICS Adult Patient Database (ANZICS APD)
- Aplastic Anaemia and other Bone Marrow Failure Syndromes Registry (AAR)
- Lymphoma and Related Diseases Registry (LaRDR)
- Myeloma and Related Diseases Registry (MRDR)

Monash University in collaboration with subject-specialist clinicians and researchers performs data management (aligning with FAIR principles) involving harmonisation, integration, linkage and analysis. The Australian Research Data Commons supports the project.

Results: Initial data from Ambulance Victoria and pilot hospitals (The Alfred, Flinders Medical Centre) have been incorporated into the NTD and analysis has commenced. The first linkage with the AAR has been successfully undertaken, demonstrating feasibility, and the high volume and complexity of transfusion support for this patient group. Additional sites (hospitals and prehospital services) are in preparation. Plans are in place to expand the NTD with CogStack, a natural language processing platform to incorporate unstructured data from patient medical notes (such as administration, and adverse event reports) into the NTD, and to link with haemovigilance data.

Conclusion: The NTD is underway, and will deliver a complete picture of transfusion practice from donor to product to patient, provide evidence on blood use to support evidence-based policy decisions, continue to provide information on massive transfusions, and improve blood utilisation and clinical outcomes for Australian patients.

Evaluation of full blood count samples from Lifeblood's blood or plasma donors tested under two conditions of storage and transport.

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Aim: Lifeblood completes full blood count samples (FBC) for selected donors to assess their suitability for future donations. Removing the current requirement for storage and transport of these FBC samples at refrigerated temperature and aligning with room temperature storage and transport of other donor blood samples would produce significant efficiencies in blood donor centres. This study aimed to compare the results of donor full blood count samples stored and transported at refrigerated (2-8°C) and room temperature (4-25°C).

Method: Five hundred full blood count samples were collected from 250 whole blood or plasma donors. These were paired for storage and transport to the processing laboratory at either refrigerated or room temperature. Samples were tested on arrival at the processing centre and the following day, after being stored at either refrigerated or room temperature. The primary outcomes of interest included differences between mean cell volume (MCV), haematocrit (HCT), white cell count (WCC), white blood cell differential counts and the need to produce blood films based on existing criteria.

Results: The results comparing the two storage and transport conditions showed a statistically significant ($p<0.05$) difference between MCV, HCT, WCC on both day one and two. Blood films were required from 16 donors due to numerical flags of results and 13 donors due to automated analyser morphology flags. The number of films required was similar in each group.

Conclusion: While statistically significant differences were demonstrated between the data sets, the clinical significance of the small numerical differences is considered minimal. Furthermore, the number of blood films required remained similar under either temperature condition. Given the significant reductions in time, processing and costs associated with room temperature over refrigerated storage and transport, we recommend a further pilot study to monitor the broader impacts, with the intent to implement national transport of FBC samples at room temperature within Lifeblood.

Red Cell Antibodies: Frequency in the Australian blood donor population.

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Aim: Australian Red Cross Lifeblood (Lifeblood) performs red blood cell (RBC) antibody screening on every new blood donor. Red cell antibody screening is a critical step to identifying unexpected non-ABO antibodies in donor plasma. The reactivity of these antibodies can be variable and have the potential to cause haemolytic transfusion reactions (HTR) or shortened red cell survival when transfused.

Method: A retrospective desktop analysis of the red cell antibody screening results was performed on all new blood donors collected by Lifeblood between 1/1/2020 and the 31/12/2021.

Results: Lifeblood registered 201,005 new donors between 2020-2021. The presence of red cell antibodies was confirmed by antibody identification panels in 517 donors (0.3%). Red cell antibodies were more likely to be detected in female donors (80%) compared to male donors (20%). The proportion of female donors with red cell antibodies exceeded the overall proportion of new donors that were female. 0.4% of new female donors were antibody positive compared to 0.1% of new male donors.

There were 28 different allo antibody specificities identified, 66 donors had multiple antibodies and 247 (48%) donors had allo antibodies with Rh specificity. There were 112 (22%) donors with auto antibodies only and a further 2 donors with allo antibodies and an auto antibody.
Previous pregnancy was declared by 326 (79%) of the female donors at donor interview. A history of transfusion was declared by 11, 5 males and 6 females. 5 of the females with a history of transfusion also had a history of pregnancy.

Conclusion: Antibodies in blood donors are more likely due to pregnancy or acute transfusion rather than transfusion due to a chronic illness. This cohort would be reflective of an otherwise healthy population. The frequency and range of antibodies in this cohort may assist in understanding the risk of transfusion reaction in emergency setting for patients that do not have a history of chronic transfusion.

Covid-19 and blood transfusion – minimising blood wastage

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Aim: To develop a plan directed towards minimising blood wastage and ensuring appropriate blood handling during Covid -19 pandemic.

Method: The frequency of blood donation in Australia declined dramatically due to escalating Covid-19 cases, recurring lock downs and staff shortages. To decrease risk of infection of blood units delivered to potential Covid-19 infectious (red zone) areas, and to minimise wastage, key stakeholders from Transfusion Medicine, infection control, anaesthesia, intensive care, emergency, haematology, orderlies, RFDS, Emergency Helicopter Retrieval were consulted for blood management best practice. The plan included development of a staff education poster for use during teaching huddles, and labelling of blood shippers within hospital as well as disposable outer packaging of shippers for intersite transport. The poster was distributed by hospital global message, on Health Information Hubs and to external blood users. Covid-19 blood wastage was recorded on the Laboratory Information System and monitored for trends to determine if further education was required.

Results: Despite a great deal of information being readily available with regards to Covid-19 regulations, this was not the case for blood product management. Hence, it was vital to develop an education plan.

To date, blood wastage due to potential Covid-19 infection has been limited to Albumex 4% and 20% = 6 vials, IVIG = 2 vials, RBC =3 and plasma =2

Conclusion: The insufficiency of comprehensive blood product management information for Covid-19 patients lead to the development of a well-structured poster on this topic. The availability of the education poster and roll out plan was key to success to inform all staff of their duty to manage blood judiciously to minimise waste and ensure safety of all patients. The result is minimised blood wastage in a large tertiary hospital during this pandemic. The poster was shared to West Australian Transfusion Education group.

A five-year review of the RCPAQAP Antigen Phenotyping EQA

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Introduction: It is vital for Transfusion laboratories to correctly identify red cell phenotypes in patient samples and donor units to ensure compatible red cells are provided to patients with clinically significant antibodies and prevent alloimmunisation.
The RCPAQAP offers an Antigen Phenotyping option (AP) as a part their General Transfusion programs. Participating Transfusion laboratories perform red cell phenotyping to confirm the presence or absence of a range of red cell antigens.
We reviewed how well the participants performed phenotyping on red blood cells using serological methods.

Materials and Methods: A total of 20 whole blood samples (4 per year per site) suspended in a red cell preservative were provided to an average of 204 laboratories enrolled for the AP program over a five-year period (2017 – 2021).
Participants were asked to perform extended red cell phenotyping on the sample.
The returned results were analysed using in-house statistical software.

Results: Over the five years, we noted an increasing number of survey participants and improved overall performance in confirming the presence or absence of red cell antigens; however, there are areas requiring improvement. These included the need for more comprehensive antigen typing to be routinely performed in every blood bank. While all sites performed the basic phenotyping, a number were referring when they should consider implementing in-house.

Conclusion: This retrospective study determined that while most participating laboratories performed red cell phenotyping competently, a number where referring the less common phenotypes which could present a risk to their patients. We recommend that all transfusion laboratories should have access to comprehensive phenotyping antisera.

A two-year longitudinal stability study of platelets cryopreserved using a novel processing method

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Aim: Cryopreservation extends the limited shelf-life of platelets from seven days to two years, leading to minimised wastage and improved availability. However, there has been a paucity of longitudinal characterization of in-vitro functional quality of cryopreserved platelets (CPPs). Additionally, the current procedure for the thawing and issuing of CPPs components is laborious and has remained challenging in emergency settings at blood banks. In this study, a novel method designed to facilitate the efficient issuance of CPPs was developed and characterized over a 2-year period in parallel with standard CPPs manufactured.

Method: A total of 27 pooled-and-split apheresis platelets units were cryopreserved at -80°C in 5-6% dimethyl sulfoxide (DMSO) to produce three matched unit pairs at three-month intervals for comparison between two processing methods. In contrast to the standard method where CPPs are frozen as standalone units, platelets are frozen in tandem with resuspending plasma in a distinct partition as a single unit in the novel method. Post-thawed platelets were assessed at T=0-, 12- and 24-hours to determine R-time and maximum amplitude using thromboelastography (TEG), and platelet recovery. Statistically significant differences were calculated using repeated measures of analysis of variance and Bonferroni post hoc tests with an alpha level of 0.05.

Results: In the overall dataset, a significantly higher mean platelet recovery was observed for CPPs produced using the new method at T=0 hrs, but significantly lower at T=12 and T=24hrs (p<0.001). Significantly shorter mean R-time (s) were also found amongst CPPs from the new method for both years (p<0.01). Clot strength, as indicated by maximum amplitude (mm), was significantly higher amongst CPPs manufactured using the novel method within and between years across thawing time points (p<0.01).

Conclusion: Our findings have demonstrated the superior in-vitro quality attributes of CPPs produced using the novel method.

Haemolytic disease of the fetus and newborn caused by a novel RhAG antigen with c.140T>C (p.Phe47Ser) missense mutation.

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Aim and background: The Rh-associated glycoprotein (RhAG) forms a core part of the Rh complex and is essential for the expression of RhD and RhCE antigens on red blood cells (RBCs). Several molecular mutations of the *RHAG* gene have been reported to result in a severe reduction (Rh_{mod}) or complete absence (regulator Rh_{null}) of Rh antigens. Here we describe a case of haemolytic disease of the fetus and newborn (HDFN) caused by an antibody to a novel low frequency RhAG antigen.

Clinical presentation: A baby born in Thailand presented with HDFN (cord blood direct antiglobulin test 4+, hemoglobin 15.3 g/dL with jaundice and hyperbilirubinemia). The maternal antibody was reactive with RBCs of the father and older sibling. Extensive antibody investigations revealed no apparent specificity.

Method: Blood samples of the infant and family members (n = 3) were collected and sent to the Red Cell Reference Laboratory. Phenotyping was performed by standard serological methods. Genomic DNA was extracted from the red cells and genotyped using the Immucor BioArray HEA Precise BeadChip kit. DNA sequencing was performed using the Custom Targeted Sequencing Panel.

Results: The patient's predicted phenotype was C+, E-, c-, e+, K-, Fy(a+b-), Jk(a+b+), M+, N-, S-, s+. Weakened Rh antigen expression was demonstrated by RBCs of the older sibling. Sequencing revealed that the infant, father and older sibling were heterozygous for a novel variant, c.140T>C (p.Phe47Ser), of the *RHAG* gene. The low frequency *GYPB*23* allele (s^D+ phenotype) was also detected in both children and the mother.

Conclusion: The presence of a novel *RHAG* c.140T>C variant at the heterozygous level results in a low frequency antigen and was responsible for this case of HDFN observed. Serological findings suggest that this variant affects the expression of RhD and RhCE antigens.

A comprehensive neonatal-paediatric intravenous immunoglobulin (IVIG) treatment plan developed to improve health care outcomes for children requiring IVIG infusions in Australia

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Aim: Children are sometimes over or under prescribed and/or administered intravenous immunoglobulins (IVIGs). Dose and rate of IVIG infusions differ according to the individual diagnosis and weight of the child. Increased rate of infusion can lead to major complications. A specific IVIG plan designed for neonatal and paediatric patients was required to guide clinicians to prescribe the correct dose and rate of IVIG administration according to the weight of the child. This is a quality improvement initiative.

Method: A new IVIG Treatment Plan was developed in accordance with national guidelines on IVIG administration and expert paediatric advice in one hospital in Perth, Western Australia. The format of the plan includes patient consent, weight of the child, IVIG prescription, diagnosis or reason for IVIG infusion, IVIG percentage with brand, total dose, and administration time. The administrative section includes the date and time of administration, with a separate area for nurses to sign during the checking process. The plan also includes a section to record the variable rate of infusion (if needed), as well as a section to document bottle usage and compatibility label/s. The final section includes information concerning infusion reactions and subsequent management. The plan was circulated amongst the paediatric multidisciplinary staff for feedback. Positive comments were received from all staff. As a result, the newly developed Neonatal-Paediatric Intravenous Immunoglobulin (IVIG) Treatment Plan was piloted within the Neonatal and Paediatric Departments in early 2021.

Results: The Neonatal-Paediatric Intravenous Immunoglobulin (IVIG) Treatment Plan was universally well-received by all staff belonging to the neonatal and paediatric multidisciplinary team. Clinician errors in prescribing the correct dose or rate of administration were reduced and staff stated the plan was easy to understand and use.

Conclusion: The two page Neonatal-Paediatric Intravenous Immunoglobulin (IVIG) Treatment Plan proved to be an effective tool in educating staff and reducing errors when prescribing and administering IVIG products for children.

Thinking outside the Blood Bank: How incorporating Fibrinogen Concentrate and the use of thromboelastography into the Critical Bleeding Protocol reduced a paediatric hospitals Cryoprecipitate waste.

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Aim: To determine if the implementation of storing Fibrinogen Concentrate and use of thromboelastography in Theatre and adding to Critical Bleeding Protocol at a tertiary paediatric hospital led to a reduction in Cryoprecipitate waste.

Method: Before Fibrinogen Concentrate was made available at the hospital, Cryoprecipitate was the blood product of choice to treat low fibrinogen during a critical bleed. Wastage of Cryoprecipitate at site was high.

The local Blood Management Committee trialled the use of Fibrinogen Concentrate and thromboelastography in August 2020, and their use was incorporated into the Critical Bleeding Protocol from November 2020. Data was extracted from the Laboratory Information system (LIS) to determine cryoprecipitate use and wastage, and the Theatre Automatic Drug Machine (ADM) for Fibrinogen Concentrate use.

Results: Between June 2018 and November 2020, there were 995 units of Cryoprecipitate issued to the hospital, with 15 (1.5%) incidents of Cryoprecipitate waste. Since November 2020 when the Fibrinogen Concentrate was made available, there has been 10 units of Cryoprecipitate wasted (1.5%) from 647 units issued. Since its introduction, 76 vials of Fibrinogen Concentrate have been used.

Conclusion: While the incidence of Cryoprecipitate wastage has remained stable (1.5%) since the introduction of Fibrinogen Concentrate and thromboelastography to the hospitals critical bleeding protocol, cryoprecipitate use has reduced by approximately 30%. Blood waste and Fibrinogen Concentrate use continue to be monitored and reviewed by the hospitals Blood Management Committee to ensure safe and appropriate practice.

Is change always safer? A review of paediatric platelet transfusion reactions post introduction of Platelet Additive Solution (PAS) in Apheresis Platelets

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Background: In March 2019, the Australian Red Cross Lifeblood introduced Apheresis Platelets in Platelet Additive Solution (PAS); prior to this Apheresis Platelets were suspended in 100% donor plasma. The introduction of PAS, which contains less plasma, was thought to reduce the incidence of allergic and other transfusion reactions.

Aim: To assess the clinical safety profile of Apheresis Platelets in PAS at a tertiary paediatric hospital.

Method: A comprehensive retrospective review of transfusion reaction information was reviewed from the commissioning of the new paediatric hospital from June 2018 to February 2022. Data were extracted from Haemovigilance spreadsheets and the Laboratory Information System (LIS). Data collected included Platelet product characteristics and type of reaction. Imputability score and severity of the transfusion reactions were determined by state and national Haemovigilance reporting guidelines.

Results: During the study period, approximately 3875 platelets were transfused of which 3867 were Apheresis Platelets. There were 23 Platelet related transfusion reactions reported. Apheresis Platelets accounted for 96% (22) of the platelet reactions, with only 1 Pooled Platelet reaction reported.
Prior to the introduction of Apheresis Platelets in PAS there were nine reactions reported with 67% classified as allergic reactions and 33% classified as anaphylactoid/ anaphylactic reactions. Imputability scores were no morbidity 1, Minor 3, Severe 4, Life threatening 1. Following the introduction of Apheresis Platelets in PAS 14 reactions were reported with 71% classified as allergic and 29% anaphylactoid/ anaphylactic. Imputability scores were minor morbidity 10, Severe and life threatening 4.

Conclusion: This review suggests an increase in the incidence of reported transfusion reactions after the introduction of Apheresis Platelets in PAS. However, there did appear to be a reduction in the severity of the transfusion reactions after the product change. The increase in reported reactions could be related to implementation of a transfusion nurse leading to improved reporting avenues within the hospital.

A comprehensive critical bleeding protocol (CBP) record developed to facilitate better staff communication and improve patient outcomes in critical bleeding scenarios

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Aim: Timely and accurate communication between clinical and laboratory staff is essential in critical bleeding situations. Miscommunication can result in less blood products arriving than initially anticipated, plus confusion as to when further products will be made available. Consequently, a detailed CBP Record was designed to improve communication between staff and provide a standardised process for the safe and rapid ordering of blood products.

Method: A new role was developed to facilitate better communication in critical bleeding situations. This role is the Emergency Transfusion Coordinator, who is also the scribe completing the CBP Record. The record was developed in accordance with national Patient Blood Management guidelines in one hospital in Perth, Western Australia. This record includes a top section to write down relevant names and contact numbers, followed by three actions. The first action instructs the scribe to activate the Critical Bleeding Protocol and order blood products guided by blood tests or rotational thromboelastometry (ROTEM). The second action allows the scribe to track blood product usage contemporaneously ensuring blood products are available in a timely manner. The final action lists the body temperature and blood test results clinicians need to normalise to reverse coagulopathy and stabilise the patient. The reverse side of the CBP Record includes space to record cell saver details, as well as a pathology communication log. The CBP Record was piloted within the Theatre and Emergency Departments in 2014.

Results: The CBP Record was widely appreciated by all theatre and emergency staff. Communication between clinical and laboratory staff improved significantly, resulting in targeted management of the bleeding patient with better outcomes.

Conclusion: The CBP Record proved to be an effective tool in improving communication between staff in critical bleeding scenarios, as well as providing a comprehensive overview of the blood products and tests involved in the management of critically bleeding patients.

Impact of governance on immunoglobulin use in Australia

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Aim: Treatments involving immunoglobulin (Ig) offer significant therapeutic benefit to people with a wide range of conditions including haematological disease. However, Ig is a high-cost product and the demand for use in Australia has been amongst the highest globally, with over 21,000 people accessing treatment annually.

For this reason, access to Ig in Australia is provided through specific governance arrangements introduced in 2014. An evaluation was undertaken in 2021 to assess the impact the governance arrangements have had on Ig use and to better understand recent trends in usage.

Method: Evaluation questions were developed and sought to understand:

1. how Ig use has changed since the introduction of governance arrangements;
    - the drivers for the change; and
    - the impact of components of governance individually and collectively on Ig demand and costs.

Results: Since the introduction of governance arrangements, the rate of growth in Ig usage has reduced from an annual average of 10.4 per cent to 7.3 per cent. There is a correlation between key components of governance arrangements and decreasing use of Ig. However, there have been no major changes in Ig use observed in the ten most commonly treated medical conditions and no reduction in the doses administered. Acquired hypogammaglobulinaemia remains the top indication for Ig use. Dosing of Ig, patient age and weight have slightly increased over the period analysed, however the number of patients being treated with Ig reduced. The effect of this moderation in usage is estimated to have saved taxpayers over $70 million so far.

Conclusion: Governance arrangements have driven standardisation and moderated the use of Ig products in Australia. The arrangements have supported the most appropriate use of nationally funded Ig for patients requiring this treatment and also delivered cost savings. Further opportunities will be explored to support the efficient, effective, ethical and most appropriate use of this precious resource and enable continued patient access to Ig therapy under nationally funded arrangements.

Genomic Characterisation of rare, weak, hybrid and novel antigens to redefine blood group profiles in Uganda.

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Aim: With approximately 85 million units of red cells transfused annually, blood transfusions remain an essential, life-saving facet of modern medicine. One such contributors is the treatment and management of sickle cell disease (SCD). SCD is highly prevalent in Africa, where approximately 45% of all people within Sub-Saharan Africa carry the SCD trait and 2% of all births suffer from sickle cell disease. These health challenges drive evolutionary pressure towards unique allelic variation, changing the blood group landscape within African communities. Next generation sequencing (NGS) can be used to provide in-depth, highly accurate characterisation of blood group antigens, overcoming shortcomings seen in serology-based assays. Adequate antigen matching in populations with higher variants may reduce the incidence of alloimmunisation. In this study, we review samples from Uganda and perform in-depth NGS and Copy Number Variation (CNV) analysis across 36 blood group systems.

Method: Genomic data from Uganda population study was accessed by the European Genome-Phenome archive (Dataset ID EGAD00001001639), where raw sequences were run on Illumina HiSeq at a low (4x) coverage. Blood group genotypes across 36 systems were analysed using RBCeq (RBCeq), a comprehensive blood typing algorithm. Additionally, CNV analysis was performed using a GATK pipeline, with a particular focus on double deletions outside of RHD, RHCE and MNS blood groups.

Results: ABO analysis revealed a large proportion of O (91%), compared to A1 at 7.5%, A2 at 0.3% and B at 0.1%, corroborating previously described frequencies. Over 40 variants were found within the RHD system. One such finding showed 43 patients with homozygous expression of RHD*01W.40, a rare weak D variant. Our findings also showed a higher prevalence of Duffy Null (FY*01N.01 variant) than previously reported.

Conclusion: Our findings offer new insights into African blood group variants for local populations and migrant populations globally. Our aim is that these insights may be used as a guide to improve accurate antigen matching for transfusion dependent patients from African communities, reducing alloimmunisation in sickle cell disease patients.

It takes a "village" to raise the standard of care

Ms Susan Ogley[1], Mrs Kobie von Wielligh[1], Mr David Peterson[1], Mrs Louise English[1], Mrs Emma McGrath[1], Mrs Trudi Verrall[1]
[1]Bloodsafe Elearning Australia, Adelaide, Australia

Background: BloodSafe eLearning Australia (BEA) has over 40 courses on patient blood management and safe transfusion practice, and additional videos, podcasts, and tools. There are more than 750,000 registered learners who have completed over 1.5 million courses. This would not be possible without a large community of reviewers, expert advisors and video interviewees. This presentation celebrates those healthcare professionals who willingly give up their time to assist in the ongoing success of this award-winning national program.

Method: An analysis of the BEA reviewer database was performed to identify different professions and specialities. Course evaluations for the last six months were also analysed, regarding impact on clinical practice, prevention of adverse events and effect on patient outcomes.

Results:
To date BEA has engaged approximately 280 experts from a wide variety of clinical and professional backgrounds including.

- Medical specialists: 198
- Nursing: 58
- Midwifery: 15
- Other: 11

Additionally, more than 100 video interviews have been undertaken for video content within the courses.

Course evaluation surveys show that respondents believe there will be an improvement in patient outcomes and reduction in near-miss events. For the period November 2021 to May 2022 there were 411 responses, with:

- 90% reporting that the BEA courses have helped them identify near misses and prevent adverse events
- 93% stating that BEA courses improve patient safety and outcomes, and
- 72% stating that they would change their practice.

Conclusion:
These demonstrate the value of a large community of professionals who willingly provide their time to improve patient safety and outcomes through education.

Specialities covered:

2. Transfusion
    - Cardiology
    - Neurology
    - Renal
    - Neonatology
    - Paediatrics
    - Haematology
    - Oncology
    - Neurosurgery
    - Gastroenterology
    - Obstetrics
    - Gynaecology
    - Critical Care
    - Orthopaedic surgery
    - Anaesthesia
    - Immunology
    - Cardiothoracic surgery
    - Vascular surgery
    - Emergency medicine
    - Academia
    - Research
    - Pharmacy
    - Dietetics
    - Governance
    - Administration
    - Consumers

Retrospective audit of transfusion practices and clinical outcomes in patients with chronic liver disease who present with acute bleeding or undergo surgical procedures at the Royal Brisbane Hospital.

Dr Gianna Pastore[1], Dr Joanne Perel[1], Dr Michelle Spanevello[1], Sue Williams[1]
[1]*Royal Brisbane And Women's Hospital, Brisbane, Australia*

Aims:

1. To examine our institution's current transfusion practice in patients with chronic liver disease and abnormal baseline coagulation studies in the perioperative setting and in patients with acute bleeding.

2. To provide effect estimates for reduction of bleeding complications and adverse events in patients who have had transfusions guided by standard coagulation testing versus ROTEM guided transfusions.

3. To produce a local hospital pathway to guide peri procedure transfusion practices to prevent procedure related bleeding and to guide transfusion practices in patients with liver disease who present with bleeding.

Method:

3.1 Study design

This observational study will be performed as a retrospective audit of transfusion practice in patients with chronic liver disease who have undergone surgical and non-surgical procedures or have been admitted to the Royal Brisbane and Women's Hospital with acute bleeding.

3.2 Study population

- Age ≥18years admitted to the Royal Brisbane and Women's Hospital with Chronic liver disease (as defined by the Child's Pugh Score (A-C)) who have received blood product transfusions in the perioperative setting or to manage acute bleeding between January 2015 and July 2021.

3.6.1. Statistical Analysis

Statistical analysis will be performed in conjunction with RBWH statisticians. We will determine baseline patient characteristics using ANOVA, chi-square and Fishers exact test, as appropriate based on available data.

Results:

Analysis and data collection still in progress. We will present our data which will hopefully confirm our study hypothesis (below).

Study hypotheses:

The use of standard coagulation studies in patients with chronic liver disease does not accurately predict bleeding risk in patients undergoing procedures and the use of ROTEM reduces the need for blood product transfusion in this setting.

Conclusion:

Conclusions to be drawn from results once statistical analysis have been performed.

Prevalence of anaemia in cardiac surgery patients and the effect on intra-operative and post surgery transfusion practice

Prof David Roxby[1], Dr Tina Noutsos, Dr Romi Sinha, Prof Rob Baker
[1]*Flinders University, Adelaide, Australia*

Aim: Evidence suggest that a significant gap exists between the release and adoption of patient blood management guidelines. The aim of the study is to examine the prevalence of preoperative anaemia and anaemia on hospital discharge in patients undergoing cardiac surgery including the incidence of transfusion of blood and blood products intraoperatively and postoperatively in the Intensive Care Unit

Method: Data were retrospectively collected for all consecutive patients who underwent cardiac surgery at a tertiary hospital between January 2014 and June 2019. Data collection included patient demographics, cardiac surgery type, blood and products transfused and haemoglobin levels.

Results: There were 2339 cardiac surgery admissions, including 1178 cardiac artery bypass graft, 1029 cardiac valve and 132 other surgeries included during the study period. Intraoperatively, 8.2% (192/2339) admissions received red cells, 2.7% (62/2339) fresh frozen plasma (FFP), 8.6% (200/2339) platelets and 1.8% (42/2339) cryoprecipitate. In ICU, 27.3% (638/2339) admissions received red cells, 12% (318/2339) FFP, 3.6% (318/2339) platelets and 4.6% (107/2339) cryoprecipitate. 732/2339 (31.3%) admissions were anaemic pre-surgery and 1139/2130 (53.5%) had a haemoglobin <100 g/L at hospital discharge. There was a significant difference in the median, interquartile (IQR) haemoglobin levels prior to surgery [142(132-151) vs 115 (102-123, p <0.001], nadir haemoglobin intraoperatively [98 (89-106) vs 76 (70-86), p <0.001], and during ICU stay [95 (82-106) vs 79 (72-88, p <0.001], and on discharge [100 (92-111) vs 94 (86-102), p <0.001], from hospital between non-anaemic and anaemic admissions respectively (Figure 1). Anaemic patients at admission had significantly higher red cell transfusions intraoperatively (20.8% vs 2.5%, p<0.001) and in ICU (43.6% vs 19.8%, p<0.001). Overall in-hospital mortality was 1.3%

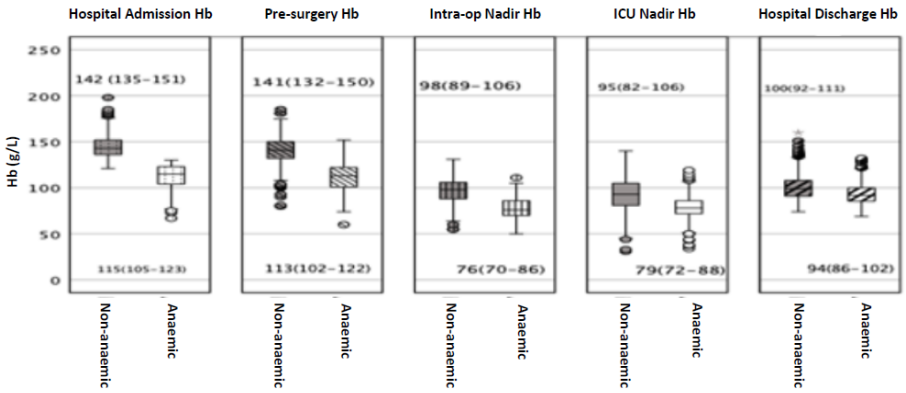


Figure 1. Pre-surgery, discharge, and intra-operative and ICU nadir median haemoglobin levels

Conclusion: Preoperative anaemia was present in 31% of cases and significant anaemia was prevalent at hospital discharge. Addressing causes of pre-admission anaemia may assist in reducing transfusion requirements and preventing significant anaemia at discharge.

iTEM, a Mobile Application-Based Thromboelastometry (ROTEM) Educational and Interpretation Tool

Prof David Roxby[1], Dr Romi Sinha
[1]*Flinders University, Adelaide, Australia*

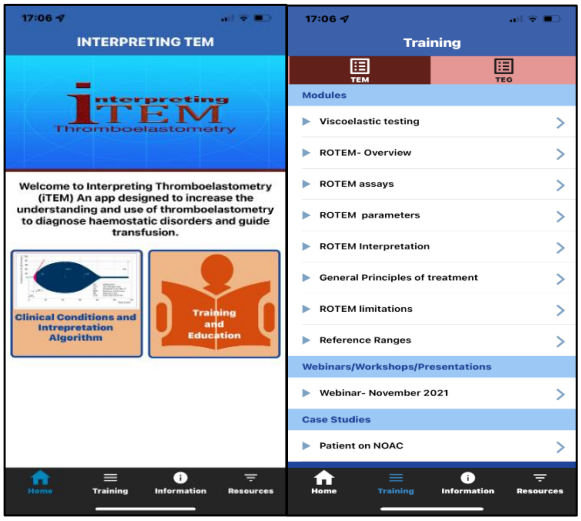
Aim: Thromboelastometry (ROTEM) is a functional whole blood viscoelastic assay that provides dynamic global assessment of the coagulation process. ROTEM has been implemented in many centres in Australia and internationally to monitor haemostasis in critical bleeding patients and guide appropriate blood product replacement. Being a dynamic test it requires competency in interpreting the traces for all the assays and understanding the relevant haemostatic defect and their clinical implications.

Method: A mobile application was developed to assist with clinical interpretation and education of health professionals using ROTEM in management of bleeding patients.

Results: The Interpreting TEM (iTEM) App has two modules – a Training and Education Module and an Interactive Interpretation Module. The Training Module has several sections including the ROTEM Assay section that briefly explains the various assays including EXTEM, INTEM, FIBTEM, HEPTEM and APTEM and their use in assessment of haemostatic disorders. The ROTEM Parameters section describes several different ROTEM parameters including the significance of Clotting Time (CT), Clot Formation Time (CFT), alpha angle (α), Amplitudes (A5, A10, A20), Maximal Clot Firmness (MCF), Lysis Index (LI 30) and Maximum Lysis (ML) and the Interpretation section explains how to interpret a temogram (Figure 1). Whereas the Interactive Interpretation Module, is logic based and developed using current peer-reviewed published algorithms. It allows for direct entry to the App of patient specific ROTEM parameter values, then displaying the interpretation of normal or abnormal results such as clotting factor, platelet or fibrinogen deficiency, hyperfibrinolysis or heparin effect and subsequent recommendations for appropriate blood product use.

Figure 1. iTEM interpretation and educational modules

Conclusion: The App is readily available to all laboratory and medical staff and will assist with the diagnosis of coagulopathy and guide appropriate blood product use in different clinical situations



Detection of Treponema pallidum DNA in blood from donors seropositive for syphilis consistent with current risk modelling

Dr Lina Rustanti[1], Dr Veronica Hoad[1], Ms Claire Styles[1], Prof Iain Gosbell[1,2], Prof Robert Flower[1], Dr Helen Faddy[1,3], Dr Eileen Roulis[1]
[1]Australian Red Cross Lifeblood, West Melbourne, Australia, [2]School of Medicine, Western Sydney University, Penrith, Australia, [3]School of Biomedical Sciences, University of Sunshine Coast, Petrie, Australia

Aim: *Treponema pallidum* bacteraemia carries a risk of transmitting syphilis through transfusion. Australian Red Cross Lifeblood manages this risk using donor screening and serological testing in combination with modern blood processing practices. A recent risk model estimated ~12% of seropositive donors are bacteraemic at time of donation. As it is difficult to culture *T. pallidum*, and serology test results do not necessarily equate to infectivity, nucleic acid detection could be used as a surrogate for detection of the pathogen in blood and indication of potential infectivity. The aim of this study is to determine the presence of *T. pallidum* nucleic acid in serologically syphilis reactive donations and pre-index donations.

Method: Syphilis reactive blood samples from 2014-2019 (n=34) and, for repeat donors, pre-index donations (within 12 weeks prior; n = 24) were retrieved from Lifeblood archive. These samples were selected from donors that tested positive for *T. pallidum* haemagglutination confirmed by specific test positive as well as non-specific, rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test positive. To detect *T. pallidum* nucleic acid, DNA was extracted and tested by quantitative real time PCR for two conserved species-specific regions, *pol-A* and *16S*.

Results: *T. pallidum pol-A* DNA was found in 7 of 58 retrieved plasma samples, and 4 of the *pol-A* positive samples were also positive for *T. pallidum 16S* DNA. Positive tested samples were either high in RPR titre (64) or VDRL titre (32).

Conclusion: Our study demonstrates that the prevalence of *T. pallidum* nucleic acid (12%) is close to the previous risk modelling in Australian blood donors. As these samples had high RPR/VDRL titres and were discarded, the risk of syphilis transfusion transmission is negligible. This indicates that our existing strategy is sufficient to identify donations at potentially higher risk of transmission via transfusion.

A quality assurance analysis of fetomaternal haemorrhage testing across Australia and New Zealand and the accuracy of these methods for the dosing of RhD Immunoglobulin.

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Aim: There is little standardisation in the laboratory techniques used to estimate fetomaternal haemorrhage (FMH). The RCPA Quality Assurance Program (QAP) results historically demonstrate wide variations in FMH methodologies across participants. The recently released revised ANZSBT Guidelines for the Laboratory Estimation of Fetomaternal Haemorrhage provide additional recommendations to address in response to a survey of laboratories across Australia and New Zealand in 2019. The study aims to understand the current laboratory practices for FMH quantification and perform a quality assurance analysis of FMH testing and its impact on RhD Immunoglobulin (RhD Ig) dose recommendations of Australia and New Zealand laboratories participating in the RCPAQAP.

Method: A retrospective analysis was performed on pre-collected and deidentified data from the survey performed by the ANZSBT Transfusion Science Standing Committee and the RCPAQAP FMH Estimation Surveys from 2018-2020. Data was collated using MicrosoftExcel. Quantitative analysis of the RCPAQAP data was performed using simple statistics. Responses from the ANZSBT survey were assessed manually.

Results: In the ANZSBT survey, 85% of participating laboratories perform Kleihauer-Betke (KB) compared to flow cytometry (FC) for quantitation of FMH - laboratory practises are discussed in detail. In the RCPAQAP survey, at least twice the number of laboratories utilised KB. The FC method demonstrated lower mean, standard deviations and coefficient of variations within each run when compared to KB for each sample. The was a tendency towards a higher number of recommended vials of RhD Ig using KB compared to FC, although overall, the median FMH results and number of recommended RhD Ig vials are similar.

Conclusion: FC offers technical advantages for FMH quantitation however KB is the most common method used and remains an adequate method for FMH testing due to availability, staffing proficiency and cost. Our hypothesis is standardisation through the new guidelines will improve the accuracy of KB.

The national Thrombotrol-VF audit: recent trends and current practice in New Zealand

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Aim: To investigate New Zealand's requirements for antithrombin III concentrate (Thrombotrol-VF), its clinical use and efficacy across the country, so that the New Zealand Blood Service can ensure adequate ongoing supply and provide recommendations on its future use.

Method: A national retrospective audit was conducted in two parts. First part pertains to the national demand for Thrombotrol-VF; this included all Thrombotrol-VF requests in NZ between 1st of January 2015 and 31st of December 2020. Part two included all Thrombotrol-VF requests in NZ between 1st of July 2020 and 30th of June 2021. The corresponding patient demographics, treatment indications, appropriateness of requests and post-treatment ACT or ATIII levels were analysed.

Results: Part I: A total of 984 Thrombotrol-VF vials (each vial contains 1000IU of antithrombin) were issued between 2015 – 2020. There was a trajectory towards increasing total vials per annum and total patients per annum. Significant differences in the demand for Thrombotrol-VF exist between different regions of NZ. Interestingly, Canterbury region has consistently required the most vials (41%), yet Auckland region accounts for most patients (33%).

Part II: Within the 12-month timeframe, there were 201 separate requests for Thrombotrol-VF, corresponding to a total of 233 vials and issued to a total of 71 patients. Thromboprophylaxis following L-Asparaginase induced antithrombin deficiency was the most common indication for Thrombotrol-VF use (46.4%). There are significant variations in clinical practice for this indication across the country, and no national standardised guideline exists. Lastly, 80% of the Thrombotrol-VF requests were appropriate, and only 60% met the target ACT or ATIII level for each of their locality.

Conclusion: This is the first national audit on Antithrombin III concentrate use in New Zealand and has provided significant insight into its use. In particular, it has demonstrated the increasing demand for this product and the need for nationally standardised guidelines.

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Utility of an improved haemovigilance review process utilising a standardised proforma guide in an Australian tertiary hospital.

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Aim: To describe the utility of a locally developed and systematic haemovigilance review process utilising a standardised proforma guide to improve quality and safety of transfusion practice at an Australian tertiary metropolitan centre.

Method: Reported cases of suspected transfusion reactions, transfusion-related adverse events, use of uncross-matched O RhD-negative red cells (RBCs) and massive transfusion (MT) episodes are reviewed fortnightly in a haemovigilance review subcommittee. A key improvement of this process is a standardised proforma guide. Details captured include patient demographics, clinical details and outcomes of any events, comorbidities, time from patient arrival to pre-transfusion specimen collection and receipt in laboratory, time from arrival in specimen collection to transfusion laboratory, time from blood component/product request to release and transfusion, frequency of full blood examination and coagulation testing, total component provision and ratios (in MTs), component waste, communication between all clinical teams involved and the transfusion laboratory staff, details of clinical symptoms and signs of suspected transfusion reaction and findings/likely diagnosis/recommendations from transfusion reaction investigations, made available in the patient's medical record. A document summary is provided to the Hospital Transfusion Committee (HTC) and incidents are reported to Victorian Serious Transfusions Incident Reporting (STIR) as per their guidelines.

Results: A total of 348 cases between March 2020 and April 2022 were reviewed. Of these cases, 139 were MT cases, 93 were instances of use of emergency uncrossmatched O RhD-negative red cell units and 166 cases of suspected transfusion reaction. Areas identified for improvement include communication issues, delays in specimen delivery and blood component waste minimisation.

Conclusion: The haemovigilance review sub-committee of the HTC continues to review events to optimise transfusion safety. Use of an improved standardised proforma guide has provided a streamlined process to review each transfusion-related event in a systematic manner ensuring that every step of the transfusion chain is monitored.

#GotBlood2Give: Exploring the experiences of Black men who have sex with men (cis and trans) with blood donation in Canada

OmiSoore Dryden[1], **Mx Jad Sinno[1,2]**, Abdul Cadri[3], Dr Edward Ou Jin Lee[4], Dr Zack Marshall[3], Dr Lawrence Mbuagbaw[5], Dr LaRon Nelson[6]
[1]Dalhousie University, Halifax, Canada, [2]University of Toronto, Toronto, Canada, [3]McGill, Montreal, Canada, [4]Universite de Montreal, Montreal, Canada, [5]McMaster University, Hamilton, Canada, [6]Yale University, New Haven, USA

Aim: In Canada, there is a paucity of research aimed at understanding the experiences of Black gay, bisexual, queer and trans men (GBQTM) in relation to health, including barriers to becoming blood donors. Black GBQTM face intersecting forms of erasure and silencing due, in part, to racism, sexism, homophobia, transphobia in both queer communities and the wider Canadian community. The HIV epidemic has uniquely shaped the way that Black GBQTM have been thought about and presented in research, which have informed specific questions in the Canadian Blood Services (CBS) donor questionnaire. While the donor questionnaire continues to evolve – with questions being removed, rewritten, and updated – questions about GBQTM remain contentions. The aim of this project was to better understand the experiences of Black GBQTM in relation to blood donation in Canada.

Method: #GotBlood2Give is an ongoing mixed-methods three-part research project conducted in Halifax, Montréal, Ottawa, and Toronto. We report findings from part one – an online quantitative survey distributed to Black GBQTM. Parts two and three consist of interviews with Black GBQTM.

Results: 286 Black GBQTM completed the online survey. Only 16.4% (n=47) of participants reported having ever donated blood. The most frequent reasons for having donated blood were that blood donation was something they believed in (n=30, 63.8%) and they felt that they were helping others (n=27, 57.4%). Among those who did not donate blood (n=210, 73.4%), the most reported reasons were that CBS did not allow them to donate (n=49, 23.7%) and that they had never been asked to donate blood (n=40, 19.3%). The remainder (n=29, 10.1%) skipped/preferred not to answer these multiple response questions.

Conclusion: Our findings suggest that Black GBQTM experience intersecting forms of discrimination reflecting broader CBS donor policies. In 2022, CBS introduced a new behaviour-based policy, which we believe still falls short in identifying low-risk Black GBQTM who should be eligible to donate blood. Recommendations from this study highlight suggested changes to the CBS donor questionnaire that would improve blood donation experiences for Black GBQTM.

Group O whole blood product retains haemostatic potential for at least 21 days of cold storage

Dr Joanne Tan[1], Ms Htet Htet Aung[1], A/Prof Denese Marks[1,2]
[1]Australian Red Cross Lifeblood, Alexandria, Australia, [2]University of Sydney, Camperdown, Australia

Aim: Australian Red Cross Lifeblood does not currently supply a whole blood (WB) product. Group O WB has been shown to improve outcomes in military settings, and early administration of blood products to trauma patients with severe bleeding improves their survival, hence WB could be suitable for Australia's pre-hospital or regional locations. The aim of the study was to evaluate the quality and function of RBCs, platelets and plasma proteins from cold-stored WB product.

Method: WB (n=24) was collected into CPD anticoagulant, held overnight, processed through a platelet-sparing filter, and stored at 2-6°C for 42 days. Samples were taken on day 1, 4, 7, 14, 21, 28, 35 and 42, and RBC, platelet and coagulation factor quality and function were measured.

Results: WB units were effectively leucoreduced, with 85% recovery platelet count following filtration. One third of the WB units processed were significantly lipaemic, with a visible lipid layer appearing after overnight cold storage. Haemoglobin levels remained constant throughout storage ($p=0.122$). Lipaemic units were more turbid with a higher percentage of haemolysis when compared to non-lipaemic units ($p=0.003$), and subsequently failed to meet the 0.8% haemolysis specification. Platelet count decreased during storage, and the R time and the maximum amplitude (thromboelastography) decreased during cold storage (both $p<0.0001$), although not affected by the presence of lipaemia. Fibrinogen concentration remained constant ($p=0.0127$), whereas both FVIII and FV decreased during storage (both $p<0.0001$). There was an increase in platelet-derived and RBC-derived microparticle numbers during WB storage ($p=0.00014$ and $p=0.023$, respectively).

Conclusion: WB retains haemostatic potential for at least 21 days of cold storage, and with further development, may be suitable for transfusion in Australia. However, the effects of lipaemia need to be considered if WB is to be used routinely, as it can interfere with quality control measurements such as haemolysis.

Emergency blood coordinator: a formal role for emergency department massive transfusion protocol resuscitations.

Mr Daniel Van Vorst[1], Ms Amy Ward, Mr Christopher Partyka
[1]SWSLHD, Liverpool, Australia, [2]Western Sydney University, Liverpool, Australia

Background; In six-months (from September 2020), 83 blood product units were wasted during massive transfusion protocol (MTP) activations in Liverpool Emergency Department (ED). Five additional blood-related incidents were reported on the Incident Management System (IMS). Investigation discovered cold-chain breaches in ED and during patient transfer from ED. Issues with administration and the coordination of MTP shipments from blood bank were also discovered. The aim of this project was to reduce MTP blood wastage and improve cold-chain management, administration and patient safety along with blood product communication and handover processes.

Method: Following multidisciplinary stakeholder engagement a Blood Coordinator role was implemented in March 2021. The Blood Coordinator is a designated resuscitation team member whose primary role is to act as the direct point of contact between blood-bank and ED. They are to assist with the cross check and administration of MTP blood products and must be competent with the rapid infuser. They are required to maintain cold-chain and formalise transfusion documentation within ED and upon transfer. Communication and education were provided to stakeholders with MTP activation now including the addition of a portable whiteboard to assist with tallying blood products, an alarming timer attached to MTP shipments and a blood coordinator phone for direct communication.

Results: Post implementation, blood product wastage reduced from 13.8 units/month to 8.6 units/month. IMS reports also decreased from 5 incidents during six-months to only 2. Communication between teams has also improved. This demonstrates a significant reduction in blood product wastage in an MTP and shows an improvement in teamwork and patient safety.

Conclusion: Allocation of a Blood Coordinator for an MTP is embedded in practice in Liverpool ED and has reduced blood wastage and improved patient safety. Other facilities with high MTP activations could implement a similar role to reduce blood wastage, improve patient safety and cold chain management.

Management of group O RhD negative red blood cells

Associate Professor David Roxby[2], Ms Lyndsay Wall[1], Ms Sandra Cochrane[1]
[1]National Blood Authority, Canberra, Australia, [2]Flinders University, Bedford Park, Australia

Aim: The use of group O RhD negative red blood cells (RBC) has increased to unsustainable levels over the last few years. Only 6.5%[1] of the Australian population are group O RhD negative, however, group O RhD negative RBC currently represent over 17%[2] of total RBC issued to Australian health providers. The National Blood Authority (NBA) has commenced a number of projects to address group O RhD negative RBC use.

Method and Results:

O RhD negative national statement

The NBA has formed a group O RhD negative RBC expert working group consisting of representatives from key professional organisations and jurisdictions. The working group will develop a joint statement on group O RhD negative RBC use and emergency issue practices. The scope of the expert working group is twofold; the first stage to issue a joint statement is underway. The second stage will be to formulate guidance for managing red blood cell inventory, transfers, policies and management.

Posters

The NBA has created two posters available to download from the NBA website on general group O RhD negative RBC management and emergency group O RBC issues. The posters are the first stage of creating an awareness in the Australian health sector regarding the unsustainable rise in group O RhD negative issues.

Tailored jurisdictional discussion papers

The NBA has undertaken tailored data analysis for each jurisdiction on the issue, transfer and discard patterns of RBC and group O RhD negative. Discussions have commenced with the aim to enable each jurisdiction opportunities to address the areas of concern.

Conclusion: These projects complement the *National Blood Product Management Improvement Strategy 2018-2022* and allow the NBA to work in partnership with the Australian health sector and jurisdictional governments. The collaborative approach is key to achieving viable and ongoing results.

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Increasing the time-to-freezing for clinical apheresis plasma

Dr Kelly Winter[1], Ms Rachel Webb[1], Ms Eugenia Mazur[1], Ms Sue Ismay[1], A/Prof Denese Marks[1]
[1]Australian Red Cross Lifeblood, Alexandria, Australia

Aim: The vast distances between blood collection centres and blood processing facilities make it challenging to align clinical plasma supply with demand. Increasing the time-to-freezing for clinical plasma would alleviate many of these issues. This study aimed to compare the quality of clinical apheresis plasma frozen within 6 and 12 hours of collection.

Method: Apheresis plasma (n=20) collected at donor centres was immediately transported to a blood processing facility, where the plasma was stored at 26°C, to replicate a worst-case scenario for shipping plasma during high external temperatures. Plasma was sampled aseptically at 6, 8 and 12 hours post-collection and frozen immediately in a rapid plasma freezer. Upon thawing, coagulation factors were measured using a coagulation analyser, and complement C3a and C5a were measured by ELISA.

Results: FVIII concentration declined in plasma frozen at 6, 8 and 12 hours post-collection (122±27, 121±25, and 116±24 % respectively) but did not reach a level of significance (p=0.3338). Importantly all components met the Council of Europe specifications for FVIII (≥0.7 IU/mL). Fibrinogen and vWF concentrations remained constant from 6 hours to 12 hours (p=0.3100 and p=0.1281 respectively). There were no significant differences in coagulation factors II, V, VII and XIII in plasma frozen at 6, 8 or 12 hours post-collection. C5a declined between 6, 8 and 12 hours (58±12, 56±11, 56±11 µg/mL respectively; p=0.2123), whilst C3a was stable. Activated partial thromboplastin time, prothrombin time, antithrombin or protein C concentration were also not significantly different in plasma frozen within 6, 8 or 12 hours from collection.

Conclusion: Clinical apheresis plasma can be frozen within 12 hours of collection, thus allowing collection from more donor centres further from blood processing centres and increasing supply. Submission will be made to the regulator, Therapeutic Good Administration, for review and approval to introduce this change to Lifeblood processes.

Extending the post-thaw shelf-life of cryoprecipitate

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Aim: Cryoprecipitate has a short post-thaw shelf-life of 6 hours, leading to very high rates of wastage. It may be feasible to extend this. The aim of this study was therefore to evaluate the quality of thawed cryoprecipitate stored at 4°C for up to 14 days.

Method: Three whole blood (WB) or two apheresis cryoprecipitate components were pooled and split into nine paediatric packs (n=20), and stored at 4°C. One paediatric pack from each pool was sampled at 6, 24, 48 and 72 hours, and day 7 and 14 post-thaw. Coagulation factors and fibrinogen were measured by coagulation analyser. Fibronectin and complement C3a and C5a were measured by ELISA. Thrombin generation was measured by calibrated automated thrombogram. The remaining samples were screened for bacterial contamination.

Results: FVIII declined significantly in WB ($p=0.0002$) and apheresis cryoprecipitate ($p<0.0001$) after 6 and 24 hours respectively. Despite these decreases all cryoprecipitate met FVIII specifications on day 7 post-thaw. Fibrinogen was stable for 72 hours, then gradually decreased in both WB and apheresis cryoprecipitate, still meeting specifications on day 14. There were minor decreases in FII, FIX and FXIII over the 14 days of storage, whereas FV decreased significantly by 48 hours post-thaw for both WB and apheresis cryoprecipitate ($p<0.0001$, $p=0.0047$ respectively). Fibronectin, vWF and C5a were stable, whilst C3a increased 9-fold over the 14 days ($p<0.0001$). There were small but significant decreases in thrombin generation lag time, endogenous thrombin potential and time to peak for both WB and apheresis cryoprecipitate. Importantly, there was an increasing amount of reprecipitation observed in the cryoprecipitate during post-thaw storage at 4°C, which became more challenging to redissolve later in storage. All cryoprecipitate components were negative upon bacterial culture.

Conclusion: WB and apheresis-derived cryoprecipitate still meet the Council of Europe specifications after 7 days post-thaw storage at 4°C.

Novel insight into platelet refractoriness

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Aim: Platelet refractoriness remains a significant burden in patients with solid and haematological malignancies. Despite the introduction of leucodepletion, 12-18% of transfused patients still develop alloantibodies against human leucocyte antigen (HLA).

We aim to 1) elucidate the unexplored Fc-gamma (Fcy) pathway in allo-antibody induced platelet clearance; 2) investigate Fcy inhibitor's capability in alloantibody binding prevention; 3) establish a murine model to examine patients' antibody effect on donor platelets; 4) demonstrate Fcy inhibitor's *in vivo* effectiveness in platelet preservation in the presence of allo-HLA antibody.

Method: The study was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee and the Animal Ethics Committee UNSW. Sera were collected with informed consents from patients with proven HLA alloimmunisation. Healthy donor platelets were incubated with patients' IgG with or without prior treatment with Fcy inhibitor IV.3, followed by labelled anti-human IgG and flow cytometric analysis. A nonobese diabetic/severe combined immunodeficient murine model of platelet refractoriness was established. Donor platelets were transfused into the NOD/SCID mice, followed by examination of human platelet number in the presence of patients' antibodies.

Results: Platelets pre-treated with IV.3 showed substantial reduction in alloantibody binding in all patients (P=0.03 Wilcoxon matched-pairs signed rank test), indicating the importance of Fcy pathway in platelet refractoriness. *In vivo,* HLA alloantibodies induced significant destruction of transfused human platelets, in a dose-dependent fashion. Further murine experiments are in progress, to examine if pre-treatment of donor platelets with healthy immunoglobulins, which non-specifically inhibit the Fcy receptors, can reduce platelet destruction.

Conclusion: We demonstrated that HLA alloantibodies induce platelet destruction via the Fc-gamma pathway. *In vitro* study confirmed the efficacy of Fcy inhibitor in preventing antibody binding. *In vivo experiments* are currently underway. Perspective clinical trials to test its activity in patients are needed

Use of half RBC units in oncology patients during severe RBC shortage to extend hospital supply

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Background/Case Studies: Blood supply during the COVID-19 pandemic was at record lows due to blood drive cancellations, fear of contracting COVID-19, and COVID-19 donor deferrals. Splitting platelet units is a well-known method of extending platelet supply. Due to the blood type O RBC shortage during the pandemic, we split one RBC unit into two half-units to extend the RBC supply. RBC splitting has been utilized in pediatric and fluid overloaded patients, however there is no research demonstrating the effectiveness of RBC splitting to extend RBC supply.

Study Design/Methods: We examined transfusion data on half and whole RBC units transfused from May 21, 2021 to November 1, 2021. The criteria for half-unit transfusion were dependent on the blood supply. In general, if there was less than one day supply of RBC units on hand, half-units were issued for stable, non-bleeding patients with hemoglobin above 7.0 g/dL in outpatients and 6.5 g/dL in inpatients. During the study period if a patient received any half RBC units, the time between the first half-unit transfused to the next RBC transfusion within the next 90 days was noted. If a patient received only whole units during this time, we observed the time from the first RBC transfusion to the next RBC transfusion in the subsequent 90 days. Pre-transfusion hemoglobin was obtained the day of the transfusion and post-transfusion hemoglobin was obtained either the day of or day after the RBC transfusion.

Results/Findings: Over 6 months, 276 patients received only whole units and 229 patients received at least one half-unit. The median number of days to next transfusion in patients who received a transfusion within 90 days after a half-unit was 3 (mean 6.7 ± 11.4) and whole unit was 5 (mean 11.8 ± 16.7) ($p < 0.001$). There were 38 (16.6%) patients who did not receive a transfusion within 90 days of first transfusion after a half-unit and 62 (22.5%) patients after a whole unit. The median pre-transfusion hemoglobin in those transfused half-units was 6.9 (mean 6.9 ± 0.5) g/dL and whole units 7.0 (mean 7.2 ± 1.3) g/dL ($p < 0.001$). The median hemoglobin prior to the second transfusion was 6.8 (mean 6.8 ± 0.6) g/dL in those previously transfused half-units and 7.0 (mean 7.2 ± 1.1) g/dL after a previous whole unit ($p < 0.0001$). Of those transfused half-units, 46.7% received a second unit within 3 days, 56.8% within 5 days and 65.9% within 7 days. After a whole unit, 30.4% received a second unit within 3 days, 37.3% within 5 days and 44.9% within 7 days.

Conclusion: Our study demonstrates the use of half RBC units can extend RBC inventory in the short term. Patients transfused half-units received a second transfusion earlier than those who received a whole unit, median 3 days versus 5 days after whole unit ($p < 0.001$).

THANZ Poster Presentations (Poster Board No T001 – T057)

Quality Study to evaluate a recently adopted secondary standard calibrator for intrinsic coagulation factor assays

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Aim: RCPA QAP reports in 2020 for our laboratory revealed a positive bias for FIX one-stage clotting assay for the STA Unicalibrator group as compared to other calibrators. At the time, the Unicalibrator was calibrated against the ISTH secondary standard calibrator SSC4 (Uni-SSC4). Our aim was to assess assay performance for intrinsic coagulation factors using a batch of Unicalibrator with values assigned against the more recent SSC5 (Uni-SSC5) and compared against the Uni-SSC4. Two different aPTT reagents were also compared.

Method: Twelve RCPA FIX samples with median assigned values and a further 22 lyophilised samples were tested for factors VIII, IX, XI and XII on a Stago coagulation analyser and compared using both the Uni-SSC4 and Uni-SCC5 calibrators. The samples were tested using Triniclot aPTT S reagent and STA CK Prest reagent in parallel. The results were analysed using linearity graphs and Altman-Bland plots to assess agreement and bias. Where available, the assigned values by RCPA were used as the reference to assess performance of 12 of those samples and Relative Percentage Difference (RPD) was calculated.

Results: There was a strong correlation between results obtained with Uni-SSC4 and Uni-SSC5 for all factors with both reagents. The Coefficient of Determination (r^2) was >0.95 and the slope was between 0.90-1.12 with both aPTT reagents. For the Triniclot aPTT S reagent, the FIX calibration using Uni-SSC4 and Uni-SSC5 showed an average RPD of 21% and 18% respectively when the RCPA-assigned FIX values were used as a reference. With the CK Prest reagent, the average RPD 10% and 8% respectively.

Conclusion: Studies confirmed that for the Triniclot aPTT S reagent, the Uni-SSC5 slightly reduced the positive bias seen with Uni-SSC4. However, with the CK Prest reagent, the bias was lowered substantially. Diagnostica Stago has now replaced SSC4 with SSC5 for STA Unicalibrator value assignments and introduced it to all STA immuno-deficient plasma.

Evaluation of initial bivalirudin dosing used off-label at a quaternary intensive care unit

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Aim: To determine whether a modified bivalirudin dosing strategy results in timely attainment of therapeutic APTT and the impact on clinical outcomes.

Methods: Single-centre, retrospective, observational cohort study conducted in the intensive care unit of a major tertiary referral centre. From January 2019 to December 2021, 31 patients prescribed bivalirudin as off-label anticoagulation for indications of suspected/confirmed heparin-induced thrombocytopenia (HIT) or vaccine-induced thrombocytopenia (VIT) were identified via pharmacy dispensing records. Guidance for dosing bivalirudin in this context – particularly in continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) – is limited. The local protocol therefore implemented a conservative starting dose regimen (*Table 1*). Relevant clinical data was extracted from medical records. Data were reported descriptively, with subgroups analysed using an unpaired t-test for continuous variables. A p-value <0.05 was considered statistically significant.

Results: Baseline demographics included patients on CRRT (45%) and ECMO (58%). Overall, 74% (n=23) of patients reached therapeutic APTT. The average time to achieve target APTT from bivalirudin initiation was 21.2 hours (median duration of therapy 67 hours), with a mean ratio of initial bivalirudin dose to first therapeutic dose of 1.4 (range 1-7.4). There were no significant differences between subgroups for these outcomes, including for HIT compared with VIT. Two events of bleeding (6.5%) were identified during or within 24 hours of ceasing bivalirudin and no episodes of new or progressive thrombosis. Local protocol compliance was 39% (12/31).

Conclusion: The current bivalirudin dosing algorithm provides a reasonable timely attainment of target APTT in critically ill patients. However, the starting dose could be increased by up to 40% to achieve a therapeutic APTT quicker. Bivalirudin appears to be a relatively safe anticoagulant, though further investigation with a larger sample size is warranted.

Table 1: Local protocol – initial bivalirudin dosing algorithm

Renal function **(estimated creatinine clearance)**	**Starting dose** **(mg/kg/hour)**
>60mL/min	0.10
30-60mL/min	0.05-0.08
<30mL/min	0.02-0.05
Continuous renal replacement therapy (CRRT)	0.03-0.05

Evaluating the incidence of hospital-acquired postoperative venous thromboembolism identified from hospital coding

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Aim: Determine accuracy of hospital coding for the incidence and extent of postoperative venous thromboembolism (VTE).

Method: Single-centre retrospective study at a major quaternary health service in Melbourne, Australia. From May 2017 to April 2018, there were 232 patients diagnosed with VTE post-surgery according to ICD-10 coding at discharge from hospital. Accuracy of coding for incidence and severity of VTE was extracted from medical records. Data were analysed descriptively.

Results: Of the 232 included patients, 52 (22.4%) were determined to be incorrectly coded data with no diagnosis of hospital-acquired VTE identified. The remaining 180 patients experienced a total of 208 objectively confirmed VTE events (median age 60 years, length of stay 21 days). The episodes of VTE consisted of lower limb deep vein thrombosis (DVT) (n=100, 48%), pulmonary embolism (n=56, 27%), upper limb DVT (n=31, 15%) and isolated lower limb superficial vein thrombosis (n=21, 10%). Virtually all patients (99.5%) had one or more risk factor for VTE. 157 patients (87.2%) were managed with therapeutic anticoagulation. Approximately one-third of all VTE events (n=68) were asymptomatic, diagnosed incidentally by routine surveillance imaging.

Conclusion: Coding data overrepresents the true number of VTE and accurate classification of events is an area in need of improvement. Substantial numbers of postoperative VTE events were observed though upon further investigation, a large proportion were of low clinical significance or identified incidentally. Further review of our local thromboprophylaxis is required to reduce the burden of postoperative VTE.

Interim analysis from B-MORE, a 24-month prospective, multicentre, non-interventional study on effectiveness and usage of recombinant factor IX Fc (rFIXFc) in haemophilia B

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Aim: Extended half-life rFIXFc has a well-established safety and efficacy profile demonstrated by phase 3 trials in patients with haemophilia B (HB; ≤2 IU/dL FIX) across all age groups. The ongoing B-MORE study prospectively evaluates real-world effectiveness and usage of rFIXFc in HB patients in Europe and the Middle East. B-MORE interim data are described.

Method: This 24-month prospective, multicentre, non-interventional study includes patients prescribed prophylactic or on-demand rFIXFc treatment prior to or at study enrolment. Baseline characteristics, 12-month retrospective data on previous FIX treatment prior to rFIXFc switch, rFIXFc prescribed dose and annualised bleed rate (ABR) are reported.

Results: At interim data cut-off (22nd October 2021), 117 patients (2 female) from 25 centres were included in the effectiveness analysis. The median (range) age at enrolment was 16 (1–81) and 80% (n=93) had severe haemophilia. Most patients (63%, n=74) were on prophylaxis before rFIXFc initiation. One (1%) patient had history of inhibitors (tolerized) and 7 (6%) patients had a target joint at rFIXFc initiation.

Patients with ≥6 months documented prophylaxis with standard half-life FIX prior to rFIXFc had a median (IQR) of 2.0 (2.0–2.0) injections/week with FIX (n=69), median (IQR) factor consumption of 74.9 (58.4–92.1) IU/kg/week (n=65) and median (IQR) overall ABR of 1.0 (0.0–2.0) (n=69).

Mean (range) overall duration of rFIXFc treatment from initiation to data cut-off was 824 (42–3650) and 457 (15–1207) days for prophylactically (n=106) and on-demand (n=11) treated subjects, respectively. Dosing and ABR on rFIXFc prophylaxis are shown (Table 1).

Conclusion: Interim data from B-MORE indicate rFIXFc prophylaxis can provide and maintain excellent bleed protection in this HB population including a large number of paediatric patients. These real-world data show a median ABR close to zero on rFIXFc prophylaxis with a low factor consumption mainly based on a once-weekly regimen.

Table 1. Prescribed prophylactic dosing and ABR on rFIXFc prophylaxis[1]

Prophylactic dosing with rFIXFc	
Prophylactic injections/week, median (IQR) (n=106)	1.0 (1.0–1.0)
Factor consumption, IU/kg/week, median (IQR) (n=104)[2]	47.6 (37.6–52.3)
ABR by pre-rFIXFc treatment regimen[3]	
Prior prophylaxis, median (IQR) (n=72)	0.0 (0.0–0.5)
Prior on demand, median (IQR) (n=5)	1.2 (0.7–2.9)

[1]Includes both retrospective and prospective follow-up periods on rFIXFc
[2]Data on factor consumption was missing for n=2
[3]Of the n=106 patients receiving rFIXFc prophylaxis, the n=77 with reported pre-rFIXFc treatment regimen are shown

The journey to secure funded access to a life changing haemophilia treatment

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The journey to secure funded access to a life changing haemophilia treatment

Aim: The National Blood Authority (NBA) responded to an application to add Hemlibra® (emicizumab) to the list of products funded under Australia's national blood arrangements.

Method: People with severe or moderate haemophilia A require treatment with FVIII products to help prevent and stop bleeding episodes which can be severely disabling and cause recurrent joint damage. Conventional Factor VIII therapy requires frequent intravenous infusions and can also lead to the development of antibody responses.

Hemlibra® is a bispecific, factor VIII (FVIII)-mimetic monoclonal antibody product that substitutes for part of the cofactor function of activated FVIII (FVIIIa) by bridging activated factor IX (FIXa) and factor X (FX).

Hemlibra® can be used prophylactically in adult and paediatric haemophilia A patients, including those with or without inhibitors. It can be self-administered subcutaneously, and may require less frequent administration when compared to alternative products.

In September 2020 the NBA sought to add Hemlibra® to the national product list funded under Australia's national blood arrangements. This was based on the outcome of assessment by the Medical Services Advisory Committee which considered comparative safety, clinical effectiveness, and cost effectiveness. The NBA was able to negotiate supply arrangements with Roche Pharmaceuticals for the supply of Hemlibra® to provide value for money for funding governments. The NBA consulted with clinical and patient groups to inform the transition steps for its introduction.

Results: Supply commenced on 2 November 2020 and there has been over 2.5 million milligrams of Hemlibra® distributed to March 2022. There has also been an observed change in the demand for other FVIII products since its introduction.

Conclusion: Feedback from health centres, patients and their carers about the introduction of the supply and funding of Hemlibra® has been very positive to date and has indicated that Hemlibra® has had a huge impact on the lives of patients in Australia with haemophilia A, especially paediatric patients.

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Using the EMR to improve compliance with venous thromboembolism prophylaxis guidelines in obese inpatients

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Aim: The aim of this study was to improve compliance with institutional VTE prophylaxis dosing guidelines for obese inpatients in our network. We performed a clinical decision support intervention by adjusting order sentences of prophylactic enoxaparin within our EMR and compared compliance rates pre and post intervention.

Method: Clinical records were evaluated pre- (June 2019 - August 2020) and post-intervention (September 2021 - February 2022) analysis of obese (weight > 120kg) inpatients at a multicentre, quaternary healthcare network. Records were reviewed for compliance to local thromboprophylaxis guidelines based on documented weight. The intervention involved adjusting order sentences for dosing of prophylactic enoxaparin within the EMR to filter appropriate doses, according to the patient's documented weight. Improvement in the pre- to post-intervention compliance was compared using Chi squared as indicated. A p-value of <0.05 was considered significant.

Results: Prior to the intervention, 187 patients were identified with a median weight of 143kg (median BMI 47.8kg/m^2). Following the intervention, 68 patients were identified with a median weight of 143kg (median BMI 49.4kg/m^2). The post-intervention group was younger, less likely to have active cancer or be postoperative. Follow up to 90 days was complete for 84.4% of all patients. Thromboprophylaxis dosing was compliant with hospital guidelines in 71% of cases in the pre-intervention group. This improved to 87% following the intervention ($p = 0.01$).

Conclusion: The simple addition of weight-based filtering to our existing EMR medication orders significantly improved appropriate dosing for thromboprophylaxis in obese inpatients. Adoption of this EMR based change could be applied to other similar weight-based therapeutics including antimicrobial and anticonvulsant agents.

Impact of novel therapies on musculoskeletal outcomes for adults with moderate to severe haemophilia.

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Aim: To describe how the treatment of adults with moderate to severe haemophilia A and B, at a state-wide Haemophilia Treatment Centre in Victoria, changed from 2015 to 2021, and the subsequent impact on utilisation of invasive interventions for haemophilic arthropathy.

Method: All patients with moderate to severe haemophilia A and B, defined by either a baseline factor level below 5% of normal or the presence of inhibitors, treated at the Victorian state-wide haemophilia service for adults in 2015, were identified from the Australian Bleeding Disorders Registry (ABDR). Data was extracted from the Alfred Health electronic medical record for 2015 and 2021, including patient demographic, treatment strategy (on-demand replacement, prophylaxis or gene therapy), treatment agent (standard half-life (SHL) factor, extended half-life (EHL) factor, emicizumab and other novel therapies), and utilisation of invasive musculoskeletal interventions including intra-articular cortisone injections, yttrium radiosynovectomy and surgery.

Results: 132 patients were identified. On preliminary analysis, 63% of patients underwent a change in treatment between 2015 and 2021. This included switching from on-demand therapy to routine prophylaxis (16%) as well as alterations in prophylaxis regimen including increased factor dose (8%), transition from SHL to EHL factor (4%) or transition to emicizumab (20%). 8% of patients received gene therapy during this period as part of clinical trials underway at the service.

Review of procedures conducted over the same period demonstrates a concurrent decline in the use of invasive musculoskeletal interventions. Intra-articular cortisone injections decreased from 84 joints across 30 patients in 2015, to 18 joints across 10 patients in 2021. Likewise, the use of yttrium radiosynovectomy declined by 56% from 30 joints in the 5 years prior to 2015, to 15 joints in the 5 years following. Further planned analysis will evaluate joint function as assessed by Haemophilia Joint Health Scores (HJHS) recorded in 2015 and 2021.

Conclusion: This study illustrates the changing landscape of haemophilia treatment and quantifies the impact of developments in prophylaxis on musculoskeletal outcomes to inform future planning and resource requirements for optimal haemophilia musculoskeletal care.

A Phase 1 sequential pharmacokinetic (PK) evaluation of octocog alfa, rurioctocog alfa pegol, and efanesoctocog alfa in severe hemophilia A

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Aim: Efanesoctocog alfa (BIVV001) is a novel factor VIII (FVIII) replacement therapy designed to decouple recombinant FVIII from endogenous von Willebrand factor. Once-weekly dosing (50 IU/kg) provided high sustained FVIII activity in the normal to near-normal range (>40 IU/dL) for 3–4 days and at 10 IU/dL on Day 7 post dose. Here, we evaluated the PK profiles of efanesoctocog alfa, a standard half-life FVIII, octocog alfa, and an extended half-life FVIII, rurioctocog alfa pegol.

Method: Thirteen previously treated adult males with severe hemophilia A (<1 IU/dL endogenous FVIII) were enrolled in this Phase 1 study (NCT05042440). After appropriate washout periods, each patient sequentially received single 50 IU/kg doses of octocog alfa, rurioctocog alfa pegol, and efanesoctocog alfa. The primary objective was to assess the elimination half-life ($t_{1/2z}$) for each product. Secondary objectives were characterization of additional PK parameters and evaluation of safety and tolerability of efanesoctocog alfa.

Results: Geometric mean $t_{1/2z}$ of octocog alfa, rurioctocog alfa pegol, and efanesoctocog alfa were 11.0, 15.4, and 43.3 hours, respectively (Table). Corresponding values for area under the curve extrapolated to infinity (AUC_{inf}) were 1670, 2820, and 10,100 IU × h/dL. Efanesoctocog alfa maintained mean FVIII activity levels >40 IU/dL for up to 4 days and ~10 IU/dL at Day 7. Corresponding times >40 IU/dL and >10 IU/dL were <1 and <2 days for octocog alfa and ~1 day and <3 days for rurioctocog alfa pegol. No serious or severe treatment-emergent adverse events were reported.

Conclusion: Single-dose efanesoctocog alfa had a 3–4-fold longer $t_{1/2z}$ and 4–6-fold greater AUC_{inf} than the other 2 products. Efanesoctocog alfa maintained high sustained FVIII activity in the normal to near-normal range for a longer duration compared with currently marketed FVIII therapies and has potential to improve bleed protection with less frequent dosing.

Table. Geometric mean (CV) PK parameters following a single dose (50 IU/kg) of octocog alfa (SHL FVIII), rurioctocog alfa pegol (EHL FVIII), and efanesoctocog alfa

PK parameters[a,b]	Octocog alfa (n=13)	Rurioctocog alfa pegol (n=13)	Efanesoctocog alfa (n=13)
$t_{1/2z}$, h	11.0 (39)	15.4 (35)	43.3 (24)
AUC_{inf}, IU × h/dL	1670 (41)	2820 (31)	10,100 (15)
CL, mL/h × kg	2.99 (45)	1.77 (33)	0.496 (19)
C_{max}, IU/dL	118 (12)	148 (20)	139 (12)
IR, IU/dL per IU/kg	2.36 (12)	2.96 (20)	2.78 (12)
MRT, h	13.2 (46)	19.2 (38)	62.7 (15)

aPTT, activated partial thromboplastin time; AUC_{inf}, area under the activity time curve extrapolated to infinity; CL, clearance; C_{max}, maximum FVIII activity; CV, coefficient of variation; EHL, extended half-life; FVIII, factor VIII; IR, incremental recovery; MRT, mean residence time; PK, pharmacokinetic; SHL, standard half-life; $t_{1/2z}$, elimination half-life.
[a]Baseline-corrected FVIII activity was determined by the one-stage aPTT-based clotting assay. [b]PK sampling was performed over a period of 3, 5, and 14 days after the administration of octocog alfa, rurioctocog alfa pegol, and efanesoctocog alfa, respectively.

Retrospective single centre review of upper extremity deep vein thrombosis

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Aim: Upper extremity deep vein thrombosis (UEDVT) accounts for 5-10% of all deep vein thromboses (DVTs)[1-3], up to 80% of which are provoked by an indwelling venous catheter[4]. The aim of this study was to describe risk factors, treatment and complications associated with non-catheter related UEDVT.

Method: Patients seen at our tertiary centre thrombosis clinic with UEDVT were identified retrospectively from April 2019 to April 2022 using the electronic medical record. Data was obtained from clinic letters and electronic results system.

Results: 30 patients were identified. 47% were female with an average age of 38 years. 87% UEDVTs involved the subclavian vein. 10% were associated with bilateral pulmonary emboli at diagnosis (one had concurrent left ventricular thrombus, another was symptomatic two days post UEDVT diagnosis and the third was incidentally found). All three were unprovoked.

Seven patients had a history of prior DVT, six of which were UEDVTs. The commonest risk factors included thoracic outlet obstruction (37%) and effort thrombosis (33%).

Three patients had thrombolysis +/- stenting; seven had surgical intervention including rib resection. Most patients were anticoagulated with rivaroxaban or apixaban, one had clexane and four used warfarin. At follow-up, ten patients had ceased anticoagulation and four had reduced intensity anticoagulation. Median duration of therapy was 4.5 months. Five patients had minor bleeding, four had post-thrombotic syndrome, three had progression while on anticoagulation (one at three months, one day 8 post thrombectomy and rib resection, and the other at 21 days with active cancer) and one had a contralateral subclavian DVT at 10 months while on warfarin with a therapeutic INR. Three patients had subsequent DVTs at other sites.

Conclusion: Non-catheter related UEDVT is associated with significant morbidity. Our study suggests that patients with unprovoked UEDVT should have thoracic outlet obstruction excluded. Studies are needed to improve the outcome of patients with UEDVT.

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External quality assurance challenges of a Factor XIII deficient sample

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Aim: To investigate an alternate model to analyse and report RCPAQAP Factor XIII (FXIII) Assay data on a FXIII immune deficient plasma where erroneously high results have shifted the median.

Method: A FXIII deficient sample (HA-FXIII-22-01) was included in the 2022 FXIII program. Data from 26 participants was processed by RCPAQAP software to obtain the median, mean, SD, CV, APS and Z-scores. The APS is calculated as +/- 5.0 up to 20.0 or +/- 25% > 20.0 based on the median of the analytical principle. Due to small sample size and erroneously high results skewing the median and its related APS, a specific target was introduced to override the medians and correct the APS to a clinically significant range.

Results: The 'Chromogenic' analytical principle group (n=19) had a median of 5.7% and an original APS of 0.7-10.7%, while the 'Liatest' group (n=7) had a median of 0.4% and an original APS of 0.0-5.4%. By overriding the target from group medians to a specific target of 0%, the APS corrected to 0.0-5.0% for both groups as seen in Figure 1. The Liatest group was unaffected as all results fell between 0 and 2%. For the Chromogenic group, two results marked 'Low' in the original report were now 'Within APS' and 9 results marked 'Within APS' changed to 'High' in the updated report. Two results are marked 'High' in both reports.

Conclusion: This sample was a FXIII immune deficient plasma with a theoretical FXIII activity of 0%. Severe FXIII deficiency is classified as <5% (<5U/dL)[1], therefore it is clinically significant that laboratories can identify a FXIII activity of <5%. By updating the APS of this sample to 0.0-5.0%, we are both highlighting those participants returning results above 5% as problematic and correctly reporting those participants submitting 0% to be marked as within APS.

References:
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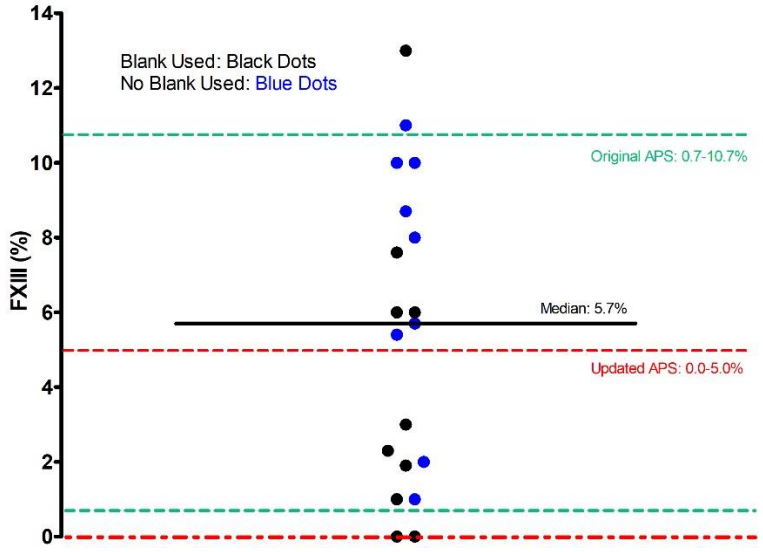
Figure 1: Chromogenic Method FXIII Results (HA-FXIII-22-01)



Factor concentrate treatment for haematuria in people with haemophilia is associated with low rates of complications

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Background and Aim: Evidence guiding optimal management of haematuria in people with haemophilia (PWH) is scarce. There has been concern that treating haematuria with factor concentrates may contribute to development of ureteric obstruction. This retrospective review was designed to contribute to the available contemporary data regarding optimal management of haematuria in PWH, including underlying aetiology, complications and outcomes.

Method: This single-centre retrospective observational study was conducted at the State Haemophilia Treatment Centre in Victoria, Australia. We identified 28 haemophilia patients admitted with haematuria using ICD codes, between January 2012 and December 2020. Data regarding demographics, severity, aetiology, treatment, and complications was collected and analysed. The median follow-up was 62 months from initial diagnosis.

Results: The baseline characteristics of our population are shown in Table 1. Three (10.7%) patients experienced major bleeding as per ISTH definition, and an underlying cause was found in 13 patients (46.4%), of which ureteric calculi were most common. The median duration of haematuria and length of stay (LOS) in hospital were both 5 days. Those receiving regular prophylaxis had a slightly shorter duration of haematuria (5.0 vs 6.0 days, p=0.74) and LOS (2.5 vs 6.5 days, p=0.06) compared to those receiving on-demand. While treatment of the haematuria with factor replacement did not reduce LOS (4.0 vs 5.0 days, p=0.64) or duration of haematuria (5.0 vs 5.0 days, p=0.44), there were few complications, in particular rates of ureteric obstruction or clot retention (1 patient that received factor, 2 that did not). Patients with more comorbidities (>/=2) had longer LOS (10.0 vs 4.0 days, p=0.12) and haematuria duration (8.0 vs 4.0, p=0.12).

Conclusion: Treatment of haematuria with factor concentrates appears to be safe with low rates of complications among PWH presenting with haematuria. The strongest predictor of LOS and duration of haematuria is the number of comorbidities.

Table 1: Baseline characteristics

	n	(%)
Type of haemophilia		
Haemophilia A	19	(67.9)
Haemophilia B	9	(32.1)
Total	28	
Severity		
Mild (>5%)	8	(28.6)
Moderate (1-5%)	2	(7.1)
Severe (<1%)	18	(64.3)
Age, years *Median (IQR)*	34.5 (25-58.3)	
Sex		
Male	27	(96.4)
Female	1	(3.6)
Regular Haemophilia Treatment		
Prophylaxis	14	(50.0)
On Demand	14	(50.0)
Inhibitor Present		
Yes	4	(14.3)
No	24	(85.7)
Comorbidities		
Smoking	3	(10.7)
Hypertension	3	(10.7)
IHD	3	(10.7)
Diabetes	1	(3.6)
CKD	1	(3.6)

Targeting anticoagulation threats in hospital with Anticoagulation Stewardship Service (ACS)

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Aim: Anticoagulation mismanagement can result in significant morbidity and mortality. In an effort to reduce anticoagulation-related errors, an Anticoagulation Stewardship Service (ACS) was implemented in October 2020 at Northern Health, Victoria. The anticoagulation steward is a pharmacist, supported by the Clinical Thrombosis Fellow and Consultant. We describe the role of ACS and review the impact of ACS on inpatient care and the organisation.

Method: A 12-month retrospective analysis of the database of inpatient referrals to ACS (October 2020 – September 2021), and review of venous thromboembolism (VTE) and anticoagulation-related hospital acquired complication (HAC) was conducted. This was compared to the preceding 12 months prior to the implementation of ACS.

Results: ACS provides governance, advice and education about anticoagulation to clinicians and patients and conducts quality improvement audits. Inpatient referrals by clinicians to ACS are reviewed to ensure evidence-based prescribing and administering of anticoagulants, in order to reduce preventable harm and optimise patient outcomes. High-risk VTE patients commenced on anticoagulation are also consulted by the ACS pharmacist via telehealth within a week following discharge as a safety interim prior to Thrombosis Outpatients. Over a 12-month period, 216 inpatients (median age 69 years, 46% (n=99) females) were referred to ACS. Median weight of patients was 88.1kg (range 30-260kg) including 31% (n=66) >100kg. Eighty-four (39%) patients had eGFR<60mL/min/1.76m^2. 71% (n=154) were referred by ward pharmacists. Some changes recommended by ACS include optimising the dose of anticoagulation (n=65, 20%), recommendations on how to commence anticoagulation (n=65, 20%) and rotate anticoagulation (n=40, 13%). Since the ACS implementation, VTE HAC rates have reduced by 18%, bleeding HAC by 67% and the rates of INR >4 by 22%.

Conclusion: Overall, the ACS has improved the organisational HAC performance and patient care. This availability of the service should be expanded to include after-hours, and be considered for other organisations.

The relationship between coagulation factor activity level and bleeding severity and quality of life in patients with rare bleeding disorders

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Aim: Rare bleeding disorders (RBDs) account for 3-5% of all inherited coagulation abnormalities and are mainly inherited in an autosomal recessive manner, exclusively affecting homozygous or double heterozygous individuals. The aim of this report is to investigate the relationship between coagulation factor activity levels and clinical bleeding severity and quality of life in patients with RBD.

Methods: This cross-sectional study was performed on 821 patients with RBD. Clinical and demographic data were collected using standard questionnaires. The health-related quality of life (HRQoL) of the patients was determined, and finally, the association between coagulation factor levels and the severity of disorders and HRQoL in patients with RBD was investigated.

Results: Life-threatening bleeding, including umbilical cord bleeding, gastrointestinal bleeding, and central nervous system bleeding were most frequently observed in patients with FXIII, FI, and FX deficiencies, respectively. About one-third of patients with FXI deficiency were asymptomatic, whereas CNS bleeding occurred in one-quarter of patients with FXIII deficiency and gastrointestinal bleeding was common in congenital fibrinogen disorders. The activity levels of coagulation factors that were critical for patients to remain asymptomatic were: Fibrinogen, > 0.6 mg/ dL; FV, 19U/dL; FV + VIII, 36 U/dL; FVII, 24 U/ dL; FX, 13U/dL; FXI, 26 U/dL1; FXIII, 25 U/dL. There was a strong association between coagulation factor activity levels and disease severity in factor (F) V, combined FV, and FVIII and FVII deficiencies. A weaker association was present for FI, FX, FXI, and FXIII deficiencies. Total HRQoL was lower in patients with FVII, FXI, and FXIII deficiencies and those under secondary prophylaxis or on-demand therapy.

Conclusion: There is a direct relationship between the activity of coagulation factors and the severity of the disorder in RBD. The severity of the disorder and the type of treatment may affect the quality of life of these patients.

Hemostatic results for up to 6 years following treatment with valoctocogene roxaparvovec, an AAV5-hFVIII-SQ gene therapy for severe hemophilia A

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Aim: Sustained clinical benefit was demonstrated up to 5 years following a single 6x1013 vg/kg dose of valoctocogene roxaparvovec (AAV5-hFVIII-SQ), an investigational gene therapy for severe hemophilia A, in a Phase 1/2 trial (NCT02576795). All 7 participants showed sustained improvements in factor FVIII (FVIII) activity, annualized treated bleeding rate, and use of exogenous FVIII. Similar results were seen for up to 4 years in the 6 participants who received a 4x1013 vg/kg dose. No participants chose to resume FVIII prophylaxis. Although these results indicate that valoctocogene roxaparvovec provides substantial hemostatic efficacy, longer follow-up is needed to monitor safety and determine how long the transgene will produce FVIII and protect against bleeding. The aim is to report safety and efficacy of valoctocogene roxaparvovec up to 6 years after administration in a Phase 1/2 trial.

Method: Adult male participants with severe hemophilia A who had previously been treated with FVIII received a single intravenous dose of valoctocogene roxaparvovec at 6×1013 vg/kg (n=7) or 4×1013 vg/kg (n=6).

Results: Updated, detailed safety and efficacy assessments from 6-year follow-up data from the 6×1013 vg/kg cohort and 5-year follow-up data from the 4×1013 vg/kg cohort will be shared. Presented endpoints will include summary and individual participant FVIII activity, annualized treated bleeding and FVIII utilization rates, details of bleeding events, and adverse events.

Conclusion: The 6-year data from this Phase 1/2 study of valoctocogene roxaparvovec will provide the most up-to-date, long-term follow-up data currently available for investigational use of AAV-mediated therapy for hemophilia A. Funded by BioMarin Pharmaceutical Inc.

Acute myocardial infarction secondary to pentosan-induced spontaneous HIT: a case report of clinical significance to current practices in sports medicine

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Aim: To report upon a dramatic case of spontaneous heparin-induced thrombocytopenia in the setting of "off-label" pentosan use for the management of osteoarthritis.

Method: Pentosan polysulfate (PPS) is a semisynthetic, heparin-like glycosaminoglycan composed of sulphated pentosyl polysaccharide molecules. It was developed in 1949 as a thromboprophylactic medication, but due to its weak anti-Xa inhibition, was largely superseded by other low-molecular weight heparins. Numerous cases of thrombocytopenia with thrombosis associated with pentosan were reported in the 1980s and by the mid-1990s the pathophysiology had been well elucidated. The use of pentosan eventually became limited to its use as an oral agent for management of interstitial cystitis since the glycosaminoglycan structure allowed it to adhere to the bladder wall and act as a direct barrier to bacteria and other noxious stimuli. More recently, there has been a renewed interest in the use of pentosan for its perceived analgesic effect in cases of knee and hip osteoarthritis, despite a lack of rigorous supportive evidence. We present a case of a 44-year-old woman, whose treatment with pentosan for osteoarthritic complaints lead to a complication of spontaneous heparin-induced thrombocytopenia (sHIT) precipitating an acute ST-elevation myocardial infarction (STEMI). The management of this case and the relevant laboratory investigations are discussed.

Results: In this case, we postulate that the patient's excellent clinical outcome was largely due to the early administration of tirofiban as well as prompt recognition and management of HIT.

Conclusion: Pentosan has long been linked to spontaneous HIT and with sports doctors finding renewed interest in this medication, it is timely to present this case as a caution to those who may consider prescribing it.

Efficacy of twice-daily caplacizumab and therapeutic plasma exchange (TPE) in high-risk acquired thrombotic thrombocytopenic purpura (aTTP) – a case report

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Aim: To demonstrate the safety and clinical efficacy of a twice-daily caplacizumab and TPE regimen in a high-risk aTTP patient, based on a theoretical pharmacokinetic/pharmacodynamic (PK/PD) model

Method: Case presentation of a patient presenting with severe neurological and cardiac involvement secondary to aTTP

Results: A 52-year old gentleman presented to our institution with fever, confusion, and jaundice.

Initial investigations revealed a Hb of 76g/L and a platelet count of 8 x 10^9/L. Peripheral blood film showed prominent schistocytes consistent with microangiopathic haemolysis. A Technoscreen ADAMTS13 point-of-care assay confirmed severe ADAMTS13 deficiency (<10%), an ADAMTS13 inhibitor (2.5 BU) was also subsequently confirmed.

Caplacizumab 10mg IV was administered prior to TPE, followed by caplacizumab 10mg SC immediately post-TPE as per protocol. IV methylprednisolone 500mg and rituximab 375mg/m2 was also administered. The patient's neurological state deteriorated despite therapy and required intubation with hypotension requiring inotropic support.

On Day 2, due to the complications overnight and persisting severe thrombocytopenia the patient was started on twice-daily TPE with the second session starting 5-hours after the post-TPE caplacizumab dose. The 5-hour interval is based on a theoretical PK/PD model. Prior to each TPE, VWF-Rico was measured to monitor caplacizumab activity aiming for < 20%. By Day 3, the platelets were 64 and by Day 4, patient was extubated and fully conscious with platelets at 106 and subsequently switched to daily TPE/caplacizumab. The only adverse effect of twice-daily caplacizumab was epistaxis (grade 2) on Day 4.

Conclusion: This is the first reported case demonstrating the safety and efficacy of twice-daily caplacizumab and TPE in high-risk aTTP. This may be a therapeutic option for refractory high-risk aTTP patients.

A comparison study of ROTEM® Sigma and ROTEM® Delta in a major tertiary hospital

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Aim: Implementation of a new blood management device in the Transfusion Medicine Unit of a tertiary hospital requires careful assessment of potential differences to ensure continuity of service and consistent patient management.

This study aimed to rule out potential measurement bias resulting from replacement of ROTEM Delta with ROTEM Sigma within the Fiona Stanley Network, and to verify manufacturer reported reference ranges. Study outcomes to be used to address suitability of current transfusion algorithms.

Method: Blood from 51 healthy donors and 22 control samples manipulated with heparin to mimic a significant cohort of our patient population were run on the Delta and Sigma devices in tandem. Correlation across clinically relevant parameters derived from our ROTEM algorithm for critical bleeding were evaluated. (EXTEM $_{CT+A5}$, INTEM $_{CT}$, FIBTEM $_{A5}$ and HEPTEM $_{CT}$). The precision between two SIGMA instruments was also evaluated.

Results: EXTEM, INTEM and HEPTEM CT values displayed modest correlation (0.5, 0.7 and 0.45). Clot firmness at 5 minutes showed good correlation between devices (EXTEM $_{A5}$ 0.89 FIBTEM $_{A5}$ 0.98). A negative bias of 10.0% was recorded on the Sigma FIBTEM $_{A5}$ ($p<0.00001$). Normal ranges derived from this study were in correlation with those reported by Werfen group. Precision between Sigma analysers was very good.

Conclusion: Parameters produced by both ROTEM devices used in the Algorithm for Critical Bleeding showed some statistical variation with no clinical significance. Slight bias in FIBTEM A5 unlikely to be reflected in clinical intervention as decision for administration of cryoprecipitate would be made with clinical circumstance and not algorithm alone

Persistence with oral anticoagulant therapy in people with atrial fibrillation: a cohort analysis of general practice data

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Aim: Oral anticoagulants (OACs) are important to reduce the risk of ischaemic stroke in people with atrial fibrillation (AF). Although patients need to continue their OAC to achieve this benefit, little is known about persistence with anticoagulant therapy in Australia. The study aimed to investigate the rate of OAC non-persistence in the first 12 months of use and its predictors in patients with AF, using national data from Australian general practices.

Method: We analysed data obtained from the NPS MedicineWise dataset, MedicineInsight. We included patients with a recorded diagnosis of AF who newly initiated an OAC between 1 January 2013 and 30 December 2017. Persistence with therapy was defined as continued prescription of any OAC within 60 days after the exhaustion of the previous prescription. The follow-up period was 12 months post-initiation. Predictors were assessed using logistic regression.

Results: Of 16,075 patients (47.3% females) with a mean age of 74.6 ±10.2 years, 27.9% were initiated on warfarin, 10.3% dabigatran, 32.2% rivaroxaban, and 29.6% apixaban. Overall, 2,116 (13.2%; 95% confidence interval [CI] 12.6-13.7%) patients were potentially non-persistent within 12 months of initiation. The non-persistence rates for warfarin-, apixaban-, dabigatran- and rivaroxaban-users were 18.3% (95% CI 17.2-19.5%), 10.1% (95% CI 9.2-11.0%), 10.9% (95% CI 9.4-12.5%) and 12.2% (95% CI 11.4-13.2%), respectively. The rate of non-persistence with direct-acting OACs (11.2%) as a group was lower than for warfarin ($p < 0.001$). Factors that increase the risk of stroke (e.g., older age, hypertension, diabetes) were associated with better persistence, as was a higher CHA_2DS_2-VASc score and lower ORBIT bleeding risk score.

Conclusion: Over 10% of patients were potentially non-persistent with OAC therapy within 12 months. Positively, persistence was higher for patients most at risk of stroke. It was also higher in those prescribed direct-acting OACs rather than warfarin, perhaps indicating their relative ease of use.

Multi-laboratory validation of new APTT and Dilute Russell's viper venom test methodology for identification of lupus anticoagulants.

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Aim: New reagents and analysers have recently been introduced into NSWHP laboratories for special haemostasis testing. An inter-laboratory lupus anticoagulant (LA) testing exercise was conducted to assist haemostasis laboratories in the method validation process and to determine inter-laboratory agreement of clotting time ratios and final interpretations.

Method: One site (RPAH) prepared multiple sets of six frozen plasma samples for testing by five different laboratories. Three samples were positive for LA and three were negative for LA, including one sample mimicking Haemophilia A without LA, and another being warfarinsed plasma with LA. Participants used Hyphen APTT reagents: LA sensitive (Cephen LS, or 'APTT screen') and LA insensitive (Cephen 5, or 'APTT confirm'), and dilute Russell's viper venom screen and confirm reagents from Instrument Laboratories. Tests were run on ACLTOP 750 or 550 analysers using local choice of pooled normal plasma (PNP). All tests were run on neat plasma and as 1:1 mixes with PNP. Neat and mix normalised ratios (NMR) were calculated.

Results: All six samples were correctly identified by all five laboratories as being either LA positive or LA negative using a mix NMR cut off for positivity of 1.20. The mean (range) APTT mix NMRs for LA positive samples were 1.45 (1.38-1.52), 1.52 (1.45-1.61) and 2.90 (2.77-3.03), and for DRVVT method mix NMR values were 1.32 (1.28-1.36), 2.04 (1.94-2.11) and 2.12 (1.99-2.25). For the LA negative samples all APTT and DRVVT mix NMR values were ≤1.10.
Median between laboratory CVs for APTT mix NMR were 4.0% (range 2.9-4.5%) and for DRVVT mix NMR 4.1% (range 2.8-5.9%).

Conclusion: There was good agreement between laboratories in determination of positivity or negativity to LA using the new reagent/analyser combinations, combined with good between laboratory precision for clotting time NMRs.

Fitusiran, an investigational siRNA therapeutic targeting antithrombin: a phase 3 study to evaluate efficacy and safety in people with haemophilia (PwH) A or B without inhibitors (ATLAS-A/B)

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Aim: Fitusiran, a subcutaneous investigational siRNA therapeutic, targets antithrombin to rebalance haemostasis in PwH, irrespective of inhibitor status. We evaluated the efficacy and safety of fitusiran prophylaxis versus on-demand (OD) treatment with clotting factor concentrates (CFC) in PwH A or B without inhibitors.

Method: In this Phase 3, multinational, open-label study (NCT03417245), males aged ≥12 years with severe haemophilia A or B without inhibitors previously treated OD with CFCs were randomised 2:1 to once-monthly 80 mg subcutaneous fitusiran prophylaxis or OD CFCs for 9 months. Primary endpoint: annualised bleeding rate (ABR) for treated bleeds in the efficacy period. Secondary endpoints included annualised spontaneous bleeding rate (AsBR) and annualised joint bleeding rate (AjBR) for treated bleeds in the efficacy period. Safety and tolerability were assessed throughout the study.

Results: Overall, 120 participants were enrolled (fitusiran, n=80; OD CFC, n=40); baseline characteristics were similar between arms. Median ABR was 0.0 in the fitusiran arm and 21.8 in the OD arm. In the fitusiran arm, 40 participants (50.6%) experienced zero treated bleeds and 66 participants (83.5%) experienced ≤3 treated bleeds versus two (5.0%) and six participants (15.0%) in the OD arm, respectively. Median AsBR and AjBR were both 0.0 in the fitusiran arm and 16.1 and 15.9, respectively, in the OD arm. The most common treatment-emergent adverse event (TEAE) in the fitusiran arm was increased alanine aminotransferase (n=18; 22.8%). A total of five treatment-emergent serious adverse events (TESAEs) were reported in five participants (6.3%) in the fitusiran arm; nine TESAEs were reported in five participants (12.5%) in the OD arm. No TEAEs of thrombosis and no fatalities were reported.

Conclusion:
Fitusiran prophylaxis resulted in a significant reduction in ABR in PwH A or B without inhibitors. Reported TEAEs were generally consistent with previously identified risks of fitusiran.

Novel immediate direct targets of EPO signaling in human erythropoiesis

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Aim: Erythropoietin (EPO) regulates expression of genes that drive proliferation, survival and differentiation of erythroid progenitor cells into mature erythrocytes. The EPO receptor signals via the JAK2-STAT pathway. Only a few direct target genes of these pathways have been identified to date.

Method: To examine EPO-induced target genes in human erythroid cells, we employed an EPO-dependent erythroid progenitor model (HUDEP-2 cells) and performed ChIP-seq against pSTAT5 and ATAC-seq. The novel metabolic labelling technique and bioinformatic pipeline, BodySLAM-seq, was used to determine the immediate transcriptional target genes of EPO.

Results: EPO stimulation resulted in rapid phosphorylation of STAT5, but not STAT1 or STAT3. ChIP-seq identified 3128 EPO-induced pSTAT5 binding sites. The majority of peaks contain a palindromic 'GAS' motif, and are located at intronic (50%), distal (29%) and intergenic (15%) enhancers; only 3% are located at promoters. *De novo* motif discovery identified significant enrichment of DNA-binding motifs for GATA and KLF transcription factors (TFs), suggesting co-operativity between EPO signaling and the essential basal erythroid TFs, GATA1 and KLF1.
To examine STAT5-independent changes in chromatin, analysis of ATAC-seq identified 14,535 differential EPO-responsive regions, mostly at promoters. Surprisingly, only ~8% overlap with pSTAT5 ChIP-seq peaks, suggesting EPO-mediated phosphorylation and DNA-binding of undiscovered TFs. By searching for enriched motifs within these regions, we identified binding sites for TFs of the NFY, EGR, and NRF1 families and others, suggesting a hidden complexity of transcription factors that mediate responses to EPO. In addition, BodySLAM-seq identified direct pSTAT5 target genes such as BCL2L1, PIM1, and CISH; others are novel targets involved in transcription regulation, erythropoiesis and signaling.

Conclusion: Our finding reveals that pSTAT5 binds in close proximity with other TFs to coregulate gene expression. The majority of chromatin accessibility changes induced by EPO are STAT5-independent. SLAM-seq identified novel immediate EPO-induced transcriptomic changes that is otherwise not detected by conventional RNA-seq

Treatment strategies and outcomes in May Thurner Syndrome

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Aim: In May Thurner syndrome (MTS), there is extrinsic compression of the left common iliac vein against the lumbar spine by the right common iliac artery. This leads to venous outflow obstruction and increased risk of iliofemoral deep vein thrombosis (DVT). There is no consensus on management of MTS. In this study, we examined the treatment strategies and outcomes of those with MTS at our institution.

Method: Between January 2013 and February 2020, patients with potential MTS were identified on Monash Health's radiology database using "May Thurner" and "iliac vein stenosis" as keywords. The medical records of patients with suggestive or positive scans (USS, CT or MRI) were reviewed further to confirm diagnosis and treatment outcomes.

Results: 30 patients with MTS were identified. Of these, 23 patients (median age 54.0, 20 females) had confirmed DVT; 18 (78%) had at least 1 additional VTE risk factor. Treatment is shown in the table. These patients were all treated with antithrombotic medication. Some additionally received endovascular intervention (5/23 patients; 22%), with no documented complications.

Summary of treatment in MTS patients with DVT (N = 23)		
Antithrombotic agent	LMWH	2
	VKA	3
	DOAC	17
	Aspirin	1
+ Stenting		1
+ Thrombectomy/stenting		2
+ Thrombolysis/thrombectomy/IVC filter		2

18 patients received indefinite antithrombotic therapy, while the other 5 patients received limited courses of anticoagulation. There was no recurrence of DVT in the 21 patients who attended follow up (median 13 months, range 0–122 months). 9 patients developed post-thrombotic syndrome (8/18, 44% on antithrombotic therapy alone; 1/5, 20% receiving additional endovascular intervention). The 7 patients without DVT at diagnosis received no treatment. 4 of these patients attended follow up (median 26 months, range 5–32 months), none of whom had developed DVT.

Conclusion: There remains no consensus on management of MTS. Conventional antithrombotic therapy appears to be appropriate with acceptable outcomes. Endovascular intervention may have a role in select scenarios, but these procedures are not without risk[1,2]. Further studies are required to determine the best management approach for MTS.

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A Rare Case of Acquired Factor VIII Inhibitors Exacerbated by Immune Checkpoint Inhibitors

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Abstract: Immune checkpoint inhibitors are used for solid organ or haematological malignancies. The blockade on immune inhibitory signals enhance anti-tumour T cell response, however it can exacerbate immune-related adverse effects.

We report a case of an 82 year old man with metastatic prostate cancer presenting with immunotherapy induced nephritis and post-renal biopsy haemorrhage. He had an subacute onset of prolonged APTT which was not correctable with normal plasma. He received second cycle of immune checkpoint inhibitors one week prior. Factor VIII assay with one-stage APTT showed a level of 1%, and inhibitor assay demonstrated presence of a strong factor VIII inhibitor (10 BU). Further investigations demonstrated biochemical progression of his metastatic cancer, while radiological investigation showed minor progression. Patient became transfusion dependent and did not show clinical response to immunosuppression. He was discharged to community with palliative care input.
Immune checkpoint inhibitors are associated with multi-organ toxicities due to immune activation. Disorder of coagulation had been reported, but predominantly an increased risk of venous thrombosis. There had been case reports of bleeding complication as a result of immune-mediated coagulation factor inhibitor. This case further supports the role of immune-checkpoint inhibitors in exacerbating acquired factor inhibition.

Antiprothrombin/antiphosphatidylserine antibody testing in Antiphospholipid Syndrome investigation - a laboratory experience

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AIM: The laboratory criteria for diagnosis of antiphospholipid syndrome includes detection of anti-beta-2-glycoprotein I and anticardiolipin antibodies, in conjunction with detection of lupus anticoagulant. The presence of antiprothrombin and/or antiphosphatidylserine antibodies are increasingly being considered an important fourth marker of antiphospholipid syndrome, particularly in patients which do not demonstrate other markers of antiphospholipid syndrome.

METHOD: Retrospective case review of patients presenting for combined lupus anticoagulant and anti-beta-2-glycoprotein I, anticardiolipin and antiprothrombin/antiphosphatidylserine antibody testing in between October 2021 and April 2022 in a single pathology practice.

RESULTS: A total of 708 patient cases were reviewed. Of this number, 560 patients were negative for lupus anticoagulant, 31 showed equivocal lupus anticoagulant results and 20 patients demonstrated a lupus anticoagulant. The remaining patients could not have their lupus anticoagulant status determined due to concurrent anticoagulant use. Of the lupus negative patients, 29 demonstrated positivity in one or more of anti-beta-2-glycoprotein I, anticardiolipin and antiprothrombin/antiphosphatidylserine antibodies. Higher proportions of antibody positivity were observed in patients with equivocal lupus anticoagulant results and lupus anticoagulant detected, with half of patients with a lupus anticoagulant detected also demonstrating additional antibody positivity. Patients demonstrating positivity to all three antibodies were only observed in patients with lupus anticoagulant detected.

CONCLUSION: From the data reviewed, antiprothrombin/antiphosphatidylserine antibody testing can provide additional information contributing to the diagnosis of antiphospholipid syndrome, however further correlation with clinical data is required.

A Ten-Year Review of the Impact of the Transition from Warfarin to Direct Oral Anticoagulant - Has Venous Thromboembolism Treatment Become Safer?

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Aim: The introduction of direct oral anticoagulants (DOAC) has resulted in a paradigm shift in the management of venous thromboembolism (VTE). We evaluate the impact of the transition to DOAC, over the last decade, on overall VTE clinical outcomes including in first unprovoked major VTEs.

Method: A retrospective analysis of all VTE admissions in non-cancer patients from January 2011 to December 2020 at Northern Health, Victoria, Australia. “Warfarin era” included events that occurred between January 2011 and December 2014 and “DOAC era” from January 2015.

Results: There were 2687 cases involving 2508 patients (45.9% males; median age 63 years). 98% were symptomatic and 1261 events (47%) were unprovoked. 1003 events occurred during the warfarin era (79% warfarin, 6% DOAC) and 1684 during the DOAC era (22% warfarin, 66% DOAC). While recurrent thrombosis within 12 months from index event was comparable, there were fewer recurrence beyond 12 months in the DOAC era compared to warfarin era (HR 0.482, 95% CI: 0.329-0.706, p<0.001). Clinically significant bleeding events were lower in the DOAC era (HR 0.628, 95% CI: 0.407-0.970, p=0.036). A subanalysis of first unprovoked major VTE events (n=602) demonstrated a significant reduction in recurrent VTE beyond 12 months from the index event in the DOAC era (HR 0.354, 95% CI: 0.147-0.854, p=0.021) with no difference in clinically significantly bleeding rates (HR 1.711, 95% CI 0.753-3.885, p=0.199) between the eras.

Conclusion: Treatment outcomes for VTE have improved over time with reduced rate of thrombotic and clinically significant bleeding complications in the DOAC era.

Health-related quality of life over 2 years following valoctocogene roxaparvovec adeno-associated virus gene transfer for severe haemophilia A: Results from GENEr8-1

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Aim: We report change in health-related quality of life (HRQOL) for men with severe haemophilia A in a phase 3 trial (GENEr8-1, NCT03370913) at 104 weeks post-treatment with valoctocogene roxaparvovec gene transfer.

Method: Men with severe haemophilia A (FVIII ≤1 IU/dL) on FVIII prophylaxis and negative for FVIII inhibitors and anti-AAV5 antibodies received a single $6x10^{13}$ vg/kg valoctocogene roxaparvovec infusion, leading to endogenous expression of B-domain−deleted FVIII. Participants completed the haemophilia-specific Haemo-QOL-A questionnaire at baseline, week (W)52, and W104. Total and domain scores range from 0–100; higher values indicate better HRQOL. An anchor-based clinically important difference (CID) of 5.5 was used for Total Score. Change from baseline was assessed with two-sided t-tests. Missing data were not imputed.

Results: For the modified intent-to-treat population (N=132), mean±standard deviation (SD) Haemo-QOL-A Total Score increased from 75.7±16.7 at baseline to 82.1±15.4 at W52 and 82.8±15.3 at W104. Mean±SD change from baseline was 6.3±12.0 at W52 and 7.0±12.6 (P <0.0001) at W104, exceeding the anchor-based CID of 5.5 at both time points. The domain with the greatest improvement was Consequences of Bleeding (CoB), which includes anxiety around bleeding. In the CoB domain, baseline mean±SD score was 73.6±21.7 and improved by 9.7±15.5 at W52 and 10.3±17.7 at W104 (P <0.0001).

Conclusion: For men with severe haemophilia A, improvements in HRQOL observed at W52 were maintained and significant at W104 after valoctocogene roxaparvovec gene transfer.

The SAXOPHONE study; a multi-center, multi-national randomized trial of apixaban versus standard of care anticoagulation for thromboprophylaxis in children with congenital or acquired heart disease

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Aim: Vitamin K antagonists (VKA) or low molecular weight heparin (LMWH) are currently standard of care (SOC) for chronic anticoagulation in children with heart disease. Direct anticoagulants are the preferred SOC for thromboembolism prevention (TE) in adults due to their proven efficacy and safety without need for monitoring. SAXOPHONE compared safety and tolerability of apixaban versus SOC for TE prevention in children with heart disease and assessed pharmacokinetics/pharmacodynamics (PK/PD).

Method: Children 29 days to < 18 years of age with heart disease requiring chronic thromboprophylaxis were randomized 2:1 apixaban:SOC for ≤12 months in this open-label, phase 2, multi-center trial. The primary safety endpoint was major or clinically relevant non-major (CRNM) bleeding. Secondary endpoints were PK/PD and TE. Safety and efficacy events were reviewed by a blinded independent Event Adjudication Committee. Ethics committee review and informed consent were obtained. SAXOPHONE was funded by the Bristol Myers Squibb and Pfizer Alliance, with scientific leadership from NIH's Pediatric Heart Network.

Results: 198 participants were screened, 192 randomized, 188 treated (126 apixaban, 62 SOC) and included in the analysis across 33 sites in 12 countries (including Australia) over 4 years. Primary diagnosis was single ventricle in 72.9% of apixaban subjects and 76.2% of SOC. Overall 66.7% were post-Fontan. One apixaban subject had 2 primary safety events (incidence rate [IR] 1.8/100 person-years exposure [P-Y]) versus 3 subjects in SOC with 4 events (IR 6.8/100 P-Y). Serious adverse event rates were similar (apixaban 20.6% versus SOC 21.0%) but mild hematomas and epistaxis were reported more frequently with apixaban (6.3% versus 1.6%, and 15.9% versus 9.7%, respectively). There were no adjudicated TE events.

Conclusion: Thromboprophylaxis with apixaban was found to be safe and well tolerated in children with heart disease with a numerically lower rate of major/CRNM bleeding versus SOC. PK/PD data will inform apixaban dosing for thromboprophylaxis in children.
*The primary disclosure of this study will take place at ISTH in London July 2022.

A case report of quinine-induced thrombotic microangiopathy treated with eculizumab

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Case: A 55-years-old female presented with 4 days of back pain, dark urine, agitation, and diarrhoea within 24 hours of consuming quinine for cramps. Blood tests are presented in Table 1. Note deranged LFT and elevated ferritin atypical for TMA. She received 2 sessions of plasmapheresis and subsequently a dose of methylprednisolone and 6 months of eculizumab. Her thrombocytopenia and anaemia resolved by 1 and 6 weeks, respectively. She required haemodialysis for a month followed by full recovery of renal function. A strongly positive quinine-dependent platelet associated antibody was subsequently reported.

Table 1. Blood tests on presentation and 4 months after diagnosis

Test	Initial	4 months	Reference range
Hb (g/L)	145	138	115-165
WCC (x 10^9/L)	22.2	5.6	3.9-11.1
Plt (x 10^9/L)	37	395	150-400
Blood film	Moderate polychromasia, schistocytes, spherocytes.		
LDH (u/l)	7020	119	30-110
Creatinine (µmol/L)	peak 507	49	45-90
Urea (mmol/L)	peak 52	4.2	3.5-8
Bilirubin (µmol/L)	267	6	≤19
ALT (u/l)	187	21	10-35
ASP (u/l)	730	15	10-35
GGT (u/l)	678	30	≤35
ALP (u/l)	536	119	30-110
Ferritin (µg/L)	157700	)	30-300
ADAMTS13 (%)	34		61-131

Discussion: Quinine is the most common cause of immune-mediated drug-induced thrombotic microangiopathy (DITMA) with high morbidity and mortality outcomes (1). In a case series (n=19), acute kidney injury occurred in all patients with 17 of 18 requiring short-term dialysis. Chronic kidney disease occurred in 14 patients, 3 with end-stage renal disease, and 8 patients died of disease (2).

While Eculizumab has proven efficacy in complement medicated TMA, there is limited experience in DITMA, specifically no reports in quinine-induced TMA (3).

Conclusion: Our case demonstrates successful treatment of quinine-induced TMA with complete recovery of renal function. We recommend further studies to assess the efficacy of complement inhibition in quinine-induced and other DITMA.

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Management of rivaroxaban- and apixaban-associated major bleeding – a retrospective cohort study

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Aim: To assess the management and outcomes of rivaroxaban- and apixaban-associated major and clinically relevant non-major bleeding (CRNMB), according to ISTH criteria, in patients presenting in the South West Sydney Local Health District (SWSLHD).

Method: A retrospective analysis was performed by identifying consecutive patients presenting to hospitals in the SWSLHD from 2015 – 2019 through the South West Sydney Area Pathology Service (SWSAPS) laboratory information system database (PathNet) with rivaroxaban or apixaban associated bleeds. Only patients with confirmed detectable rivaroxaban or apixaban levels at the time of bleeding were included in the analysis. Clinical and laboratory datapoints were retrospectively extracted through the SWSLHD electronic medical record system and blood bank database (PowerChart and Patient Product Enquiry).

Results: During the 5-year study period, a total of 248 patients presented with a major bleed/CRNMB. 106/248 patients (43%) received pro-haemostastic agents. Of the 106 patients whom received pro-haemostatic agents, 43% received Prothrombinex (3-factor PCC), 20% received Prothrombinex + fresh frozen plasma (FFP), 16% received FFP alone, 13% received FEIBA, 5% received FEIBA + Prothrombinex, 2% received FEIBA/Prothrombinex/FFP, and 1% received FEIBA + FFP.

66/248 (27%) were intracranial bleeds. There were 29/248 deaths (12%) related to the primary bleeding event. 15/106 patients (14%) whom received pro-haemostatic agents died from bleeding-related complications. No patients whom received pro-haemostatic agents developed thrombosis during that presentation. Mean apixaban level in the pro-haemostatic group was 134, and 137 in the non-interventional group. Mean rivaroxaban level in the pro-haemostatic group was 213, and 183 in the non-interventional group.

Conclusion: Patients presenting with rivaroxaban- and apixaban-associated major/CRNMB demonstrate a mortality rate of 12%. The use of pro-haemostatic agents did not appear to improve mortality in our cohort, and is also not associated with thrombotic complications.

Acquired haemophilia A in South Australia: a case series and shift in treatment paradigm.

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Aim: To review the incidence and clinical features of acquired haemophilia A (AHA) between 2019 and 2021 in South Australia.

To review the change in upfront management of AHA as compared to a previous case series published in 2009[1] and its effect on bleeding, remission rates, durability of remission, and treatment side effects.

Method: A retrospective review was conducted of consecutive patients diagnosed with AHA managed in South Australia between 2019 and 2021. Patients were identified through the Australian Bleeding Disorders Registry.

Results: A total of 13 patients with AHA were identified. This equates to an incidence rate of 2.55 cases per million per year compared to previously reported 1-1.5 cases per million per year. At diagnosis, median APTT was 60s (range 47-96s), median FVIII level 5.5% (range <1% to 14%) and median Bethesda inhibitor titre of 11U/ml (range 2.2-352U/ml). Eleven out of thirteen patients (85%) received anti-CD20 monoclonal antibody Rituximab, predominantly in the upfront setting, compared to 5/24 patients (21%) in the historical cohort. Two patients had septicaemia and associated bleeding at initial presentation. Three patients developed infective complications within 6 months post immunosuppression. One patient had prednisolone induced psychosis. There was one death from sepsis, which was possibly due to AHA treatment.

Conclusion: The use of upfront immunotherapy may improve outcomes of acquired haemophilia and tolerability of treatment in elderly age groups compared to conventional immunosuppression.

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Detection of inhibitory effect of Caplacizumab on VWF activity is assay dependent

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Background/Aim: Acquired Thrombotic Thrombocytopenic Purpura (aTTP) is a thrombotic microangiopathy caused by autoimmune antibodies against "a disintegrin and metalloproteinase with a thrombospondin type 1 motif (ADAMTS13)". This leads to the accumulation of ultra-large multimers of von Willebrand factor (VWF), which induces platelet aggregation resulting in disseminated microvascular thrombosis. Caplacizumab, an anti-VWF humanized nanobody has recently been approved for use in aTTP. Its mechanism of action is attributed to binding of the A1 domain of VWF, thus inhibiting its interaction with platelet glycoprotein 1b-alpha (GP1b-α). Platelet-dependent VWF activity can be used to assess the inhibitory effect of caplacizumab. We describe a case report of a patient with refractory aTTP treated with caplacizumab and its effect on different VWF activity assays.

Method:

1. Two samples from a patient with aTTP on caplacizumab were sent to different laboratories (Lab 1 and Lab 2) on 2 different occasions and the following VWF assays performed:
   - Lab 1: Performed on ACL TOP 750 analyser using HemosIL™ reagents (Werfen Instrumentation Laboratory, Bedford, USA)- Immunoturbimetric VWF:GPIbR (VWF:RCo Activity),VWF collagen binding (VWF:CB),VWF Antigen (VWF:Ag), Factor VIII (FVIII)
   - Lab 2:
     - Performed on Sysmex 5100 CS analyser using Siemens reagents (Siemens Healthcare Diagnostics, Marburg, Germany)- VWF:RCo (ristocetin and fixed formalised platelets) (BC-VWF:RCo), VWF:GPIbM (gain-of-function recombinant (INNOVANCE® VWF Activity), VWF Ag (INNOVANCE® VWF Ag), FVIII.
     - Performed on Acustar analyser using HemosIL™ reagents (Werfen Instrumentation Laboratory, Bedford, USA)- VWF:CB

Results: On both occasions, VWF activity was significantly reduced/undetectable using VWF:RCo and VWF:GPIbM assays and within the normal range using the VWF:GPIbR assay.

Conclusion: Detection of inhibitory effect of Caplacizumab on VWF activity is assay dependent with most sensitive tests being VWF:RCo and VWF:GPIbM assays. As therapeutic monitoring of caplacizumab may be required in bleeding situations/refractory TTP, clinicians should be aware especially given the availability/use of different VWF activity assays in Australian laboratori

Severe Pregnancy Associated Acquired Thrombotic Thrombocytopenic Purpura (aTTP) Refractory to Steroids, Rituximab, and Plasma Exchange Successfully Treated With Caplacizumab, Bortezomib And Mycophenolate.

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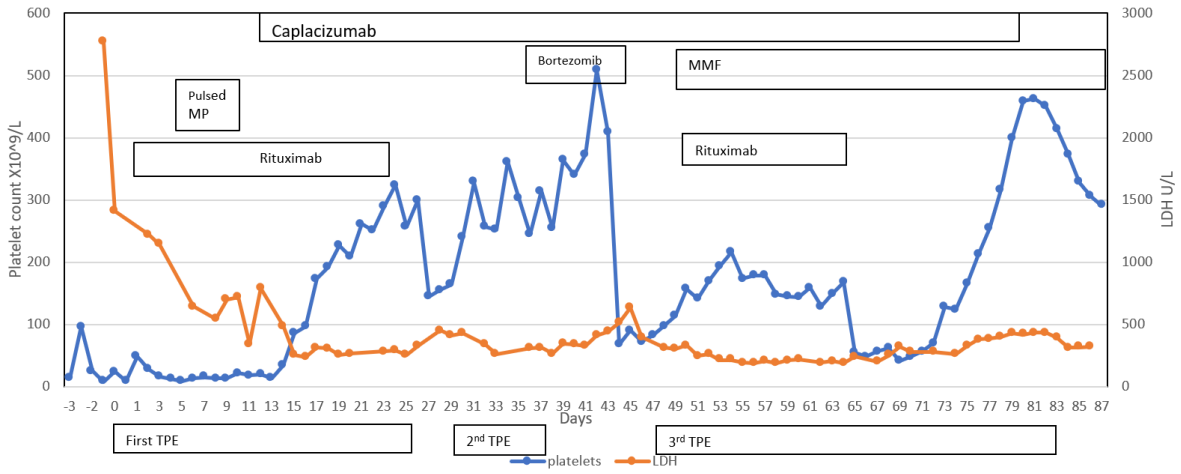
Background: The standard of care for aTTP is therapeutic plasma exchange (TPE) and immunosuppressive therapy with corticosteroids. However, 10-42% of patients do not respond to TPE and corticosteroids requiring additional therapies while 34–37% relapse after initial response.

Case Report: A 28-year-old pregnant lady of Indian descent (G1P0) underwent emergency caesarean section at 35 weeks gestation for preeclampsia. Pre-operatively, she was noted to have severe thrombocytopenia (platelet count 14x10^9/L). Plasma exchange was commenced due to persistent thrombocytopenia. Pre-exchange testing confirmed a diagnosis of aTTP with ADAMTS13 activity of <1% and inhibitor titre 1.7 BU. She was commenced on prednisolone 1mg/kg and weekly Rituximab. She developed acute right basal ganglia stroke manifested by blurred vision on Day 6 of TPE prompting escalation of immunosuppression with pulsed methylprednisolone 1g daily for 3 days. She remained thrombocytopenic and clinical course was further complicated by necrotising pancreatitis with multiple peripancreatic collections, focal seizure and acute renal failure requiring continuous renal replacement therapy. She was commenced on compassionate-access Caplacizumab on Day 14 and by Day 17 achieved platelet count normalisation (174x10^9/L). Repeat ADAMTS-13 activity was 38% with inhibitor titre <0.5BU. Despite this, she had 3 subsequent exacerbations (recurrent thrombocytopenia within 30 days of ceasing TPE) requiring re-initiation of TPE with the addition of Bortezomib, further Rituximab and mycophenolate (Figure 1). She was successfully weaned off TPE on Day 83, with repeat ADAMTS-13 activity of 38% and undetectable inhibitor titre. She remains in remission 60 days post TPE cessation.

Conclusion: This case describes an effective multimodal therapeutic approach in the management of refractory pregnancy associated acquired TTP. Immunosuppressive therapy remains important to reduce anti-ADAMTS13 autoantibody formation when Caplacizumab is used.

Figure 1: Platelet count and LDH trend



Safety and Efficacy of Idarucizumab for Dabigatran Reversal – A Regional Hospital Experience

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Background: Idarucizumab, a humanised monoclonal antibody fragment that binds to dabigatran, acts as a specific reversal agent for the direct thrombin inhibitor in emergency perioperative settings or acute bleeding.

Method: We performed an audit of patients who received Idarucizumab for reversal of dabigatran over the last 5 years between 2017 and 2021 at Launceston General Hospital in Tasmania.

Results: 8 patients received Idarucizumab (Table 1). 5 patients (62.5%) prior to emergency surgery/invasive interventional procedures, 1 (12.5%) prior to thrombolysis for acute stroke, however complicated by post-thrombolysis intraparenchymal haemorrhage, 1 (12.5%) for acute intracranial bleeding, 1 (12.5%) given pre-emptively following traumatic cervical spine fracture, that was eventually managed conservatively. Prior to Idarucizumab, 5 patients had blood tests for Thrombin Time (TT) with 4 of them recorded above the upper limit of normal detection (>55s). APTT and PT were tested in all 8 patients with 3 of them above the upper limits of normal for both PT and APTT. Fibrinogen levels were normal. Underlying renal impairment was noted in 2 patients of which one patient underwent haemodialysis.
Testing for dabigatran levels using dilute thrombin time was not available in our laboratory and hence there was difficulty in laboratory monitoring in our patients.

All patients were monitored clinically after administration of Idarucizumab. In all the 5 patients who underwent surgery / invasive procedures clinically significant bleeding complications were not observed. All the patients who received Idarucizumab for active bleeding demonstrated clinical improvement. No mortality was recorded in both the groups. No significant adverse effects due to Idarucizumab were observed in any of the patients.

Conclusion: In regional hospitals, rational use of Idarucizumab for reversal of dabigatran in emergency settings has been proved to be safe and effective, despite limitations in proper laboratory monitoring of dabigatran levels.

Comparison between full dose and reduced dose enoxaparin in the management of cancer-associated venous thromboembolism

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[1]*Monash Health,*

Treatment of cancer-associated venous thromboembolism (VTE) is challenging due to high rates of both recurrent thrombosis and major bleeding. Low molecular weight heparin remains the preferred anticoagulant in select patients. Trials evaluating dalteparin have reduced the dose after one month. The optimal enoxaparin dosing regimen for cancer-associated VTE remains uncertain.

Aim: To compare the efficacy and safety of full dose enoxaparin (1mg/kg twice daily or 1.5mg/kg daily) versus reduced dose enoxaparin (≤1mg/kg daily) in the management of cancer-associated VTE.

Method: A single-centre, retrospective audit was performed on patients with active cancer and acute VTE between January 2014 and December 2018. All patients received full dose enoxaparin for at least the first 28 days. Following this, patients either remained on full dose enoxaparin or were changed to reduced dose enoxaparin, at their treating clinician's discretion. The primary outcome was recurrent VTE at six months. All suspected recurrences were blindly adjudicated by two reviewers. Secondary outcomes were rates of ISTH-defined major bleeding and mortality. The study received institutional ethics committee approval.

Results: 257 patients (median age 64, 53% female) were identified with active cancer and acute VTE. 141 patients (55%) remained on full dose enoxaparin and 116 patients (45%) received reduced dose enoxaparin. There was no difference in rates of recurrent VTE at six months between reduced dose enoxaparin and full dose enoxaparin (5.2% versus 5.7%, p=0.86). There was also no difference in major bleeding events (9.5% versus 7.1% p=0.49). Mortality was lower in patients who received reduced dose enoxaparin (16% versus 39%, p<0.01), likely because patients who died had less opportunity to have their enoxaparin dose reduced. There were no deaths attributable to recurrent VTE or bleeding.

Conclusion: The efficacy of reduced dose enoxaparin appears comparable to full dose enoxaparin in the management of cancer-associated VTE, though without reduction in major bleeding.

A single centre experience of port-a-cath removals for paediatric patients with severe haemophilia A (SHA) on Emicizumab (Hemlibra®).

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Aim: To assess the outcomes of port-a-cath removals for patients with SHA (with and without inhibitors) on Emicizumab prophylaxis. The primary outcome assessed was haemostatic response with or without pre-operative factor concentrate. Secondary outcomes assessed were factor concentrate usage (i.e., unplanned factor replacement) and length of stay for monitoring.

Method: A retrospective review of fourteen male patients (three with inhibitors) who had their port-a-cath removed between February 2021 and April 2022. Outcomes were assessed according to whether they received pre-operative factor concentrate prior to port-a-cath removal. The haemostatic response was assessed using the ISTH haemostatic response for surgical procedures scale.

Results: 7 /14 patients received no pre-operative factor concentrate including one inhibitor patient. The other seven patients were given pre-operative factor concentrate including two inhibitor patients. In the group that received pre-operative cover 6 /7 had a good to excellent haemostatic response. However, in the group with no pre-operative replacement 5/7 had a fair haemostatic response and required unplanned factor concentrate. All fourteen patients received Tranexamic acid (20 – 25mg/kg TDS PO). The total bed length of stay was ten nights for the group with no pre-operative factor compared to thirteen nights for those who received pre-operative factor.

Conclusion: Overall, we observed better haemostatic outcomes in patients who received pre-operative factor concentrate than those who had no pre-operative factor. We propose factor concentrate support in addition to Emicizumab will give improved haemostasis, and further study of the optimum dosing regimen is warranted.

Venous Thromboembolism in Delta and Omicron variants of Covid-19

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Background: Coronavirus Disease 2019 (Covid-19) manifests primarily in respiratory compromise, however it has also been associated with high rates of venous thromboembolism (VTE). Current data demonstrates reduced severity of illness and hospitalisations with Omicron compared to the Delta variant. Whilst the risk of VTE in Covid-19 has been shown to increase with severity of illness, the incidence and relative risk of VTE between different strains is yet to be elicited.

Aim: To investigate the incidence of VTE in patients infected with the Delta variant of Covid-19 in contrast to those infected with the Omicron variant using a retrospective cohort study.

Methods: Data was extracted from Western Sydney Local Health District data bases for all patients diagnosed with Covid-19 in 2020 and 2021. Patients were eligible for inclusion if they had a positive test for Covid-19 (Rapid antigen test or Polymerase chain reaction) and radiological evidence of VTE. Patients were excluded if they had concurrent prothrombotic haematological disease. A separate sub-group analysis was conducted for patients who were pregnant or up to 12 weeks post-partum. Data were analysed for baseline characteristics, incidence and location of VTE, and variant of Covid-19.
Results were reported using descriptive statistics.

Results: Data collection remains in progress. At the time of abstract submission 22 patients are included in the study (14 male, 8 female). The median age at time of Covid-19 diagnosis was 60years (Range 33-89years). The median time for development of VTE from Covid-19 diagnosis was 18.5 days. Pulmonary embolism was the most common VTE being found in 11/22 patients. This was followed by Lower limb VTE in 9/22, Upper limb in 6/22 and Ischemic cerebral event in 5/22.
Delta variant was found in 80% cases of VTE whilst Omicron was found in 20% cases of VTE.

Conclusions: Preliminary data suggest that the occurrence of VTE in patients with Covid-19 is more likely in those with Delta strain when compared with Omicron strain. Pulmonary embolism is the most common type of VTE found in patients with Covid-19 infection.

Efanesoctocog alfa half-life and clearance are independent of von Willebrand Factor (VWF) in severe hemophilia A: a post hoc analysis from Phase 1/2a studies

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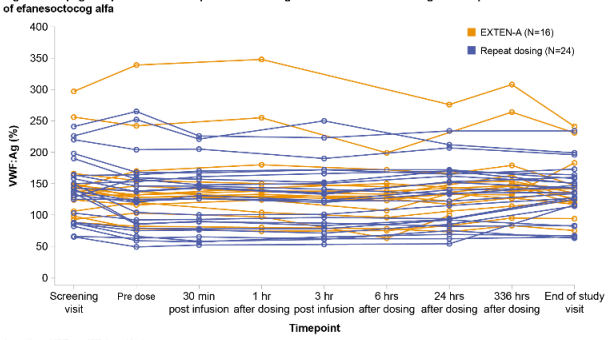
Aim: Efanesoctocog alfa (BIVV001) is a new class of factor VIII (FVIII) replacement designed to decouple FVIII from endogenous VWF. This post hoc analysis evaluated the relationship between endogenous VWF antigen levels and efanesoctocog alfa half-life and clearance in patients with severe hemophilia A.

Methods: Forty previously treated adult males with severe hemophilia A (<1 IU/dL FVIII) and ≥150 prior FVIII exposure days enrolled in the EXTEN-A single-dose (NCT03205163) and repeat-dose (EudraCT No: 2018-001535-51) studies. Subjects received either a single intravenous dose of 25 IU/kg (n=7) or 65 IU/kg (n=9) efanesoctocog alfa in EXTEN-A or 4 once-weekly doses of either 50 IU/kg (n=10) or 65 IU/kg (n=14) in the repeat-dose study. Primary objectives were safety and tolerability. Pharmacokinetics was a secondary objective. Half-life and clearance of efanesoctocog alfa were evaluated as a function of pre-dose VWF antigen levels. VWF antigen levels were assessed at various time points. Linear correlations were calculated using Pearson's correlation coefficient.

Results*:* Overall, mean (range) age was 39 (19–63) years (n=40). Mean (range) pre-dose VWF antigen levels were 151% (74%–297%; n=14) and 128% (49%–265%; n=24) for the single- and repeat-dose studies, respectively. Individual patient antigen levels of endogenous VWF were relatively stable over time (Figure 1A). Similar results were observed for VWF:RCo activity levels. Thirty-seven subjects were included in the pooled correlation analyses; 3 had missing values. No correlation was observed between VWF antigen levels and efanesoctocog alfa half-life (R^2=0.0007; *P*=0.88) (Figure 1B) or clearance (R^2=0.0493; *P*=0.19).

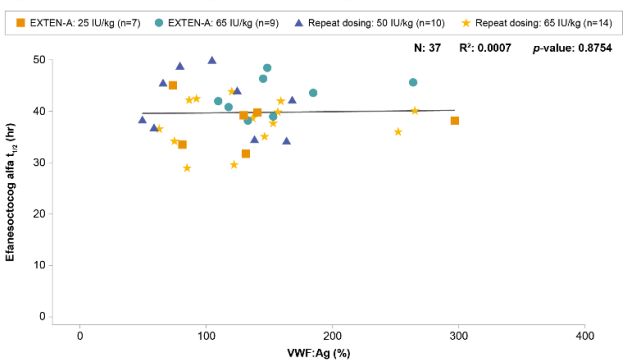
Conclusions: Endogenous VWF levels are unaffected during and after treatment with single or repeat doses of efanesoctocog alfa in previously treated patients with severe hemophilia A. Half-life and clearance of efanesoctocog alfa were independent of endogenous VWF levels. This is consistent with preclinical data and supports the Phase 3 trials (XTEND-1, NCT04161495; XTEND-Kids, NCT04759131; XTEND-ed, NCT04644575).

Figure 1A. Spaghetti plot of individual patient VWF antigen levels[a] over time for single and repeat doses of efanesoctocog alfa



Ag, antigen; VWF, von Willebrand factor.
[a]The value for pre-dose VWF was taken from Day 1 of the single-dose study and Day 22 (dose 4) of the repeat-dose study.

Figure 1B. Correlation of efanesoctocog alfa half-life by VWF antigen levels[a,b]



R^2 is the square of Pearson's correlation coefficient.
Ag, antigen; $T_{1/2}$, half-life; VWF, von Willebrand factor.
[a]The value for pre-dose VWF was taken from Day 1 of the single-dose study and Day 22 (dose 4) of the repeat-dose study.
[b]Three subjects had missing values and were excluded from analysis.

Correlation of Emicizumab levels with clinical experience in Paediatric and Adult Haemophilia A patients

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Aim: There is a growing body of evidence that Emicizumab in patients with moderate to severe Haemophilia A is as efficacious as factor prophylaxis in preventing bleeds, with the advantage of convenience of use[1]. There is limited data on steady state Emicizumab levels and corresponding clinical response to treatment.

Method: Moderate to severe Haemophilia A patients who had transitioned to Emicizumab were identified from the paediatric and adult Haemophilia centres in Perth, Western Australia. Bleeds requiring factor replacement were recorded 12 months prior to transition and up to 12 months following. These were obtained from the Australian Bleeding Disorders Registry and patient hospital notes. Available steady state Emicizumab levels were also recorded.

Results: 31/32 paediatric patients had the same or improved bleeding rates since transition to Emicizumab. No patient had a spontaneous bleed since transition. Emicizumab levels were not available for the one patient who had a trauma related haemarthrosis on Emicizumab, despite no bleeds 12 months prior to transition. One patient continued to have high bleeding rates (annualised bleeding rate of 6 vs 5 post transition) due to adherence issues, with an Emicizumab level of 10µg/ml. Of the 31 patients (and excluding the non-adherent patient), Emicizumab levels were measured in 16, with a mean of 55.54µg/ml (range 38.8 – 81).
20/22 adult patients experienced the same or improved bleeding rates post transition. The two patients with worse bleeding rates since transition both have only had 1 bleed each in 12 months of follow-up, and their Emicizumab levels were 58.54µg/ml and 79.15µg/ml respectively. Of the 20 patients, Emicizumab levels were recorded in 10, with a mean of 50.58µg/ml (range 22.77 – 85.22).

Conclusion: In both our paediatric and adult Haemophilia A patients, Emicizumab was an effective treatment in preventing bleeds. The mean and range of Emicizumab levels in both cohort groups who had an effective response was very similar. This wide range of therapeutic Emicizumab levels may be of important for dosing changes, particularly with the paediatric cohort.

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Experience with Thromboelastography use at Royal Hobart Hospital: A retrospective cohort study

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Background: Royal Hobart Hospital (RHH) commenced using thromboelastography (TEG) in 2019 and we aimed to determine its role in our transfusion laboratory.

Methods: All TEGs performed from 1st July 2019 to 31st May 2020 were analysed. Bleeding patients were divided into- Cardiac surgery, Surgical non-cardiac, Trauma, Obstetric and others.
Two Haematologists were retrospectively provided 24 paired TEG and conventional coagulation tests (CCT) independently and the transfusion advice was collated.

Results: Fifty-five TEGs were performed on 50 patients, of which 46 (84%) had concurrent CCTs performed. Thirty-two (70%) out of the 46 TEGs were normal. Nineteen (59%) of these had normal CCTs. Strongest correlation was seen between Clauss fibrinogen assay and CFF MA with Spearman's correlation coefficient (rs) of 0.87. The median time to CCT results in our institution was 39 minutes. The time to delivery of preliminary TEG results were between 10 to 20 minutes.
Blinded assessment by 2 Haematologist showed that an average of 13 (54%) patients were recommended to have FFP in the CCT arm and 2 (8%) in the TEG arm. An average of 4 (17%) patients were recommended protamine in the TEG arm and 1 (4%) patient in CCT arm. TEG and CCT transfusion advice were concordant in 6 out of 24 patients (25%) with Haematologist 1 and 12 out of 24 (50%) with Haematologist 2.

Conclusion: CFF MA is a reliable marker of fibrinogen activity and TEG directed therapy is likely to lead to less FFP use. Heparin effects were more readily detected in the TEG arm. These benefits should be balanced against the cost of TEG while also considering the comparable turnaround time of CCT at RHH. The study also highlights the need for development of local data driven consensus algorithm.

Phenotypic characterisation of congenital fibrinogen disorders: a single centre experience.

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Aim: To evaluate the clinical phenotype, molecular profile and treatment approaches for patients with a congenital fibrinogen disorder (CFD) at a statewide haemophilia service (Alfred Health).

Method: Data were retrospectively extracted from the Australian Bleeding Disorders Registry (ABDR) and Alfred Health's electronic medical record (EMR) including demographics, fibrinogen level/activity at diagnosis, clinical presentation, bleeding and thrombotic history, molecular profiling and treatment.

Results: The Alfred Health cohort of CFD patients constitutes 26% (44/167) of all Australian CFD patients (1 afibrinogenemia, 16 hypofibrinogenemia, 25 dysfibrinogenemia, 1 hypodysfibrinogenemia, and 1 not classified). Median age at diagnosis was 45 years old. 68% of patients were female vs 32% male. At presentation, 30% (13/44) were diagnosed by an incidentally discovered low fibrinogen, 20% (9/44) from familial screening due to an affected family member, 41% (18/44) due to a bleeding event and 2% (1/44) due to a thrombotic event (3/44 not specified). Prior to diagnosis, thrombotic events had occurred in 11% (5/44), bleeding events had occurred in 33% (15/44) and pregnancy loss in 9% (4/44). 53 procedures were recorded; of these 19% (10/53) were major and 81% (43/53) were minor procedures. Plasma-derived fibrinogen concentrate (RiaSTAP®) was used in 42% (22/53). Peri-operative outcome data was available for 27/53 procedures; of these greater-than-expected bleeding occurred in 19% (5/27) and thrombosis in 11% (3/27). Molecular testing had been performed in only 7 patients.

Conclusion: This initial retrospective study characterises the largest cohort of CFD patients at a single site in Australia. The clinical heterogeneity of this cohort is similar to findings previously published (1). Peri-operative bleeding and thrombotic rates were higher than expected, noting however the small numbers of procedures evaluated. Further evaluation at a national level, including prospective molecular typing and structural studies, will be required to better characterise this rare bleeding disorder.

References

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Evaluation of real-world bleeding outcomes in patients with haemophilia A (HA) with or without inhibitors on emicizumab prophylaxis in Australia.

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Aim: The National Blood Authority approved use of emicizumab through the governance of haemophilia treatment centres (HTCs) in Nov 2020 for patients with severe or moderate haemophilia A without inhibitors and in severe haemophilia A with inhibitors. We aim to perform nation-wide assessment on number and type of bleeding events in HA patients who have commenced emicizumab prophylaxis.

Method: Data were extracted from the Australian Bleeding Disorders Registry (ABDR) regarding demographics, severity, treatment, inhibitors and number and type of treated bleeds since commencing on emicizumab prophylaxis.

Results: There are currently 463 HA patients on emicizumab in Australia: 86% (397/463) with severe disease, 12% (57/463) moderate and 2% (9/463) mild. 32% (146/463) have a current or past inhibitor. The median length of time on emicizumab was 61 weeks (IQR 42-75).

Recorded bleeds were a combination of patient-reported and HTC-reported events. 28% (128/463) of patients had a bleed, with total number of bleeds equalling 265. Median number of bleeds per person was 0 (IQR 0-1). Figure 1 shows the bleed site where specified [note (175/265) were not specified]. Figure 2 shows treatment location where specified. Regarding provoking factors: 37% (97/265) bleeds were spontaneous, 59% (156/265) provoked and 4% (12/265) not specified. There was no association between a weekly versus fortnightly/monthly dosing regimen or presence of inhibitor and bleeding events on univariate analysis (based on Chi squared test).

Figure 1: Bleed site where specified

Conclusion: These results suggest low rates of bleeding events with the use of funded emicizumab prophylaxis in Australia. Planned comparison to number of bleeding events prior to widespread rollout of funded emicizumab and evaluation of QoL data will further inform the utility of emicizumab as a key treatment modality in HA patients moving forward.

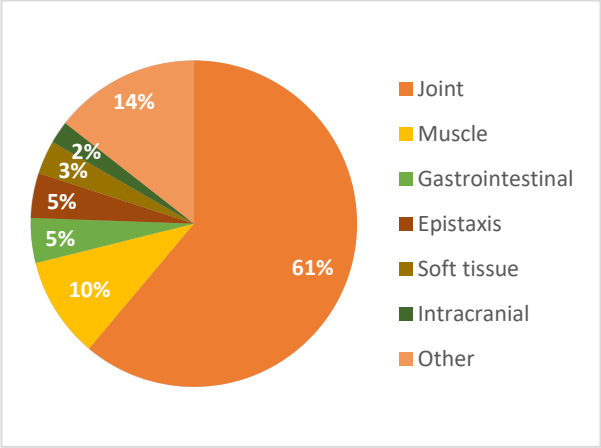

Figure 1: Bleed site where specified

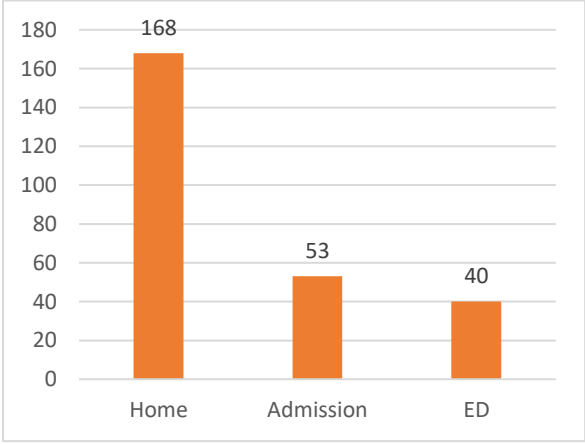

Figure 2: Treatment location where specified

Evaluation of real-world peri-operative outcomes in patients with haemophilia A (HA) with or without inhibitors on emicizumab prophylaxis in Australia.

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[1]Alfred Health, Melbourne, Australia, [2]Monash University, Melbourne, Australia, [3]Australian Haemophilia Centre Directors' Organisation, Melbourne, Australia

Aim: The National Blood Authority approved use of emicizumab in Australia through the governance of haemophilia treatment centres (HTCs) in Nov 2020 for certain HA patients. We aim to perform nation-wide assessment of peri-operative outcomes in HA patients who have commenced emicizumab prophylaxis.

Method: Data were extracted from the Australian Bleeding Disorders Registry (ABDR) regarding demographics, severity, treatment, inhibitors, number and type of surgical procedures in HA patients since commencing emicizumab. Further peri-operative detail for the HA patients treated through the Alfred Health HTC was obtained from electronic medical record (EMR) review, including data on adverse peri-operative outcomes and emicizumab-specific FVIII levels.

Results: There are currently 463 HA patients on emicizumab in Australia; 36 are treated through the Alfred Health HTC.

In the Alfred cohort, 92% had severe disease and 25% had a history of an inhibitor. The median length of time on emicizumab was 368.5 days. Surgery was performed in 11%; 5 procedures in total (4 elective, 1 emergency; 3 minor and 2 major) were recorded, with no adverse outcomes (including unexpected peri-operative bleeding or thrombotic complications) reported. Emicizumab-specific FVIII levels were performed in 3/5 procedures.

In the wider Australian cohort: 107 procedures were performed since change to emicizumab. Of these, 81% (87/107) were elective, 19% (20/107) were emergent. Of the 104 procedures with further detail available, 24% (25/104) were major and 76% (79/104) were minor procedures. See Figure 1 for breakdown of procedure type.

.Figure 3- Procedure type

Conclusion: Single centre data on peri-operative outcomes suggest a reassuring safety profile for HA patients on emicizumab prophylaxis. The nation-wide data confirms a large number of procedures have been performed in this cohort and planned exploration of associated peri-operative outcomes will further inform the safety/risk profile in this setting.

Diagnosis of antiphospholipid syndrome: an audit of clinician laboratory test ordering practices across various medical specialties

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Aim: Antiphospholipid syndrome (APS) is a complex autoimmune disorder. The revised Sapporo criteria are used to guide clinical and laboratory diagnosis. However, significant heterogeneity can exist in antiphospholipid antibody (aPL) test ordering which impacts on the applicability of results. A retrospective audit was conducted to assess clinician ordering practices of aPL tests.

Method: A retrospective audit was conducted of patients who had an aPL test ordered between January and December 2019 in a regional tertiary hospital. Data collected included number of aPL tests ordered, test results, presence of clinical history suggestive of antiphospholipid syndrome, anticoagulation history and follow up test requests.

Results: Data was obtained for 1180 aPL test orders. Median age was 38 years (range 0-93). Eighty one percent of test orders were for female patients. Fifty nine percent of tests were ordered by medical subspecialties with immunologists ordering the highest numbers of tests. Clinical information was provided for 63% of tests ordered. Only 42% of lupus anticoagulant orders also had anticardiolipin antibody and anti-ß$_2$ glycoprotein I antibody testing ordered, with obstetrics and gynaecology being the most likely specialty to order all three tests. Patients who fit clinical criteria for antiphospholipid syndrome were more likely than those not fitting criteria to have a positive test result ($p = 0.013$). Patients on anticoagulation were more likely than those not on anticoagulation to have difficult to interpret results ($p<0.0001$). Of the 287 tests requiring follow up testing (with either positive or borderline results), 16% were done at an incorrect interval of less than 12 weeks.

Conclusion: Laboratory diagnosis of APS can be complex and therefore requires a methodical approach. This audit shows that practices around test ordering and follow up are highly variable. Improvements could be made through measures such as clinician education.

Colchicine effects on platelet function: results of a systematic review

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Aim: There is wide interest in the ancient anti-inflammatory drug colchicine as a novel treatment to prevent heart attacks and strokes, with most mechanistic studies focusing on its effects on microtubule and inflammasome function in leukocytes. However, studies dating back more than 50 years have investigated the effects of colchicine on platelet function, in mostly *in vitro* settings under inconsistent, often supraphysiological concentrations. We have systematically reviewed this literature, with a particular focus on pharmacologically relevant concentrations.

Method: We searched Embase, Medline and PubMed and screened 428 papers to find primary research articles either testing platelets after incubation with colchicine or reporting a clinical effect of colchicine treatment on platelet function. Of 98 relevant articles, 10 included incubation with colchicine concentrations in the nanomolar range (commonly observed *in vivo*).

Results: Nanomolar concentrations of colchicine reduced platelet aggregation in response to collagen or calcium ionophore but not ADP, epinephrine or thrombin, and inhibited intracellular signalling in response to collagen-related peptide and thrombin (ROS generation and protein phosphorylation, respectively). It supported vinblastine binding to platelets and decreased thrombin-induced formation of platelet-leukocyte aggregates, but had no effect on platelet degranulation or procoagulant platelet formation. However, uptake of colchicine by platelets increased with incubation time, suggesting that intracellular accumulation may occur, and that inhibitory effects on platelet aggregation, granule release, clot retraction and extracellular vesicle formation shown in studies using short incubation times with higher concentrations of colchicine may also be physiologically relevant. There were very few high-quality *in vivo* studies defining the effects of colchicine on specific platelet activation pathways.

Conclusion: Colchicine has plausible antiplatelet effects at low concentrations, particularly in relation to platelet aggregation stimulated by collagen, and thrombin-induced platelet-leukocyte formation. There is a pressing need for clinical studies exploring mechanistic aspects of platelet inhibition by colchicine relevant to its cardiovascular protection.

Acquired Thrombotic Thrombocytopenic Purpura: relapse rates post initial episode in large cohort of Victorian patients

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Aim: Relapse of thrombotic thrombocytopenic purpura (TTP) is common (30-50% of patients) and is associated with significant morbidity and mortality[1].Conjecture remains, however, regarding the role of ADAMTS13 monitoring in TTP clinical remission to prevent relapses.

This study was performed to establish the rates and risk factors for clinical and biochemical relapses of TTP after initial treatment with a view to optimise frequency of ADAMTS13 monitoring and help inform treatment approaches.

Method: A retrospective audit was conducted of ADAMTS13 levels between 2011-2022 and corresponding hospital records from two tertiary hospitals in Melbourne, Australia. Adult patients with ADAMTS13 levels less than 20% were included in this study. Patients with inherited TTP or TTP secondary to a concomitant condition (e.g. malignancy, stem cell transplant) were excluded. Clinical discretion was used to determine a TTP diagnosis for patients with a ADAMTS13 level between 10-20%, and only those deemed to have clinical features diagnostic of TTP were included in this study.

Results: Between 2011 and 2022, 27 patients were diagnosed with TTP. One patient was excluded from this study as they had TTP secondary to immunotherapy for a solid organ malignancy. One patient died during their acute presentation.

In our study, 54% achieved a complete clinical and biochemical remission of TTP (defined as a achieving an ADAMTS13 level □ 20%). Of this cohort, 44% (11 patients) subsequently suffered at least one biochemical relapse of their TTP, at a median time to relapse of 31 months (range 3-300 months).

Conclusion: Whilst majority of patients achieve remission of their acute TTP, relapse rates still remain high within this group. Further prospective analysis is required into the best approach to achieve sustained clinical remission.

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Pathological findings in rotation thromboelastometry associated with thromboembolic events in COVID-19 patients.

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Aim: In addition to typical respiratory symptoms, COVID-19 is associated with coagulation abnormalities that lead to thromboembolic complications.

Method: Retrospective study of critically ill patients admitted to an intensive care unit (ICU) a cause of severe COVID-19 pneumonia (Group 1) and we evaluated coagulation function using coagulation standard parameters on day of admission (T0) and 10 (T10) days after admission to ICU and rotational thromboelastometry (ClotPro). In addition, we compared coagulation standard parameters to patients with severe non–COVID-19 pneumonia (Group 2).

Results: Eighty-four patients participated in our study. Traditional coagulation parameters were similar between group 1 and group 2. Only D-dimer levels (2442.11 ng / ml vs 370 ng / ml, p = 0.03) were significantly higher in COVID-19 pneumonia than in non-COVID-19 pneumonia. In addition, we concluded an increase in D-dimer levels during the hospital stay (T0 = 2442.11 ng / ml vs T10 = 8564.39 ng / ml, p = 0.000). Finally, patients with SARS-CoV-2 pneumonia exhibited hypercoagulant thromboelatometry profiles, characterized by elevated maximum clot firmness (MCF) values.

Conclusion: The results observed in our study support hypercoagulability in a severe inflammatory state, rather than a disseminated intravascular coagulation (DIC). More studies are needed to allow a better understanding of the coagulopathy produced in patients with severe COVID-19 pneumonia

Laboratory Challenges: A case presentation of a bleeding patient with confounding results

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Case Study: We report the case of a 76 year old male who presented with bleeding. The APTT was prolonged in the initial coagulation screen. Our investigative protocol used a panel of tests, including Factor Assays (VIII, IX, XI, XII, XIII), von Willebrands Screen and assays for Lupus Anticoagulant. The results left the laboratory with more questions than answers.
Published literature offered limited or mixed guidance regarding standardised procedures for multiple dilutional analysis of one-stage factor assays and interpretations of Bethesda assays. In this case, these inconsistencies contributed to a wide range of possible outcomes being considered. And in the setting of an actively bleeding patient, this could have significant consequences.
The laboratory utilised every tool within their scope of practice and expertise in the hope of providing clinicians with a definitive diagnosis, however the complexity of the case leaves the diagnostic door open and provides an educational opportunity for all laboratories.

Conclusion: This case highlights the complexities a laboratory can face when determining a diagnosis in an acute patient. It is the hope that this case can generate discussions regarding standardisation as well as alternative methods, approaches and interpretations that could assist laboratories in making a diagnosis in this intricate setting.

Efficacy and safety of fitusiran prophylaxis, an siRNA therapeutic, in a multicenter phase 3 study (ATLAS-INH) in people with hemophilia A or B, with inhibitors (PwHI)

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Aim: Hemophilia A and B are rare bleeding disorders characterized by ineffective clot formation due to insufficient thrombin generation caused by deficiency of FVIII or FIX, respectively. Fitusiran is a subcutaneously (SC) administered investigational siRNA therapeutic targeting antithrombin. Here, we present the efficacy and safety of fitusiran prophylaxis for people with hemophilia A or B with inhibitors (PwHI) in an open-label, phase 3 study (ATLAS-INH; NCT03417102).

Method: 57 eligible males ≥12 years receiving on-demand treatment with bypassing agents (BPA) were randomized 2:1 to receive once monthly 80 mg SC fitusiran prophylaxis or continue with on-demand BPA. The primary endpoint is annualized bleeding rate (ABR). Secondary endpoints include spontaneous ABR, joint ABR, and quality of life (QoL) measured by Haem-A-QoL. Results were analysed as a negative binomial regression model.

Results: A statistically significant reduction was observed in ABRs of treated bleeds, as well as spontaneous and joint bleeds, with fitusiran vs BPA on demand ($P<0.001$) (Table 1). 25 patients on fitusiran (65.8%) had zero treated bleeding events. Statistical significance was also achieved for improvement in HRQoL. Overall, 38 patients (92.7%) on fitusiran and 11 patients (57.9%) receiving BPA on-demand experienced ≥1 treatment emergent adverse event (TEAE). A total of 13 treatment emergent serious adverse events (TESAEs) were reported in 7 patients (17.1%) on fitusiran and 8 TESAEs in 5 patients (26.3%) receiving BPA on-demand. One patient (2.4%) on fitusiran experienced TEAEs that resulted in study drug discontinuation. No fatal TEAEs were reported.

Conclusion: Once-monthly 80 mg fitusiran prophylaxis resulted in a significant reduction in treated bleeds among PwHI, and improved HR-QoL. Reported TESAEs were generally consistent with the previously identified risks of fitusiran or what is anticipated in adult and adolescent PwHI. A revised fitusiran dosing regimen with reduced dose and dose frequency is currently being evaluated in ongoing clinical studies.

Efficacy and safety of valoctocogene roxaparvovec gene transfer for severe hemophilia A: Results from the GENEr8-1 two-year analysis

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Aim: GENEr8-1 is a phase 3, single-arm, open-label, sponsor-blinded trial evaluating safety and efficacy of adeno-associated virus (AAV)-based gene transfer with valoctocogene roxaparvovec in severe hemophilia A (NCT03370913). We report results from the year two analysis of the ongoing GENEr8-1 study.

Method: This prospective study included men with severe hemophilia A (FVIII ≤1 IU/dL), AAV5 antibody and FVIII inhibitor negative, on FVIII prophylaxis who received a single 6x1013 vg/kg valoctocogene roxaparvovec infusion (ITT population; N=134). Of those, 132 were HIV negative (mITT population), 112 enrolled from a prospective noninterventional study (rollover population), providing baseline data for annualized bleeding rate (ABR) and FVIII use. The primary efficacy endpoint was change from baseline in ABR for treated bleeds from five weeks post-infusion or three days after the end of FVIII prophylaxis, whichever was later, to last visit by data cut-off (efficacy evaluation period, EEP).

Results: Mean ABR decreased by 4.1 treated bleeds per year ($p<0.0001$; N=112; median follow-up 110 weeks), an 85% reduction from 4.8 (median 2.8) at baseline. Mean AFR was reduced by 133 infusions per participant ($p<0.0001$), a 98% reduction from 135.9 (median 128.6) at baseline. Mean FVIII activity at week 104 was 23.0 (median 11.8) IU/dL by chromogenic substrate assay, an increase of 22.0 IU/dL ($p<0.0001$; N=132). By one-stage assay, mean FVIII was 36.1 (median 21.6) IU/dL at week 104.

No new safety signals emerged and no treatment-related SAE were reported during year two. Eighty-three percent of participants received immunosuppressive treatment in response to liver enzyme elevations. Ninety-nine percent of these participants were off immunosuppression (IS) by week 104. There were no IS-related serious adverse events (SAE) in year two.

Conclusion: A single treatment with valoctocogene roxaparvovec was well-tolerated and led to stable and durable annualized bleed control superior to prior prophylaxis through two years post gene transfer.

Final study report of andexanet alfa for bleeding with factor Xa inhibitors

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Background: Andexanet alfa is a modified recombinant inactive form of factor Xa (FXa) that reverses FXa inhibitors. ANNEXA-4 was a cohort registration study evaluating andexanet in patients with acute major bleeding. We present the final data.

Method: We evaluated 477 patients with acute major bleeding within 18 hours of FXa inhibitor administration. Co-primary outcomes were percent change in anti–FXa activity from baseline to nadir during andexanet treatment and percentage of patients with excellent or good hemostatic efficacy 12 hours after andexanet treatment.

Results: Mean age was 78 years. Bleeding was predominantly intracranial (329 patients [69%]) or gastrointestinal (109 patients [23%]). In apixaban-treated patients (n=172), median anti–FXa activity decreased from 147 to 10 ng/mL (93% reduction; 95% CI, 94 -90%); in rivaroxaban-treated patients (n=130), it decreased from 214 to 11 ng/mL (94% reduction; 95% CI, 95-93%); in edoxaban-treated patients (n=28), median anti–FXa activity decreased from 121 to 24 ng/mL (71% reduction; 95% CI, 82-65%); and in enoxaparin-treated patients (n=17), it decreased from 0.48 to 0.11 IU/mL (75% reduction; 95% CI, 79-67%). Excellent or good hemostasis occurred in 272 of 340 evaluable patients (80%, 95% CI 75-84%). Within 30 days, thrombotic events occurred in 50 patients (11%) and death in 81 patients (17%).

Conclusion: In acute major bleeding patients on FXa inhibitors, andexanet treatment reduced anti–FXa activity and resulted in good/excellent hemostasis in 80% of patients.

Venous thromboembolism in obese patients: a ten-year experience

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Aim: To review the impact of obesity on VTE treatment and outcomes.

Method: A retrospective analysis was conducted of VTE presentations (DVT +/- PE) to Northern Health, Victoria, Australia, from January 2011 to December 2020. Morbidly obese patients (defined as >120kg) were compared to those ≤120kg. Patients with malignancy and those without documented weight were excluded. 2362 VTE cases, including 194 patients with weight >120kg were identified (see Table 1). The median follow-up was 55 months.

Results: Morbidly obese patients were younger (median age 47 years) and more likely to have previous history of VTE (n=78, 40%). They were more likely to present with unprovoked VTE (59% vs 45%, p< 0.001) and major VTE (75% vs 67%, p=0.028) compared to those ≤120kg. Warfarin was the most common choice of anticoagulant in patients >120kg. The morbidly obese patients had the highest rates of VTE recurrence off anticoagulation (7.8/100- patient years; HR 2.0 (95% CI 1.3-3.0)) when comparing to patients ≤120kg. There were no differences in clinically significant bleeding rates.

A subanalysis of enoxaparin anti-Xa levels performed on patients >120kg (see Table 2) demonstrated no differences in the rate of therapeutic levels achieved using uncapped (1mg/kg twice daily) or reduced (< 1mg/kg twice daily) strategies, with no differences in thrombosis or bleeding rates across strategies.

Conclusion: Morbid obesity is associated with increased clot burden and higher rate of VTE recurrence off anticoagulation without increased clinically significant bleeding. No differences were seen between uncapped or reduced enoxaparin dosing strategies in these patients. As the prevalence of global obesity rises, it is important to optimise the anticoagulation strategies in this population

Idiopathic upper extremity deep vein thrombosis: a systematic review

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Aim: To assess the effects of anticoagulation alone compared to anticoagulation with additional interventions such as thrombolysis or decompressive surgery on the incidence of recurrent upper extremity deep vein thrombosis (UEDVT) and post thrombotic syndrome (PTS) in patients with idiopathic UEDVT (including those associated with the oral contraceptive pill).

Method: A systematic search was conducted for studies which focused on acute UEDVT treatment defined as therapies starting within four weeks of symptom onset. We limited studies to those that recruited 10 or more subjects and involved at least 6 weeks to 12 months anticoagulation alone or together with additional interventions with at least 6-month follow-up. Primary outcomes were symptomatic recurrent radiologically confirmed UEDVT and PTS. Secondary outcomes were symptomatic venous thromboembolism, bleeding and mortality.

Results: We found seven studies which reported recurrent UEDVT rates and five that reported PTS rates. All studies were retrospective or cross-sectional. None compared anticoagulation alone to anticoagulation with additional intervention. Study heterogeneity precluded meta-analysis and risk of bias was moderate to serious (Figure 1). Recurrent UEDVT occurred in 0 to 12% post anticoagulation alone and 0 to 23% post additional interventions. PTS was limited to mild/moderate occurring in 4 to 32%. Few studies reported secondary outcomes.

Conclusion: Given the limited evidence behind idiopathic UEDVT management, prospective comparative studies are essential.

Figure 1. ROBINS-I assessment of all included studie

Audit of thrombophilia screen ordering practices at a regional hospital network in New South Wales

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Aim: To evaluate the rate of inappropriate ordering of screening for inherited and acquired thrombophilias and summarise the main indications given. This data will be used to create local guidelines to promote greater judiciousness in thrombophilia screen ordering.

Method: We retrospectively reviewed all inherited and acquired thrombophilia tests performed on inpatients at Pathology North across Gosford and Wyong Hospitals in 2021. The records of all individuals having some or all of the following tests were screened: Factor V Leiden mutation, prothrombin gene mutation, Protein C level, Protein S level, antithrombin level, factor VIII level, von Willebrand Factor level, lupus anticoagulant, anticardiolipin antibodies, beta-2-glycoprotein antibodies. The electronic medical record was reviewed for clinical indication for testing, whether testing changed management and whether appropriate counselling was given on the rationale for the test and any anticoagulation commenced. Testing for autoimmune disorders and vasculitis were excluded from the analysis. Clinical appropriateness for ordering these tests was determined based on two existing guidelines: The Choosing Wisely Guideline adopted by Waikato Haematology in New Zealand and the British Society of Haematology criteria for inherited thrombophilia testing.

Results: Preliminary analysis has indicated the majority of thrombophilia screens were normal. Thrombophilia screens ordered in the context of acute stroke in patients over 50 years old, provoked venous thromboembolism and less than 8 weeks postpartum formed the majority of inappropriate tests. A significant proportion of screens were performed whilst the patient was on anticoagulation. Haematology advice was not always sought prior to ordering the screen.

Conclusion:
Thrombophilia screening is a blunt tool wielded by clinicians. This analysis forms the impetus for initiatives to promote more selective use of testing in patients, including education and the creation of a local guideline.

Delayed onset of disseminated intravascular coagulation following Stanford Type A aortic dissection repair: A case report and literature review

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Aim and method: Disseminated intravascular coagulation (DIC) is a recognised complication of large aortic aneurysms (0.5 to 6%), but is much less frequently reported in association with aortic dissection. We report a case of spontaneous resolution of DIC in the context of chronic Stanford type A aortic dissection. We review the literature and postulate the mechanism for aortic dissection related DIC and its resolution.

Results: An 83-year-old man presented with spontaneous bruising and intramuscular haemorrhage six months after surgical repair of a type A dissection extending from the aortic root to the iliac arteries.

Investigations for a bleeding diathesis were consistent with a consumptive coagulopathy; platelet count 28 $x10^9$/L, D-dimer >20 mg/L (<0.50) and fibrinogen 0.8 g/L (2.0-4.0). His haemoglobin and haptoglobin were normal and his LDH was 278 U/L (<250). A CT aortic angiogram demonstrated the repaired ascending aorta with the false lumen (left subclavian artery to L2/L3 level) having increased in diameter at the distal arch containing mural thrombus. Additional investigations excluded active malignancy and infection and the mechanism for his coagulopathy was considered to be secondary to an extension of his aortic dissection triggering platelet adherence to the exposed subendothelium and activation of coagulation and fibrinolysis.

Surgical intervention was not considered possible. He developed haemorrhagic complications despite blood product support, and he was subsequently made palliative with no further therapeutic transfusion or anticoagulation. Six months following discharge, his coagulation studies, platelet count and fibrinogen level had normalised.

Conclusion: We postulate that this man developed DIC secondary to an extension of his aortic dissection and that gradual endothelialisation of the false lumen led to the spontaneous correction of his DIC.

Nursing Poster Presentations (Poster Board No N001 – N017)

The haematology patient voice - understanding patient and whanau needs through treatment and the Covid pandemic

Ms Emma Barker[1], Ms Deborah Tomlin[1]
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Aim: As an NGO providing psycho-social and financial support to haematology patients, Leukaemia & Blood Cancer New Zealand conducted a patient survey in late 2021 to better understand patient and whanau needs during Covid, to gather feedback on our service, to measure referral needs and to identify any gaps and unmet needs that we could address. We also wanted to gage online vs in-person support preferences to inform our future service strategy in a pandemic world.

Method: Utilizing a Survey Monkey survey, both online and postal, we surveyed 3000 members on our database, nationwide. We had a 20% return of 594 responses with a reasonable representation across all demographics, including regions, blood cancers, age (over 18 years old) and ethnicity.

Results: There were several key findings - of note was a significantly greater need for mental health support during Covid, as well as significant need for earlier referral for psychosocial support particularly at diagnosis, with 92% saying that referrals to NGO psychosocial support should be automatic. Another significant measured impact on patients was financial issues. Patients and whanau showed an increasing willingness to opt for online support compared to previous years.

Conclusion: We found several common themes that enabled us to tweak our service provision and adjust things to better meet the needs of patients and whanau, particularly to address isolation requirements for our vulnerable patients during Covid with improving our online services, expanding our family/whanau support and increasing our financial support budget.

Including the patient voice: engaging myeloma patients in the selection of patient reported outcome measures

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Background: With rapid advances in treatments for myeloma patients, there is need to ensure that patient reported outcome measures (PROMs) chosen to assess health-related quality of life (HRQoL) in clinical trials, target issues that matter most to patients. In a systematic review of PRO data reported in 32 myeloma randomised controlled trials (RCTs) between 2014-2021, no studies included patient input when selecting PROMs to use. The EORTC QLQ-C30 and QLQ-MY20 were the most commonly used tools in this review.[ix]

Aim: To establish a suite of validated, patient endorsed PROMs for use in future real-world trials.

Method: An exploratory, descriptive study using semi-structured, telephone-based interviews with myeloma patients. Patients who had completed at least one line of therapy were invited to provide feedback on 10 validated, commonly used PROMs. Interview data were collected using summary statements, analysed using a manifest content analysis approach.

Results: Twenty-six participants were recruited (13 male, 13 female) with a mean age of 67 (range 54-76). Although all PROMs were deemed acceptable, the My-POS was preferred over the EORTC QLQ-C30 and QLQ-MY20 because of its free text component. Fatigue and financial impact were identified as important domains not adequately covered by the My-POS. Therefore, the Brief Fatigue Inventory and COST-FACIT PROMs were included in the final suite.

Conclusion: Ability to contribute what matters most via free text is important to patients when completing PROMs. No single PROM fully captured the wide range of concerns prioritised by our participants. We will use the set of PROMs in a future study to assess impact of bortezomib, lenalidomide and dexamethasone on the HRQoL of the newly diagnosed, transplant ineligible patients

A multi-centre analysis of infusion reactions with the use of subcutaneous daratumumab injections.

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[1]ICON Cancer centre, Gold Coast , Australia

Aim: Daratumumab is a human IgG kappa monoclonal antibody that targets CD38 and has proven to be highly efficacious against multiple myeloma when used alone or in combination with other anti-myeloma medications. Recently daratumumab was approved to be administered by sub-cutaneous injection within Australia with non-inferior outcomes when compared to intravenous administration. Infusion related reactions have been reported to be within 7% to 13%, with a majority grade 1-2. The aim of this study was to assess our patient reported reactions throughout Icon Cancer Centres in Australia compared to those of the major published trials.

Method: Using pharmacy prescribing software, we were able to retrospectively identify 29 patients across 6 ICON treatment centres who had been prescribed subcutaneous daratumumab. Patient information was de-identified and the bedside nursing observation charts, progress notes and risk assessment analysis were reviewed. Data specifically relating to signs of immediate infusion related reactions were collected which included respiratory and cardiac symptoms (rhinorrhoea, sneezing, cough, throat irritation, wheezing, chest discomfort), febrile episodes, puritis, chills, nausea and vomiting, erythema at injection site and vital signs.

Patient were monitored for any potential infusion reactions using ICON's standard chemotherapy nursing assessment form at the time of the infusion and for 2 hours post completion.

Conclusion: Grade 1 injection site erythema and puritis were the most common reported infusion reaction occurring in 5% of patients; with over 50% having resolved at discharge (2 hours). Other reported reactions were grade 1 respiratory reactions including cough, rhinorrhoea and throat irritation. No patients were reported experiencing grade 3 or above adverse outcomes. Subcutaneous daratumumab has been well tolerated within our patient population. Our results are comparable to those published in the APOLLO and COLUMBA trial.

Chronic graft versus host disease is a major risk factor for chronic fatigue and physical and functional decline in long-term survivors following allogeneic stem cell transplantation.

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Aim: To examine health related quality of life (HRQOL) domains following haemopoietic stem cell transplantation (HSCT) comparing individuals with and without a history of chronic graft versus host disease (cgvhd) to develop patient centred long-term follow up care priorities.

Method: Individuals more than two years post HSCT attending a late effects clinic completed the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT) – Fatigue scale[1] and Functional Assessment of Cancer Therapy - Bone Marrow Transplant (FACT-BMT)[2] scale. Results were compared between participants with and without cGvHD. Study questionnaires were returned via hard copy with informed consent. Results were analysed using a comprehensive HSCT database. Multiple linear regression analysis was performed using Stata/IC 16.

Results: FACIT-Fatigue and FACT-BMT questionnaires were completed and returned by 135 of 146 individuals from June 2017 - June 2019. The most common indications for transplant were leukaemia (54%), lymphoma (10%) and myeloma (9%). Table 1 shows characteristics of the participants and FACIT-Fatigue and FACT-BMT scale scores between the non GvHD and cGvHD cohort. Compared to individuals without a history of cGvHD, individuals with cGvHD had a significant reduction in HRQOL measures by; 4.7 points on the fatigue scale (95% CI -9.2, -0.2, p=0.04), 2.4 points on the physical sub-scale (95% CI -4.2, -0.6, p = 0.01), 2.6 points on the functional sub-scale (95% CI -4.7, -0.65, p = 0.01) and 3.9 points on the BMT sub-scale (95% CI -6.0,-1.7, p=0.001). There was a trend to lower scores on the emotional and social sub-scales, but these were not significant

Table 1: Characteristics of participants and FACIT-Fatigue and FACT-BMT scale scores between non GvHD and cGvHD cohort.

	Non GvHD cohort	cGVHD cohort	cGvHD coefficient	Std.err	95% CI	p
Number	73 (54%)	62 (46%)				
Female (%)	46	48				
Age at time of assessment	41±18	50±15.2				
Time since transplant	9.9±6.1	7.5±4.8				
FACIT-Fatigue score	41.7±11	36.4±13.5	-4.7	2.3	-9.2, -0.2	0.043
FACT-BMT Emotional subscale score	20.4±3.1	18.9±5.1	**-1.4**	**0.8**	**-0.04, 0.05**	**0.062**
FACT-BMT Social subscale score	23.1±5.3	21.6±5.7	**-1.6**	**1.0**	**-3.7, 0.4**	**0.12**
FACT-BMT Physical subscale score	24.6±4.3	21.9±5.6	-2.4	0.9	-4.2, -0.6	0.01
FACT-BMT Functional subscale score	22.9±5.1	20.0±6.0	-2.6	1.0	-4.7, -0.6	0.01
FACT-BMT subscale score	32.6±5.4	28.4±6.3	-3.9	1.1	-6.0, -1.7	0.001

Conclusion: Results from this study demonstrate individuals with a history of cGvHD require long-term follow up care focused in positive physical and functional outcomes. Identifying key domains within HRQOL measures to key groups post HSCT allows patient centred targeted support programs to be developed. Late effects clinics are ideally situated to move towards better management of patients with greater care needs as measured by poorer HRQOL measures; with focus of limited resources on encouragement of physical activity, behavioural counselling and energy conservation strategies.

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Is oral calcium supplementation adequate to prevent and manage citrate toxicity with single needle red blood cell exchange?

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Aim: To evaluate whether oral calcium is effective in preventing and managing citrate reactions during single needle red blood cell exchange. Apheresis procedures, such as red blood cell exchanges are commonly required in Sickle Cell Disease to remove defective red blood cells and replace with donated red blood cells. Anticoagulant, acid citrate dextrose solution A (ACD-A) is essential to prevent clotting of the extracorporeal circuit of the Spectra Optia system. ACD-A binds to free calcium ions to prevent the activation of platelets and clotting cascade within the apheresis circuit. The patient receives some of the calcium-binding citrate during the procedure which may cause citrate-induced hypocalcaemia. Intravenous calcium infusions are contraindicated during single needle procedures due to an increased risk of clotting of the circuit. A new method using only oral calcium was developed.

Method: The transition of two Sickle Cell adolescent patients from paediatric to adult service provided the opportunity for adult apheresis nurses to implement single needle access for prophylactic red cell exchange. Assessments include monitoring pre- and post-procedure corrected calcium with and without oral calcium supplementation, signs and symptoms of hypocalcaemia during the apheresis procedure and impact of procedure times.

Results: Impact of ACD-A on corrected calcium will be presented. Side effects associated with hypocalcaemia during red cell exchanges, including tingling or numbness of lips, fingers and toes, muscle twitching, tetany, nausea or vomiting will be discussed as well as the impact of oral calcium premedication prior to the apheresis procedure. The method will be presented.

Conclusion: This study will describe the outcomes of implemented strategies to prevent and manage citrate reactions during single needle red cell exchanges. Greater understanding of citrate management with oral calcium will impact on future patient management. Apheresis nurses will feel confident to initiate single needle access on future patients with difficult venous access or therapeutic plasma exchange.

Personal Experience on the Impact of Covid-19 on Research

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Aim: The aim of this abstract is to look at the personal experiences on the impact of Covid-19 on a PhD research project.

Background; When the first pandemic lockdown occurred, the impact of this reverberated throughout all haematology departments around the world. Australia followed guidelines published from other parts of the world and new Australian guidelines were quickly put in to action. This included withdrawing stem cell transplants. This resulted in increased stress by patients, health providers and researchers.

The PhD project 'Wellness in Stem Cell Transplant' went through several delays and changes to the main research. Nearing the end of the project and in the last phase, the study was broken in to two groups, the first was a data collection group obtaining data on patients receiving usual treatment while having an autologous stem cell transplant. The second group involved the intervention of an exercise program prior to stem cell transplant. An initial power study concluded that 32 participants needed to be recruited in each group.

Method: Outline the experience of the researcher and the impacts on several areas of an interventional study.

Results:
Lockdown 1:

1. Multiple delays in candidature – did not require to meet milestones
    - Didn't put ethics on hold – still able to collect data on existing patients
    - Change in the number of participants
    - Increased participant stress and anxiety
    - Reduction in the number of participants – what would be the effect on results?
    - Changes in Protocol

Lockdown 2:

- Change in hospital practices – physiotherapy exercises stopped as no-one allowed in the department.

Conclusion: There were multiple delays in Candidature which extended the duration of the study. Multiple changes made to the study protocol. Physiotherapy developed an online exercise program; this will need to be studied to show the effectiveness on this delivery method.

COVID-19 vaccine hesitancy, acceptance, and informational needs among an Australian oncology population: a cross-sectional survey

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Aim: The COVID-19 pandemic has demonstrated that people with cancer are at significantly higher risk of morbidity and mortality from this disease. The vaccination rollout has been compounded by delays, safety concerns and widespread misinformation.

Method: A cross-sectional survey was conducted in a large tertiary hospital in Brisbane, between 10th May and 31st July 2021 and assessed health beliefs, experiences of the pandemic, vaccine hesitancy and informational needs.

Results: Two hundred and one participants completed the survey. The majority (84%) of participants were planning to receive the vaccine. Participants aged under 60 years were significantly overrepresented in those not planning to receive the vaccine. Men, people who had experienced anxiety during the pandemic and those who felt they had received adequate information were more likely to receive the vaccine. Over 52% of participants stated they were “worried about vaccine side effects”. Only 58% and 63% of participants “agreed” that the vaccines were safe and effective, respectively. However, over 82% of respondents stated they would have the vaccine if recommended by their oncologist. 50.2% of individuals who decided to complete the survey were from haematology services and when asked about cancer-specific vaccine information the most common questions were regarding interactions with cancer treatments, those with a previous history of blood clotting and those undergoing BMT. Those undergoing BMT wanted to know about the timing with their post BMT re-vaccinations and if it would affect their GVHD.

Conclusion: Cancer patients have unique concerns and informational needs regarding the COVID-19 vaccines. Although most participants did plan on receiving the vaccine, high levels of hesitancy remain. There is a need for tailored and effective communication that capitalises on existing relationships of trust between patients and clinicians.

Priming intravenous tubing with monoclonal antibodies reduces chair time in the outpatient setting: preliminary results from a randomised controlled trial

Ms Francesca Boyte[1], Ms Robyn Matthews[1], Dr Elise Button[1,2], Ms Lee Jones[2], Ms Therese Hayes[1], Mr Grant Partridge[1], Ms Emilly Egan[1], Ms Amanda Sutherland[1], Ms Marianne Fenton[1], Mr Michael Smith[1,2], Associate Professor Glen Kennedy[1], Dr Melissa Eastgate[1], Dr Nicole Gavin[1]
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Aim: There is a limited evidence-base around priming practices in the haematology-oncology setting. Furthermore, there are safety concerns around priming intravenous (IV) tubing with monoclonal antibodies (MABs), however this practice could reduce chair time.

Method: Patients prescribed single-agent Daratumumab, Obinutuzumab, Pembrolizumab or Nivolumab infusions were consecutively randomised to either standard priming with saline/glucose *versus* priming lines with 16mL MAB. Primary outcome was chair time utilization. Secondary outcomes included incidence and severity of MAB-reactions. A sample size of 128 episodes of care was calculated to detect a medium effect size of 0.5 (Cohen's d) with 80% power and alpha of 0.05.

Results: From July 2021 to January 2022, 52 patients were recruited equating to 128 episodes of care (32 episodes of care to each MAB which are infused over various time frames ranging from 30 minutes to 3 hours). There was a 3% reduction in chair time between control and intervention groups for Daratumumab, representing a 7-minute difference between groups which was not statistically significant ($p=0.523$). A greater reduction in chair time was seen for Obinutuzumab, with a 16-minute reduction in the control group, equating to a 6% change ($p=0.032$). Pembrolizumab and Nivolumab both had a 7-minute reduction between control and intervention groups ($p<0.001$), this accounted for a larger percentage of change between control and intervention groups, 16% and 15%, respectively. No difference in MAB-infusion reactions were noted between groups.

Conclusion: The results of this study demonstrate that priming the IV tubing with MABs reduces chair time for patients without increasing adverse events. More chair time could be reduced if this priming practice was implemented with other IV MABs, chemotherapy and blood products.

Developing a myeloma nurse link program in regional and rural Australia: a six month review of the pilot study

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Aim: Education and support for myeloma patients in regional and remote parts of Australia is often more disparate than in metropolitan areas. The aim of this project was to help close this gap by offering mentorship and education opportunities to regional haematology nurses by establishing the Myeloma Australia (MA) Nurse Link (NL) Program.

Method: Expressions of interest (EOI) were sort by MA for a six-month pilot including provision of resources and monthly professional development opportunities. An evaluation survey incorporating qualitative and quantitative data was conducted at the end of the pilot.

Results: Of the ten EOI received, eight nurses enrolled, with seven ongoing from NSW, ACT, TAS and VIC. Six nurses completed the evaluation. Their experience in haematology nursing ranged from five to over twenty years. The primary reasons for participation in the program was to gain knowledge to better support myeloma patients. The link nurses were passionate about myeloma and had a desire to raise awareness about myeloma.

A total of seven online sessions were during the pilot and covered myeloma education, debriefing and networking opportunities with experts in the field. During the pilot, several nurses delivered in-service education although this aspect of the program was heavily impacted by COVID and subsequent demands on the workforce.

All nurses indicated that the meeting frequency was sufficient although three found it difficult to attend due to clinical workload. Four of the five agreed their myeloma knowledge had improved. Other key benefits of the program included access to resources, networking and learning about new treatments.

Conclusion: Following the successful pilot and evaluation of the Program the next phase will include improvements such as incorporation of face to face meetings and expanding the number of link nurses to fiftee

More than skin deep: care collaboration for complex cutaneous graft versus host disease

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Chronic graft versus host disease (GVHD) is experienced by approximately 40% of allogeneic haematopoietic stem cell transplant (HSCT) recipients. It can manifest in almost any organ, however is most commonly reported to affect the skin, mouth, liver, lung and eyes. Complex disease requires comprehensive assessment and specialised, holistic management.

Aim: The initial aim of this collaboration was to effectively manage an individual's wound, however secondary aim developed to initiate pathways to optimise early interventions.

Method: The initial patient with extensive wounds was referred to the haematology nurse practitioner (NP). The haematology NP liaised with the plastics wound advanced nurse consultant, and a comprehensive wound care plan was initiated with regular review and sharp debridement. Wounds are objectively monitored using photography with consent, with detailed measurements and descriptions. Further collaboration identified opportunities to improve skin care education and incorporate as a standard of care.

Results: The initial individuals wound has, and continues to, significantly improve as evident by decrease in slough, increase in granulation and advancing wound edges. The judicious use of topical antimicrobial dressings have assisted in management of immunosuppressed patient needs. As the wound has improved and dressing frequency has reduced (from daily to twice weekly) opioid requirements have reduced. Opioid, antibiotic and wound management has been led by the nurse specialists.
Post HSCT skin care pathways are in development, and skin assessment at day 100 post transplant has been accepted to be incorporated in standard of care to improve monitoring, patient education and early intentions for chronic cutaneous GVHD.

Conclusion: Complex GVHD wounds have been managed by comprehensive, collaborative care. Collaboration was essential to develop pathways to initiate early interventions leading to improving outcomes. GVHD care is complex and skilled, specialist nurses have a pivotal role in best supporting the patient and navigation to achieve best outcomes.

Not ‘that’ jab, all the other ones: Reviewing and refining our post-transplant vaccination program

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Background: When referring to vaccines in current times, an assumption is that discussion will focus on the COVID-19 vaccine, however for people undergoing stem cell transplantation, discussion needs to incorporate the requirement to undergo a post-transplant revaccination program. Following autologous or allogeneic stem cell transplantation, protective immunity to vaccine-preventable diseases is partially or completely lost, thereby a revaccination program is required.

Aim: Imperative to reviewing the current vaccination program was reviewing adherence/success with our current initiative.

Method: Review of the program included an audit, exploration around enablers and barriers to workflow, and reviewing evidence to ensure best practice adherence.
Allogeneic transplant recipients transplanted in 2019 without relapse surviving beyond 6 months (n=29) were identified for audit. This population was selected to enable analysis to include live vaccination (measles, mumps, rubella vaccine and/or varicella vaccine) administration data, which is scheduled for administration consideration from 2 years post-transplant.
Vaccination schedule documentation was correlated with administration data and clinical notes to assess cause for withholding or delay. Seminars were held with the haematology transplant group to review current and evidence-based practice. Protocols were compared within the state aiming for harmonisation to enable regional centre administration.

Results: 100% of patients commenced the post-transplant vaccination schedule. 80% completed the transplant program. 100% of the patients who did not complete had nursing review with documentation and rationale for not administering. For patients continuing program at 2 years (n=17), live vaccines were administered for 59%, with 41% not requiring live vaccines due to serological testing demonstrating immunity.

Conclusion: This audit confirmed the program has great uptake of the post-transplant vaccination program, despite the unexpected disruptions from the COVID-19 pandemic. This encourages us to continue with our program, as well as continue with initiatives to ensure ongoing adherence, utilise best practices and patient centred opportunities

Putting a cap on CLABSI: Can a disinfecting cap reduce central line infections?

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Aim: Central line associated blood stream infections (CLABSI) have significant impact on the morbidity and mortality for our vulnerable haematology and bone marrow transplant (BMT) patients. Our aim is to reduce CLABSI rates via the use of a disinfecting cap containing 70% isopropyl alcohol. We would review the CLABSI rates pre, during and post the trial period

Method: All haematology and BMT patients with a central access venous device (CVAD) admitted to 7B at the Royal Melbourne Hospital during the month of March and April 2021, were assigned a central line disinfecting cap. This cap was to be used for the entirety of their admission and any subsequent admission/s during the trial period. Based on the bed location on admission, patients were assigned either the '3M Curos disinfecting port protector' or the 'ICU medical SwabCap'. Approximately 50 patients were involved in the trial. CVAD removal date, blood culture collection date, relevant pathology and diagnosis were collected. CLABSI was determined using CDC and VICNISS definitions.

Results: In the 4 months prior to the trial, we had an average CLABSI rate of 5.5%. During the 2-month trial the rate dropped significantly to 1.5%. Following the trial, the next four months gave us an average CLABSI rate of 4.4%, indicating that the disinfecting caps used successfully reduced our CLABSI rates.

Conclusion: CLABSI rates were significantly reduced with the introduction of the disinfecting cap. A reduction in CLABSI correlates with reduced patient morbidity and mortality and reduced cost to the organisation. Given the positive results, we have implemented the ICU medical SwabCap full time on our ward to improve patient outcomes for our haematology and BMT cohort.

GP Cancer Support Line - set up of new specialist cancer nurse operated service

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Introduction: Establishment of the centralised 'GP Cancer Support Line' as a component of the Enhancing
Cancer Management in Primary care project across the CESPHN region is to address access barriers to specialist cancer advice and service navigation knowledge gaps. The line will improve communication between specialist hospital-based cancer care teams and primary care, to enhance best practice person-centred cancer care within the primary care setting and across the cancer care continuum.

Objectives/Aims: To establish a telephone support line for general practitioners and practice nurses to access high quality advice and information from credible specialists to enhance the management of cancer in primary care.

Description/Methodology: Employment of specialised cancer nurse to establish and operate a new support line service
supported by part-time staff specialists to respond to enquiries from general practice in relation to cancer management across the CESPHN region. The service will address call enquires from GPs for navigation and cancer related enquires such as: Treatment and symptom management, cancer service navigation and general patient advice, psychosocial care, survivorship care, palliative care and advance care planning, assistance with referral pathways and advice relating to the care of patients prior to specialist consultations, in particular for cases requiring rapid referrals.

The nurse and project team proactively engaged with key stakeholders across our local Health Network and collaborating Local Health Districts, and liaised with public and private hospital services, community services, cancer organisations and primary health care teams in order to map and deliver relevant and up to date service navigation and specialist advice.

Conclusion: Establishing our new support line service has begun to address access barriers to effective communication and access to specialist cancer advice and service navigation for GPs, and
promote partnerships across the acute and primary care settings to enhance cancer care across the care continuu

Lymphoma care for all communities

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Introduction: At least 6,500 Australian's are diagnosed with Lymphoma/CLL annually. Many are from regional, rural or remote locations (RRR), adding complexity to their treatment journey for health professionals (HPs), patients and carers.

Australian studies demonstrate rural patients with B-cell lymphomas have inferior survival rates compared to big city counterparts (Wright, et al., 2018). This is echoed internationally, with higher mortality rates in underdeveloped areas with lower socioeconomic demographics, despite lower incidence rates (Zhou, et al., 2019).

Aims: This pilot project will map, scope, and reveal diverse needs of RRR patients. It will provide a platform to develop structures and initiatives supporting HPs education and RRR lymphoma patients' needs, aiming to improve patient outcomes.

Description: A multiphase approach is being implemented over three years. Firstly, identifying stakeholders and understanding how hospitals provide care to RRR patients. Treatments were reviewed and cross referenced against a Modified Monash Model (MMM) targeting RRR sites. Secondly, engaging stakeholders in target states (WA and QLD) to understand nursing educational needs, deliver targeted education, scoping relevant lymphoma subtypes, while learning about RRR models of care. Thirdly, establishing an advisory group of patients and nurses to provide insight into unmet needs.

This will lay groundwork to develop specific resources for RRR communities, addressing unmet informational and supportive care needs. Resources and nursing education will be available on a dedicated "resource hub" through Lymphoma Australia's website.

Outcomes: Expected outcomes include:

1. Increasing nursing networks, best practice sharing and education
    - Identifying and understanding RRR patient unmet needs
    - Improving education and awareness amongst patients
    - Improved health literacy for RRR nurses and patients
    - Increased referral for clinical trials for RRR patients
    - Improved patient outcomes
    - Greater access to standard of care

Conclusion: Lymphoma care for all communities aims to improve RRR patient outcomes, by increasing support, education, side-effect management and patient resources, improving equity in clinical trials, and awareness of lymphoma to assist in earlier diagnosis.

Collection efficiency comparison of CMNC versus MNC procedures for autologous stem cell collection

Mr Andrew Steele[1]
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Aim: This study was aimed to be a comparative study of the collection efficiency of Continuous Mononuclear Cell Collection (CMNC) versus Mononuclear Cell collection (MNC) in autologous stem cell collection to establish the most efficient and effective collection process both for the collection centre and for laboratory processing. To do this we aim to study efficiency averages of both methods of collection and bag processing volumes sent to the laboratory. The initial hypothesises was that the volume of bags was significantly higher in CMNC thus leading to increased processing and storage needs within the laboratory and increase reinfusion volumes and to show if the collection efficiency was also improved in CMNC.

Method: The collection centre uses Terumo Optia machines and had historically been MNC collectors only. In 2021, the centre switched to CMNC collections but increased bag volumes were noted by the labs and the efficiency of the procedure was questioned. Using a designated collection efficiency calculation Absolute CD34 in Bag (x10*6) / ((total inlet volume X0.001) X PreCD34+ve cells in blood) X100. We retrospectively calculated the efficiency of collection for CMNC collects from 01/01/22 until 24/02/22 (n= 20) when we changed practice and commenced collecting with MNC. This data was then compared against ongoing MNC collections to produce average efficiency and bag volume.

Results: CMNC had a collection efficiency percentage ranging from 33% to 134% and MN from 11% to 94%. The study is ongoing, but early results show slightly increased collection efficiency rating for CMNC collections (60.8/57.8) and an average Volume of collect bags only 20mls more for CMNC vs MNC.

Conclusion: The data would suggest that CMNC does give superior collection efficiency over MNC and only increases the collection volume by a small amount, making it a viable alternative for ongoing therapy. In addition CMNC has been preferred anecdotally by practitioners.

CSL Behring Cares: Supporting Patient with Secondary Immunodeficiency (SID) to use Subcutaneous Immunoglobulin (Hizentral®) in the Home

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Objectives: Treatment for secondary immunodeficiency (SID) includes intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg), which have both traditionally been administered in hospital. In 2018, the CSL Behring CARES patient support program (PSP) for Hizentra® was established to help educate patients and their carers to provide SCIg treatment in their home environment. CARES is managed by an independent provider, Aesir Health, and offers in-home education and support services using qualified registered nurses. Through the PSP, patients can receive the required in-home educational visits from a nurse trained in the administration of SCIg. An analysis of SID patients enrolled in CARES is presented here.

Methods: Patient competence in SCIg self-administration was assessed on completion of each nurse home visit using a standardised form. Patient's skills and knowledge were rated in relation to the preparation, infusion and post-infusion care.

Results: At time of writing, 412 patients with SID had been enrolled in CARES, ranging from age 10 to 92 years. The average weekly dose of Hizentra® was 10.1 g and the average weekly volume was 43.3 mL. Prior to enrolling in the PSP, 78% of patients were receiving IVIg, 4% were receiving SCIg and 16% were treatment naïve. For patients who were receiving SCIg, 40% had received self-administration training in the hospital. Competency was achieved by 92.2% of all enrolled SID patients. On average, patients became competent in self-administration after 2.4 nurse visits (range 1–9 visits).

Conclusion: Patients of variable ages with SID may be suitable for home-based therapy with Hizentra®. These patients can be effectively transitioned from hospital-based Immunoglobulin treatment to weekly home-based therapy with Hizentra® using CARES. Further analyses of CARES are planned to determine how to best continue to support patients with their ongoing home-based treatment.

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Frail but not forgotten: nurse-led management of older patients with myeloma

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Multiple myeloma is the second most common haematological malignancy diagnosed in Australia, predominantly occurring in people aged over 70 years. With our aging population, the incidence of Myeloma is projected to increase. It is estimated that approximately 60% of patients diagnosed with myeloma experience symptoms of frailty. Managing myeloma is complex and requires an understanding of the concept of frailty to determine and individualise treatment. **The involvement of a myeloma cancer nurse improves patients' quality of life,** facilitates early identification of therapy related toxicities, and enhances medication adherence resulting in improved quality of life.

Aim: To establish a myeloma nurse specialist led program for newly diagnosed or relapsed patients with myeloma aged 65 and older.

Method: Eligible patients were given the opportunity to have a nurse specialist involved in their care. Baseline frailty screening was conducted, and referrals made if needs identified. The nurse offers a point of contact to patient and caregivers whilst providing ongoing counselling and individualised supportive care and education including medication management.

Results: As of May 2022, 100% of patients invited to enrol consented to participate (n=100). Over 25 emergency department/hospital presentations have been avoided attributing to the involvement of the myeloma nurse specialist. 1/3 of enrolled patients have reported toxicities to the nurse, receiving prompt assistance and management. Feedback has identified feelings of support and a greater sense of confidence in disease management with the involvement of a nurse specialist.

Conclusion: The myeloma nurse has facilitated early identification of frailty and needs, helping to prevent confusion and mitigate errors. Despite ongoing recruitment, the role has already shown to improve the quality of life and treatment outcomes of older patients with myeloma. There is the hope that this role can be expanded to include care provision to all patients diagnosed with myeloma.

BMTSAA Poster Presentations (Poster Board No B001 – B003)

CliniMACS Plus CD34 selection – Westmead BTCT Lab's experience

Mr Daochen Tong[1], Dr YiVee Chew[1], Kenneth Yehson[1], Melina Kariotis[1], Heather Lucas[1], Dr Seray Adams[1], Dr John Kwan[1], A/Prof Kenneth Micklethwaite[1], Vicki Antonenas[1]
[1]Westmead BTCT Lab, Westmead, Australia

Aim: This validation retrospectively analysed the efficiencies of the Miltenyi CliniMACS Plus CD34 selection procedure.

Method: One-hundred and forty CD34 selections were performed on the CliniMACS Plus device between 8/3/2000 and 29/7/2021 at Westmead BTCT Lab. 122 haematopoietic progenitor cell (HPC) sources were apheresis and 18 were bone marrow. Selection was carried out on either large scale (LS) or regular size kits according to according to manufacturer's cut-offs.

Viable CD34 (vCD34) recovery, purity and vCD3 and vCD19 depletions were compared using two-sided unpaired t-tests or Wilcoxon rank-sum test depending on normal distribution of data. Effects of loaded total nucleated cell (TNC) and CD34 numbers on selection outcomes were analysed by Kendall's correlation. $P<0.05$ was considered statistically significant. Statistical analyses were performed in R version 4.1.0 and RStudio version 1.4.1717.

Results: The selection procedures achieved an average (±SD) vCD34 recovery and purity of 65±12% and 80±13% respectively. vCD3 and vCD19 depletions of $-\log_{10}$ 4.7±0.61 and 3.6±0.52 were attained respectively.

Apheresis as the starting HPC source gave superior vCD34 recovery ($p<0.0001$), purity ($p<0.05$) and vCD3 depletions ($p<0.0001$). LS compared to regular kit performed better in vCD34 recovery ($p<0.0001$), vCD3 depletion ($p<0.0001$) and vCD19 depletion ($p<0.05$).

Both loaded TNC and vCD34 numbers correlated with increased vCD34 purity ($p<0.01$, $p<0.0001$ respectively), vCD3 depletion ($p<0.0001$, $p<0.01$ respectively) and vCD19 depletions ($p<0.0001$, $p<0.05$ respectively), while TNC also correlated with better vCD34 recovery ($p<0.0001$).

Conclusion: The CliniMACS Plus CD34 selection has been a reliable procedure utilised for over 20 years at the Westmead BTCT Lab, with better selections from using HPC apheresis products and LS kits.

Optia Bone Marrow Processing is highly effective at volume and RBC reductions with excellent recoveries of CD34 and CD3 cells.

Mr Daochen Tong[1], Dr YiVee Chew[1], Kenneth Yehson[1], Heather Lucas[1], Melina Kariotis[1], Dr Seray Adams[1], Dr John Kwan[1], A/Prof Ken Micklethwaite[1], Vicki Antonenas[1]
[1]Westmead BTCT Lab, Westmead, Australia

Aim: This retrospective validation aimed to demonstrate the performance of Optia Bone Marrow Processing (BMP) at the Westmead Blood Transplant and Cell Therapies (BTCT) Lab.

Method: Forty-one bone marrow (BM) samples were processed using the Terumo Optia BMP based on manufacturer instructions at the Westmead BTCT Lab between 1/1/2015 and 17/8/2021. One sample was processed twice due to insufficient CD34 recovery first time round.

White blood cell count (WBC) and haematocrit (Hct) were measured by automated haematology analysers, while viable CD34 (vCD34), viable CD3 (vCD3) and mononuclear cells (MNC) were enumerated by single platform flow cytometry.

For correlation between predictor and outcome variables, parametric Pearson's correlation or non-parametric Kendall's rank correlation was used depending on Gaussian distribution of variables. Kruskal-Wallis test was used for multiple comparisons between operating scientists and individual comparisons were made against the median using Wilcoxon rank-sum test. Statistical tests and graphs were made in R version 4.1.0 and RStudio version 1.4.1717. Significance was defined as $p<0.05$.

Results: Average (± SD) reductions of 91±2.7% and 98±0.9% were achieved for volume and RBC respectively. MNC, vCD34 and vCD3 recoveries were 88±8.8%, 88±9.2% and 86±10.1% respectively.

Total nucleated cell recovery had a negative correlation with WBC (Pearson's $r = -0.57$, $p<0.0001$), RBC depletion had a positive correlation with Hct (Kendall's $tau = 0.27$, $p<0.05$) and vCD34 recovery had negative correlation with initial CD34 concentration (Kendall's $tau = -0.24$, $p<0.05$).

There was no significant variability between the 7 operators.

37/41 products were transplanted and from available data, 32/33 patients achieved haematological recovery. Median days to neutrophil and platelet recoveries were 21 (range 13–36) and 26 (12–68) days, respectively.

Conclusion: The Optia BMP is highly effective in volume and RBC reductions of BM, while retaining vCD34 and vCD3 cells for stem cell transplants.

Overnight storage of PBSC without dilution

Ms Linda Welschinger[1], Ms Cathie Milton[2], Dr Asma Ashraf[2]
[1]Nsw Health Pathology North, Waratah, Australia, [2]Calvary Mater Newcastle Hospital, Waratah, Australia

Aim: To assess the effect of nucleated cell numbers (NCC) on viable $CD34^+$ recovery ($vCD34^+$) and early engraftment kinetics in peripheral blood stem cell products that are refrigerator stored overnight.

Method: This retrospective study involved 426 adult haematology patients, with 753 collections and 338 autologous stem cell transplants (ASCT), that occurred at Calvary Mater Newcastle Hospital between January 2010 and December 2021. Patient collections were grouped by overnight storage and NCC of </≥300 x 10^6/mL or those immediately processed. Each collection was assessed for $vCD34^+$ post cryopreservation using single-platform flow cytometry, and each ASCT was assessed by the storage and NCC of the products used and time to neutrophil and platelet engraftment. Statistical analysis was by unpaired t-Tests, and by single factor one-way ANOVA with post-hoc Bonferroni Correction. Pearson correlation was used to assess the strength of association between continuous variables. Data were summarised by median and range. Non-parametric tests were conducted on sample medians when data was non-normally distributed. *P*-value of <0.05 was considered significant.

Results: Collections that were stored overnight with a NCC of ≥300 x 10^6/mL had reduced thawed viable $CD34^+$ recovery (*P*=0.01) when compared with products stored overnight with a lower NCC or those immediately processed. There was no difference in median time to neutrophil or platelet engraftment between the stored and immediately processed groups. A graphical lag to recovery was noted in 30% of patients whose ASCT consisted of products that had been stored overnight with NCC of ≥300 x 10^6/mL, but this was found not to be statistically significant. Only the thawed $vCD34^+$ cell dose given had any effect on engraftment.

Conclusion: From our results we find that there are no patient or product safety issues with overnight storage of PBSC without dilution. Although referring to the thawed $vCD34^+$ is recommended when calculating the dose for ASCT.

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