Abstract Details: Associations between various inherited factors and the development of myeloid malignancies have been recognized for many decades. In some instances, patients diagnosed with recognizable constitutional disorders such as Down syndrome, neurofibromatosis type 1 (NF1), and Fanconi Anemia (FA) were shown to have a markedly elevated risk of developing myeloid malignancies compared to general population. Other individuals at substantial risk of developing myeloid malignancies compared to general population. Other individuals at substantial risk of evolution to myelodysplastic syndrome (MDS) or AML are patients with primary hematologic disorders such as Shwachman–Bodian–Diamond syndrome (SBDS), severe congenital neutropenia (SCN), and familial platelet disorder with predisposh medosition to acute myelogenous leukemia (FPD/AML). A final broad category includes multi-generational kindreds in which multiple individuals without other obvious developmental or hematologic phenotypes present with MDS and/or AML. One confusing aspect of the literature is that some investigators refer to these patients as having “familial leukemia” and distinguish them from individuals who develop MDS or AML in the context of either an inherited developmental syndrome or an antecedent hematologic disorder. Indeed, rapid advances in genome-wide sequencing technologies have uncovered common mutations in what were previously thought to be distinct subsets of patients with inherited predispositions to MDS/AML. Furthermore, many of the genes mutated in the germ line of individuals with familial leukemia are also targets of somatic alterations in de novo MDS. Finally and importantly, comprehensive sequencing of MDS and AML clones from patients with inherited predispositions uncovered cooperating somatic mutations in many of the same genes found in sporadic MDS and AML. These data implicating germ line mutations as “sowing the first seed” in the development of myeloid malignancies provide a satisfying explanation for the variable age of onset and incomplete penetrance observed in many inherited predispositions to MDS and AML. Two broad clinical, morphologic, and molecular patterns emerge when patients who develop MDS or AML in the context of a germ line mutation are considered in toto. The first group of disorders is characterized by mutations that compromise hematopoietic stem and progenitor cell (HSPC) function, which frequently results in impaired differentiation and peripheral blood cytopenias. SBDS, SCN, and FPD/AML are relevant examples. Perhaps not surprisingly, the causative germ line mutations often inactivate one allele of genes that encode proteins that function as “master regulators” of HSPC fate such as RUNXI, GATA2, CEBPA, and ETV6. A smoldering MDS phase is a common initial manifestation of leukemic transformation in these syndromes, and loss of one chromosome 7 homolog or a deletion of the long arm [monosomy 7/7(7q)] is a recurring acquired cytogenetic abnormality. Thus, these cases of MDS and AML exhibit striking similarities to myeloid malignancies that arise in the context of aplastic anemia and to cases of therapy-induced MDS and AML that develops after treatment with alkylating agents. Although inherent dysfunction of or damage to normal HSPC is a unifying feature of these disorders, it is unknown how this predisposes to myeloid transformation, selects for outgrowth of a clone with monosomy 7/del(7q), and promotes intrinsic drug resistance. A second and distinct group of myeloid malignancies develop in infants and young children with NF1, Noonan syndrome, and other so-called “Rasopathies”. Here the causative mutations affect the NRAS and KRAS proto-oncogenes and other genes involved in Ras signaling. These mutations can either dominantly activate the encoded protein (e.g. PTPN11 mutations that increase basal SHP-2 phosphatase activity) or can result in loss of function (e.g. in NF1 or CBL). Consistent with the known role of Ras in driving proliferation in response to cytokine growth factors, children with Rasopathy disorders typically present with juvenile myelomonocytic leukemia (JMML), an aggressive MDS/myeloproliferative neoplasm (MDS/MPN) overlap syndrome. Approximately 30% of JMML bone marrow specimens exhibit monosomy 7 at diagnosis, while other patients acquire this cytogenetic abnormality after progression to AML. JMML is largely refractory to conventional AML treatment. Although MEK inhibitors have shown promise in genetically engineered mouse models, hematopoietic stem cell transplanation remains the only effective treatment. Importantly, the JMML–like MPN that arises in children with Noonan syndrome frequently regresses without treatment. This observation, which has important implications for clinical management, is likely explained by the fact that the causative germ line PTPN11 and KRAS mutations are biochemically
less activating than the somatic mutations in these genes found in JMML and other cancers. An intriguing paradox is why young children with NF1 are predisposed to JMML, while older patients with this disorder are not at increased risk of developing de novo myeloid malignancies.

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Abstract No. 2
Abstract Title: A donor-specific epigenetic classifier for acute graft-versus-host disease severity in hematopoietic stem cell transplantation
Full Name: Professor Stephan Beck
Institution/Company: Professor of Medical Genomics, Director, PGP-UK, UCL Cancer Institute, University College, London, UK

Abstract Details: Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for many hematological conditions. Acute graft-versus-host disease (aGVHD) is a prevalent immune-mediated complication following HSCT. Current diagnostic biomarkers that correlate with aGVHD severity, progression, and therapy response in graft recipients are insufficient. Here, we investigated whether epigenetic marks measured in peripheral blood of healthy graft donors stratify aGVHD severity in human leukocyte antigen (HLA)-matched sibling recipients prior to T cell-depleted HSCT.
Methods: We measured DNA methylation levels genome-wide at single-nucleotide resolution in peripheral blood of 85 HSCT donors, matched to recipients with various transplant outcomes, with Illumina Infinium HumanMethylation450 BeadChips. Results: Using genome-wide DNA methylation profiling, we showed that epigenetic signatures underlying aGVHD severity in recipients correspond to immune pathways relevant to aGVHD etiology. We discovered 31 DNA methylation marks in donors that associated with aGVHD severity status in recipients, and demonstrated strong predictive performance of these markers in internal cross-validation experiments (AUC = 0.98, 95% CI = 0.96–0.99). We replicated the top-ranked CpG classifier using an alternative, clinical DNA methylation assay (P = 0.039). In an independent cohort of 32 HSCT donors, we demonstrated the utility of the epigenetic classifier in the context of a T cell-replete conditioning regimen (P = 0.050).
Conclusions: Our findings suggest that epigenetic typing of HSCT donors in a clinical setting may be used in conjunction with HLA genotyping to inform both donor selection and transplantation strategy, with the ultimate aim of improving patient outcome.

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Dirk Paul et al. Genome Medicine 2015 7:128

Abstract No. 3
Abstract Title: Stem Cell Gene Therapy for Monogenic Diseases
Full Name: David A. Williams
Institution/Company: Chief of the Division of Hematology/Oncology, Director of Clinical and Translational Research, Boston Children’s Hospital, Associate Chairman, Department of Pediatric Oncology, Dana-Farber Cancer Institute, Leland Fikes Professor of Pediatrics, Harvard Medical School, Boston, MA, USA

Abstract Details: Integrating viral vectors have been developed for the treatment of genetic diseases. Targeting of hematopoietic cells, particularly hematopoietic stem cells (HSC) and T lymphocytes have led to proof-of-principle trials with successes in several monogenic diseases and in treatment of leukemia. However, integrating vectors also carry risks of insertional genotoxic mutagenesis and previous trials in children with rare immunodeficiency diseases were associated with treatment-related myelodysplasia with monosomy 7 and frank acute lymphoblastic leukemia with inappropriate activation of proto-oncogenes, such as LMO2. Thus, the challenge facing the field is to reduce the risk of insertional activation while maintaining efficacy. Recent advances in vector platforms and vector design are being tested in current human trials for a number of monogenic diseases. In a multi-institutional, international trial, we have recently demonstrated efficacy and safety of the use of an enhancer-deleted (ie SIN) designed γ-retrovirus vector in a human trial treating X-linked severe combined immunodeficiency disease (X-SCID). Interim analysis on the initial 9 patients has been reported (Hacein-Bey, Pai et al. NEJM, 2014). This trial will be updated. We have also recently defined vector architecture required for application of shRNAs to human trials (Guda et al. MT, 2015). This approach is being utilized to modulate expression of BCL11A, a key transcription factor regulating repression of γ-globin in hemoglobinopathies. Effective knock-down of BCL11A is associated with significant induction of fetal hemoglobin (HbF), which is protective for sickling conditions. Pre-clinical
data utilizing for a humanized mouse model of SCD and SCD primary bone marrow CD34+ cells show induced levels of Hb F of ~70% in HbSS red cells and a reduction in sickle-induced hemolysis. A planned clinical trial in sickle cell disease will be presented. Gene editing for SCD is also moving toward clinical testing. The results of vector redesign in preclinical and clinical studies and the opportunities and challenges of gene editing for clinical applications will be discussed.

Abstract Details: The concept of using Haematopoietic Stem Cell Transplantation (HSCT) in autoimmune diseases originated in basic science and serendipitous clinical cases several decades ago. Over the last 20 years, HSCT has been progressively used as a specific treatment for patients with severe treatment resistant autoimmune diseases. In the vast majority of patients autologous HSCT has been performed, although occasionally allogeneic HSCT has been used, particularly in paediatrics. The EBMT Autoimmune Diseases Working Party (ADWP) has been central to the evolution of this therapy in Europe and has maintained a database which now contains over 2000 procedures for a wide variety of diseases. In addition, the EBMT ADWP has produced guidelines and recommendations for clinical and research practice. Currently the main indications for autologous HSCT are multiple sclerosis, systemic sclerosis and Crohn’s disease, which are supported by large series and randomised controlled trials, whereas retrospective registry analyses have supported benefit in rarer indications. In association, mechanistic studies have provided insight into how tolerance may be achieved with HSCT. Although allogeneic HSCT is essentially a means of replacing an aberrant immune system, long-term responses to autologous HSCT may be explained in some diseases by ‘rebooting’ of the immune system through thymic reprocessing, T-cell repertoire changes and increased T-regulatory cell activity. Further research will be facilitated by the recent EBMT ADWP guidelines for biobanking and immune reconstitution studies. HSCT may therefore not only result in clinical benefit, but also provide insights into the pathophysiology of various autoimmune diseases. In summary, the evolution of HSCT in severe autoimmune diseases has been gradual, but the recent publication of a clinical and scientific studies, as well as evidence-based guidelines and recommendations, has added momentum to the field as reflected by growing activity in autoimmune diseases where other treatment options are limited. Multidisciplinary appraisal of individual cases, including alternative therapeutic avenues and patient fitness for HSCT, is central to decision making. Where possible, patients should be enrolled on prospective clinical trials. Close inter-speciality working is essential at both patient care and specialist society levels.

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Abstract No. 5

Abstract Title: Chemotherapy-free Allogeneic Hematopoietic Stem Cell Transplantation for Adult Patients with Sickle Cell Disease (SCD)

Full Name: Damiano Rondelli, MD
Institution/Company: Division of Hematology/Oncology, University of Illinois Hospital & Health Sciences System, Chicago, IL, USA

Abstract Details: Allogeneic hematopoietic stem cell transplantation (HSCT) is the only therapy that can cure SCD. Standard myeloablative conditioning regimens, mostly in pediatric patients, showed in the past that this procedure is associated with risks of morbidity and mortality. The experience of HSCT in adult patients has been very limited and small series of patients transplanted with chemotherapy regimens at reduced intensity produced disappointing results. Two recently published limited series of patients receiving a non-myeloablative regimen showed encouraging results with high rate of cure rates without transplant mortality. Only one of these two small studies, performed at the National Institute of Health, was designed without any chemotherapy, and using alemtuzumab (anti-CD52 monoclonal antibody) and low-dose total body irradiation (TBI) as conditioning regimen. Because this approach resulted in a 90% success in a small cohort of HLA and ABO matched related transplants, we tested it in an independent clinical trial, only for patients between age 16 and 60 and including also ABO mismatched donors. The chemotherapy-free regimen included: Alemzumab (anti-CD52 monoclonal antibody) i.v. at 0.03 mg/kg on Day -7, 0.1 mg/kg on Day -6, 0.3
mg/kg/day on Days -5 to -3 and TBI as a single dose of 300 cGy on Day -2. Immunosuppressive therapy with oral sirolimus was started on Day -1. To be eligible for the study, patients needed to be at high risk with a history of any of the following complications: 1) stroke, 2) ≥3 vaso-occlusive crises (VOC) per year requiring medical attention, 3) ≥2 life-time episodes of acute chest syndrome, 4) ≥2 episodes of priapism per year requiring medical attention, 5) red blood cell (RBC) alloimmunization during chronic transfusion therapy, 6) bilateral proliferative retinopathy with major visual impairment in at least one eye, 7) ≥2 joints with avascular necrosis, 8) chronic kidney disease, 9) stage I or II chronic lung disease, or 10) pulmonary hypertension defined as symptoms consistent with pulmonary hypertension and mean pulmonary artery pressure >25 mmHg. Between November 2011 and June 2014 13 high risk SCD patients were transplanted. Patients received matched-related donor G-CSF mobilized peripheral blood stem cells that in 2 cases were ABO incompatible. Quality-of-life (QoL) measurements were performed at different time-points after HSCT. All patients initially engrafted. Over 12 months, a mix but stable donor/recipient chimerism was observed in 11 patients (85%), slowly reduced in 1 patient, while another patient who was not compliant experienced a secondary graft failure. With a median follow-up of 15 months (range: 11–37 months) there was no mortality, no acute or chronic GVHD and no grade 3-4 extramedullary toxicity. At 1 year post-transplant, 12 patients with any persistent level of donor cell chimerism normalized the hemoglobin concentration regardless of ABO matching; improved cardio-pulmonary parameters and QoL parameters such as bodily pain, general health, and vitality. In four patients sirolimus was stopped without rejection or SCD complications. These results validate for the first time the successful use of a chemotherapy-free regimen in MRD HSCT for high risk SCD, here also in ABO mismatched cases, and demonstrate an improvement in QoL without risk of GVHD or mortality. No conflict of interest to disclose.

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Abstract No. 6

Abstract Title: Allogeneic stem cell transplantation: Still a role in CLL/lymphoma?
Full Name: Professor Dr. Peter Dreger
Institution/Company: Heidelberg University Hospital, Germany

Abstract Details: The field of lymphoma treatment is rapid changing due to the advent of molecular pathway inhibitors and monoclonal antibodies. In this presentation, we will analyze the impact of these novel treatment options on the role of allogeneic stem cell transplantation in the treatment algorithms of lymphoma and chronic lymphocytic leukemia. A particular focus will be put on the interaction of novel drugs with transplantation if used pre-, peri, or post-transplant. Finally, future perspectives of allogeneic transplantation in relation to further drug development and novel cellular therapies (CART cells) will be discussed.

Abstract Category: Debate ‘Chemo Free’ in Follicular Lymphoma

Abstract No. 7

Abstract Title: How Biology of Follicular Lymphoma will inform future therapy
Full Name: Daniel Hodson
Institution/Company: University of Cambridge, UK

Abstract Details: Recent years have seen a dramatic increase in our understanding of FL biology and revealed multiple potential therapeutic opportunities. The t(14:18) BCL2 translocation, originally thought to be the genetic basis of FL has since been detected in the memory B cells population of more than half of healthy, elderly donors(1). These memory cells recirculate back through the germinal centre, seemingly without conferring any significant risk of FL and suggesting the requirement for subsequent (or preceding) genetic hits. Several next generation sequencing studies have identified high frequency mutations of histone modifier genes including the lysine methyl transferase KMT2D and lysine acetyl transferases CREBBP and EP300(2-4). Mutation of at least one of these genes is found in more than 85% of cases of FL. The B cell receptor (BCR) signal has also emerged as an important survival pathway for FL(5). Activating mutations have been identified in

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multiple BCR components along with FL-specific patterns of immunoglobulin glycosylation that suggest a mechanism of ligand independent activation of the BCR by interaction with microenvironmental lectins(6). The microenvironment provides essential growth and survival factors for FL cells whilst at the same time is modified by FL(7). Of particular importance is the modification of the T cell activity by FL, in part through the PD1-PDL1 pathway(8). There is also an increased understanding of the mechanism of action of our “targeted” therapeutic agents such as lenalidomide. This and related drugs bind the E3 ligase Cereblon and enhances its ubiquitination, and thence the proteasomal destruction, of the transcription factors Ikaros and Aiolos(9-11). This in turn leads to reduced expression of IRF4 in the B cell and increased IL2 in T cells. Similar drugs might be selectively designed to target Cereblon any desired transcription factors in a customisable way, as has already been achieved for BRD4(12). However, our increased knowledge comes with increased complexity and unresolved questions. For instance, which of the many identified mutations are currently driving the malignant phenotype as opposed to being innocuous passengers or evolutionary remnants from an earlier stage of lymphomagenesis. Several sequencing studies have revealed that FL is not a homogeneous tumour but rather a collection of evolving competing subclones where transformation and relapse may arise not from the primary tumour but from a common inferred progenitor. Finally, co-operation and interaction between intracellular signalling pathways suggests that FL cells may find ways to compensate for the effects of pharmacological molecules designed to target a single component of a signalling pathway and rationally designed synergistic combinations will be needed. The answers to these questions will come from continued improvements in our understanding of lymphoma biology.

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years, with the best results seen in those patients with a negative PET scan after the conclusion of induction chemotherapy. It is against this background that any non chemotherapy based therapy will need to be judged. Long term follow up data on the use of single agent Rituximab as first line therapy with 2 year maintenance therapy may be associated with prolonged PFS with a small cohort of patients remaining disease free for up to 8 years, but the majority of these patients had a low tumour burden and the time of diagnosis with no immediate clinical requirement for chemotherapy. More promising are the data on the combination of the immunomodulatory agent lenalidomide in combination with Rituximab, one retrospective analysis from MDACC showing an equivalent PFS with the R2 regimen compared to multiagent chemotherapy, and a prospective phase II trial from the same institution showing high response rates with this chemotherapy free regimen, but as Buske points out in an accompanying editorial “Rituximab plus chemotherapy combinations are uniformly accepted as standard treatment for follicular lymphoma, underlining that we are still dependent on a chemotherapy backbone if we want to offer patients with follicular lymphoma the most effective treatment possible”. A similar prospective study from the SAKK group shows a high response to this combination but no long term PFS data are yet available. There are now limited data from small phase II trials where Rituximab is combined with the bcl2 inhibitor “venetoclax” or the PI3kinase inhibitor Idelalisib, but there are no definitive results that would enable us to conclude that we can yet discard chemotherapy from first line treatment for Follicular Lymphoma. We also have to remember that even if impressive data are published in the near future, cost, toxicity and the side effects of long term usage of novel agents have to be set against the considerable achievements possible with short course non toxic chemo-immunotherapy.

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Abstract Category: Iron/ACD
Abstract No. 9
Abstract Title: Pathways for iron loading beyond hemochromatosis and blood transfusion
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Abstract Details: Iron is an essential nutrient because it is a central component of heme, iron–sulfur cluster-containing enzymes, and proteins involved in mitochondrial respiration and DNA synthesis. The importance of iron is linked to its redox reactivity, which enables reversible binding of oxygen, transfer of electrons and mediation of catalytic reactions. However, iron can also catalyse the formation of toxic hydroxyl radicals, which can cause cellular damage. Therefore, tight regulation of iron homeostasis is needed to avoid both iron deficiency and overload. Dietary heme-bound and elementary iron are absorbed in the duodenum and transferred to the circulation, where the iron is bound to transferrin and is mostly transported to the bone marrow to be used for erythropoiesis. After a mean half-life of 120 days, senescent erythrocytes are taken up by spleen macrophages and degraded (i.e. erythrophagocytosis), resulting in the extraction of iron and transfer of the metal from the macrophage to the circulation. This re-utilisation of the metal meets 90-95% of the body’s iron needs.
daily needs for iron while only 5-10% originate from dietary iron absorption. The co-ordination of iron absorption and macrophage iron release is orchestrated mainly by a small peptide known as hepcidin. Hepcidin is mainly produced by hepatocytes in response to iron loading but also by inflammatory stimuli, whereas its expression is reduced by iron deficiency, hypoxia and anaemia. Hepcidin exerts its regulatory effects by binding to the only known cellular iron export protein, ferroportin, leading to ferroportin degradation and blockade of iron release from macrophages or enterocytes. Therefore, an increased formation of hepcidin either by iron loading or during inflammation leads to the inhibition of duodenal iron absorption and macrophage iron retention. By contrast, the lack of hepcidin, as a consequence of anaemia or iron deficiency, promotes ferroportin expression and iron transfer from enterocytes and macrophages to the circulation and the erythron. Inflammation has multiple effects on iron homeostasis resulting in typical diversion of iron traffic characterized by low circulating iron levels and increased concentrations of the major iron storage protein ferritin, further leading to the development of anaemia, known as anaemia of chronic disease or anaemia of inflammation which is found in patients with an activated immunity; for example, in people with infections, cancer, autoimmune disease, congestive heart failure or on dialysis. Specifically, cytokines such as interleukin (IL)-1 and 6 induce the expression of hepcidin in the liver which blocks duodenal iron absorption and iron egress from macrophages. In addition, these cytokines but also IL-10, TNF-alpha or IFN-gamma increase the uptake of iron into macrophages via multiple routes and promote its storage within ferritin, whereas ferroportin transcription is blocked thus resulting in macrophage iron loading and circulatory iron deficiency, a mechanism which is further aggravated by the autocrine formation of hepcidin by macrophages. Hyperferritinemia with normal or mildly elevated transferrin saturation and mild hepatic iron deposition is found in subjects with non-alcoholic fatty liver disease (NAFLD) whereas excess iron is observed in approximately one third of NAFLD patients and is commonly referred to as the “dysmetabolic iron overload syndrome”. Iron loading aggravates the clinical course of NAFLD with regard to liver-related and extrahepatic disease complications such as diabetes via formation of toxic hydroxyl-radicals. Inflammatory cytokines, hepcidin and copper deficiency contribute to iron loading, whereas in subjects regularly consuming alcohol iron loading is a consequence of alcohol mediated inhibition of hepcidin expression with a subsequent increase of duodenal iron absorption. A decreased formation of hepcidin is key to the development of secondary iron overload in “iron-loading anemias,” which include thalassemia intermedia and congenital dyserythropoietic and inherited nonsyndromic sideroblastic anemias. Thalassemia intermedia is characterized by ineffective erythropoiesis and high iron stores. Thereby, hepcidin expression is suppressed by erythropoiesis derived factors such as GDF-15 or erythroferron resulting in increased iron absorption and iron loading in the presence of anaemia.

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Abstract No. 10
Abstract Title: How should we investigate new cases of hyperferritinemia?
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Abstract Details: Raised serum ferritin (SF) or hyperferritinemia (HF) is becoming an increasingly frequent reason for referrals to haematology clinics. A simple pathway for discerning whether the raised SF is associated with raised body iron is required. While a low SF is almost invariably caused by iron deficiency (except in severe vitamin C deficiency), a raised SF has important causes other than iron overload. Thus Investigation of HF by haematologists should aim to distinguish true iron overload from inflammatory or hepatic causes. Investigation using transferrin saturation (TfSat) is a simple and underused test providing clues as to whether iron overload is causative of HF. The upper limit of non-fasting TfSat is 45% and is an effective way of screening for hereditary hemochromatosis (HH). A value of >50% on two samples suggests iron overload. If there is a clear family history of HH, and TfSat is increased and genetic markers for C282Y and/or H63D are positive the diagnosis of HH (type 1) is likely. The level of HF is critical to prognosis: if SF <1000 μg/L this predicts the absence of cirrhosis. Whereas a SF >1000 μg/L together with an elevated aminotransferase or aspartate aminotransferase level and platelets <200 x10^9/L predicted the presence of cirrhosis in 80% of C282Y homozygotes. Common causes of raised SF without raised TfSat include: non-inflammatory liver disease, alcoholic liver disease [ALD], chronic hepatitis B and C, non-alcoholic-fatty liver disease [NAFLD], or non-alcoholic steatohepatitis.
Learning objectives

- To understand the role of transferrin saturation in the investigation pathway for hyperferritinaemia
- To understand the role of liver iron concentration estimation (LIC) in the investigation pathway for hyperferritinaemia
- To understand when it is appropriate to refer for a hepatology opinion

Abstract Category: Immune Thrombocytopenia

Abstract No. 11

Abstract Title: Approach to refractory ITP in adults

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Abstract Details: Immune thrombocytopenia (ITP) in adults is an autoimmune disorder characterized by reduced platelet count and possible bleeding. Steroid ± IGIV represent the front line treatment for symptomatic ITP but, unfortunately, only 20 to 30% of patients achieve durable response, so that most of them need salvage treatments (1). Splenectomy remains the standard salvage therapy for patients with active disease with nearly 60% cure rate (2). According to accepted standardization, the definition of refractory ITP regards patients who have failed 1L therapy, splenectomy and have active symptomatic disease (3). However, splenectomy is not always feasible owing to medical comorbidities or patient unwillingness. Therefore the use of other medical options in the new diagnosis, persistent or chronic phases of disease is often necessary. Different therapeutic options are available which can be offer with curative or palliative purpose according to patients’ characteristics and expectations. Rituximab has short and long-term effect in 50-60% and 20 to 40% of cases (4-6), respectively. Patients selection seems important: younger age, female sex and shorter ITP duration are associated with better results (6-7). Possible toxic effects are represented by the development of infusional reactions and serum syndrome during the first month of treatment and infectious complications later on. The thrombopoietin receptor agonists (TPO-RAs) Romiplostin and Eltrombopag results active to increase the platelet count long-term in nearly 60-70% of patients (8-9). These agents should be administered at the dosage sufficient to achieve a safe platelet count, effect that is generally treatment dependent, even if the maintenance of the response upon TPO-RAs suspension has been reported in some patients. The switch from one TPO-RA to the other is feasible and may overcome the condition of resistance or intolerance to Romiplostin or Eltrombopag. Thrombotic events, liver toxicity (only for Eltrombopag) and an increase of reticulin in the bone marrow are possible side effects. Several other agents as Dapson, Danazol and other immune suppressive agents as Cyclospirin-A, Azathioprine, Cyclophosphamide, Mycophenolate mofetil may represent alternative therapeutic options for patients with symptomatic ITP. Unfortunately no prospective controlled studies have been performed with these...
agents which use is generally associated with platelet count improvement in nearly 20 to 40% of patients.

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Abstract No. 12
Abstract Title: Is there a role for Splenectomy in the management of ITP today?
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Abstract Details: There are numerous treatments for ITP, both medical and surgical. Splenectomy, which is often recommended for disease refractory or relapsed from first-line therapy, has been shown to cause an immediate increase in platelet count in up to 80% of patients. Despite this, the response is not always sustained and relapses often occur, overall results depending on the length of follow-up but in meta-analysis no better than 60%. Extra caution must be taken when splenectomies are carried out on ITP patients, as they are more likely to bleed during surgery due to the nature of the disease, usually requiring pre-operative preparation. There are other complications of splenectomy, based on the immunological functions of the spleen. These include a higher risk of infections and pneumococcal sepsis post-surgery. In the UK, the Department of Health recommends that antibiotic prophylaxis is taken for life after splenectomy surgery, although not all countries recommend this. There is also the increasing recognition of longer term cardiovascular effects, in particular pulmonary hypertension and an increased incidence of cardiovascular disease. Splenectomy has for a long period been considered the “gold standard” of ITP treatment but there has been a decrease in its popularity, primarily as a result of newer medical treatments which are an effective alternative to surgery. Even though some of the drugs have a wide spectrum of side effects, they are preferred to surgery with potential complications followed by a lifelong risk of infection. The 2010 International Consensus on ITP Diagnosis and Treatment, listed splenectomy as a second line therapeutic option but there has been increasing controversy about the appropriateness of this as the clinical usefulness of splenectomy in the management of ITP has been questioned and which has led to a large discrepancy in practice internationally. Our own study was conducted through the analysis of secondary data collected by the UK ITP Registry. The UK ITP Registry has data on patients with ITP from multiple sites in the UK. There are currently 48 active centres and data has been collected for 1369 patients. Data on treatments has been collected since 2002. Data collection has been both current and retrospective. The ITP Registry collects data regarding patients with primary ITP, and only collects data from adults. As a rare disease the Registry allows the use of data from multiple sites, which would not have otherwise been possible in the given timeframe. The main drawback of secondary data is the lack of control of data quality. Over the period covered by patients reported to the Registry, based on the year of ITP diagnosis, there has been an increased wait before splenectomy surgery is carried out. It has increased from under one year to over three years. Whilst the mean interval between diagnosis and splenectomies carried out between 1970 and 1975 was approximately 6 months, the mean for splenectomies carried out in 2010 onwards was over 3 years.

Diagnosed Pre-guidelines
Diagnosed Post-Guidelines

Since the publication of the 2010 guidelines there has been a substantial 6.5-fold decrease in splenectomy use. Both groups are of a large size however it should be noted that those diagnosed post-2010 guidelines, have had a smaller time frame for potential surgery. The increasing interval to splenectomy tends to suggest that patients are being offered alternate therapies before splenectomy and the use of surgery is increasingly
being downgraded in the option list. It is however arguably the only curative form of treatment and the question is whether patients likely to respond can be targeted. Our own studies indicate that Indium labelled platelet scanning is of value before performing splenectomy in ITP. Patients with pure or predominant splenic uptake respond well to splenectomy. Among patients with a pure splenic pattern, 95% showed an excellent immediate response to splenectomy and 88% maintained a good long-term platelet count at six months post-surgery. In contrast, 60% of patients with a mixed pattern of sequestration displayed an excellent immediate response but only 16% maintained a good platelet count at six months. No patients with a hepatic pattern of sequestration underwent splenectomy since previous reports had suggested that the response rate in this group was very low. These results are being increasingly supported by other European studies which show the responses are maintained. Splenectomy clearly has a place in the management of ITP however its position as an early option in the steroid relapsed or refractory patient can be questioned. Alternate therapies are now available and increasingly it is recognised that some, such as the thrombopoietin agonists, may be associated with long-term responses and as their risk profile is increasingly understood may be a better alternative to the removal of a healthy organ. Splenectomy should be reserved for those where predictive studies indicate an increased chance of long term response.

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Abstract No. 13
Abstract Title: Immune thrombocytopenia in pregnancy
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Abstract Details: Thrombocytopenia occurs in around 6% of pregnancies, although most of these have platelet counts above 100x10^9/l and do not cross the paths of haematologists. The most common causes of a low platelet count in pregnancy are gestational thrombocytopenia (GTP) and pregnancy induced hypertension (PIH), accounting for 75% and 20% respectively. Around 5% are due to ITP. The diagnosis of ITP is one of exclusion and largely rests on the antenatal history, including previous thrombocytopenia or autoimmune disease (or a clinical history suggestive of such), and the timing and severity of the thrombocytopenia. GTP and PIH develop in the latter half of pregnancy, leading ITP to be the most common cause of isolated thrombocytopenia in the first trimester. In later pregnancy, the lower the platelet count, the greater the likelihood of it being ITP; thrombocytopenia associated with PIH is usually moderate and with GTP rarely falls below 70 x10^9/l. However, other, life-threatening, causes of severe thrombocytopenia need to be ruled out. Fortunately, many women with ITP do not require treatment in pregnancy but for those that do, the optimal use of steroids, intravenous immunoglobulins (IVIG) and third line agents is unknown. Steroids impair autoantibody production and reduce phagocytosis of the opsonised platelets and are effective in 80-90% of cases. To limit maternal side effects, the approach to treatment involves the minimally effective dose for the minimal duration possible. Indeed it is rarely necessary to give treatment in early pregnancy unless the platelet count is below 20 x10^9/l, although it would need to be raised above 50 x10^9/l for delivery, or higher to allow regional anaesthesia. Although the optimal dose and preparation is unknown, prednisolone 20mg daily is a reasonable starting dose, to balance efficacy with avoidance of adverse effects. If time is short, a higher steroid dose may be preferred and/or IVIG 1g/kg. Women who do not respond to these treatments may benefit from laparoscopic splenectomy, if in the second trimester, or a choice of third line agents, each with its own limitations, which need to be carefully considered and discussed with the patient. Maternal IgG is actively transported to the fetal circulation via the neonatal Fc receptor on sycntiotrophoblasts. Binding to corresponding fetal platelet antigens may result in fetal thrombocytopenia and potentially, intracranial haemorrhage. Studies have shown this risk to be low, with only around 4% of newborns having cord platelet counts of <20 x10^9/l and very few with bleeding. However, the effect on the neonate cannot be predicted unless information is available from previous births and the nature of the maternal ITP is unchanged. For most cases, the mode of delivery should be dictated by obstetric indications, however those with a previous history of severe neonatal thrombocytopenia have a high chance of recurrence and the optimal mode of delivery for these women is unknown.
Abstract No. 14

Abstract Title: New treatment options for ITP

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Abstract Details: ITP treatment is based upon the understanding that platelets are being destroyed at an increased rate by anti-platelet antibody and not being produced at an adequate rate due to immune inhibition of megakaryocytes. Current therapies attempt to decrease the rate of platelet destruction or increase the rate of platelet production and include corticosteroids, IVIG, rituximab, splenectomy, and TPO receptor agonists. Except for splenectomy, none of these therapies provides long term remission and newer treatments are needed. Ongoing ITP research is focused on altering the immune response or reducing the effect of anti-platelet antibody on platelet destruction. A number of new therapeutic modalities are about to enter the clinic and are the subject of this brief review. Upon their production, anti-platelet antibodies bind to platelet antigens, are then bound by macrophage Fc receptors, internalized and destroyed along with the platelets they coat. Current research efforts target the major steps in this process:

- Anti-CD40 ligand antibodies. CD40 ligand is important in B cell development and inhibition of CD40 ligand decreases B cell activation. IgG class switch and inflammatory cytokines. Treatment with an early anti-CD40 ligand antibody reduced anti-GPIIb/IIIa antibody producing B cells and raised the platelet count in ITP patients. However a part of the Fc region of the antibody caused thromboembolism and studies stopped. A new anti-CD40 ligand antibody, BMS-986004, has been engineered without this thrombogenic Fc region and is currently in clinical studies in ITP.

- FcRn pathway inhibitors. The 28 day half-life of IgG is due to neonatal Fc receptor (FcRn) that protects it from degradation. Inhibition of FcRn reduces IgG half-life to 1-2 days and mice lacking FcRn are protected from autoimmune disease because of accelerated catabolism of pathogenic IgG. In two mouse models, monoclonal antibody against FcRn decreased clinical symptoms of myasthenia gravis and increased the platelet count in ITP. Increased catabolism of anti-platelet IgG may treat ITP by providing a continuous endogenous "plasmapheresis".

- Modified IgG – sialylated IVIG. Anti-platelet antibody-coated platelets bind macrophage FcγRIII receptors and are internalized and degraded. But FcγRIII function is inhibited when the FcγRIIb receptor appears. Animals deficient FcγRIIb fail to respond to IVIG in ITP models suggesting that this inhibitory FcγRIIb receptor is necessary for IVIG to work. The clearance of an opsonized platelet from the circulation can be thought about as being regulated by the extent of FcγRIIb inhibition of FcγRIII on the macrophage surface. Sialylated IVIG comprises 1-5% of total IVIG and appears to be the active component of IVIG by inducing FcγRIIb expression. By creating IVIG enriched with sialylated molecules, a "super IVIG" can be produced.

- Recombinant Fc multimers (stradomers). Some studies of IVIG have suggested that only the Fc portion is required and that IgG aggregates may be more effective than monomers. Infusion of IgG Fc fragments instead of IVIG increased platelets in children with ITP and had an immunomodulatory effect. In other studies IgG aggregates where more active than non-aggregated IgG. Stradomers are multimeric IgG Fc structures that bind to the FcγRIIb and SIGN-R1 receptors as effectively as IVIG. Stradomers do not raise the platelet count in FcγRIIb deficient mice, suggesting that they work through upregulation of FcγRIIb.

- Syk kinase inhibition. Once bound to the FcγRIII receptor, internalization of opsonized particles requires a number of signal transduction changes including activation of the spleen tyrosine kinase, Syk. In mice models, Syk inhibitors like fostamatinib abrogated autoimmune ITP and autoimmune hemolysis. In a small human trial, fostamatinib increased the platelet count in ~40% of ITP patients and a phase 3 trial is nearly completed.

The studies above focus on various stages of the clearance mechanism of platelets by anti-platelet antibody and each shows an ability to raise the platelet count in animals or humans with ITP. But these molecules may have more extensive effects on down-regulating anti-platelet antibody production and thereby have the potential for more extensive effects on the ITP process than just ameliorating platelet clearance.

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Abstract No. 15

Abstract Title: The Management of Acute Myeloid Leukaemia in Pregnancy

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Abstract Details: Diagnosis of a haematological malignancy during pregnancy poses a huge challenge to the pregnant woman, her family and the medical team. A pregnant woman diagnosed with a haematological malignancy should be managed jointly by consultant haematologist, obstetrician, midwife, anaesthetist and neonatologist. The published data indicate that pregnancy is not an independent risk factor influencing cancer survival. (1) Chemotherapy can be administered from 14 weeks gestational age onwards. Long term outcome of children exposed in utero to chemotherapy is comparable to children of the same age. Nevertheless, a higher rate of neurodevelopmental problems was encountered after preterm birth. (2) Treatment delays may compromise maternal outcome without improving the outcome for the pregnancy. (3) Without treatment maternal death can occur within weeks or months. (4) In addition leukaemia in a pregnant woman carries an increased risk of miscarriage, fetal growth restriction, and perinatal mortality. (4, 5, 6) The earlier in gestation the diagnosis of leukaemia is made, the higher the incidence of spontaneous miscarriage, premature labour, and fetal growth restriction. Suspected causes of fetal death include maternal anaemia, disseminated intravascular coagulation or leukaemic cells affecting blood flow, nutrient exchange and oxygen delivery in the intervillous spaces of the placenta. (4) When pregnancy is not advanced enough to consider early induction of labour, combination chemotherapy should be offered. Induction with daunorubicin and cytosine arabinoside as per standard AML protocols should be offered. The teratogenic risk following chemotherapy during pregnancy appears to be lower than commonly estimated. However first trimester exposure to chemotherapy has been associated with 10-20% risk of major malformation. The risk is lower with single chemotherapy compared to combination regimen. It is still a matter of debate whether in utero exposure to anthracyclines in general is cardiotoxic to the fetus. However, serial prenatal sonographic assessment of fetal cardiac function might have a role in monitoring anthracyclines cardiotoxicity or cardiac failure. Experience of cytarabine administration during pregnancy is limited. As with the use of anthracyclines, most fetal malformations seem to occur after exposure during the first trimester. Congenital malformations including limb malformation have been associated with its use in the first trimester, either alone or in combination with other chemotherapies (7,8,9) Transient cytopenias, intraperitoneal fetal death, fetal growth restriction and neonatal death secondary to sepsis have been reported with its use during all trimesters (10,11) though the risk is relatively small. Planned delivery is preferable to allow timely administration of subsequent chemotherapy. Plans should be made for elective delivery as soon as foetal maturity allows but should be carefully timed and delivery should be avoided during the maternal nadir period, usually two to three weeks after treatment. This should allow the mother’s blood counts to be improving rather than deteriorating. Vaginal delivery is preferable to caesarean section because of the lower risks of infection and elective caesarean section only being advised for obstetric indications. After delivery, appropriate AML consolidation therapy should be planned to be completed as soon as feasible.

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Abstract No. 16

Abstract Title: Chronic Myeloid Leukaemia in Pregnancy

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Abstract Details: Recent advances in CML therapy have dramatically improved survival and offer most patients durable molecular response and normal life expectancies. However, the management of CML during pregnancy remains a clinical challenge. Management of CML in pregnancy should be individualised based on the relative risks and benefits to the mother and fetus, focusing on survival of the mother, while limiting treatment-related toxicity to the developing fetus. Imatinib and dasatinib exposure during pregnancy have been associated with an increased risk of spontaneous abortions and serious congenital malformations. There are still limited data on the effects of TKI on fertility, pregnancy and embryo-fetal development. The current consensus is to avoid all TKI during pregnancy. We recommend physicians to encourage their patients to initiate and complete fertility preservation prior to commencing any cancer therapy that may impact on gonadal function. Women of childbearing potential should be advised to practice effective contraception and avoid becoming pregnant whilst on TKI therapy. Women who want to interrupt treatment in order to become pregnant should be counseled and advised of the risk of suboptimal response or relapse even if they have achieved deep and durable molecular response. Molecular monitoring should be carried out at regular intervals throughout pregnancy and consideration given to introducing IFN-α in the presence of increasing tumour load. There are several factors to be taken into consideration when faced with a patient who has become pregnant whilst receiving TKI. These include the disease status, alternative treatment options and the probability of achieving disease control following a prolonged period off treatment. The advice given to patients will differ according to their disease response particularly with respect to previous or current accelerated phase or blast crisis. Patients who present with chronic phase disease during pregnancy can safely continue their pregnancy to term and can be successfully managed with leukaapheresis if necessary during the first and subsequent trimesters, with IFN-α being introduced if necessary in the second trimester onwards. Patients presenting in advanced phase disease should be counseled with respect to consideration of elective termination of pregnancy in order to commence induction chemotherapy and/or a TKI. Management of CML in pregnancy requires a multidisciplinary approach requiring close collaboration with the obstetricians.

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Abstract No. 17

Abstract Title: Thrombophilia Testing & Obstetrics – Who to test and what tests

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Abstract Details: Thrombophilia refers to laboratory abnormalities that increase the risk of venous thromboembolism (VTE). Over the last decades numerous of such factors have been identified. The most prevalent examples of hereditary forms of thrombophilia include the Factor V Leiden and Prothrombin G20210A mutations, deficiencies of the natural anticoagulants antithrombin, protein C and protein S, persistently elevated levels of coagulation factor VIII, and mild hyperhomocysteinemia. Taken together, some form of hereditary thrombophilia can be identified in over 50% of patients with VTE. Moreover, hereditary thrombophilia has been associated with arterial cardiovascular disease and obstetric complications such as (recurrent) pregnancy loss and preeclampsia. The high yield of thrombophilia testing has led to widespread testing for these abnormalities in patients. Nevertheless, thrombophilia testing remains a topic of ongoing debate, mostly because of the lack of therapeutic consequences. While hereditary thrombophilia is a clear risk factor for a first VTE, the risk for recurrent episodes is hardly increased compared with non-affected patients and prolonged anticoagulation is not warranted. A similar lack of therapeutic consequences applies to patients with obstetric complications. Thrombophilia testing in asymptomatic relatives of patients with VTE may be useful in families with antithrombin, protein C or protein S deficiency, or for siblings of patients who are homozygous for factor V Leiden, and is limited to women who intend to become pregnant or who would like to use oral contraceptives. Careful counselling with knowledge of absolute risks helps patients to making an informed decision in which their own preferences can be taken into account. This presentation will review the epidemiology of thrombophilia and pregnancy-related VTE. The current recommendations for thrombosis prophylaxis will be reviewed, with a focus on thrombophilia. Furthermore, the association of both hereditary and acquired (i.e. antiphospholipid syndrome) thrombophilia with pregnancy
complications such as preeclampsia and recurrent miscarriage will be summarized, as well as current evidence on treatment with aspirin and/or heparin in women with thrombophilia. Learning objectives At the conclusion of this presentation, participants should be able to

1. Describe the impact of thrombophilia on risk of pregnancy-related venous thrombosis
2. Describe the association between pregnancy complications and thrombophilia both quantitatively and qualitatively
3. Describe if and how the presence of thrombophilia affects recommendations regarding thrombosis prophylaxis in pregnancy and puerperium, or during puerperium only

Learning objectives
Describe the state of the evidence with respect to prevention of pregnancy complications with aspirin and/or heparin in women with antiphospholipid syndrome and with hereditary thrombophilia

Abstract No. 18
Abstract Title: Thrombotic microangiopathies & pregnancy
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Abstract Details: Thrombotic microangiopathies (TMA’s) describe the clinicopathological effects of thrombosis in small vessels producing thrombocytopenia and microangiopathic haemolytic anaemia (MAHA). These changes often produce end-organ damage. Laboratory Haematologists are often alerted to this condition first, because review of the blood film of an anaemic & thrombocytopenic patient confirms the microangiopathic process, with evidence of red cell fragmentation. Thrombotic thrombocytopenic purpura (TTP) is the most feared TMA and was first described in pregnancy in 1955. The pentad of TTP includes thrombocytopenia, MAHA, neurological signs, renal impairment and fever. However, a diagnosis is often made if MAHA and thrombocytopenia are present, in the absence of any other identifiable cause. In some series of TTP patients pregnancy is present in approximately 5-25% of TTP cases, and can reflect late onset adult congenital TTP or acute idiopathic TTP. The problem with TMA’s in pregnancy is that the differential diagnosis may be very difficult and often clinical suspicion in conjunction with laboratory parameters requires differentiation from other TMA’s which are specific to this period. The diagnostic challenge of TMA’s in pregnancy is the differentiation from Acute Fatty Liver of Pregnancy (AFLP), pre-eclampsia (PET) or eclampsia, HELLP (Haemolysis, elevated liver enzymes, low platelets), antiphospholipid syndrome (APLS), systemic lupus erythematosus (SLE), haemolytic uraemic syndrome (HUS), and disseminated intravascular coagulation (DIC).

The distinction between the diagnoses is particularly difficult post partum, when the situation may be complex with pregnancy related TMA’s, such as pre-eclampsia / HELLP and hemolytic-uraemic syndrome occurring with TTP as a result of placental damage due to TTP. In initial reports of TTP in pregnancy, maternal survival was rare and fetal mortality due to placental infarction approached 80% Plasmapheresis has transformed the outcome of TTP, including those associated with pregnancy, although mortality may still occur During 2003–2008 there were 556 maternal deaths in the UK, of which six (1%) were due to TTP. Thrombosis occurs in the placenta in untreated TTP pregnancies and results in fetal growth restriction, intrauterine fetal death and pre eclampsia. Women presenting with TTP during pregnancy appear to fall into two groups; those with congenital TTP and those with acquired, antibody mediated TTP. Congenital TTP may first present during pregnancy and these women are more likely to relapse in subsequent pregnancies. In recognition of the difficulty in differentiating TTP from other TMA’s in pregnancy and especially post partum, (and recognising that pre-eclampsia and HELLP can present in the postnatal period), BSH guidelines recommend that plasma exchange should be started urgently. Pre-treatment ADAMTS13 assays will distinguish congenital and acquired TTP from other pregnancy-associated TMA’s. Diagnosis is confirmed with ADAMTS 13 activity <5%, no evidence of an inhibitor and confirmation by mutational analysis of the ADAMTS 13 gene. In pre-eclampsia and HELLP syndrome ADAMTS13 activity is reduced (median 31% range 12-43%) but antibodies to ADAMTS13 are not found. If TTP develops in the first trimester, regular PEX may allow continuation of pregnancy with delivery of a live infant. Delivery is the definitive treatment of choice for pregnancy-associated TMA’s, although delivery does not guarantee remission of TTP. Close liaison with an obstetrician with expertise in thrombosis and fetomaternal medicine is required. Serial fetal monitoring with uterine artery Dopplers should be used to assess if there is adequate fetal growth and to assess placental blood flow. Plasma infusions alone may be sufficient in mothers with congenital TTP. However, at delivery PEX may be required to ensure adequate levels of ADAMTS13. The ideal frequency of plasma replacement during pregnancy is unknown. In acquired TTP, it is difficult to predict future relapse in
pregnancy. A reduction in ADAMTS13 activity (<10%) at the start of pregnancy may require elective therapy to prevent microvascular thrombosis during pregnancy.

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Abstract Category: Transfusion Practice: Delivering Patient Blood Management

Abstract No. 19

Abstract Title: Patient blood management – the view from Pittsburgh

Full Name: Mark Yazer, MD

Institution/Company: Professor of Pathology, University of Pittsburgh, Medical Director, RBC serology reference laboratory, Centralized Transfusion Service, Associate Medical Director, Centralized Transfusion Service, Pittsburgh USA

Abstract Details: Patient blood management (PBM) is an umbrella term for techniques that are performed on potential transfusion recipients in order to optimize their condition such that transfusion might be avoided and when it is necessary, to use only the smallest amount of blood product to achieve the clinical endpoint. The scope of PBM activities are not limited to direct patient interventions, but can also involve the construction and optimization of the hospital and/or transfusion service’s infrastructure to support clinical decision making in transfusion medicine. The following are some examples of PBM initiatives that can help ensure that transfusions are provided at the right time and in the right dose.

1. Evidence based transfusion practice

   This truly is a golden age of high quality transfusion medicine research. From randomized controlled studies on RBC transfusion thresholds,1-3 to platelet dose studies,4 and advances in the knowledge base about plasma transfusion,5 the situations in which patients will benefit from transfusion (and when they will not) has never been clearer.

2. Electronic enhancements to assist implementing evidence based transfusion practice

   Simply having high quality literature available does not mean that it will have been read by blood product prescribers. Interventions such as creating alerts in the computerized physician order entry (CPOE) have been demonstrated to reduce the number of transfusions administered to patients whose laboratory criteria do not suggest that a transfusion is warranted.6-8 Requiring prescribers to select an indication for the transfusion and having the CPOE verify that those conditions are actually present in the patient is an effective way of educating prescribers about the latest transfusion evidence at the moment when they are deciding if a transfusion is needed.

3. Pre-operative optimization of hemoglobin

   Many patients are anemic before surgery, and anemia is a major risk factor for poor surgical outcomes. Identifying anemic pre-surgical patients and correcting the deficiency is an important method of avoiding transfusion.9 Along this line, restricting autologous donation to the very uncommon patient with severe allergies to allogeneic blood or the highly alloimmunized for whom compatible RBCs cannot be found, is another important means of preventing (not fixing) pre-operative anemia.

4. Minimizing blood product waste

   The gift of a blood donation by a volunteer donor is precious. Thus wasting a unit represents a waste of a donor’s time and effort. Simple interventions such as indicating on the unit how it should be stored once issued from the blood bank, when it expires, and generally increasing prescribers’ awareness that the donated units come from altruistic donors have been shown to significantly reduce wastage.10,11 Reduced wastage saves the hospital money, and helps to ensure that products will be available for patients who need them.

5. Use of pharmaceuticals instead of blood products

   Clearly using hematinc therapy to correct anemia has many advantages over using blood products, but so can using medications such as tranexamic acid to reduce and prevent surgical bleeding, and vitamin K and (in the right situations) prothrombin complex concentrates to quickly reverse an elevated INR, can all effectively reduce the need for, and adverse effects of, allogeneic transfusion. It is likely that allogeneic blood product transfusions will be required for many years to come. Applying the principles of PBM can help ensure that they are used appropriately when the clinical benefits outweigh their risks.

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Abstract No. 20

Abstract Title: The management of coagulopathy in postpartum haemorrhage

Full Name: Dr Peter Collins

Institution/Company: Cardiff University School of Medicine, Cardiff, Wales, UK

Abstract Details: The management of major obstetric haemorrhage (MOH) relies on a multi-disciplinary team approach with haematologists often asked to advise on the management of coagulopathy. The haemostatic management of MOH remains challenging and current published guidance relies heavily on experience from major trauma in the non-pregnant population and expert opinion. There is evidence that haemostatic impairment in the pregnant population is different from trauma-induced coagulopathy and that the type and rate of onset of coagulopathies depends on the underlying cause of obstetric bleeding.

In many cases of MOH coagulation remains normal but in some women catastrophic haemostatic impairment occurs. In recent years interest in the implications of relative hypofibrinogenaemia, point of care monitoring of coagulation abnormalities and the potential to give goal-directed therapy to correct coagulopathies has created the possibility to change treatment strategies. Fibrinogen reaches critically low levels earlier than other coagulation factors during MOH and has been shown to be a predictive biomarker for progression of obstetric bleeding. A point of care surrogate measure of fibrinogen (Fibtem) is also a rapidly available useful predictive biomarker for progression. The optimal target fibrinogen level during MOH is not known but recent guidelines suggest that the level should be maintained above 2 g/L during active bleeding. Fibrinogen can be replaced with cryoprecipitate or fibrinogen concentrate and ongoing studies are investigating these treatment options. A prothrombin time (PT) and/or activated partial thromboplastin time (aPTT) prolonged more than 1.5 times normal are associated with established haemostatic failure. Recent guidelines recommend that FFP should be infused if the PT or aPTT are prolonged above the normal range and bleeding is continuing. This is to prevent progression to haemostatic failure and takes into account the time taken for laboratory results to become available.

The time taken to obtain laboratory coagulation results has led many experts to recommend formulaic fixed-ratio transfusion of red cells and FFP, although this policy results in many women being transfused FFP whilst their coagulation is normal. Recent guidelines to obtain laboratory coagulation results has led many experts to recommend formulaic fixed-ratio transfusion of red cells and FFP, although this policy results in many women being transfused FFP whilst their coagulation is normal. Recent guidelines suggest infusing early FFP in situations where coagulopathy is likely such as placental abruption or amniotic fluid embolus or if the diagnosis of bleeding has been delayed. With other causes of bleeding, if 4 units of red cells have been transfused and no coagulopathy is likely such as placental abruption or amniotic fluid embolus or if the diagnosis of bleeding has been delayed. With other causes of bleeding, if 4 units of red cells have been transfused and no coagulopathy is present, point of care viscoelastometric tests to guide haemostatic replacement during MOH and that use of tranexamic acid to treat MOH is increasing and trials are ongoing that should provide a clear indication of the benefits and risks of this treatment.

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Abstract No. 21

**Abstract Title:** Choosing Wisely Campaigns: Improving outcomes by doing less

**Full Name:** Dr. Jeannie Callum

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**Abstract Details:** Transfusion practice for red blood cells, platelets, plasma and cryoprecipitate is highly variable country to country, hospital to hospital within the same country, and between physicians within the same institution. The most common metric used to compare countries is the number of red blood cells transfused per 1000 people in the population. The majority of countries currently reside in the range of 30 to 40 red blood cell units per 1000 population, but the variability is huge with many countries below 30 and other countries above 40. Similarly, clinical studies looking at pre-transfusion triggers note wide variability in practice. Recent reports have shown approximately 22% of red cell units, 58% of plasma transfusions, and 42% of platelet transfusions are unnecessary. It is unknown what is driving the variability in transfusion practice but likely the top two contributing factors are: (1) physicians are unclear as to when blood products are indicated; and (2) additional clinical trials are needed to help refine transfusion practice. Evidence to support the first etiology is the poor performance of resident physicians on standardized transfusion exams. Due to the wide variability in clinical use of laboratory tests, diagnostic imaging, and procedures, multiple different organizations worldwide have launched “choosing wisely campaigns” in attempts to generate change. In the United States, the American Board of Internal Medicine launched a campaign that now has statements from 71 medical societies, including 13 transfusion-related statements. In Canada, Choosing Wisely Canada, in partnership with the Canadian Medical Association has published 29 society statements including 14 pertaining to blood transfusion. The majority of the statements pertain to three themes: (1) Stop liberally transfusing patients; (2) Don’t use blood products to reverse warfarin except in emergencies; (3) Stop doing so much unnecessary blood work that is contributing to high transfusion rates. The American Association of Blood Banks in 2014 published its five statements through the American Board of Internal Medicine program. Those statements are: (1) Don’t transfuse more units of blood than absolutely necessary; (2) Don’t transfuse red blood cells for iron deficiency without hemodynamic instability; (3) Don’t routinely use blood products to reverse warfarin; (4) Don’t perform serial blood counts in clinically stable patients; (5) Don’t transfuse O-negative blood except to O-negative patients and in emergencies for women of childbearing potential with unknown blood group. The details of these five statements will be discussed. The reason for these recommendations will be reviewed. Data from pertinent studies will be reviewed. The goal of each of the choosing wisely statements are to foster worldwide change in our quest to reduce unnecessary tests and procedures. Each institution needs to take one or more of the choosing wisely transfusion statements and obtain baseline data for compliance with guidelines. Next, the data needs to be presented to senior leadership at that hospital, preferably with peer benchmarking data for comparison. Then, an evidence based approach to quality improvement needs to be undertaken with serial measurements to ensure your hospital is meeting quality expectations.

**Abstract Category:** LMIC (1) Anaemia & Infection

Abstract No. 22

**Abstract Title:** Anaemia, iron deficiency and infections

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**Institution/Company:** Consultant Paediatric Infectious Diseases, Head of the Global Child Health Group, Emma Children’s Hospital / Department of Global Health, Academic Medical Centre, University of Amsterdam

**Abstract Details:** Infections, anaemia and iron deficiency are major causes of childhood morbidity and mortality predominantly occur in resource limited settings such as sub-Saharan Africa. These three conditions could interact. As an example, iron deficiency may lead to anaemia, but also may increase susceptibility to infection by suppressing the host immune response. The complex interaction is illustrated by the fact that iron is an important component, as an essential nutrient, in erythropoiesis. But iron is also essential for proper functioning of the host immune system as well an important factor for growth of various pathogens, including non-typhoid salmonella. This has resulted in a treatment dilemma in which iron is needed to treat the iron deficient...
anaemia and improve the immune system of the host (child), but the same treatment may also put the child at an increased, potentially fatal, infection risk. A key outstanding questions is: How does the iron status of a child influences their susceptibility to infections, like malaria? A more practical question for the doctor treating children in an African setting may be: Is it safe to treat HIV infected anemic children with iron and does it have any effect on their haemoglobin recovery? In other words, can you safely start iron supplementation in these children or should you combine it with antibiotics and/or antimalarial prophylaxis? These and other questions will be addressed during the presentation.

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Abstract No. 23
Abstract Title: Safety and efficacy of iron supplementation in pregnancy in Kenya
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Abstract Details: Background: Antenatal iron supplementation leads to increased haemoglobin concentrations and reduced risk of anaemia at term. Iron deficiency is associated with severe anaemia and maternal death, but causal evidence from randomized trials is inconclusive. Potential effects of iron interventions on malaria are likely to be most pronounced in pregnancy, when iron absorption is very high. Plasmodium infection in pregnancy is usually asymptomatic, but associated with adverse outcomes. In infants, there can be reduced birth weight, intraterine growth retardation, preterm delivery, increased neonatal mortality while pregnant mothers may be prone to increased risk of severe anaemia and death. The World Health Organization guidelines state that children in settings with high prevalence of malaria and other infectious diseases should not receive universal iron supplementation. Whereas coverage of antenatal iron supplementation is abysmally low in most lower and middle income countries and benefits are uncertain, there is evidence that it can increase the burden of malaria. We aimed to measure the effect of iron supplementation during pregnancy on maternal Plasmodium infection assessed at delivery, birthweight, gestational duration, foetal growth and maternal and infant iron status. Methods: 470 rural Kenyan women with singleton pregnancies, gestational age 13–23 weeks and haemoglobin concentration ≥90g/L were randomized to supervised daily supplementation with iron (60mg as ferrous fumarate) or placebo until 1 month postpartum. To prevent severe anaemia, both groups additionally received 5.7 mg iron/day through flour fortification. Intermittent preventive treatment against malaria was given as usual. Plasmodium infection was assessed at birth by dipstick tests, PCR and histological examination of placental biopsies. Results: Primary outcome was maternal Plasmodium infection at birth. Predefined secondary outcomes were birthweight and gestational age at delivery, intrauterine growth, and maternal and infant iron status at 1 month after birth. Among the 470 participating women, 40 women (22 iron, 18 placebo) were lost to follow-up or excluded at birth; 12 mothers were lost to follow-up postpartum (5 iron, 7 placebo). At baseline, 190 of 318 women (59.7%) were iron-deficient. In intention-to-treat analysis, comparison of women who received iron vs placebo, respectively, yielded the following results at birth: Plasmodium infection risk: 50.9% vs 52.1% (crude difference, −1.2%, 95%CI, −11.8% to 9.5%; P = .83); birthweight: 3202 g vs 3053 g (crude difference, 150 g, 95%CI, 56 to 244; P = .002); birth-weight-for-gestational-age z score: 0.52 vs 0.31 (crude difference, 0.21, 95%CI, −0.11 to 0.52; P = .20); and at 1 month after birth: maternal haemoglobin concentration: 12.89 g/dL vs 11.99 g/dL (crude difference, 0.90g/dL, 95%CI, 0.61 to 1.19; P < .001); geometric mean maternal plasma ferritin concentration: 32.1 μg/L vs 14.4 μg/L (crude difference, 123.4%, 95%CI, 85.5% to 169.1%; P < .001); geometric mean neonatal plasma ferritin concentration: 163.0 μg/L vs 138.7 μg/L (crude difference, 17.5%, 95%CI, 2.4% to 34.8%; P = .02). Serious adverse events were reported for 9 and 12 women who received iron and placebo, respectively. There was no evidence that intervention effects on Plasmodium infection risk were modified by intermittent preventive treatment use. Conclusions: In a mixed population that included women with anaemia and iron deficiency at baseline, iron supplementation produced major gains in birth weight, with no apparent effect on Plasmodium infection. The coverage of universal antenatal iron supplementation must be increased. “There was no evidence that gains in birth weight depended on gravidity, maternal age, HIV infection, anaemia, and IPT use, suggesting benefits from iron for all subgroups thus defined, including primigravidae and those who did not receive IPT. Thus, our results may apply to pregnant women in other low- and middle-income countries, although the
effect on birth weight can vary depending on the prevalence of iron deficiency.” – Mwangi et al. 2015 JAMA. 2015;314(10):1009-1020. doi:10.1001/jama.2015.9496 Keywords: iron; anaemia; malaria; Plasmodium; pregnancy; birthweight; foetal growth; Kenya clinicaltrials.gov identifier:NCT01308112

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Abstract No. 24

Abstract Title: From red cell antigens to vaccines: Progress and prospects with new vaccines for malaria

Full Name: Simon J. Draper

Institution/Company: Associate Professor & Wellcome Trust Senior Fellow, Jenner Institute, University of Oxford, UK, Email: simon.draper@ndm.ox.ac.uk

Abstract Details: Plasmodium falciparum malaria affects 200-300 million people annually, resulting in the death of about 0.6 million individuals. Another species of malaria parasite, P. vivax, also causes severe and relapsing malaria illness, but less mortality. P. vivax is more geographically widespread than P. falciparum, and is found largely in South America and Asia. Thus, despite increasing implementation of control measures, the burden of malarial disease remains far too high. The most advanced subunit vaccine against P. falciparum, called RTS,S, has been tested in Phase III clinical trials across Africa with results showing modest short-term efficacy against clinical disease in young children (1), whilst no effective vaccine exists for P. vivax. More recently, calls have been made for a second generation vaccine to exert 75% efficacy over two years against both species of parasite (2). If this ambitious rhetoric is to be realised, new approaches to malaria vaccine design are required. Vaccines against the parasite’s asexual blood-stage have the potential to reduce mortality, morbidity and transmission of malaria, however no vaccine has proven convincingly protective in clinical trials. Significant challenges have included antigenic polymorphism; redundancy of red blood cell (RBC) invasion pathways used by the parasite; the apparent requirement for exceptionally high antibody concentrations to mediate protection, and the lack of validated in vitro assays that associate with in vivo protection in humans. We have developed vaccines targeting the full-length reticulocyte-binding protein homologue 5 from P. falciparum (PfRH5) and the Duffy-binding protein from P. vivax (PvDBP), both of which mediate essential non-redundant RBC invasion pathways. PvDBP has been known for many years to bind the Duffy antigen receptor for chemo- kines (DARC or Fy) on the RBC surface (3), whilst PfRH5 was recently shown to bind to basigin/CD147 (4, 5). We have previously reported that vaccines based upon the full-length PfRH5 induce antibodies which neutralise all tested laboratory-adapted parasite lines (6), and have shown that neutralisation of recently-isolated parasites by anti-PfRH5 antibodies is more potent than with antibodies against historical candidate antigens (7). We have also confirmed that vaccines based on PfRH5 can mediate heterologous strain efficacy in a stringent Aotus nancymaeae non-human primate – P. falciparum challenge model (8). These data have supported the prompt clinical testing of PfRH5-based vaccines. This talk will describe the on-going development of new PfRH5-based vaccine candidates (9), and will report the data from the first Phase Ia PfRH5 vaccine clinical trial in healthy UK adults that completed in Oxford in late 2015. In parallel, we have also recently completed the first ever trial of a candidate PvDBP vaccine against blood-stage P. vivax (10) – data from this study will also be presented.

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leukemia cell survival and growth. IgM and IgD are the BCR isotypes that are characteristically expressed on the surface of CLL cells, and they have distinct non-overlapping function in BCR signaling. IgM signaling promotes CLL cell survival and transcriptional activation of CCL2, whereas IgD signaling causes upstream activation of the cytoskeleton. Turning off BCR signaling with selective inhibitors of the BCR-associated kinases Bruton’s tyrosine kinase (BTK)3, 4, 5, and phosphoinositide 3-kinases (PI3K)6, such as ibrutinib or idelalisib, induces high rates of durable responses in patients with CLL, and these novel agents currently are transforming the CLL therapeutic landscape. Characteristically, CLL patients treated with these agents experience rapid shrinkage of enlarged lymph nodes, along with a transient rise in peripheral blood CLL cell counts due to re-distribution of CLL cells from the tissues into the blood7. Responsible for this phenomenon is the disruption of CLL trafficking and homing mechanism, based on the role of BTK and PI3K in signaling and function of chemokine receptor and adhesion molecules8, 9.

Deuterated (heavy) water labeling of CLL cells before treatment with ibrutinib established profound effects of kinase inhibitor therapy on leukemia cell birth and death rates. Development of resistance to the new kinase inhibitors is a rare event which typically occurs in high-risk patients, with the emergence of clones carrying BTK, PLCγ2 mutations10, or del(8p). Analysis of clonal evolution during ibrutinib therapy demonstrates that resistant sub-clones are already present at the beginning of therapy. These sub-clones then are selected and expand during ibrutinib therapy, indicating that this fundamental mechanism of drug resistance also applies to the BCR-associated kinase inhibitors. In the CLL frontline setting ibrutinib induces durable responses in the vast majority of patients4, 11, with improved progression-free and overall survival when compared to chlorambucil8. So far, combination trials failed to demonstrate any major added benefit from combining kinase inhibitors with conventional chemotherapy agents, i.e. bendamustine. Collectively, discoveries related to the CLL microenvironment and BCR signaling, along with the clinical success of ibrutinib and idelalisib have fundamentally changed our understanding of CLL disease biology, and CLL patients, especially patients with high-risk disease, greatly benefit from these new therapeutic options.

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**Abstract No. 26**

**Abstract Title:** Advances in Molecular Stratification of Chronic Lymphocytic Leukaemia

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**Abstract Details:**

Chronic Lymphocytic Leukaemia (CLL) is characterized by considerable clinical and biological heterogeneity. Overall survival of the 30% of patients relapsing less than 3 years following 1st line chemo-immunotherapy is just over 2 years (Tam et al., 2015). On the other hand, some patients with hypermutated immunoglobulin status might be cured with chemo-immunotherapy alone (Fischer et al., 2015). Highly effective targeted agents are now being evaluated and introduced into clinical practice (Byrd et al., 2014) (Byrd et al., 2015) (Furman et al., 2014) (Hillmen et al., 2015) (Goede et al., 2014) and there is considerable interest to try to stratify CLL patients according to their molecular signature (Rossi et al., 2013) (Stilgenbauer et al., 2014) (Baliakas et al., 2014) (Stilgenbauer et al., 2015) (Guieu et al., 2015) (Ljungstrom et al., 2015). Currently, only fluorescent-in-situ hybridization (FISH) of del17p is used to make treatment decisions. We will discuss the clinical significance of TP53 mutation analysis (Rossi et al., 2014) (Zenz et al., 2010) and the potential clinical and health-economic value of additional molecular testing in CLL. The second part of the talk will focus on whole genome analysis of CLL. We will review recently published (Schuh et al., 2012) (D. A. Landau et al., 2015) (D. a. Landau et al., 2013) (Puente et al., 2011) (Quesada et al., 2011) and unpublished data on the genomic landscape of CLL revealing fascinating insights into CLL pathogenesis and the potential significance of mutations in the non-coding regions of the genome (Puente et al., n.d.).

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Abstract Category: BSH Presidential Session
Abstract No. 27
Abstract Title: The Unexplained Evolution of the Megakaryocyte/Platelet Lineage
Full Name: Jack Levin, M.D.
Institution/Company: Univ. of California School of Medicine, San Francisco, CA USA

Abstract Details: The mammalian platelet is derived from the cytoplasm of megakaryocytes, the only polyploid hematopoietic cell. Polyploid megakaryocytes and their progeny, nonnucleated platelets, are found only in mammals. In all other animal species, cells involved in hemostasis and blood coagulation are nucleated. The nucleated cells primarily involved in nonmammalian, vertebrate hemostasis are designated thrombocytes to distinguish them from nonnucleated platelets. In many invertebrates, only one type of cell circulates in the blood (or hemolymph), and this single type of cell is typically involved in multiple defense mechanisms of the animal, including hemostasis. These cells are capable of aggregating and sealing wounds. This process is probably the earliest cell-based hemostatic function. A comparison of amebocytes (the only type of circulating cell in the hemolymph of the horseshoe crab, Limulus polyphemus) with human platelets provides a basis for understanding the many nonhemostatic functions of platelets. Platelets appear to possess many of the multiple capabilities that characterize “primitive” circulating amebocytes, whose functions include hemostasis. For example, platelets possess rudimentary bactericidal and phagocytic activity. They have been shown to interact with bacteria, endotoxins, viruses, parasites, and fungi. Platelets are not only important for the maintenance of hemostasis but are also inflammatory cells. Despite these overall similarities in function, there exists no proof that invertebrate blood cells evolved into platelets. Nonmammalian vertebrates have nucleated, often spindle-shaped thrombocytes, the first cells to evolve that specialize in hemostasis. Thrombocytes are found in fish. There is a central round or elongated nucleus and a rim of cytoplasm. Avian thrombocytes are similar in appearance to fish thrombocytes and are believed to be produced by mononuclear precursors in the bone marrow. Similar to platelets, avian thrombocytes contain serotonin (5-hydroxytryptamine) and release what appears to be beta-thromboglobulin during the release reaction. Serotonin is also present in the thrombocytes of birds and reptiles, but not in fish. The thrombocytes of at least some birds, amphibians, reptiles, and fish have a membrane system referred to as the surface-connected canalicular system (SCCS). This system is also a feature of mammalian platelets and has been linked to their derivation from the cytoplasm of megakaryocytes. The presence of nonnucleated platelets and their polyploid megakaryocyte progenitors in the bone marrow only in mammals suggests that some important feature of mammalian physiology benefits from this unique mechanism for the production of anucleate cells from the cytoplasm of a larger cell, for the apparently major purpose of supporting hemostasis. However, because both monotremes, which are egg-laying mammals, and marsupials, which have a nonplacental pregnancy, possess megakaryocytes and platelets, it is apparent that neither live birth nor the presence of a placenta accounts for the evolution of platelets in mammals. Therefore, the biological advantage gained from the generation of nonnucleated platelets by polyploid megakaryocytes remains unidentified. The evolutionary event or events that resulted in the appearance of mammalian megakaryocytes and platelets remain elusive. Comparative molecular genetic studies are likely to provide further insights.

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Abstract Details: The treatment options and our knowledge of the biology of chronic lymphocytic leukaemia (CLL) are in the midst of momentous and revolutionary change. The modern era began with the observations of the natural history of CLL, and introduction of chlorambucil by Galton, the FAB morphological classification together with Catovsky and others, and the staging systems of Rai and Binet. Therapy was revolutionised with the progressive introduction of immunochemotherapy, and now again recently with the introduction of B-cell receptor signal pathway receptor inhibitors (BCRi), and bcl-2 inhibition. Novel antibodies, particularly oblimersen and novatoclax, have also contributed to significant progress in CLL, especially patients with co-morbidities shown with the CLL11 study. The median age of diagnosis of CLL is $>70$ years, but only recently has the typical elderly patient group been the focus of clinical trials. Drugs that block molecules within the BCR pathway such as Bruton’s tyrosine kinase, particularly ibrutinib, and PI3Kinase, particularly idelalisib have both shown dramatic effectiveness in patients with relapsed and refractory (R/R) CLL. These agents have a characteristic occurrence of a lymphocytosis in a high proportion of patients concurrent with the sometimes dramatic beneficial effects with major reduction in lymphadenopathy and splenomegaly, together with improvement in bone marrow function. These agents appear to function primarily by blocking BCR signalling within the lymph node microenvironment proliferation centre, the principal location for maintenance of CLL cell survival and proliferation. Btk is a member of the Tec-kinase family which also includes Inducible T-cell kinase (ITK) and Tec-kinase and off (Btk) target Tec-kinase inhibition may be responsible for some of the adverse events seen with ibrutinib such as bruising and atrial fibrillation. A number of other inhibitors of Btk are under investigation, particularly ACP-196 and BG-3111 which inhibit Btk more selectively. BCRi’s may cause diarrhoea, and with idelalisib, some develop colitis. The activity of these agents is effective across all CLL adverse risk groups although follow-up is remains relatively short. Several large clinical trials comparing ibrutinib plus rituximab versus the fludarabine, cyclophosphamide, rituximab (FCR) combination are in progress. A proportion of patients develop secondary resistance to Btk inhibition and some have acquired mutations in either Btk or PLCγ2. A number of small molecule inhibitors of other BCR pathway molecules including dual inhibitors are under investigation. The bcl-2 anti-apoptotic protein is over-expressed in CLL and several attempts to block this machinery have been made with oblimersen and novatoclax. Venetoclax (Abt-199) is the only agent in ongoing development in this class but shows extremely promising results. Early problems with tumour lysis syndrome (TLS) appear to have been largely resolved with an incremental dosage schedule over 5 weeks. Clinical trials with this agent in 17p-deleted and R/R CLL are recently reported, and combination trials are beginning. The BCRi and bcl-2 inhibitors are already crucial in the management of R/R CLL, and will no doubt change the way in which we treat CLL over the coming years.
Multiple Myeloma (MM), however a majority of patients continue to relapse and survival improvement has not been forthcoming in high risk disease. Therapeutic approaches targeting high risk disease including long term proteasome inhibitor therapy have provided benefit, albeit incomplete. Significant efforts have therefore been made to better understand the genetic landscape of MM, with more than 1000 MM exomes sequenced. Based on analysis of this data we developed a MM specific 88 gene Mutation Panel (M3P) that includes all of the most commonly mutated genes, actionable drug targets and genes targeted by current standard of care (SOC) therapies and that allows tracking of clonal evolution by measuring tumor clone size at different timepoints, as well as copy number and sample purity estimation. Overall, tumor samples from 504 MM patients have been characterized. Overall coverage per mutation averaged >500x depth. We identified 945 variants (1.9 per patient) and in 83% of the investigated samples a mutation was found. Clonal heterogeneity of sequencing reads suggesting the presence of a significant number of subclones (21% of mutations <10% of the tumor). These subclones change over time in response to therapy in a phenomenon we have termed clonal tides and it can be a minor clone at diagnosis that is ultimately drug resistant and lethal. These data provide a biologic basis for in vitro drug library screening as a tool for therapy selection, particularly in high risk disease.

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Abstract No. 31
Abstract Title: Classifying and Returning Diagnostic, Uncertain and Incidental Genomic Results
Full Name: Dr Gail Jarvik
Institution/Company: Head, Division of Medical Genetics, The Arno G. Motulsky Endowed Chair in Medicine Professor of Genome Sciences, University of Washington Medical Center, Seattle, WA USA

Abstract Details: As we approach genomic medicine there are numerous challenges to overcome. These include the pathogenicity classification of very rare capability for utilisation of next generation sequencing in clinical care we will train with 530 person years of Masters Training the next generation of clinicians and scientists to ensure that NHS capacity to harness Genomic Medicine is the most advanced in the world. An example of how this system is being deployed is our chronic lymphocytic leukaemia pilot where the strength of the UK haematological Oncology Network has been used to investigate across multiple trials drivers to malignancy, response, relapse and outcomes.

Abstract No. 30
Abstract Title: Genome guided therapy in Multiple Myeloma
Full Name: Dr. A. K. Stewart
Institution/Company: Vasek and Anna Maria Polak Professor of Cancer Research, Carlson and Nelson Endowed Director Center for Individualized Medicine, Mayo Clinic, Scottsdale, AZ USA

Abstract Details: Introduction of novel therapeutic agents has dramatically improved survival in Multiple Myeloma (MM), however a majority of patients continue to relapse and survival improvement has not been forthcoming in high risk disease. Therapeutic approaches targeting high risk disease including long term proteasome inhibitor therapy have provided benefit, albeit incomplete. Significant efforts have therefore been made to better understand the genetic landscape of MM, with more than 1000 MM exomes sequenced. Based on analysis of this data we developed a MM specific 88 gene Mutation Panel (M3P) that includes all of the most commonly mutated genes, actionable drug targets and genes targeted by current standard of care (SOC) therapies and that allows tracking of clonal evolution by measuring tumor clone size at different timepoints, as well as copy number and sample purity estimation. Overall, tumor samples from 504 MM patients have been characterized. Overall coverage per mutation averaged >500x depth. We identified 945 variants (1.9 per patient) and in 83% of the investigated samples a mutation was found. Clonal heterogeneity of sequencing reads suggesting the presence of a significant number of subclones (21% of mutations <10% of the tumor). These subclones change over time in response to therapy in a phenomenon we have termed clonal tides and it can be a minor clone at diagnosis that is ultimately drug resistant and lethal. These data provide a biologic basis for in vitro drug library screening as a tool for therapy selection, particularly in high risk disease.
variants, the possibility of incidental (also called additional or secondary) findings that were not expected by the patient or physician, and the important task of communicating both the testing plan and the expected results to patients. Dr. Jarvik will review recent results of the Clinical Sequencing Exploratory Research (CSER) Consortium that address these challenges. The recently published American College of Medical Genetics and Genomics / Association for Molecular Pathology (ACMG/AMP) proposed guidelines (Richards et al 2015, PMID: 25741868) attempt to improve and standardize variant pathogenicity classification. While efforts to centralize variant pathogenicity data, such as ClinVar, are an important resource, many variants will have little data to guide the understanding of pathogenicity. CSER tested the consistency of usage of the ACMG/AMP guidelines across 9 labs and identified important clarifications and suggested improvements (Amendola et al, submitted). These lessons will be reviewed. Dr. Jarvik led an effort to identify the expected rate of incidental findings when ordering a genomic test based in 6500 persons exomes (Amendola et al 2015, PMID:25637381). This work suggests a 1-3% rate of actionable adult onset disease incidental findings for an individual exome or genome test and highlights which gene-disease pairs are most common among incidental findings. Finally, Dr. Jarvik will address patient perspectives and clinical practices in genomic medicine. Return of diagnostic and incidental findings will be address, along with the issue of variants of uncertain significance (VUS; Amendola et al 2015, PMID: 26478737). While the ACMG position of return of incidental findings (Green et al, 2014, PMID:23788249) suggests that a VUS should not be returned in that case, VUS results are common in diagnostic tests. It is important that the patient understand the likelihood that a VUS is pathogenic.

Abstract Category: Training discussion

Abstract No. 32

Abstract Title: The future landscape of medical training and practice in the UK

Full Name: Professor Ian Cumming
Institution/Company: Chief Executive, Health Education England

Abstract Details: Direction Haematology exemplifies the changing world of laboratory and clinical medicine, embracing cutting 21st century technology with sophisticated analytical platforms that deliver rapid, cost effective and high quality diagnostics, enhancing patient care pathways. Modern haematology appears far from the original discipline. With an ever increasing focus on the management of haematological disorders, haematologists can now utilise dual clinical training in medicine and pathology to deliver an increasingly complex service, with subspecialisations including transfusion, coagulation and haemoglobinopathies. Such developments have allowed a holistic, patient-centred approach, whilst delivering world class outcomes in both treatment and research. Workforce: In September 2014, the Health and Social Care Information Centre indicated that there were 768 whole time equivalent Haematology consultants employed in the NHS. In recent years, this number has grown an average of 2% per year, (slower than the average medical specialty), and this increasingly complex service requires the development of more than just the medical field. The scientific laboratory workforce must now acquire skill sets such as bioinformatics and genomics, gained, for example, through ‘Modernising Scientific Careers,’ a programme that provides a clear pathway for clinical scientists through the levels of BSc, MSc, and the recently developed Doctorate, allowing the development of knowledge and skills to consultant level. The introduction of science apprenticeships will also allow bands 2 to 4 staff to develop skills that complement the clinical science workforce and allow individuals a framework to progress to professional clinical scientist training if they wish. Such entry also supports our ‘widening participation’ agenda in this exciting and fast developing workforce. Cancer: Genome-based diagnostics is a rapidly developing field that affects the delivery of haematology services. Cancer treatment is at the forefront of benefiting from this advancement, as genetic tests stand to significantly improve cancer diagnoses and influence treatment decisions, thus curriculums will move to reflect these advancements. As such, HEE will continue to take forward relevant recommendations set out in the Independent Cancer Task Force (CTF) report, which focuses on effective prevention, earlier diagnosis; informed choices and convenient care; access to treatments with minimal side effects, holistic support and quality of life (including end of life). Furthermore, in 2016/17 HEE will scope the development of a pathology workforce to ensure that future training needs and quality management issues are aligned with the NHS strategic vision and cancer plan deliverables. 7DS: One of the ten clinical standards that contribute towards the implementation of 7 day services focuses on access to diagnostics. High quality haematology services are pivotal to this, but these are not without cost. Overall, pathology services cost the NHS an estimated £2.5 billion per annum, of which the single largest element is the workforce. Diagnostic laboratory equipment is also a significant capital investment for the NHS, thus it is imperative that they are run efficiently. NHS laboratories already provide a 7 day service, so with a greater emphasis on the drive to integrate diagnostics into primary care, further improvements to patient care will be achieved.
Abstract Category: BSH Guidelines and Practice Session - The global applicability of BSH guidelines

Abstract No. 33

Abstract Title: British Committee for Standards in Haematology (BCSH) practical guideline for the management of major haemorrhage

Full Name: Beverley Hunt, Prof of Thrombosis & Haemostasis, Kings College London

Institution/Company: Consultant, Guy's & St Thomas' NHS Trust, London, UK

Abstract Details: Of all the guidelines the committee have been involved in producing, this has been the most difficult! Before starting we actively withdrew the previous guidance on the management of massive blood loss, written 10 years previously, because day-to-day practice had changed substantially following the retrospective data from the American military in the Iraq war. This had shown that the upfront use of fresh frozen plasma alongside red cells had reduced mortality when compared to using red cells alone in the initial resuscitation in traumatic massive bleeding (the old guidance essentially advised red cells first and the management of coagulation problems later). The second problem was that the CRASH-2 trial had shown that the use of tranexamic acid reduced mortality in those with traumatic bleeding, but not necessarily massive blood loss, so we wanted to cover any patient with significant bleeding, so we could ensure tranexamic acid reached all those who benefit. After much discussion we changed the title from management of “massive” bleeding to “major” bleeding. We also recognised that Haematologists were not usually involved in the general resuscitation of a bleeding patient: indeed Clinical Haematologists were not usually present in the Emergency Dept or theatre where the patient was, and the Laboratory Haematologist by definition would not be there. However in most hospitals the Haematologists are the policemen for the release of blood products and lead in writing the clinical and laboratory protocols in these areas. We felt we had to offer therefore on concentrating on the use of blood products especially those altering haemostasis. An ongoing problem during the writing of this guideline was that key papers were produced which led to major changes in the final product.

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Abstract No. 34

Abstract Title: DLBCL Controversies and Global Challenges

Full Name: Dr. Sridhar Chaganti

Institution/Company: University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Birmingham, UK

Abstract Details: Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) accounting for 30-40% of all cases. A majority of patients are cured with R-CHOP (Rituximab with Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) chemotherapy. However, a significant minority have primary refractory disease and a further 20-30% relapse after achieving complete remission. Outcome for elderly, frail patients, not suitable for R-CHOP, also remains poor, representing another area of unmet need. Much effort is currently focussed on defining high-risk patients likely to fail R-CHOP and developing alternative treatment strategies for this group. Various clinical and biologic factors have been reported to predict inferior outcomes in R-CHOP treated patients. The revised international prognostic index (R-IPI) uses clinical parameters to identify a poor-risk group where the chance of cure with R-CHOP is only about 50% (1). Dose intensive chemotherapy regimens and/or upfront high dose therapy have been used to improve survival in this group (2,3,4,5), but currently there is no consensus on the optimum approach. Disease bulk is another clinical feature predicting for worse outcome (6). Though previous studies have reported improved survival with addition of radiotherapy consolidation to initial sites of bulk (7,8), it remains unknown if it adds any further benefit for patients achieving a complete metabolic remission following a course of R-CHOP. Gene expression profiling (GEP) has also been used to risk stratify patients, with DLBCL arising from activated B cells (ABC-type) reportedly carrying a worse prognosis compared to those from germinal centre B cells (GCB-type) (9). As a surrogate for GEP, several immunohistochemistry (IHC) algorithms have been developed to ascertain cell of origin (10, 11, 12), but their prognostic significance in R-CHOP treated patients has been variable (13). Thus, the clinical relevance of determining cell of origin remains uncertain at present. Rearrangements of the MYC gene with or without BCL-2 and/or BCL-6 gene rearrangements are seen in 5-10% of DLBCL and are known to confer adverse prognosis (14,15). Over expression of MYC and BCL-2 protein on IHC is a much more frequent occurrence and also affects outcome though to a lesser extent than the corresponding gene rearrangements (16,17,18). Whilst testing for MYC rearrangements helps risk stratify
patients, much controversy surrounds the best therapeutic approach in this setting. In recent years, positron emission tomography (PET) scan has emerged as a valuable tool for imaging DLBCL. PET scan is superior to conventional computed tomography (CT) scan for staging, particularly in delineating extranodal disease and has promising efficacy in identifying bone marrow involvement (19), though it remains unclear if it can replace a staging bone marrow biopsy altogether. Interim PET scan, during R-CHOP chemotherapy, has also been evaluated as a predictor for risk of progression (19), but results have been variable and its use outside of a clinical trial remains controversial. The challenge for the future is to be able to better define the high-risk patient and develop alternative treatment strategies. Rapid advances are being made in our understanding of disease biology and mutational landscape in DLBCL which may lead to incorporation of promising novel non-chemotherapy based approaches.

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groups of patients while clinicians are often required to take decisions affecting individual patients. Therefore, it is up to the clinician applying the guideline to determine how similar a particular patient is to those in the research population. To enable the clinician do this, guidelines should provide an accurate description of the population on which they are based. There is a paucity of appropriately designed clinical guidelines in many low income countries (LICs) and where these are available they are not regularly revised. As a result, clinicians in LICs depend on guidelines developed in more affluent countries. In haematology, guidelines developed by the BSH are possible options, though it is not known how widely they are used in LICs. Unfortunately, most guidelines (including BSH guidelines) are based on research evidence from the Western world (Europe and America) and occasionally from Asia. Also, the search criteria often exclude publications not written in English. Thus, if there is research evidence published for example in French (widely spoken in many LICs) it would not be considered. Similarly, BSH guidelines are primarily designed with the British patient or/and resident in mind and designed by experts drawn more often than not from a pool of UK based consultants. Since there are marked differences in socio-demographic, cultural, economic and possibly genetic factors between the population of Western countries and those of LICs. It is unlikely that the population from which evidence for any BSH guideline is based and for which it was designed would bear any similarity to the population found in most LICs. The feasibility of implementing the guideline is another important factor; for example financial barriers may limit implementation due to additional costs of procuring relevant equipment or for further training. So while clinicians in many LICs may use the BSH guidelines due to the absence of well-designed locally applicable alternatives; it is not clear if the BSH wants or intends for these guidelines to be used outside Britain. However, if they do, there is the need for BSH to involve local experts from LICs in guideline development and also include as a minimum suggestions on how BSH guidelines can be adopted to local situations in under-resourced countries.

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Abstract Category: Acute Lymphoblastic Leukaemia

Abstract No. 36

Abstract Title: BCR-ABL1 like acute lymphoblastic leukemia (ALL) in adults, insights and potential therapeutic targets

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Abstract Details: Overall survival of adults with ALL has improved over the last 20 years and is around 40% after 5 year follow-up1. In contrast, in children the overall survival after 5 years is above 90%2. Current risk groups in adult ALL are based mainly upon cytogenetic abnormalities3. However, approximately 25% is not classifiable. New genetic insights in ALL showed the prognostic value of e.g.ikaros deletion (IKZF1-/-), CRLF2 overexpression, and also BCR-ABL1-like signature. Monique den Boer (the Netherlands) and also St. Jude Children’s Research Hospital, identified the BCR-ABL1-like or Philadelphia-like ALL subtype45. BCR-ABL1-like ALL got its name because it has a gene expression profile similar to BCR-ABL-positive ALL. The resulting oncogenic protein drives cancer proliferation and survival through aberrant tyrosine kinase signaling. This oncprotein can be targeted with tyrosine kinase inhibitors (TKI), providing a treatment option combined with chemotherapy for this specific subgroup of patients. BCR-ABL1-like ALL lacks the characteristic BCR-ABL fusion that defines BCR-ABL positive ALL. Strikingly, BCR-ABL1-like ALL was also an independent adverse prognostic factor and prognosis seems as bad as in BCR-ABL positive patients. Recently, extensive molecular analyses of patients with BCR-ABL1-like ALL uncovered rearrangements or sequence mutations deregulating tyrosine kinase signalling suggesting TKI as a potential treatment option for patients within this ALL subgroup. In 15% of all BCR-ABL1-like patients a tyrosine kinase fusion was found; In 10% of these patients PDGFRb, CSF1 or ABL fusions were detected, susceptible to imatinib and dasatinib. While in 5% of the BCR-ABL1 like patients, JAK2 fusions were found. Several cases have been described with an EBF1-PDGFRb fusion protein and these cases showed in vitro and in vivo sensitivity to imatinib and dasatinib. Moreover, JAK2 fusions might be sensitive to JAK2 inhibitors, like ruxolitinib, although the in vivo evidence is scarce and mainly seen in vitro or ex vivo. In conclusion, a new high risk group has been identified in children as well as in adults. Extensive
evaluation of the genome, detected tyrosine kinase fusions and therefore targeted treatment might be an option in this subgroup with a bad prognosis.

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5. Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A trial work has focused on patients with relapsed or refractory T-ALL. Much of the clinical work has focussed on B-precursor ALL. CD38 is a potential target, which may expand therapeutic options for patients with T-ALL. Much of the clinical trial work has focused on patients with relapsed or resistant B-precursor ALL where the extremely poor long-term outcome is well described and the only known curative approach is allogeneic haematopoietic stem cell transplant (alloHCT). A pre-requisite for alloHCT is the achievement of complete remission (CR). Novel approaches such as the CD19/CD3 T cell engaging “bispecific” antibody blinatumomab, the CD22-targeted inotuzumab (antibody coupled to the DNA-binding, anti-tumor antibiotic calicheamicin) and CD19-targeted chimeric antigen receptor T cells have all demonstrated, in single arm studies, higher rates of CR in patients in whom conventional chemotherapy approaches would be predicted as most likely to fail; patients with primary refractory disease, very early relapse and even relapses following alloHCT. To date, although randomised controlled trials (RCT) in relapsed ALL with both blinatumomab and inotuzumab have been completed, the data are neither fully analysed nor published. There are two notable features of immunotherapeutic approaches to date, which indicate their promise in treating relapsed ALL. First, their relative lack of ‘conventional’ chemotherapy-related toxicities can make them more widely applicable than standard intensive re-induction chemotherapy regimens. Second, is their propensity to obliterate minimal residual disease (MRD) in responders, which is of particular interest, although long-term survival data in these MRD-negative situations are lacking. As a counterbalance, the cost is vastly more than that of standard of care. The overall place of most of these novel agents in the therapy of de-novo ALL is completely unknown but is now beginning to be investigated. The immunotherapeutic approach with the most data in de-novo ALL is the antiCD20 antibody, rituximab, which has been studied in combination with chemotherapy and compared to standard of care in RCT. The talk will explore the preliminary and published data on novel therapeutic approaches in Ph neg ALL, discuss on-going trials and highlight the possibilities and pitfalls of exploring these agents in de-novo Ph neg ALL.

Abstract No. 37

Abstract Title: Relapsed ALL

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Abstract Details: The previous 5 years have seen an almost unprecedented era of therapeutic exploration of non-chemotherapy agent for the treatment of Philadelphia chromosome-negative (Ph neg) acute lymphoblastic leukaemia (ALL). All of the novel approaches include an immunotherapeutic component, targeted to molecules displayed on the surface of the leukaemia blast population. CD19, CD22 and CD20 have been the major targets to date, so the majority of the work has focussed on B-precursor ALL. CD38 is also a potential target, which may expand therapeutic options for patients with T-ALL. Much of the clinical trial work has focused on patients with relapsed or resistant B-precursor ALL where the extremely poor long-term outcome is well described and the only known curative approach is allogeneic haematopoietic stem cell transplant (alloHCT). A pre-requisite for alloHCT is the achievement of complete remission (CR). Novel approaches such as the CD19/CD3 T cell engaging “bispecific” antibody blinatumomab, the CD22-targeted inotuzumab (antibody coupled to the DNA-binding, anti-tumor antibiotic calicheamicin) and CD19-targeted chimeric antigen receptor T cells have all demonstrated, in single arm studies, higher rates of CR in patients in whom conventional chemotherapy approaches would be predicted as most likely to fail; patients with primary refractory disease, very early relapse and even relapses following alloHCT. To date, although randomised controlled trials (RCT) in relapsed ALL with both blinatumomab and inotuzumab have been completed, the data are neither fully analysed nor published. There are two notable features of immunotherapeutic approaches to date, which indicate their promise in treating relapsed ALL. First, their relative lack of ‘conventional’ chemotherapy-related toxicities can make them more widely applicable than standard intensive re-induction chemotherapy regimens. Second, is their propensity to obliterate minimal residual disease (MRD) in responders, which is of particular interest, although long-term survival data in these MRD-negative situations are lacking. As a counterbalance, the cost is vastly more than that of standard of care. The overall place of most of these novel agents in the therapy of de-novo ALL is completely unknown but is now beginning to be investigated. The immunotherapeutic approach with the most data in de-novo ALL is the antiCD20 antibody, rituximab, which has been studied in combination with chemotherapy and compared to standard of care in RCT. The talk will explore the preliminary and published data on novel therapeutic approaches in Ph neg ALL, discuss on-going trials and highlight the possibilities and pitfalls of exploring these agents in de-novo Ph neg ALL.

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Abstract No. 38

Abstract Title: The present role of ICSH in Standardisation and International Guideline activities

Full Name: Samuel J. Machin

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Abstract Details: The International Committee for Standardisation in Haematology (ICSH) was initially formed in 1963 as a Standardising committee with international membership to produce evidence based laboratory guidelines and international primary and secondary working standards. The ICSH is a not-for-profit organisation, mainly funded by unrestricted educational grants from commercial companies in the field of laboratory haematology. The activities and publications of ICSH are all available free of charge via www.icsh.org. All guidelines and recommendations are published in prime review journals (usually IJLH or Cytometry), which are available free of charge internationally for at least 5 years after publication. These documents are all suitable for laboratories in the developing world. In 1994 ICSH first published guidelines for the evaluation of blood cell analysers. This included notes on differential leucocyte and reticulocyte counting and cell marker applications. Over the last 20yrs or so, technology in instrumentation has progressed considerably with now at least 10 different manufacturers having developed their state of the art automated counters presenting a wide range of novel features with new parameters which should present the end-user with exciting challenges in their laboratory testing schedules. The 2014 (Briggs et al. IJLH 36,613-627) guideline was published primarily to allow independent laboratories to evaluate internally the performance, advantages and limitations of any individual instrument for all the parameters, which are available. Other related guidelines/recommendations have also been published over the last few years. These included a reference flow cytometric method based on the RBC/platelet ratio. The previous reference method still relied on the manual phase contrast microscope chamber count with its high imprecision in the order of 10-25%. Then a technical report on a new reference material for haemoglobin bincyanide for use in standardisation of blood haemoglobin measurements. In conjunction with a commercial partner, a new haemoglobin standard became available for calibration using this material on all haemoglobinometers and automated counters throughout the world. The leucocyte differential on automated counters has always relied on comparison with the CLSI 2×200 cell manual differential. Different analysers assess nucleated red cell (NRBC) counts and immature granulocytes now by sophisticated counting techniques, where as previously these were only indicated by an abnormal cell flag. Preparatory work has been undertaken on developing a panel of monoclonal antibodies for producing an immunophenotypic leucocyte differential reference method. This should allow manufacturers and users to assess their morphological classification of different cell types and improve the true/false positive/negative flagging on any automated system. Verification and performance of all cell counters for analysis of body fluids has also been assessed. Further work is still required on several aspects of the white cell, red cell and platelet parameters. These include standardisation of MPV (mean platelet volume) and immature platelet fractions, reticulocyte fractions and red cell inclusion bodies and identification/quantitation of blast cells and differentiation of atypical viral lymphocytes during various stages of infection. The performance assessment of sample mode, precision, within run precision, carry over, linearity, sample stability, accuracy and comparability all need to be constantly considered today. ICSH is determined to remain focussed on the assessment and development of new automated blood cell counters and works with all manufacturers and an international panel of clinical/scientific assessors to produce regular, meaningful, modern advice. Comments and updates on work in progress/future meetings may be obtained from the administrator at admin@icsh.org.

Abstract No. 39

Abstract Title: Epidemiology, Diagnosis and Prevention of Thalassaemias in Hong Kong and Mainland China

Full Name: Professor Jason So

Institution/Company: Clinical Associate Professor, Department of Pathology, Faculty of Medicine, University of Hong Kong

Abstract Details: The prevalence of thalassaemias is very high in China, which is estimated at 3.6%, or 4.6 million of the 1.3 billion national population. The distribution, however, is very heterogeneous within this vast country. Most carriers are found in the southern provinces where malaria was once endemic, and in the north western provinces along the Silk Road where thalassaemia mutations were introduced from the Middle East and Mediterranean region. With such a large number of carriers, the disease burden is considerable. An estimate of 20,000
thalassaemia major patients will be born annually. The accessibility to red cell transfusion, iron chelation therapy and haemopoietic stem cell transplantation is very variable. Significant morbidity and mortality is still observed. Therefore, disease prevention is of utmost importance to reduce the adverse impact at a personal, family and society level. Large scale prevention programmes incorporating carrier screening, genetic counselling and prenatal diagnosis are in place in the southern provinces where severe thalassaemias are most prevalent. Carrier screening is performed in the antenatal setting, with a very good uptake rate in large cities. Therapeutic termination of a severely affected pregnancy is culturally acceptable and is legal before the end of second trimester. Preimplantation genetic diagnosis is an alternative option but it is not widely available. Late booking, incomplete family study, difficulty in phenotype prediction (e.g. Hb E-beta thalassaemia) and changing parental expectations are the challenges facing health care providers. Better public education is essential to achieve a better control of thalassaemias. Carriers of severe thalassaemia mutations are effectively screened using a low red blood cell mean corpuscular volume (MCV) as a screening parameter. Accurate determination of MCV is therefore crucial. With modern blood cell analysers and a good internal quality control programme this is achievable. A phenotypic diagnosis can then be made using relatively simple methods such as supravital staining to detect Hb H inclusions for diagnosis of alpha thalassaemia and Hb A2 quantitation for diagnosis of beta thalassaemia. Genetic analysis is indicated when the phenotype is atypical and when prenatal/preimplantation diagnosis is contemplated. When the prevalent types of globin gene mutation in the local population are known, targeted genotyping using routine diagnostic techniques is able to characterise the mutations efficiently. Although the current screening and diagnostic algorithm for thalassaemias generally performs well, it is not without its limitations. False negativity may be encountered during phenotypic or genotypic testing, which can arise from the nature of the underlying globin gene mutations or from an interaction of co-existing globin and non-globin defects. A good understanding of the pathophysiology of thalassaemias and the principles of the tests employed for their detection are required to appreciate the potential diagnostic pitfalls. Test standardisation, application of appropriate special tests, development of new and better tests, external quality assessment and laboratory accreditation are ways to further improve our diagnostic service.

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Abstract No. 40

Abstract Title: Past Present and Future of Quality in Haemostasis Testing

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Abstract Details: Many tests performed in Coagulation laboratories have a direct impact on patient management and inaccurate results in relation to familial and acquired bleeding and thrombotic disorders could have very serious consequences for patients. Accurate and reliable results are needed when testing is performed in relation to possible familial haemostatic disorders where laboratory error may lead to misdiagnosis. Proficiency testing (PT) or External Quality Assessment (EQA) in clinical laboratories is an integral part of quality management systems used to ensure that laboratory test results are safe for patient management purposes. After it was realised that divergent results could be obtained when the same specimen was analysed in different laboratories there was a small regional distributions of samples amongst 10 -15 centres in the Philadelphia region of USA in 1945. The College of American pathologists was formed the following year and early projects included national PT surveys. These early days were reviewed by one of the main protagonists (Sunderman 1992). The results of the first 2 surveys in the 1940s were described as “exceptionally disquieting” and were never released. Over the years it has been increasingly recognised that unsatisfactory laboratory work can and will occur and that regular EQA is a fundamental part of the process of a suitable quality management system in all areas of clinical laboratory. The pre analytical, analytical and post analytical phases of testing are all of great importance. Assessment of analytical quality should include participation in independent external quality assessment programmes. For a laboratory testing to reach the quality required for accreditation against ISO standards it is a requirement that the laboratory participates in an appropriate inter-laboratory comparison programme appropriate(ISO 15189 2012). The ISO 15189 standard requires that the programme chosen by the laboratory should provide clinically relevant challenges that mimic patient samples and have the effect of checking the entire examination process, including pre-examination and post-examination procedures, where possible. EQA programmes have focussed on the analytical component but studies and articles always show that more errors occur in the pre-analytic phase than any other. EQA programmes are encouraged by ISO to address the pre-analytic phase. This can be done in a number of ways and in future this will increasingly be included in EQA repertoires (ISO 17043). One approach is to
use questionnaires about practice with feedback on how an individual centre compares to other centres. Another option could be use of EQA materials that contain interfering substance such as haemoglobin. The third option is to record error rates supplied by participants which can be compared to quality standards. All of these will likely increase in future. Perhaps the most important component of laboratory testing is the post-analytical interpretation since it is the way that results are interpreted that impacts most on patient management. Some post analytical EQA is already undertaken for example in relation to D-dimer to exclude possible VTE in the UK NEQAS Point of Care D-dimer programme where participants their local EQA result along with a clinical scenario and pre test probability score to decide whether VTE can be excluded or not. Their interpretation is then assessed. In future EQA programmes will have to address the post analytical phase more in this way.

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Abstract Details:
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Abstract Title: DOAC in clinical practice real world audit data
Full Name: Sarah Bond
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Abstract Details: The Anticoagulant Service at GWH currently provides counselling and dose adjustment of all patients commencing vitamin K antagonists (VKAs), discharge planning for inpatients and a telephone advice line for patients and all healthcare professionals. In June 2012 we adopted the UK NICE-TA for dabigatran and rivaroxaban for treatment of non-valvular AF in stroke prevention (SPAF) and in September 2013 apixaban was included. Agreement was made with the local commissioners to continue to counsel patients commenced on the Direct oral anticoagulants (DOACs). Continuing care is undertaken by the GP including annual renal function checks. Use of a decision aid ensured suitability of any proposed anticoagulant including checking for contra-indications, specialist groups where advice is required before prescribing and risk factors for bleeding (HAS-BLED) and a proforma was developed for monitoring these patients. Patients are reviewed at 3 months and annually thereafter to check for any problems including bleeding, deteriorating renal function, episodes of dyspepsia or any other adverse event. Data is also collated for patients on a DOAC for treatment of venous thromboembolism. Result data that has been updated to March 2016 will be presented and will include the number and type of all adverse events experienced by patients on a DOAC. Example data from June 2015 is shown below: Results (June 2015) 422 patients receiving a DOAC for AF (10.5% of our total anticoagulant population) 66 on dabigatran of which 63 have had at least 1 review with 17 (27%) having an adverse event (2 major bleeds). 203 on rivaroxaban of which 179 have had a review with 25 (14%) having an adverse event (2 major). 153 on apixaban of which 131 have had a review with 3 (2.2%) having an adverse event (1 major). Conclusions: In our patients’ experience the DOACs appear to be well tolerated. All adverse events ranged from 2.2% - 27% but serious adverse events are low and similar ranging from 0.6 – 1.6%. Previous local adverse event data for patients receiving VKAs showed there was a 6% chance of an adverse event with a 1% risk of a major/fatal bleed and a 3% risk of a minor bleed. No patient has had an embolic event. Benefits of this scheme will be discussed.
a two-year period of follow-up. Consistent with the findings of two other trials comparing 3 months to 12 months of anticoagulation after a first episode of unprovoked DVT or PE (4,5), the main implication of the PADIS-PE trial is that, more than ever, only two treatment options are warranted in patients with unprovoked VTE who should be treated for either a short duration (3 or 6) months or indefinitely. One of the interpretations of this randomized trial is that the majority of patients with a first unprovoked VTE should remain indefinitely on anticoagulant therapy. However, prolonged use of warfarin with a target International Normalized Ratio (INR) ranged from 2 to 3, the reference treatment for indefinite anticoagulation, is associated with a significant risk of bleeding. Thus, some evidence suggests that reduced dose of direct oral anticoagulant therapy (DOAC) was superior to placebo without any major concern regarding safety and was possibly as effective as, and safer than, full dose of DOAC (6). However, direct comparison of reduced dose of DOAC with full dose of warfarin (INR 2-3), the reference treatment for unprovoked VTE, has not been performed yet. The second interpretation is based on the observation that only one-third of patients with unprovoked VTE will really benefit from indefinite anticoagulation; identifying the remaining two-third patients with a lower risk of recurrences who do not need extended anticoagulation is therefore a major objective. If the use of D-dimer alone was not found enough discriminant in order to identify low or high risk patients (7), conversely, promising scores, including D-dimer in combination with clinical variables, have been derived; however prospective validation is still needed (8).

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Abstract No. 43

Abstract Title: Hospital Acquired v Community Acquired VTE: comparison of risk factors and 5 years follow up

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2University of Plymouth, UK research fellow in statistics

Abstract Details: This was a retrospective review of all Venous thromboembolism (VTE) events diagnosed within a large teaching hospital in 2010. Subsequently, the patients were followed up for five years to the end of 2015 reviewing VTE recurrence and all-cause mortality. Thrombotic events for hospital acquired thrombosis (HAT) are compared with community acquired thrombosis (CAT) in this study. A further smaller VTE group of incidental-finding thrombosis (IFT) was identified later in the study, predominantly comprising patients with active cancer being scanned for staging or response. These were included after reviewing patient information systems retrospectively. Radiology data was used to identify positive VTE events and these were crosschecked with the patient information system to identify whether criteria for HAT were met. The groups were carefully matched to identify difference in VTE type, risk factors (using the national VTE risk assessment tool) and demographic information. The 2010 study cohort consisted of 703 patients, of which 486 were CAT events (251 Deep Vein Thrombosis [DVT] and 235 Pulmonary Embolism [PE]). 217 were HAT events (84 DVT & 133 PE) demonstrating a significant relative association of PE with HAT (x^2 8.57: p = 0.001). Analysis of risk factors and demographic information were compared for all HAT with all CAT events, looking for significant differences using a multiple logistic regression model, calculating odds ratio with 95% confidence intervals (CI). Regarding risk factors, age > 60 years, and mean age, was significantly associated with HAT over CAT events (OR 2.625, 95%CI 1.754-3.937, p < 0.001) whilst family or personal VTE history and obesity were more associated with CAT events (p=0.001 & p=0.001 respectively). In addition active cancer was significantly associated with HAT events (p=0.008) whilst a significant medical history and sex do not differ
between diagnosis source. These patients were followed up for 5 years to review mortality rates and VTE recurrence with IFT findings also included. Overall mortality was 39% (274/703) whilst both HAT, 98/194, 51% and IFT 63/77, 82% were significantly greater than that for CAT 113/364, 31% (p=0.001) as might have been expected. Using Kaplan-Meier survival curves CAT patients had significantly higher 5-year survival. In addition, mortality rates were highest within the first 12 months after diagnosis with 59% of all deaths occurring within this period. Overall there were 69 recurrent VTE events, the majority (56) being previous CAT events with 75% (52/69) of recurrent VTE events occurring at the same site as the initial event. The crude incidence rate was 1.56 per 1000 patient years (95% CI 1.45-1.68) for all events. This compares with findings from Silverstein et al (1998) of 1.17 from a 25 year retrospective review and from Heit (2008) showing 1.14 for community VTE rates. The total CAT rate of 31% compares to that seen in the Riet registry at 29% (Monreal & Trujillo-Santos, 2009) with a crude incidence rate of 2.09 per 1000 patient admissions (95% CI 1.81-2.37) for the HAT group. Findings from Roberts et al (2011) demonstrated a rate of 1.26 per 1000 admissions though there are differences in the age of populations served, being lower within London compared to the hospital geographical area (Office of National Statistics, 2011) with advanced age being the most significant factor associated with VTE (Cushman et al., 2004). This study provides evidence that VTE risk factors for CAT were different to HAT. All-cause mortality is higher for HAT events, in common with other studies. The site of VTE recurrence is frequently the same as previously and the majority of VTE are community events.

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Abstract No. 44

Abstract Title: Limited vs whole-leg assessment of the deep venous system in outpatients with suspected deep vein thrombosis: the PALLADIO study

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Institution/Company: Short Medical Stay Unity and Thrombosis Center, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy

Abstract Details: Compression ultrasonography (CUS) represents the mainstay for the diagnosis of deep vein thrombosis (DVT). Two different approaches have been validated: limited-CUS and whole-leg CUS. With the former strategy, only the proximal veins are explored, whereas with the latter strategy the entire venous system, including the below-knee veins, is explored. When directly compared in two clinical trials, the diagnostic accuracy of the two strategies was shown to be equivalent and both approaches are currently recommended by international guidelines. The use of either one approach in real-world clinical practice varies from center to center, and from country to country. Limited-CUS is faster, readily available in the emergency setting, and has a better reproducibility. However, when initially negative this approach requires repeat testing after 5 to 7 days, or the negative results of additional tests such as pre-test clinical probability (PTP) or D-Dimer (DD) to safely rule out DVT. Whole-leg CUS can be conclusive after a single evaluation, but requires experienced operators and advanced scanners. Furthermore, the routine investigation of the below-knee veins often leads to the detection of low risk isolated DVT, thus exposing patients to often unnecessary anticoagulation. In the PALLADIO study, we aimed to assess the accuracy of an algorithm combining extended and limited CUS. PALLADIO was a multicenter, prospective cohort study enrolling consecutive outpatients with clinically suspected DVT. All patients underwent DVT measurement and pre-test clinical probability (PTP) assessment. DVT was ruled out with no further testing in patients with PTP unlikely and negative DD (group 1). Patients with PTP likely or positive DD underwent limited CUS only (group 2), patients with PTP likely and positive DD underwent extended CUS (group 3). Patients in group 1 and patients with a negative CUS underwent a 3-month follow-up. The primary outcome was the incidence of objectively documented DVT or pulmonary embolism (PE) in patients in whom DVT was ruled out. A sample of 1100 patients was calculated on the assumption that the primary outcome would not exceed 1%, and the upper limit of the 95% confidence intervals (CI) would not exceed 2%. Of 1162 recruited patients, 351 were in group 1, 401 in group 2, and 410 in group 3. In the whole group, the median age was 66 years, and 60% of patients were females. Limited-CUS was positive in 12 patients (3%) in group 2;
extended CUS was positive in 200 patients (48%) in group 3; 38% of diagnosed DVT were isolated distal DVT. The three-month incidence of VTE in untreated patients after a negative diagnostic strategy was 0.87% (95% CI, 0.44-1.70). We concluded that by combining the two diagnostic strategies in a single algorithm, we were able to simplify the diagnostic approach to patients with suspected DVT. Using the PALLADIO algorithm, DVT can be safely ruled-out without the need for repeat CUS and only selected, higher risk patients require whole-leg CUS. This approach is likely to reduce the overdiagnosis of low risk isolated distal DVT.

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Abstract Category: Transfusion (Science)

Abstract No. 45

Abstract Title: The clinical impact of RBC storage age: findings from clinical trials

Full Name: Dean Fergusson
Institution/Company: Senior Scientist & Director, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Centre for Practice-Changing Research, Ottawa, Ontario, Canada

Abstract Details: Transfusion of red blood cells is one of the most common medical interventions administered in hospitalized patients. In North America, donated red blood cells can be stored for up to 42 days. It has been suggested that prolonged storage of red blood cells may explain adverse consequences associated with transfusion. Until recently, the clinical impact of prolonged red blood cell storage has not been firmly established. Reported adverse consequences of prolonged storage have been attributed to the generation of cytokines in the storage medium. Changes to red cell membranes that alter deformability of red cells and an inability to scavenge nitric oxide and biochemical changes such as decreased levels of 2,3 DPG, may be even more important than the generation of cytokines as they impair the ability of red cells to deliver oxygen to meet tissue needs. In vulnerable patients such as the critically ill, transfusing older red blood cells may result in higher rates of organ dysfunction and morbidity because of the deleterious oxygen deficits, or the pro-inflammatory effects of bioactive materials that accumulate during red cell storage. Laboratory evidence, including animal studies, supports the hypothesis that prolonged storage may be deleterious. In terms of human studies, a number of observational studies suggest that prolonged storage affects clinical outcomes such as mortality and risk of infection. A systematic review of observational studies found that the transfusion of older red-cell units was associated with a 16 percent increase in mortality. Yet, observational studies assessing the association of storage age have major shortcomings such as the ability to account for multiple transfusions of varying storage ages and confounding by indication whereby sicker patients receive more transfusions. Properly conceived and conducted, large clinical trials overcome these limitations by their ability to randomize patients to distinct red cell storage age interventions (e.g. “fresh” vs “older”) and achieve a balance of known and unknown confounders between groups. Recently, large randomized clinical trials addressing storage age have been published. Two trials conducted in the neonatal (ARIPI) and adult (ABLE) intensive care populations compared red blood cells stored for 7 days or less to standard issue. The RECESS trial in cardiac surgery patients compared red blood cells stored for 10 days or less to those stored for 21 days or more. The ARIPI, ABLE, & RECESS trials all suggest no benefit of “fresh” red cells compared to either standard issue or “older” red blood cells in terms of major morbidities and mortality. Additional large trials conducted in all hospitalized patients, critical care, and cardiac surgery, are nearing completion. Current evidence suggests that transfusion of fresh red blood cells does not improve clinical outcomes, therefore changes to current storage time practice policy is unwarranted. Results to date also suggest that the demonstrated changes to red cells or the storage medium documented in numerous laboratory studies have limited clinical impact.
Various cell types of the human body. More recently, cell lines and ability to differentiation into all the their unlimited capacity for replication (they form stem cells (hESC) as a starting material because of consortium focussed initially on human embryonic manufacture of multiple units. The work of the Novosang able to act as the starting material for large scale man- tion capacity and it seems unlikely that they would be HSPC for this purpose however is their limited replica- cytes in the UK. One of the challenges of utilising study of adult and cord blood HSPC derived reticulo- Transplant are about to initiate a larger clinical successful recovery and survival of HSPC-derived reticulocytes. A study has been reported from the French group demonstrating robust reticulocytes can be produced. A study has known that erythroid cells can be differentiated from haematopoietic stem and progenitor cells (HSPC) in colony assays and that in two phase culture systems robust reticulocytes can be produced. A study has been reported from the French group demonstrating successful recovery and survival of HSPC-derived reticulocytes in a single volunteer and NHS Blood and Transplant are about to initiate a larger clinical study of adult and cord blood HSPC derived reticulo- cytes in the UK. One of the challenges of utilising HSPC for this purpose however is their limited replication capacity and it seems unlikely that they would be able to act as the starting material for large scale manufacture of multiple units. The work of the Novosang consortium focussed initially on human embryonic stem cells (hESC) as a starting material because of their unlimited capacity for replication (they form cell lines) and ability to differentiation into all the various cell types of the human body. More recently, attention has shifted to human induced pluripotent stem cells (hiPSC), which can be derived from adult fibroblasts or peripheral blood cells and have similar properties to hESC. However with both of these cell types there are significant challenges relating to the length and complexity of the cell differentiation process, the cost of manufacture and the production of unstable reticulocytes. This has lead the team to focus on the development of erythroid cell lines which combine the replication capacity of pluripotent stem cells lines with the relative simplicity of the differ- entiation process of a HSPC and which can produce stable reticulocytes. Many challenges remain particularly in the complex task of translation of these kinds of cellular therapies. The characterisation and stability of the starting cell line, analytic and process control over the differentiation process, detailed characterisation and preclinical assessment of the final product all represent significant barriers to successful GMP manufacture for first in man recovery and survival studies. Longer term challenges include scale up manufacture and control over the cost of goods which are essential issues to address if these kinds of technologies are going to make it to routine clinical application.

Abstract No. 46

Abstract Title: Progress on the development of cultured red cells
Full Name: Professor Marc Turner
Institution/Company: Medical Director, Scottish NBTS
HeadQuarters, Edinburgh, Scotland, UK

Abstract Details: Despite significant advances in the sufficiency, quality and safety of blood supplies in developed economies over the past few decades, substantial problems persist on a global basis in respect of the lack of appropriate donor infrastructure and the impact of globalisation on the spread of new, emergent and existing transfusion transmissible infectious diseases. In addition there are significant challenges in the provision of red cell concentrates to some groups of patients such as those with thalassaemia and sickle cell disease in terms of chronic iron loading and alloimmunisation. It has long been known that erythroid cells can be differentiated from haematopoietic stem and progenitor cells (HSPC) in colony assays and that in two phase culture systems robust reticulocytes can be produced. A study has been reported from the French group demonstrating successful recovery and survival of HSPC-derived reticulocytes in a single volunteer and NHS Blood and Transplant are about to initiate a larger clinical study of adult and cord blood HSPC derived reticulo- cytes in the UK. One of the challenges of utilising HSPC for this purpose however is their limited replication capacity and it seems unlikely that they would be able to act as the starting material for large scale manufacture of multiple units. The work of the Novosang consortium focussed initially on human embryonic stem cells (hESC) as a starting material because of their unlimited capacity for replication (they form cell lines) and ability to differentiation into all the various cell types of the human body. More recently, attention has shifted to human induced pluripotent stem cells (hiPSC), which can be derived from adult fibroblasts or peripheral blood cells and have similar properties to hESC. However with both of these cell types there are significant challenges relating to the length and complexity of the cell differentiation process, the cost of manufacture and the production of unstable reticulocytes. This has lead the team to focus on the development of erythroid cell lines which combine the replication capacity of pluripotent stem cells lines with the relative simplicity of the differ- entiation process of a HSPC and which can produce stable reticulocytes. Many challenges remain particularly in the complex task of translation of these kinds of cellular therapies. The characterisation and stability of the starting cell line, analytic and process control over the differentiation process, detailed characterisation and preclinical assessment of the final product all represent significant barriers to successful GMP manufacture for first in man recovery and survival studies. Longer term challenges include scale up manufacture and control over the cost of goods which are essential issues to address if these kinds of technologies are going to make it to routine clinical application.

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Abstract Category: LMIC (2) Oncology

Abstract No. 47

Abstract Title: The practice of clinical haemtology in an emerging economic environment
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Abstract Details: The practice of Clinical Haematology in an emerging economic environment can be both challenging and rewarding. Challenging because of some difficulties one has to overcome in order to deliver quality management and rewarding when despite the odds one can either cure or at best improve the quality of life of one’s patients. Ghana is a West African country with a total population of 25 million. Korle- Bu Teaching Hospital situated in Accra is the oldest and biggest teaching hospital in the country. It has the only well-established Haematology department equipped with the basic resources in the country. Currently there are four consultants, five specialists and 4 residents in training. Referrals to the department are received from all the ten political regions of the country and even beyond the shores of Ghana. (Togo, Liberia and Sierra Leone). Adult patients with either benign and malign-ant haematological disorders are managed. Benign disorders include nutritional anaemia haemolytic

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anaemias and coagulation disorders. Malignant disorders include leukaemias, lymphomas and Multiple Myeloma. Unfortunately majority of our patients present late and invariably irreversible complications would have already occurred. Hearing loss and priapism for example are seen in some Chronic Myeloid Leukaemia (CML) cases. Late referrals maybe due to lack of funds since the National Health Insurance though available does not cover haematological malignancies. Patients thus have to pay out of pocket. Others also seek alternative medicine before reporting. Outpatient consultation is done at the Central Outpatients Department of the hospital. With one weekly slot all other consultations are done at our day care facility. Our department has no ward of its own and has to rely on availability of beds on the Medical wards. The diagnosis of haematological disorders at our centre is mostly done using very basic tests. For example in the diagnosis of leukaemias except for CML one has to rely only on morphology. (Peripheral film and bone marrow aspirate.) Also regarding bleeding disorders one can only make a diagnosis of haemophilia. Samples for other specific confirmatory tests are sent to laboratories abroad at an expensive cost to the patient. Turn around time for results is long. Treatment modalities though present are limited especially for haematological malignancies. Chemotherapeutic drugs that are used due to cost and availability will be considered ‘ancient’ in advanced countries. None the less some successes are chalked. Despite the odds we are able to offer to our patients at best a reasonable good quality of life in a known environment, among family and loved ones even if cure is not achieved. We however look forward to a future where more haematology centres can be established nationwide and current laboratory diagnostic tests can be performed in house. We also hope to provide a wider spectrum of chemotherapeutic drugs that patients can afford and also have the opportunity to be involved in clinical trials and international multicentre research all in the bid to enhance the care of our patients.

Abstract No. 48

Abstract Title: Acute Promyelocytic Leukemia (APL) associated coagulopathy

Full Name: Eduardo M. Rego, M.D.
Institution/Company: University of São Paulo, Medical School of Ribeirão Preto, Department of Internal Medicine.

Abstract Details: Despite the significant progress in Acute Promyelocytic Leukemia (APL) treatment in the past three decades with long-term survival rates exceeding 80%, there remains a high early mortality due mainly to bleeding and thrombotic complications. In developing countries, delay in making the diagnosis, promptly establishing treatment with all-trans retinoic acid (ATRA) and providing adequate support therapy further increase early mortality. The International Consortium on Acute Promyelocytic Leukemia (IC-APL) was established in 2005 as an initiative of the American Society of Hematology to create a network of institutions in developing countries. IC-APL formulated guidelines which featured standardized approaches for specific and prompt diagnosis, along with guidelines for treatment and supportive care. According to these guidelines, ATRA treatment was initiated immediately in all cases in which the diagnosis of APL was suspected based on morphology. Considering that many patients are first admitted to emergency rooms (ERs), a small stock of ATRA was established locally and IC-APL members wrote educational material in Portuguese and Spanish aiming physicians who attend in ERs and Intensive Care Units. The provisional diagnosis of APL was confirmed using the anti-PML immunofluorescence technique, upon which daunorubicin was combined with ATRA. Platelets were transfused to maintain the platelet count above 30,000 to 50,000/μL, and cryoprecipitate was administered to maintain the fibrinogen level above 150 mg/dL. Genetic confirmation of the diagnosis was mandatory and was performed by RT-PCR, RQ-PCR, FISH or karyotype identifying the t(15;17)/PML-RARA rearrangement. The concordance between the anti-PML immunofluorescence and molecular biology tests was 100%. Regarding treatment, the IC-APL study was identical to that of the LPA2005 trial reported by the Programa Español de Tratamiento en Hematologia / Dutch-Belgian Hemato-Oncology Cooperative Group (PETHEMA/HOVON), except for the replacement of idarubicin by daunorubicin due to its better availability and lower cost in developing countries. The 2-year OS and EFS for the IC-APL were 79.4% (95% CI, 73.6-85.7%) and 76.2% (95% CI, 69.9-83.1%), respectively, with a median follow-up period from diagnosis among survivors of 28 months (range, 7–62 months). The induction mortality rate was reduced from higher than 30% prior to the IC-APL study to approximately 17%. The establishment of a network also created the possibility of the development of cooperative research. Considering that bleeding and thrombotic complications are the most frequent ones during induction and the leading cause of death, our group decided to explore APL associated coagulopathy pathogenesis and, in particular, the role of Tissue Factor (TF). APL cells express TF on their surface, and after activation by phospholipids, TF forms a complex with factor VII and converts factor X to activated factor X, thus leading to aberrant activation of the coagulation cascade. APL cells may also induce TF procoagulant activity of endothelial cells through their secretion of IL-1β. We have investigated TF expression and activity in microparticles, which are cell-derived
fragments of 0.1–1.0 μm diameter. In the plasma of patients with APL, there is an increase of microparticles containing procoagulants in comparison to healthy blood donors. The TF activity, evaluated by measuring thrombin generation, was increased in the APL microparticles. It is noteworthy that thrombin generation is increased in both the microparticles and microparticle-free plasma. Based on the fact that activity of the complex FVIIa-TF can be inhibited by the tissue factor pathway inhibitor (TFPI), and we have also measured the plasma concentrations of free-TFPI and detected significantly higher levels in APL samples compared to controls. Along with the enhanced procoagulant activity, APL is associated with increased fibrinolysis. APL promyelocytes express high levels of Annexin A2, a co-receptor for plasminogen and for tPA, capable of increasing plasmin generation. Using a murine model of APL, we showed that the infusion of the LCKLSL peptide, a competitor for the Annexin A2 tPA-binding site reversed the Thrombin-Antithrombin peptide, a competitor for the Annexin A2 tPA-APL, we showed that the infusion of the LCKLSL peptide, a competitor for the Annexin A2 tPA-binding site reversed the Thrombin-Antithrombin complexes levels, suggesting that Annexin A2 may be a target for future therapeutic interventions. Taken together, the experience of the IC-APL points out the importance of international networking for improving medical education and patient care, along with addressing relevant scientific issues.

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Abstract No. 49

Abstract Title: ‘Oncology for children: what is possible where resources are scarce?’

Full Name: E M Molyneux1

Institution/Company: Hon Professor of Paediatrics, College of Medicine, Box 360, Blantyre, Malawi

Abstract Details: Background Malawi is one of the poorest countries in the world but since the 1970s children with cancer have been cared for in the Queen Elizabeth Central Hospital Blantyre. At first the children were managed in general paediatric wards with curative treatment targeting only the most common tumour – Burkitt lymphoma (BL). In 1997 a separate paediatric oncology ward was built, extended in 2012 and now has 21 beds. Treatment options were expanded step by step. Over the last 2 decades different treatment protocols for Burkitt lymphoma have been assessed, a modified SIOP protocol for Wilm’s tumour was developed and schedules for other tumours such as retinoblastoma, Hodgkin’s disease, germ cell tumours were added. Palliative care is an essential component of care as members of the team counsel families, listen to their concerns and – importantly – provide a pain service. About 300 new patients are treated annually; 35% have Burkitt lymphoma, but a wide range of cancers are seen. Challenges It is only recently that non-communicative diseases have featured in policy making for low income countries – so funding remains inadequate. Chemotherapeutic agents have been limited in what is consistently available. Children present with advanced disease; over 90% of the children are malnourished on diagnosis; many are anaemic and have co infections such as malaria, schistosomiasis or hookworm; some have HIV infection. The children cannot tolerate aggressive chemotherapy and there is limited supportive care to manage toxic side effects. Radiotherapy is unavailable in the country. Laboratory and histopathology services are not always timely and cannot influence clinical decision-making. Until 2015 there was no paediatric oncologist, and the 5 nurses have only ‘on the job’ training in cancer care. Travel to and from the hospital is costly for families, most of whom are poor, rural farmers and abandonment of treatment is a real problem if these costs are not funded. Acute leukemias are increasingly diagnosed and as they require intense and prolonged treatments they are a great challenge to treat successfully. Collaborations Most of the nurses, many of the chemotherapy drugs, nutritional rehabilitation and travel all benefit from charitable support. World Child Cancer, Children with Cancer
in Malawi and others have given sustained support without which this service could not be maintained. The Newcastle based charity Children with Cancer in Malawi has set up a microscope camera in Blantyre with picture-upload to a dropbox in Newcastle, where a haematologist and oncologist review the cytology photos and give rapid opinions and advice. Research grants have benefited many children. A collaboration between African countries for Wilm’s tumour management is an exciting platform for working together on Wilm’s and other tumours to enable important studies, appropriate to the continent, to be carried out. Outcomes Overall 1-year survival for BL has improved from 25% to 70%; Kaposi’s sarcoma has a one year survival of over 70%; retinoblastoma cases are being referred earlier. Acute leukaemias still have a poor outcome but enhanced treatment protocols are giving better results. And at last there is a Malawian paediatric oncologist.

Abstract Category: UKMF
Abstract No. 50
Abstract Title: Integrating NGS approaches into patient care: How I manage high risk disease in presentation in transplant eligible disease
Full Name: Prof Wee Joo Chng
Institution/Company: National University Cancer Institute Singapore

Abstract Details: Significant advance in the outcomes of patients with multiple myeloma has been achieved over the last decades with the introduction of a number of new effective therapies. However, there is still a subgroup of patients with very poor outcome despite these treatments. Identifying these patients with high-risk disease requires the use of both information at baseline and post-treatment factors such as depth of response and timing of relapse. The revised international staging system utilizes genetic information, and simple blood parameters such as beta-2 microglobulin, serum albumin and lactate dehydrogenase levels. The advent of various genomics techniques has the potential to provide additional prognostic and predictive markers that can help guide therapeutic decisions. Specific genetic aberrations may be amenable to specific treatment such as BRAF mutation and BRAF inhibitors, or MYC activation and bromodomain inhibitors. In additional, gene expression profiles provide further refinement on current prognostic system. From the different clinical trials, some inference can be made on what are the best strategies to treat high-risk disease. Proteasome inhibitors appear to be beneficial particularly newer generations of proteasome inhibitor such as carfilzomib and ixazomib. Intensification with tandem transplant also seems to benefit high-risk patients. It is clear that the time have come to specifically test some of these regimens and treatment strategies in high-risk patients.

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Abstract No. 51
Abstract Title: Risk stratification in the older patient; what are our priorities?
Full Name: Sonja Zweegman
Institution/Company: Department of Hematology, VU University Medical Center, Amsterdam, the Netherlands

Abstract Details: Do new standards of care incorporating immunomodulatory agents and proteasome inhibitors benefit all elderly patients with Multiple Myeloma? The introduction of the immunomodulatory agents and the proteasome inhibitors has not only greatly improved the prognosis of younger patients with MM, also in the elderly patients ≥65 years, the addition of bortezomib, thalidomide or lenalidomide to melphalan and prednisone improved outcome. However, when considering the outcome as described in population based registries (PBR), reflecting real life, the elderly patients appear to benefit less. The limited benefit of novel agents in the elderly as described in PBR, might be explained by the fact that the majority of elderly patients are not being included in randomized clinical trials (RCT) due to not fulfilling the eligibility criteria because of co-morbidities. Usually the treatment is either not given or given without the addition of novel agents, or else with a lower dose of novel agents. That this fact (at least partly) explains the difference in outcome between RCT and PBR indeed, is supported by several observations showing that if novel therapy is given to the elderly outside of RCT, there is an increase in OS, even in the oldest patients. This indicates that also a subgroup of elderly patients benefits from novel therapies. Are there tools available to define the subpopulation of elderly MM patients that will benefit from treatment? Therefore, there is an urgent need to determine in whom therapy is feasible and in whom it might compromise the quality of life. The Comprehensive Geriatric Assessment has found to predict OS and adverse events during chemotherapy. There are however two limitations. Firstly, data on the prospective value of CGA in patients with hematological malignancies are limited, without data on MM patients in specific. Secondly, the CGA is time consuming. Therefore, several studies investigated the possibility of shorter screening versions in order to identify fit patients who are able to receive standard...
How to treat elderly MM patients in clinical practice? There is evidence that in patients ≥65 years, especially in those ≥75 years, the toxicity of anti-myeloma treatment and subsequently the discontinuation rate is higher, negatively affecting outcome. On the other hand, the addition of novel therapies. A recent publication of the International Myeloma Working Group showed that a concise frailty score, based on age (<75, 75-80, >80 years, score 0,1,2 respectively), CCI (≤1 or ≥2, score 0 or 1) and (instrumental) Activities Daily Life score (ADL >4 or ≤4, score 0 or 1, iADL>5 or ≤5, score 0 or 1), predicted non-hematological toxicity in 869 patients ≥65 years uniformly treated within 3 randomized clinical trials. These data underscore the importance of geriatric assessments as well as the need for prospective validation in uniformly treated patient populations. This will be performed in a Dutch HOVON study also implementing objectively measured criteria (physical function such as gait speed and handgrip strength, cognitive function and sarcopenia) and exploring the value of biomarkers reflecting biological age, such as the senescence marker p16INK4a. Hopefully, these biomarkers will be even more precise in predicting toxicity than calendar age. How to treat elderly MM patients in clinical practice? There is evidence that in patients ≥65 years, especially in those ≥75 years, the toxicity of anti-myeloma treatment and subsequently the discontinuation rate is higher, negatively affecting outcome. On the other hand, the addition of novel agents has been found to improve OS with months to even more than one year. Given the first data on the predictive value of geriatric scores (fit – unfit – frail) determined by limited geriatric assessments, this should be implemented in clinical practice. Unfortunately, there are no studies prospectively investigating the clinical outcome in a randomized trial either adapting the dose of anti-MM according to these geriatric assessments or not. Awaiting the results of these clinical trials practical guidelines were recently published that can be used to personalize therapy in the elderly patients being currently treated.

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Abstract Category: BSH Medal Lecture
Abstract No. 52
Abstract Title: Teaching haematology: Art, science and humanity
Full Name: Tim Littlewood

Institution/Company: Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Abstract Details: A haematologist may be a scientist, detective, psychologist, shaman, sometimes all in the same day. Hard science is what drives our healing, yet the humanity of haematology – the everyday connections we form with our patients – is what ensures they feel cared for. So how do we, as haematologists, imbue today’s students with the essential haematology knowledge, whatever discipline of medicine they finish in but also inspire the haematologists of tomorrow with the qualities and skills our specialty spans? And how do we enthuse the brightest and best to choose a career in haematology? Drawing upon filmed testimony from patients, students and junior doctors, my presentation will seek to answer these profound questions for the future of our specialty. If haematology were well taught in medical schools, we would expect newly qualified doctors to be both confident and competent in managing common haematological disorders. However, surveys of final year medical students indicate that even if well taught, haematology is considered difficult and daunting. The phrase ‘hematophobia’ was coined to describe these difficulties, capturing the sense of unease and under-confidence many young medics feel towards our discipline.* There are many reasons for the unease. The terminology that we use (e.g. anisopoikilocytosis) is old fashioned and we should be communicating in less arcane (and less Greek) vocabulary. More fundamentally, haematology contact time with medical students has decreased over the past few decades, and disappeared completely in some medical schools. The British Society for Haematology’s education sub-committee was set up in part in response to this deficit, and now provides innovative teaching at every level. What little time remains for haematology in medical school curricula must be optimally utilised to provide students with the core essential knowledge of the subject, but also to inspire and enthuse them. How? Teaching the core curriculum must come first. The molecular genetics of acute leukaemia may be exciting but we need to make sure that students understand the tests to diagnose iron deficiency. Most of the core material will be delivered by lectures and small group teaching. But how many have received any training in giving lectures or small group teaching or, indeed, feel that it is necessary for them? Outpatient clinics and ward rounds should be unmissable opportunities to engage students. What can you teach there? The core curriculum (including the old fashioned arts of taking a patient history and clinical examination skills) for sure, but also taking consent, delivering bad news and end-of-life care amongst many other vitally important generic skills. Perhaps more than anything else, patients themselves provide the most wonderful teaching material. Listening to a
patient talk about their disease, its symptomatology, its diagnosis and treatment (not to mention the patient’s recollections of the communication skills of the health care staff) is usually a far more memorable and inspiring teaching session than any talk in the absence of patients or patient material. Let us pass on our passion and understanding of haematology so that we provide the very best education to the next generations.

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Abstract Category: BSH Education Committee

Abstract No. 53

Abstract Title: Making the virtual world work for you

Full Name: Prof Beverley Hunt

Institution/Company: Guy’s & St Thomas’ NHS Foundation Trust, King’s College London & Thrombosis UK

Abstract Details: For most consultants attending this conference, the virtual world came to us as mature adults and not everyone has embraced it with open arms. But approached in a positive way it can be enormously beneficial to individuals in learning, teaching and extending one’s professional profile. For those with medical problems it can be a way of establishing contact with others who have the same problems, bridging the gap between the short interview when they attend a health professional and the questions that come up in day-to-day life. This lecture will discuss in detail the following: Facebook. So it’s not just a place to upload the latest holiday pictures. Facebook allows one to run Facebook groups and over the last few years Thrombosis UK has run a very effective Facebook group – allowing those with the same medical problems to express their concern and lack of knowledge and get advice from others in the same situation. Of course it needs someone to log in every day to ensure there is fair play and that the site has not been taken over. LinkedIn. LinkedIn is a site where individuals and groups can run a profile and connect with others. Twitter. I would strongly recommend Twitter as a way of keeping up-to-date (up to the minute!) on current views about the latest academic articles and following or expressing individual academic views. Most of the big journals will Tweet their content on their publication day and many key opinion leaders are now on Twitter and run academic tweets. I would argue that there is no concept or view that cannot be reduced to 140 characters, and being able to express concepts in a concise way allows one to think more clearly and to get to the essence of a problem. Some groups such as World Thrombosis Day might have a Twitter session where one can ask a key opinion leader questions via Twitter. Of course there are many other fun non-academic things going on Twitter that will engage and amuse you. Webinars. Webinars allow individuals to give lectures on line +/- slides and have a global audience – it’s an easy way to learn while sitting at your desk.

Wikipedia. Another way of advertising one’s individual or organisational presence is to have a Wiki(pedia) page. Wiki will check the content before allowing one to launch a page, and once up, it needs a check now and again, and updates as necessary. In Google searches, Wiki usually comes up high on the list.

Abstract No. 54

Abstract Title: ‘Social Media’ – is that enough to make you turn the page?

Full Name: Dr. Emily Graves and Dr. Andrew McGregor

Institution/Company: James Cook University Hospital, Middlesbrough, UK; Royal Victoria Infirmary, Newcastle upon Tyne, UK

Abstract Details: Many people think of social media (SoMe) as being new-fangled, frivolous, or perhaps fun but irrelevant to work. TeamHaem want to convince you otherwise. SoMe encompasses many forms of communication with ever expanding formats. Four years ago a group of haematology trainees decided to explore the various communication methods as a platform for teaching. Our target audience was undefined, but we hoped to reach a broad range of interested parties, including undergraduates, nurses, biomedical scientists, junior doctors and consultants in many specialities. As TeamHaem we began posting brief clinical scenarios as a blog, then using Twitter, Facebook (and latterly, some other media tools) to promote, develop and discuss the case. The result has been the evolution of a rich, diverse community of learners with a broad mix of skills, interests and knowledge. Such a network is not easily captured by two dimensional data, but some statistics may help: we have 1971 followers on Twitter, have an impression of 2,630,049 (the number of people who could be reached by any one tweet) and our blog has been accessed from 158 different countries: a truly ‘global community of practice’. Of our 1971 followers 551 have actively participated in cases, giving us an impressive 28% participation rate. The advantages for the learner of the blended SoMe approach are numerous, and have already been recognised in educational literature. One major advantage is the asynchronous, international nature of this learning platform. This is particularly valuable now, when increasing clinical demands are limiting access to real-time teaching for British trainees. The knowledge and skills of participants is wide-ranging.
and allows learning in a truly multi-disciplinary fashion, as the anonymity afforded by SoMe helps to overcome traditional hierarchies (Kind et al 2015). Learning in this way also encourages reflexive practice as participants discuss and debate key points and share experiences. By allowing participants to pose questions and engage in dialogue, we facilitate our followers in exploring a topic to their educational satisfaction, thus creating a more engaging experience (Batt-Rawden et al 2014). As clinicians we find SoMe is excellent for allowing us to stay abreast of developments within haematology and share this knowledge with our colleagues; the popularity of medical conference hashtags is one manifestation of this. Participants in a recent academic study of SoMe similarly appreciated the ability to keep up to date with their speciality and share interesting insights with colleagues (McGowan et al 2012). SoMe is not an educational utopia however. There is no formal editorial scrutiny of content, which could threaten the integrity of SoMe as an educational resource. Most frustratingly, there is a lack of recognition of such methods of publishing and learning from traditional educational and academic structures. The development of altmetrics (Roemer et al 2012) may be a step in the right direction to challenge the establishment’s position on this matter. Our presentation will introduce you to the basics of twitter (and other media platforms), allow you to hear from some great proponents of SoMe and explain to you why, whether a teacher or clinician, exploring the diverse world of SoMe is something you should try. Come with an open mind; smartphone and twitter handle optional.

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Abstract No. 55
Abstract Title: ‘iBlood’ - putting patients at the heart of students’ learning
Full Name: Dr Rachel Clarke
Institution/Company: John Radcliffe Hospital, Oxford University Hospitals NHSFT, Oxford, UK

Abstract Details: iBlood – the BSH’s new home for interactive, online teaching for students - will soon be hitting desktops, laptops and smartphones near you. The first online iBlood tutorials will launch later this year within the all-new BSH site. Their aim: to demystify and bring to life haematology for medical students and junior doctors. At their heart is the patient experience – brought to the students via the medium of professionally-filmed patient interviews. iBlood aims to address the lack of confidence many doctors feel in handling haematology – a major problem for the NHS since all doctors, even the most junior, will confront common and potentially life-threatening blood disorders such as haemorrhage, transfusion reactions and neutropenic sepsis. Our second, but equally important, objective is to encourage empathy among clinicians with the difficult and distressing experiences some haematology patients face, such as intensive chemotherapy, bone marrow transplants and coming to terms with a terminal illness. The iBlood team of junior doctors and consultant haematologists has the unique strength of being professionally trained not only in medicine, but also in television production, website design and photography. iBlood will launch with 10 tutorials initially, each demystifying a core disease such as acute myeloid leukaemia or venous thromboembolism. The spine of each tutorial is a broadcast quality, filmed patient interview covering the patient’s experience of his or her illness, from diagnosis to treatment and including coping with uncertainly about prognosis. The interviews are sometimes painful or moving, and raise important issues for all doctors about how best to communicate a terminal prognosis, or a diagnosis of cancer, for example. Inter cut with the patient video clips are text, diagrams, tables and photos conveying the core facts about the disease. We also include filmed interviews with consultants, providing an expert perspective. Having worked through the tutorial, students can then test their understanding with MCQs, and finally download a factsheet and podcast version of the material. All iBlood materials are quality checked by consultant members of the British Society for Haematology’s Education Subcommittee, ensuring they are of the highest calibre. iBlood will, we hope, be a unique new multimedia learning resource for students. Designed by students for students, with expert oversight from senior haematologists, it works across all platforms and devices, in online and downloadable forms, potentially paving the way for a new model for teaching haematology in the twenty-first century.

Abstract No. 56
Abstract Title: Making apps happen for haematology
Full Name: Dr. Duncan Brian
Institution/Company: University College London Hospitals NHS Foundation Trust, London, UK
Abstract Details: Apps, or software applications, are computer programs designed to assist us with our daily routines. Typically, they process a number of user inputs to facilitate the task in hand, rather than for example, simply serving reference information all at once. For haematology, online calculators, image banks and specialty guideline databases are examples of specialty-specific web apps in common use. Web apps, which run on-demand via a web browser rather than needing prior installation, have been made feasible since increased broadband speeds have allowed real-time user interaction. Sites such as YouTube, Google Docs and the Outlook web app are common examples of web applications. Apps may also exist for mobile or tablet devices, but in contrast to online apps, they require installation and are device specific. Nonetheless, owing to smartphone portability and near constant availability, the range of current and potential smartphone apps is even more diverse. In healthcare, the digital dictation platforms purchased by several NHS Trusts and a number of electronic patient record systems are examples of applications running within a web browser. For hospital staff required to use multiple laboratory, clinic or ward-based computer systems, web-based apps have clear advantages. Compared to device specific smartphone apps, web apps have the advantage that the same app may be run via a web browser on a desktop computer or a smartphone device. Additionally, user account preferences or clinical data can be stored via the app and be re-used later on a different machine. A case study focusing on the creation of an online bone marrow aspirate counter, https://cellcountr.com, is presented as an example of a web app developed by a team of junior doctors and haematologists to replace a sometimes unavailable physical counter and to enhance diagnostic reporting workflow. The software underpinning this and many other online apps is ‘open-source’ and hence is available free of charge. Events such as NHS Hack Days and the Code4Health initiative similarly provide an opportunity for clinicians to engage with software developers working pro bono. Together these resources make it realistic for individuals and organisations to develop basic / proof-of-concept applications specific to their needs for relatively little cost. The talk will give an overview of the development of the web app Cellcountr that was designed to enhance the current bone marrow aspirate reporting workflow. We will additionally explore how the use of open-source technology such as Bootstrap and ‘responsive’ web design has facilitated the development of mobile-friendly web applications. Finally, a discussion of the potential costs and approaches to scaling apps for wider use is presented along with suggestions for putting new app ideas online.

Abstract Category: Prezi – Making your presentations sing

Abstract No. 57

Abstract Title: Prezi is a free online software designed for presentations and story boarding. It was created in 2009 and presently has on 35 million users

Full Name: Ieuan Walker

Institution/Company: King’s College London School of Medicine, London, UK

Abstract Details: Currently medical education is undergoing a technology revolution with increasing emphasis placed on mobile technology and platform based tools. Today’s medical students and trainees have grown up using smart phones, tablets and social media. Meanwhile, the majority of teaching is delivered using PowerPoint software that is now 25 years old (older than most medical students in the UK!). Haematology is frequently poorly taught at medical school, with the majority of students reporting it either too complex or too dull. Highlighting the need to engage students to deliver important information concisely and develop an understanding of pathways and concepts important to the subject. Compelling evidence exists that the rise of technology has fundamentally changed how we learn. fMRI studies have shown that students born in the digital age think much more visually than previous generations, and engage better with mind mapping ideas. The traditional linear approach to presentations as delivered by PowerPoint fails to address this, with the old lexicon ‘death by PowerPoint’ frequently used to describe medical lectures. Prezi offers a number of key strengths; visual representation of a drug pathway or disease helps organisation of knowledge from the lecture. Similarly, if used correctly Prezi may help structure thinking for medical students giving them skills to problem solve in the future. Feedback from teaching is that traditional ‘chalk board’ teaching receives higher satisfaction than PowerPoint lectures. With a combination of both scoring higher still. Prezi gives us the opportunity to mind map and explore ideas visually while retaining key information in specific slides. This talk will demonstrate how to use Prezi to achieve visually stunning presentations, and provide ideas on how this powerful internet based tool can be employed to deliver educational talks. *This talk is delivered by*
Abstract No. 58

Abstract Category: Patient Advocacy Session

Abstract No. 58

Abstract Title: Now patients are living longer, we need to think about long-term sequelae and not just short-term impact

Full Name: Professor John A Snowden

Institution/Company: Sheffield Teaching Hospitals NHS Foundation Trust & University of Sheffield, UK

Abstract Details: Modern haematological cancer care is increasingly successful in either curing patients or otherwise prolonging survival for many years. Whilst celebrating these achievements, the increasing challenges of cancer survivorship cannot be ignored and late physical and psychosocial consequences following completion of treatment are increasingly recognised. Such ‘late effects’ have been defined by the US National Cancer Institute as: ‘[A] health problem[s] that occur[s] months or years after a disease is diagnosed or after treatment has ended. Late effects may be caused by cancer or cancer treatment. They may include physical, mental and social problems, and second cancers.’ While late effects were first recognised in long-term survivors of childhood cancer and leukaemia, with the improved outcomes for a range of cancers at all ages, increasing attention is also merited for late effects and survivorship in adults.1,2 Physical late effects may affect any system, ranging from relatively specific problems such as endocrine failure and infertility to more widespread complications, such as impaired immunity, alterations in body composition and long-term risks to the cardiovascular system. Psychological late effects include anxiety, fatigue, clinical depression, impairment of cognition and learning, impaired social, sexual and family relationships, and compromised education and work opportunities. Both physical and psychological late effects interact with each other and with the ageing process to produce a unique range of problems for individual patients. ‘Late effects’ are now relevant to a wide range of haematological cancers. These can be broadly categorised into cancers treated with curative intent, such as acute leukaemia and high grade lymphoma, and ‘chronic’ malignancies, such as myeloma or chronic myeloid leukaemia, where patients now often live for over a decade post-diagnosis, whilst receiving repeated lines of therapy to maintain long-term disease control in the absence of cure. Although both categories may experience the late effects of intensive chemotherapy and blood and marrow transplantation, there is increasing recognition that ‘low-dose’ therapies also carry a burden of ‘late effects’.3,4 The early recognition of late effects and effective management strategies should lead to an improvement in the management of patients with both cured and chronic haematological cancers. How to deliver this consistently in haematological cancer services remains a challenge. Various models of survivorship care are used, all of which require dedicated resource, staffing and separation of clinical focus from the routine haematology clinic for effective delivery. Although generic screening guidelines have been developed for detection of late transplant-related complications, there is little guidance for screening and managing late effects in specific haematological cancers. There is a need for more clinical trials in late effects management, including randomised trials of interventions.

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Abstract No. 59

Abstract Title: Assessing benefits and risks of new medicines from the patient perspective – methodological approaches

Full Name: Sarah Richard

Abstract Details: Objective: To discuss the challenges for patient groups in providing patient perspective on the benefits and risks of medicines in regulatory and reimbursement settings, and how new approaches could support more effective patient involvement in benefit-risk decisions. Current patient input into benefit-risk decision-making Traditionally regulators and health technology assessment (HTA) bodies seek patient perspectives on a new medicine through consulting patient groups. Regulators seek individual patient experts to attend committee meetings to share their experience of the condition and their views on the medicine’s benefit-risk balance. UK HTA bodies also invite patient groups to give evidence
about the impact of the condition and the added value to the patient community of the new medicine compared to existing options. There are challenges for patient groups in providing this input. While there is often substantial evidence on the impact of the condition it is often not possible to say with certainty that a given medicine’s benefit-risk profile will be favourable to the majority of patients. Complex patient and disease-specific factors, such as prior treatment experience, personal circumstances, preferences and approach to risk will affect the perceived value of a medicine to an individual. Qualitative input by individuals and patient groups therefore provide important depth and insight, however the generalisability of the information obtained may be limited. There is increased interest in exploring more quantitative ways to elicit perspectives on the benefits and risks of medicines that move towards a ‘science of patient input’. As yet there is no consensus on the best methods and the role of different stakeholders, including patient groups, in such activity. 

Potential of quantitative patient preference methodologies Myeloma UK is exploring the feasibility of two preference elicitation methods through a pilot with different partners using a Multi-Criteria Decision Analysis methodology and a study based on Discrete Choice Experiment techniques. Both techniques are informed by qualitative stages. They aim to describe the relative importance and weights of different treatment outcomes, assess if there are subsets of patients who value outcomes differently and the feasibility of applying these preference weights to the known profiles of new medicines during the assessment process. These approaches have significant potential but also a number of challenges. There may be a significant cognitive burden for patients in understanding language around trade-offs and likelihood of risk as well as an emotional burden in answering questions around hypothetical treatment scenarios and outcomes. There are also limitations in being able to capture every outcome important to patients while keeping the study manageable. Ideally the outcomes should directly relate to the known profile of one or more medicines. However, while clinical trials focus on clinical endpoints such as overall survival and progression-free survival we found that mode of administration, number of hospital visits, and impact on family were important considerations. While qualitative stages are key to defining the inputs for a quantitative study, the fact that clinical trial data do not necessarily reflect the most relevant outcomes to patients means that any scientific approach may be inherently limited. 

Conclusion Patient preference methodologies have the potential to add value to the process of assessing benefits and risks of medicines and improve the impact of patient input on decision-making. Further research in this area will be useful for identifying best practice and realising this potential.

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Abstract Category: UK MDS Forum
Abstract No. 60
Abstract Title: Future of diagnostics in MDS
Full Name: Dr Catherine Cargo
Institution/Company: HMDS, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Abstract Details: In the new era of molecular medicine, mutational analysis is increasingly utilised in the investigation and diagnosis of suspected haematological malignancies. The diagnosis of the myelodysplastic syndromes (MDS) however remains heavily reliant on morphology which, as a subjective approach, suffers from poor interobserver concordance1. To date cytogenetics has provided an objective marker of disease however this is uninformative in a large proportion of cases. With the advent of high throughput sequencing and array-based cytogenetics the genomic architecture of MDS is now well documented and large gene panels can detect somatic mutations in over 90% of cases2,3. The high frequency of abnormalities suggests that it may be feasible to use the presence of a genetic abnormality as a core criterion for MDS diagnosis. While a molecular approach to MDS diagnosis is appealing, this is complicated by a number of issues. The driver mutations detected are not unique to MDS and are found across the spectrum of haematological malignancies meaning these abnormalities alone may not be disease defining. There are also reports of the same somatic mutations in the blood of aging healthy individuals4-6 with the frequency of these increasing to over 10% in those >70yrs. The reported mutations overlap with three (DNMT3A, ASXL1, TET2) of the most frequently mutated genes found in MDS. The term clonal haematopoiesis of indeterminate potential (CHIP) has been proposed to encompass these patients with somatic mutations but without other evidence of disease7. While age related mutations were frequent, the risk of developing a haematological malignancy was small (~1% per year) similar to other clonal excess states such as monoclonal gammopathy of unknown significance (MGUS). This suggests that somatic mutations can be present without ever causing disease and questions
the validity of mutational analysis in the diagnostic setting. Subsequent studies have however confirmed that the frequency of mutations is considerably higher in those presenting with cytopenia, even in the absence of morphological disease. Kwok et al detected somatic mutations in large numbers of patients with idiopathic cytopenia of undetermined significance (ICUS), most frequently in samples showing some evidence of dysplasia (45-62%) though also in those without (17-20%). This increase in frequency compared to healthy individuals suggests that these mutations are indeed related to the cytope-nia. This was further supported by our retrospective study which identified a somatic mutation +/or structural abnormality in almost all (91%) ICUS patients who subsequently did progress to MDS or acute myeloid leukaemia (AML). Importantly there were notable differences in the mutational profile between those that progressed and reported healthy individuals with the former having higher allele fractions (clone size) and greater numbers of mutations. This implies that clones must expand to an appropriate level and/or acquire cooperating mutations to be disease defining and this information will be critical when developing future diagnostic algorithms. The inclusion of molecular techniques in the laboratory investigation of cytopenic patients has the potential to significantly improve MDS diagnosis, particularly in those with early disease. For patients with high risk features this would provide an opportunity for early intervention and improved clinical outcomes. Large prospective studies are however required to fully determine the clinical significance of these mutations and define diagnostic criteria.

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Abstract No. 61
Abstract Title: Towards precision medicine in myelodysplastic syndromes
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Institution/Company: Director, Myelodysplastic Syndromes Program, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts USA

Abstract Details: The terms “precision medicine”, “personalized medicine” and “targeted therapy” are among the latest biomedical buzzwords. While medicine has to some extent always been tailored to individual circumstance and to the idiosyncratic particulars of clinical presentation, what is meant by these phrases is the ability to choose treatment approaches informed by a deep understanding of disease biology, rather than empirically on the basis of tissue of origin, appearance of cells under the microscope, or other less specific disease features. Because the myelodysplastic syndromes (MDS) are so morphologically and molecularly heterogeneous – unlike the myeloproliferative neoplasms (MPN), there are no “dominant” high-frequency mutations associated with MDS akin to JAK2 and CALR in MPN – adoption of “precision” medicine in this setting represents both a challenge and an opportunity. Disease patterns already inform therapeutic choices in some MDS settings. For instance, anemic patients with deletion of chromosome 5q. preserved platelet count and low blast proportion respond best to lenalidomide, while anemic patients with serum erythropoietin levels <500 U/L (and especially <100 U/L) who are not heavily transfusion dependent are most likely to respond to epoetin or darbepoetin. Similarly, patients with serum thrombopoietin levels <600 pg/mL and minimal platelet transfusion needs are more likely to experience a meaningful platelet increment and reduction in bleeding events during treatment with thrombopoiesis stimulating agents such as eltrombopag and romiplostim. Uncertainty continues over the optimal candidates for immunosuppressive therapies: in various series, younger age, normal karyotype or trisomy 8, HLA DR15, hypocellular marrow, presence of a paroxysmal nocturnal hemoglobinuria clone have predicted response to anti-thymocyte globulin in MDS. Genomic discoveries in MDS promise to further refine choices and influence haematological practice. However, not all observations are clinically important: MDS patients with TET2 mutations are somewhat more likely to respond to therapy with hypomethylating agents, yet the difference in response rate between mutant and wild-type populations is not enough to help in clinic decision-making. In contrast, the extremely poor outcomes of patients with TP53 mutations who undergo reduced-intensity conditioning allogeneic stem cell transplant has prompted some centers to restrict transplant in this subgroup of patients outside the context of a
clinical trial. A large analysis of molecular patterns and transplant outcomes is ongoing under the auspices of the CIBMTR and may help confirm and extend these results. Among developmental therapies, the high erythropoietic response rate to the activin receptor ligand trap luspatercept (ACE-536) reported for patients with SF3BI mutations and ring sideroblasts may new light into disease biology. Rationally designed targeted agents such as AG221 and AG120, inhibitors of isocitrate dehydrogenase (IDH), may benefit a subset of MDS patients with IDH mutations. Splicing modulators such as H3B 8800 will begin trials this year, and may take advantage of clonally-restricted vulnerability to further disruption of splicing in cells bearing somatic mutations in spliceosome components, in the same way that lenalidomide’s cebrolin-mediated degradation of casin kinase affects primarily CSNK1A1 haploinsufficient cells. Many practical difficulties remain before new narrowly-targeted agents are widely adopted into MDS clinical practice. First among them is the fact that both the drugs themselves and companion diagnostics are expensive, and molecular testing is not currently performed in MDS in most clinics. Yet the potential for marked improvement in outcomes for this difficult set of diseases with “precision medicine” would seem to justify enthusiasm, and will continue to drive developments in this area.

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Abstract Category: Platelets: Function and Management

Abstract No. 62

Abstract Title: Platelet production in vitro for transfusion from human pluripotent stem cells

Full Name: Thomas Moreau, Guenaelle Bouet, Maria Colzani, Daniel Howard and Cedric Ghevaert

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Abstract Details: Platelet transfusions to thrombocytopenic patients are increasing by 7-10% per year. We are currently entirely reliant on donor-derived platelets, which have limitations: short shelf-life and precarious supply chain, risk of donor-derived transmitted infections and issues of HLA mismatch in chronic recipients. We are aiming to develop protocols to produce platelets in vitro from a renewable source of stem cells - human pluripotent stem cells (hPSCs) - using a methodology and reagents compatible with the production of a clinical grade commercially viable product. First we developed a chemically defined forward programming (FoP) approach to produce megakaryocytes (MKs) from hPSCs based on the overexpression of 3 key transcription factors (TFs; GATA1, FLI1 and TAL1) driven by lentiviral vectors. This FoP protocol generates pure MK cultures (>80% CD41 + CD42+ cells) which expanded in vitro for several months culminating on average to 2x10^9 MKs per starting hPSC with minimum cytokine requirement and cell handling. These results are now validated using clinical grade cell lines, including cell lines with “common” HLA haplotypes in order to provide matched platelets for alloimmunised patients. Second we addressed the challenge of the low platelet number produced per MKs in vitro (at best 10 platelets per MK whilst in vivo it is estimated that MKs produce >1000 platelets per cell). To improve platelet release and harvest, we recreated the characteristics of the bone marrow vascular niche in vitro. First we use collagen-based 3-dimensional porous scaffolds to recreate the physical 3-dimensional space. Second we screened a library of 50 recombinant ectodomain proteins in order to identify cell-to-cell contact signal proteins that promote platelet formation. We identified two which can be further immobilised to collagen 3D-scaffolds leading to a 5-fold increase in platelet yield. Finally we integrated the scaffolds in a bespoke parallel-flow two-chamber bioreactor to a platelet yield of >100 platelets per MK. We validated the platelets produced in vitro in a range of in vitro and in vivo assays in mice. The combination of FoP technology in hPSCs with the tissue engineering approach has paved the way for potential human studies in the next 5 years.

Abstract No. 63

Abstract Title: Platelets and Immunity

Full Name: John W. Semple.

Institution/Company: Keenan Research Center for Biomedical Sciences at St. Michael's Hospital, Toronto, ON, Canada.

Abstract Details: Platelets are the smallest and second most abundant circulating cells in the blood and their primary role is to maintain the integrity of the vasculature. When blood vessel injury occurs, platelet adhesion and activation receptors recognize subendothelial matrix proteins such as collagen and this can initiate a coordinated series of reactions leading to the formation of a fibrin clot to arrest bleeding.
It appears, however, that in addition to hemostasis, platelets also have important inflammatory and immunological functions. As early as the 1960’s, reports began to demonstrate that platelets may play an active role in inflammation and perhaps the regulation of immune responses. For example, platelets can store and secrete several pro- and anti-inflammatory chemokines (e.g. Platelet factor 4 and RANTES) and cytokines (e.g. Interleukin-1β and Transforming growth factor-β) that can affect local immune responses such as chemotactically attracting neutrophils to sites of tissue damage. On the other hand, platelets may be able to directly regulate adaptive immune responses via their ability to express and secrete CD40/CD40L co-stimulatory molecules. Of perhaps, greater interest, platelets have been shown to express the entire family of Toll-like receptors (TLR) and this may allow them to act as circulating sentinel cells that first encounter bacterial products for presentation to the innate immune system. In particular, surface expression of platelet TLR4 enables platelets to present lipopolysaccharide to mononuclear cells and neutrophils which can modulate their phagocytic capabilities. On the other hand, studies have also suggested that depending on their activation state, platelets may be able to either suppress CD8+ T cell responses or under certain circumstances, present MHC class I associated peptides to activate CD8+ T cells. More recent data from our laboratory suggests that platelet progenitors, the megakaryocytes can act as potent antigen presenting cells that can cross present protein antigens to CD8+ T cells. Taken together, these studies suggest that platelets represent a critical link between innate and adaptive immunity. Thus, elucidating the role of platelets in sepsis and a better understanding of the apparent central role they play as immune cells may be important for the potential development of efficient therapeutic modalities against infections. This lecture will highlight the many characteristics of platelets that categorize them as immune cells and will discuss how platelets may be major controllers of immune responses.

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Abstract No. 64
Abstract Title: Inherited thrombocytopenias: not only haemorrhages
Full Name: Calo L. Balduini and Federica Melazzini
Institution/Company: Università di Pavia and IRCCS Policlinico San Matteo Foundation, Pavia, Italy

Abstract Details: Inherited thrombocytopenias (IT) have been considered for a long time exceedingly rare and always characterized by severe bleeding tendency. However, recent identification of several new forms raised from a handful to 30 the number of well-defined IT and revealed that they are actually more frequent than previously thought, affecting at least 2.7:100,000 subjects (Balduini et al, 2102; Pecci, 2015; Savoia, 2015). This explosion of knowledge changed our view of IT, in that it has been shown that bleeding tendency is mild or even absent in most cases. In fact, many of the newly discovered IT on the one hand were found to be characterized by mildly or moderately reduced platelet count, on the other side were proved to be more prevalent than those known in the past. Although severe bleeding affects only a minority of patients, ITs have still to be taken seriously because advances in their knowledge revealed that many patients run a risk that remained unknown until recently: that of acquiring additional disorders that affect their quality of life and often put at risk their lives. Subjects with congenital amegakaryocytic thrombocytopenia always develop bone marrow aplasia in childhood and die if they do nor receive bone marrow transplantation (Ballmaier and Germeshausen, 2011); those with MYH9-related disease (MYH9-RD) not only often develop deafness and cataracts, but are also at risk of an evolutive glomerulonephritis causing renal failure and requiring dialysis or kidney transplantation (Pecci et al, 2014a); patients with ANKRD6-related thrombocytopenia (Noris et al, 2013) and familial platelet disorder with predisposition to acute myeloid leukemia (Liew and Owen, 2011) are at risk of myeloid malignancies, while subjects with ETV6-related thrombocytopenia (Noetzli et al, 2015) are prone to childhood lymphoblastic leukemia. Thus, recognizing patients with these disorders is mandatory in order to give effective genetic counselling, personalize follow up and be ready to give appropriate treatments if new illnesses develop. Making a definite diagnosis is important also because specific treatments for specific disorders have been identified. For instance, thrombopoietin mimetics have been shown to be effective in increasing platelet count in subjects with MYH9-RD (Pecci et al, 2010), and some patients successfully received these drugs instead of platelet transfusion in preparation to surgery or other invasive procedures (Pecci et al, 2012; Favier et al, 2013). Moreover, long-term thrombopoietin mimetics administration reduced spontaneous bleeding in some subjects with Wiskott-Aldrich syndrome and X-linked thrombocytopenia (Gerrits et al, 2015). Also for some extra hematological defects of IT effective treatments have been found. For instance, cochlear implantation was very effective in restoring hearing capacity in 8 of 10 subjects with MYH9-RD (Pecci et al, 2014b). Unfortunately, suspecting and
diagnosing IT is not always easy, and many patients are misdiagnosed with immune thrombocytopenia. Medical history (to identify other affected family members), physical examination (to recognize the additional defects of syndromic IT) and blood film examination (to detect the morphological abnormalities of blood cells that are characteristic of many IT) remain the most important tools for suspecting the genetic origin of thrombocytopenia (Balduini et al., 2013).

Abstract No. 65
Abstract Title: Advances in our understanding of TTP and current management
Full Name: Dr Marie Scully
Institution/Company: University College London Hospital, London, UK

Abstract Details: TTP is a life threatening disorder that requires prompt diagnosis and immediate treatment. The mortality remains at 10-20% during acute episode and is increased if the diagnosis is not considered, treatment is delayed and in the presence of poor prognostic factors, primarily neurological and cardiac involvement. Cardiac disease is often only evident by a raised troponin level at presentation (Hughes, et al 2009) and +/- neurological features should be a signal to intensify therapy. Plasma exchange remains the mainstay of therapy, to replenish the significantly reduced metalloprotease ADAMTS 13. In the majority of cases, TTP is caused IgG antibodies to ADAMTS 13. Antibodies are polyclonal, almost exclusively affecting the spacer domain of ADAMTS 13 and are not all inhibitory in nature as once considered. More recently, very low ADAMTS13 antigen levels appear to predict severity (Thomas, et al 2015) and the role of immune complexes appears increasingly important. Reducing the antibodies, achieves in most patients, normalisation of ADAMTS 13. The main therapies used are steroids and rituximab. Prevention of relapse can be achieved by monitoring ADAMTS 13 levels and treating with rituximab prophylactically (Westwood, et al 2013) (Hie, et al 2014). Secondary causes of TTP, also associated with significantly reduced ADAMTS 13 (<10%), require treatment of the underlying condition as well as PEX and often immunosuppression. Despite congenital TTP being rare, suggested as <1/million of the population, the majority of cases are now diagnosed in adulthood, especially during pregnancy. Furthermore, particularly within Caucasians, a specific molecular abnormality can be identified (Moatti-Cohen, et al 2012, Scully, et al 2014). There are new therapies on the horizon for TTP. Currently under clinical trials are nobody’s, preventing the binding of platelets to VWF. In a phase II study, the time to normalisation of the platelet count was 39% quicker than standard therapy. A phase III trial has been initiated. While not affecting the underlying pathophysiology, this therapy reduces new microvesicular formation and improves the time to platelet normalisation in the acute setting. Replacement of ADAMTS 13 using recombinant technology is the ideal situation. Phase I use of rec ADAMTS 13 has been completed in congenital TTP and further trials in congenital and acquired TTP are awaited.
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Abstract Category: UK Haemoglobinopathy Forum

Abstract No. 66

Abstract Title: Investigational Agents for Sickle Cell Anaemia

Full Name: Miguel R. Abboud MD
Institution/Company: Department of Pediatrics and Adolescent Medicine, American University of Beirut, Beirut, Lebanon

Abstract Details: Sickle cell disease (SCD) is a general name for a group of inherited conditions that have two features in common – sickle red cells in the blood, and clinical illness as a result of having the abnormal erythrocytes. The underlying abnormality is a point mutation, the replacement of adenine by thymidine (GAG => GTG) in the sixth codon of the gene for beta globin. The protein product of this abnormal gene is sickle haemoglobin (HbS). Deoxygenated HbS is less soluble than its normal counterpart deoxy-HbA. Therefore deoxy-HbS crystallizes when oxygen concentration is low, as occurs in the tissues, making the red blood cell adopt various abnormal shapes, such as the characteristic sickle or half-moon shape. Sickle cells and other erythrocytes containing HbS tend to stick to white blood cells, platelets and blood vessel walls, so obstructing blood flow and causing damage to various parts of the body. Blood vessel occlusion, sickling of erythrocytes, and premature destruction of red cells containing HbS (haemolysis) are the fundamental pathophysiological processes in SCD. Despite profound understanding of the genetic basis and pathophysiology, effective or curative therapy for SCD has remained elusive. Therapeutic agents that aim to interfere with pathophysiology of sickling and that currently are under investigation will be discussed in this presentation; these include selectin antagonists, adenosine receptor agonists and new anti-adhesion agents. It is hoped that the considerable insight into the nature of SCD acquired to date will be translated into efficacious treatment for this condition.

Abstract No. 67

Abstract Title: Setting up a comprehensive sickle cell care program in a low resource setting

Full Name: Dr Mohamed Cherif Rahimy
Institution/Company: Professor of Pediatrics and medical Genetics, Faculty of Health Sciences, University of Abomey-
Calavi, Director, The National SCD Institute dedicated to the care of affected Infants and Pregnant Women, Benin Republic, West Africa

Abstract Details: In developed countries, continuous comprehensive care program (CCCP) from diagnosis at birth, prior to onset of symptoms, has been shown to decrease SCD-related childhood mortality and mor-
bidity. In 1993, no data was available on such SCD programs in Sub-Saharan Africa. However, given the cultural superstitions and poor socioeconomic back-
ground of the sub-Saharan Africa countries, where the vast majority of children with SCD live, programs need substantial adaptation, tailored to the local reali-
ties which otherwise will inevitably compromise compli-
cance of parents and consequently enrollment of initially asymptomatic SCD children into a CCCP. Without follow-up, neonatal screening will have no sense in terms of public health. Facing these con-
straints, as a first step, we concentrated our effort to constitute a trained and committed team on voluntary basis including midwives and elaborated a CCCP, which includes intensive socio-medical intervention programs tailored to local constraints to overcome drawbacks and to ameliorate the disease course. In a second step, in May 1993, we implemented a strategy based on identification and active information and sensitization of the pregnant at-risk-women prior delivery, to encourage voluntary enrollment of the future babies into the screening and follow-up pro-
grams and oriented our attention towards the two main maternities in Cotonou the financial pole city of the country. During the initial period, this newborn testing was asked by 79.3 % of the targeted 736 at-risk-women of whom 81% did ask for the result of the test, which was made available before the age of three months; and 85% of eligible SCD
babies were effectively enrolled into the CCCP. Starting from 1996, more and more at-risk-mothers aware of the existence of such programs brought their offspring for testing and enrollment and increasing number of children diagnosed on the occasion of SCD-related acute events were also referred. Furthermore, several additional programs were designed and implemented: specific care to improve the poorer pregnancy outcome in SCD, cost-effective outpatient management of fever, a frequent acute event in SCD children, non-invasive management of the hip avascular necrosis. Initial analyses of the cohort; indicate a remarkable reduction of the morbidity and mortality burden and satisfactory physical growth. In our series of SCD children, the under-five mortality rate is 15.5 per 1000, which is amazingly 10 times lower than the overall under-five mortality rate in the Benin Republic; the observed maternal mortality rate is 1.8%. About 80% of enrolled children are still regular attendees. These results sustained by an advocacy strategy including organization of two international seminar held in Cotonou, festivities for SCD children, intervention in local media, a WHO supported workshop on SCD in September 1999 and top-ranked scientific papers, were important determinants in inciting our Ministry of Health to institute in year 2000, the National SCD Program and to convince the Government to create in 2010, The National SCD Institute, dedicated to the care of affected Infants and Pregnant Women, where a cohort of more than 3,000 patients are prospectively and homogenously followed from early infancy, to document the history of SCD in our settings. This National Institute, fully inside the national health system, has already set up two satellite centers at 150 and 450 km from Cotonou. Very striking, this experience demonstrates the possibility to 1) revert the community attitude toward the disease and 2) to convince the decision makers on the relevance of giving appropriate care to children with SCD, despite the Africa setting unique conditions.

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Abstract Category: Paediatric Committee / CCLG / CLCN
Abstract No. 68
Abstract Title: Genomic of Childhood ALL
Full Name: Prof Shai Izraeli
Institution/Company: Sheba Medical Center and Tel Aviv University, Israel

Abstract Details: In this educational talk I will give an updated overview on the genomic landscape of childhood ALL focusing on B cell precursor ALL and on recent discoveries. Childhood ALL is a developmental disease. It results from the unfortunate accumulation of several acquired, somatic, genetic abnormalities that block differentiation and endow properties of self-renewal of lymphoid precursors. The first initiating event occurs in-utero and result in an expansion of a large pre-leukemic clone. The genetic events causing progression to frank leukemia occur after birth. The machinery responsible to many of these genetic aberrations is the inherent “built-in” lymphoid specific genomic instability that is responsible for the V(D)J DNA recombination that generates immune diversity. Hence childhood ALL may be viewed as a “genomic developmental accident” of this sophisticated machinery. Greaves hypothesis that the progression to frank ALL may be related to immune/ inflammatory response to common infection has recently been supported by experimental evidence in transgenic mice. Recent discoveries have expanded the defining subgroups of ALL. A subgroup of ALL named “Philadelphia like”, which probably should be better named as “Kinase driven”, consists of many types of genomic lesions that activate either the ABL or the JAK-STAT signaling pathway. The diagnosis of these leukemias is important not only because of their worse prognosis but also because of the possible therapeutic role of specific kinase inhibitors. Another group among “B-others” is characterized by the expression of a short isoform of the ERG oncogene. The role of this isoform, if any, in the generation of these leukemias is unclear. This subgroup is associated with better prognosis. The primary driving events are always associated with additional secondary cooperating mutations. These may be divided in general into three types: mutations in differentiation genes (e.g. PAX5, IKZF1), activation of signaling (e.g. RAS), or epigenetic modifications (e.g mutations in CREBBP). The diagnosis primary and secondary events is important for risk classification. For
example the presence of IKZF1 deletions is generally associated with worse prognosis except when they are associated with the abnormal ERG isoforms. It is important also to stress that the prognostic significance depends on the treatment protocol. The combinatorial matrices of primary and secondary genetic events create a clonal complexity of ALL at diagnosis and relapse. Thus even at diagnosis the leukemia may be composed from several subclones. Relapse may originate in a minor subclone resistant to upfront chemotherapy. Several such examples of subclonal expansion by chemotherapy will be given. In the future, identification of specific “resistance mutations” at the time of diagnosis may tailor therapy to prevent relapse. Finally, host genomics gene wide association studies (GWAS) have been conducted to identify genetic polymorphisms associated with drug toxicity. These interesting discoveries may allow future personalized adjustment of therapy to reduce long term toxicity which is the major current challenge in treatment of childhood ALL.

Abstract No. 69

Abstract Title: Novel Treatments for Childhood ALL

Full Name: Lia Gore, MD
Institution/Company: University of Colorado School of Medicine and Children’s Hospital Colorado Aurora, Colorado, USA

Abstract Details: Overall and disease free survival for childhood acute lymphoblastic leukaemia (ALL) has continued to improve such that there are now subsets of patients with ALL who have a greater than 98% chance for cure, while some have quite dismal outcomes and remain refractory to conventional treatments. Prognostic factors are refined sufficiently to allow risk-directed categorization and disease treatment allocation, which for some patients may mean less intensive therapy and the potential for fewer short- and long-term side effects, while advances in molecular and genomic diagnostics are increasingly being used to consider alterations in primary therapy for higher risk patients. Recent developments in therapies for childhood ALL such as those presented at this meeting have altered the landscape of available options for the treatment of relapsed ALL in particular, and increasingly, practicing paediatric oncologists are challenged to place these new treatments into the context of currently established therapies and prioritize the options for relapsed patients specifically. Immunotherapy and strategies using chimeric antigen T-cells, virus-specific T-cells, bi-specific antibodies (T-cell engaging and otherwise), and immunotoxins have greatly increased in availability and sophistication, and are now more widely available, with ever-increasing potential applications, although to date, they have not been applied to newly diagnosed patients. Simultaneously, the number of available new therapeutic options is large enough that meaningful clinical trials can be difficult to conduct based on the proportion of agents to the number of available patients eligible for such trials. A pressing challenge to the field is to begin to place these therapies in the context of more conventional approaches to the currently highly successful treatment of ALL for a large majority of affected patients, and to continue to evaluate both the short- and long-term consequences of newer treatments both alone and in combination with other more conventional agents. Discussion about what constitutes a truly novel therapy for ALL and examples of currently available experimental therapies for childhood ALL will be reviewed. The context of these treatments to future strategies and trial opportunities for both single agent and combination explorations will be discussed.

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cardiovascular disease. Over the last three decades, all major pediatric and several adult HL study groups have followed the paradigm of response-based treatment adaptation and toxicity sparing through the reduction or elimination of RT and tailoring of chemotherapy. High treatment efficacy is achieved using dose-dense chemotherapy. Refinement and reduction of RT have been implemented on the basis of results from collaborative group studies, such that radiation has been completely eliminated for certain subgroups of patients. Because pediatric staging and response criteria are not uniform, comparing the results of trial series among different pediatric and adult study groups remains difficult; thus, initiatives to harmonize criteria are desperately needed. A dynamic harmonization process is of utmost importance to standardize therapeutic risk stratification and response definitions as well as improve the care of children with HL in resource-restricted environments.

Abstract Category: Laboratory Science

Abstract No. 71

Abstract Title: Challenges and opportunities for haematology diagnostic services

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Abstract Details: Haematologists will be central players in the looming clash of the two dominant philosophies in modern medicine – personalised medicine and the value in healthcare movement. Haematologists have led the way in the development of personalised medicine. Chronic myeloid leukaemia, in which the nature of the disease is dramatically changed by the use of a bespoke therapy targeting the genetic signature, has proved the concept and provided hope for the current generation of researchers across all fields of medicine. Genomic technologies and their informatics skeletons are now in various stages of development and implementation in reference and research laboratories and patient samples are outsourced to them, often across national borders into different or unknown quality framework. For the haematologists in the clinic, the chance to describe an individual patient’s disease in molecular terms is the endgame of their physician training to be curious, thorough and to regard the observation of each patient as an opportunity to contribute to the body of knowledge about disease. At the same time, governments are calling for a halt to growth in healthcare spending and for the profession to justify their use of resources with evidence that interventions provide better outcomes for patients and that they have protected patients from interventions which are of little or no value to the them. With the demand for pathology testing outstripping other medical services throughout the world in the last twenty years, both the clinical stewards of value in healthcare and the budget holders have the diagnostic laboratory in their sights. The haematologist, in this domain, has the difficult role of steward and change agent, not physician investigator. The haematologist, with one foot in the clinic and the other in the laboratory is, however, uniquely placed to lead the discussion on where testing presents value and where it is wasteful, and in the process, to address the points of weakness where errors in diagnosis arise. The challenge in front of us all is to make funding go further without compromising the individual patient’s chance to benefit from the new disease changing technologies or their safety as physician test ordering and laboratory pathways are re – engineered. Examples of new models of practice in diagnostic haematology laboratory services will be discussed.

Abstract No. 72

Abstract Title: CLL or not CLL? - Definitive diagnosis of CD5+ B-cell malignancies in an integrated laboratory

Abstract Details: CD5 has been relied upon for many years as a critical diagnostic marker for mature B-cell neoplasms and diagnostic algorithms which stratify based on CD5 expression are routinely used by haematopathology laboratories. CLL and MCL are defined as CD5-positive entities but, as phenotypic and molecular characterisation of B-LPDs has improved, it has been shown that CD5 expression can be seen in a wider range of diagnostic entities, ranging from indolent lymphomas to those with an aggressive disease course. This group of disorders can show overlap in clinical features, morphology, immunophenotype and molecular abnormalities, making definitive diagnosis challenging. Accurate diagnosis is crucial to patient outcome, especially in the case of clinically aggressive entities, and as new treatment strategies are developed this may become even more important. A more robust approach to the diagnosis of CD5+ B-lymphoproliferative disorders is required. Tissue biopsies, bone marrow aspirates and peripheral blood samples received for diagnosis of mature B-cell malignancies by a single integrated haematopathology department, HMDS, have routinely had extended B-cell immunophenotyping for over a decade. This has provided a large cohort of well-characterised CD5+ B-cell lymphomas which have been studied to define the range of B-cell neoplasms which exhibit CD5 expression and investigate any phenotypic differences between entities. Current immunophenotypic scoring systems to diagnose CLL may be inadequate when recent understanding of molecular pathway abnormalities are considered. The use
of newer antigens, such as CD200 and ROR1 expression, can improve diagnostic accuracy. CD5+ DLBCL has several distinct phenotypic characteristics which can contribute to diagnosis. Mantle cell lymphoma and CD5+ marginal zone lymphoma show the greatest amount of phenotypic overlap but, again, newer antigens, such as ROR1, can be helpful in distinguishing between the two entities. In many cases the assessment of key molecular abnormalities is also crucial and immunophenotyping can be used to direct downstream molecular testing. There is no defining molecular abnormality in CLL: deletion of 13q14 is present in approximately half of cases but is also seen in other B-LPDs. The presence of a CCND1/IGH indicates a diagnosis of MCL but absence of the translocation does not completely exclude this diagnosis. The MYD88 (L265P) mutation has been shown to be present in a substantial number of WM/LPL/MZL patients but again is not disease-specific. The additional diagnostic evidence provided by targeted molecular analysis allows a definitive diagnosis in some instances but there remains a proportion of cases for which a definitive diagnosis is not possible. In summary, CD5+ B-LPDs represent a group of disorders which can be diagnostically challenging. Both flow cytometry and molecular analysis can contribute to reaching a definitive diagnosis but a proportion of cases remain unclassifiable. This has implications for patients in terms of access to clinical trials and novel therapies and this group should be characterised further.

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Abstract Category: LMIC (3) Transfusion

Abstract No. 73

Abstract Title: A new research agenda for blood services in Africa

Full Name: Imelda Bates

Institution/Company: Liverpool School of Tropical Medicine, Liverpool, UK

Abstract Details: Introduction Chronic shortages of safe blood and inequitable access cause substantial death and disability and are major public health challenges for countries in sub-Saharan Africa (SSA). [1]. Transfusion services in SSA face high rates of family-replacement donation, dependence on secondary-school donors, low repeat donation rates, temporal variations in supply and demand, high discard rates due to transfusion-transmitted infection, predominantly emergency rather than elective transfusions and unsustainable reliance on external funding. International policies and guidelines for blood transfusion are generally based on evidence from high-income countries and are not necessarily appropriate for low and middle-income countries in Africa. There is also critical lack of indigenous transfusion researchers in SSA, which makes it very difficult for the region to generate evidence for its own priorities. Following the first SSA transfusion research prioritisation meeting in Mombasa in 2008 [2], efforts to build up research capacity within SSA’s blood services have intensified (eg. T-REC programme [3] and ISBT’s African transfusion researcher network). In 2015 at a workshop in Pretoria stakeholders from SSA’s transfusion services updated and revised the research priorities taking account of recent publications and emerging challenges (eg. Ebola epidemic). Methods The 35 workshop participants included blood service directors, researchers, clinicians, funders, policy makers, commercial organisations and non-governmental organisations. Through discussions in small inter-disciplinary groups research priorities were revised and updated for each of five themes, from biological safety to financing models, used in the 2008 Mombasa workshop. Specific research questions were proposed for each theme and prioritised through an equitable voting system. Results A revised transfusion research agenda for SSA was agreed. Examples of priorities were: pragmatic and culturally-sensitive approaches to blood donor recruitment, evidence on the costs and effectiveness of different blood service models and appropriate IT systems to optimise blood stock use and blood donor tracking. These priorities were informed by a preliminary review of published transfusion research from SSA between 2008 and 2015. The review identified ~300 primary transfusion research publications. Half of these concerned transfusion-transmitted infections; very few focused on transfusion systems, models, costs and sustainability. Discussion A revised research agenda for transfusion services in SSA was agreed [4] but it was clear that there was a mismatch between the overwhelming focus of recent publications on biological safety and an almost complete absence of much-needed ‘systems-level’ research. SSA blood services face many similar problems so there is much to be gained by developing a mechanism for sharing information and tools, and by collaborating and learning from each other.

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3. Building research capacity of blood services in Africa http://www.i-rec.eu/
Learning objectives
To understand: the challenges faced by blood services in sub-Saharan Africa (SSA) in ensuring adequate supplies of safe blood and equitable access why research from high-income countries may not be applicable to the SSA setting where most blood comes from family donors and is used for emergencies, and where transfusion-transmitted infection (TTI) prevalence is high why the current research focus on TTIs does not match the need for 'systems-level' research on, for example, how to increase repeat donors and optimise stock management and use

Abstract No. 74
Abstract Title: The challenge of providing safe blood transfusions in Sub-Saharan Africa – T-REC transfusion research in Ghana
Full Name: Henrik Ullum, Lucy Asamoah-Akuoko, Francis Sarkodie, Oliver Hassall, Imelda Bates
Institution/Company: University of Copenhagen, Denmark

Abstract Details: Blood transfusion is an essential and integral part of modern hospital based health care. Sub-Saharan African (SSA) transfusion services are faced with a multitude of challenges including: lack of blood for transfusion, shortage of financial resources and high prevalence of transfusion-transmissible infections. T-REC was an EU funded African/European collaborative network aimed at building transfusion research capacity within the two African partner countries, Zimbabwe and Ghana. Research questions in Ghana were the two top priority research areas defined at the 2008 Mombasa transfusion research workshop: 1) Reducing transfusion-transmitted infections and 2) Increasing recruitment and retention of safe donors. The first PhD project focused on defining rational ways of reducing transmission of syphilis by transfusion. In Ghana, it is estimated that around 6-8% of blood donors carry antibodies against syphilis with a corresponding high risk of syphilis transmission by unscreened blood. However, there is no national algorithm on syphilis screening of blood donors and as cold storage of blood components strongly inhibits syphilis transmission many blood banks in Ghana do not test for syphilis. A survey of 81.9% of transfusion facilities in Ghana revealed large proportions of: lack of syphilis testing 52%, usage of unvalidated quick tests 53%, lack of standard operating procedures 93% and lack of clinical care of infected donors 43.1%. Challenged by an unacceptable loss of donors by conventional syphilis screening of donors and risk of syphilis transmission without screening a simple algorithm was developed at Komfo Anokye Teaching Hospital. The blood donors were screened at the time of donation with an anti-treponemal rapid diagnostic test and blood collected irrespective of the result. Units screening negative for HIV, hepatitis B and C were released to stock. Syphilis RDT screen-positive units were quarantined and re-tested with Rapid Plasma Reagin (RPR) – units testing negative were released to stock and test-positive units discarded. With our data we concluded this that novel strategy can contribute to improving blood safety without jeopardizing blood supply in countries facing both high prevalence of syphilis and shortages of blood donors. In Ghana as in many other countries of SSA the blood supply often relies very much on family replacement donors donating for friends or relatives. It has proven difficult to obtain large populations of repeat voluntary donors. Family replacement donors could potentially be motivated to become repeat voluntary donors. Through in depth interviews and focus group discussions we identified several cultural specific beliefs and ideas that could deter blood donation. Blood having supernatural power and risk of donated blood being used for occult rituals are common beliefs; also fear of positive HIV tests deters donation of blood. In a survey of 211 blood donors at Southern Area Blood Centre only 6 returned for re-donation during 4 months follow up. Questionnaire data will be used to identify factors that may increase return rates. The T-REC collaboration is a useful example of research capacity building in low/ middle income countries to answer important health research questions relevant for local policy and practice.

Abstract No. 75
Abstract Title: REDLINE: cargo drones to expedite blood delivery and medical supplies between hospitals and clinics in emerging economies
Full Name: Jonathan Ledgard
Institution/Company: Afrotech-EPFL. Lausanne, Switzerland

Abstract Details: Redline is a consortium based out of EPFL, ETH, and Imperial Colleges which proposes to develop Unmanned Aerial Systems (UAS) technology, droneport infrastructure, logistics, and regulatory framework to enable delivery of payloads with high social value to off-grid communities that lack access to basic healthcare and economic necessities. Problem: continued lack of infrastructure in emerging economies Some 800 million people in our world will have limited access to basic health services and economic necessities for the foreseeable future. Most will live in Africa. Delivery of urgently needed supplies to off-grid communities and persistent humanitarian crises will often be slow, expensive, and poorly
accompanied by side effects, varying in frequency long with daily oral medication, which is itself.

However, unlike patients who have so far successfully stopped therapy are small, the ability to achieve deeper responses on the more potent second generation agents compared to imatinib, suggests that this figure is likely to increase over time and holds real hope of 'treatment free remissions' for many.

Abstract Category: MPD/CML

Abstract Title: Curing Chronic Myeloid Leukaemia: Hope or Reality?

Full Name: Jane F Apperley

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Abstract Details: The introduction of the tyrosine kinase inhibitors (TKI) into the clinical management of chronic myeloid leukaemia (CML), together with the adoption of rigorous, accurate and standardised molecular monitoring of disease burden, has profoundly changed the prognosis of this once fatal condition. Data derived from patients who were entered into clinical trials of frontline TKI at the MD Anderson Cancer Center, suggest that the overall survival of patients aged less than 65 at diagnosis now approaches that of the normal US population. However, unlike patients who have been 'cured' of other haematological malignancies, treatment is lifelong with daily oral medication, which is itself accompanied by side effects, varying in frequency and severity. The management of the majority of patients has now become the management of any chronic illness, with attention paid to avoiding and/ or minimising the adverse events of therapy. It is therefore not surprising that patients and physicians are questioning the need to remain on continuous therapy. Unsurprisingly, the probability of prolonged survival is associated with the ability of the TKI to induce deep and durable molecular responses. This ability is measured in terms of log reduction in tumour load using quantitative reverse-transcriptase polymerase chain reaction assays (RQ-PCR) to assess the number of BCR-ABL1 transcripts. At 12 months from the start of therapy, a three log reduction, known as a major molecular remission (MMR or MR3), is associated with prolonged survival. However, a group of patients with a very good overall survival, can be identified as early as 3 months from the start of treatment, on the basis of a one log reduction (MR1) in tumour load. Failure to achieve MR1 at 3, or MR3 at 12 months, are used to trigger a change of TKI so as to optimise the response. The depth of molecular response continues to increase over time, and a significant proportion of patients will achieve even deeper responses, reaching the limits of sensitivity of the RQ-PCR assay, at MR4.5 or MR5. In the phase III study of imatinib versus nilotinib for newly diagnosed patients (ENESTnd), the probability of MR4.5 at 4 years was 23% and 40% in imatinib and nilotinib treated patients respectively. The three year follow-up from the phase III DASISION study (dasatinib vs imatinib for the newly diagnosed), similar figures were reported with MR4.5 occurring in 22% of those treated with dasatinib compared to 12% of those on imatinib. It is in this group of very good responders that attempts at withdrawal of therapy have occurred. In the STIM study of 100 patients on imatinib who had achieved MR4.5 for a minimum of 2 years, approximately 40% could remain off therapy indefinitely. These results were reproduced in a further group of imatinib treated patients with sustained MR4.5 in the smaller Australian TWISTER trial of 40 patients. A number of other studies are now underway across the world investigating the possibilities of stopping patients with less deep responses (MR3 or MR4) for a variable period of time (I or 2 years) and/or who have been treated with dasatinib or nilotinib. Certain characteristics that might predict the patient capable of stopping therapy for a prolonged period of time, are now emerging, including early molecular response, depth and duration of deep responses, response to first line therapy and Sokal score. Although the numbers of patients who have so far successfully stopped therapy are small, the ability to achieve deeper responses on the more potent second generation agents compared to imatinib, suggests that this figure is likely to increase over time and holds real hope of 'treatment free remissions' for many.
Abstract No. 77

Abstract Title: Mutations in MPN, what do they mean, how can we use them

Full Name: Alessandro M Vannucchi

Institution/Company: CRIMM, Center for Research and Innovation for Myeloproliferative Neoplasms, AOU Careggi, Department of Experimental and Clinical Medicine, University of Florence, Italy.

Abstract Details: Recent advances in the understanding of the molecular landscape of chronic myeloproliferative neoplasms (MPN), that include polycythemia vera (PV), essential thrombocytosis (ET) and primary myelofibrosis (PMF), have contributed to a revision and, overall, a significant improvement of the diagnostic approach to these hematologic neoplasms. The three phenotypic drivers mutations, represented by mutations in JAK2V617F, MPL and CALR, are included as major by mutations in JAK2 (V617F, exon 12 mutations), the criteria for imatinib discontinuation in patients with CML. The number of mutations per patient, the mutational frequency, an ideal diagnostic pathway revision and, overall, a significant improvement of the molecular landscape of chronic myeloproliferative neoplasms (MPN), that include polycythemia vera, essential thrombocythemia and primary myelofibrosis.

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Recent advances in the understanding of the molecular landscape of chronic myeloproliferative neoplasms (MPN), that include polycythemia vera (PV), essential thrombocytosis (ET) and primary myelofibrosis (PMF), have contributed to a revision and, overall, a significant improvement of the diagnostic approach to these hematologic neoplasms. The three phenotypic drivers mutations, represented by mutations in JAK2V617F, MPL and calreticulin (CALR), are included as major by mutations in JAK2 (V617F, exon 12 mutations), the criteria for imatinib discontinuation in patients with CML. The number of mutations per patient, the mutational frequency, an ideal diagnostic pathway revision and, overall, a significant improvement of the molecular landscape of chronic myeloproliferative neoplasms (MPN), that include polycythemia vera, essential thrombocythemia and primary myelofibrosis. The three phenotypic drivers mutations, represented by mutations in JAK2V617F, MPL and calreticulin (CALR), are included as major by mutations in JAK2 (V617F, exon 12 mutations), the criteria for imatinib discontinuation in patients with CML. The number of mutations per patient, the mutational frequency, an ideal diagnostic pathway revision and, overall, a significant improvement of the molecular landscape of chronic myeloproliferative neoplasms (MPN), that include polycythemia vera, essential thrombocythemia and primary myelofibrosis.

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Abstract No. 78

**Abstract Title:** The Goals of Treatment for Myeloproliferative Neoplasm Patients

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**Abstract Details:** Patients with myeloproliferative neoplasms are a very heterogeneous group of patients regarding age, disease prognosis, and clinical impact arising from their myeloproliferative neoplasm. Indeed, the clinical spectrum from earlier myeloproliferative neoplasms such as essential thrombocytopenia (ET) and polycythemia vera (PV) can have quite a variable course and clearly can then transition into the more difficult disease-related features which can be hallmarks of primary myelofibrosis or those with post-ET or post-PV myelofibrosis. Over the past 10 years, it has been identified that these patients have several different categories of clinical burden that can exist with their disease. First, there is a variable risk of vascular events, whether they be thrombosis or hemorrhage. Second, impact of myeloproliferation, whether it leads to splenomegaly and associated difficulties, hepatomegaly, or more rarely, other areas of extramedullary hematopoiesis can be a burden. It clearly is recognized that patients can have a very disease-specific symptom burden which can include most commonly fatigue, but can frequently include pruritus and night sweats, and as the disease advances, difficulties from splenomegaly, weight loss, bone pain, and fever. Finally, there is a variable risk of disease progression either from ET and PV to myelofibrosis or from myelofibrosis to acute myeloid leukemia. Individualizing care of patients with myeloproliferative neoplasms needs to be mindful of the impact of each of these disease features in treatment planning for an individual MPN patient. Allogeneic stem cell transplant is a curative therapy for MPNs, however the time commitment to accomplish, resources required, and morbidity and mortality are significant. The appropriateness of allogeneic transplant for an individual patient requires assessment of prognosis, identification of potential donors, and thoroughly educating the patient to be involved with making the transplant decision. Medical therapies are judged based on current response criteria from both the European LeukemiaNet and the International Working Group for Myelofibrosis based on their ability to impact cytopenias and/or myeloproliferation, splenomegaly, MPN-related symptoms, and bone marrow histologic findings. The inclusion of serial assessment of symptomatic burden has joined other objective measurements such as blood counts and spleen imaging as important methods of evaluating therapy of novel agents and has been integrally involved in assessment of responses in JAK inhibitors in myelofibrosis, second-line JAK inhibitors, and polycythemia vera and new classes of agents, whether they be in combination with JAK inhibitor or of additional novel pathways such as antifibrosing agents or telomerase inhibition. Future individualization and goals of care in myeloproliferative neoplasms will likely increasingly utilize molecular markers as goals of response; however, this probably will not completely substitute the important clinical features which have been identified to date.

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Abstract Category: Acute Myeloid Leukaemia

Abstract Title: Post remission therapy by allogeneic or autologous transplantation in AML: for whom the preferred option?

Full Name: Jan J Cornelissen, MD, PhD
Institution/Company: Department of hematology, Erasmus Cancer Institute, Erasmus Medical Center, Rotterdam, The Netherlands

Abstract Details: Cancer genomics has established acute myeloid leukemia (AML) as a multiclonal disease, that develops according a Darwinian model of leukemogenesis. Immunotherapeutic approaches have recently regained interest in the treatment of multiclonal malignancies, such as the acute leukemia’s. A particular potent immunotherapeutic modality is allogeneic hematopoietic stem cell transplantation (alloHSCT), that exerts its graft versus leukemia effect across all genomic AML subsets. AlloHSCT is increasingly applied as post remission therapy (PRT) in older patients with AML, following reduced intensity conditioning regimen. Apart from matched sibling donors, an increasing number of patients receive an alternative donor graft. The last decade has witnessed major breakthroughs, challenging both the upper age limit and the application of only sibling and well-matched unrelated donors. Both umbilical cord blood and haploidentical sibling donors were shown to be associated with acceptable toxicity and largely similar outcome as compared to matched unrelated donors, and currently approach results with matched sibling donors. While alloHSCT is considered the preferred type of PRT in poor and very poor risk AML, the place of alloHSCT in intermediate risk AML is being debated and autologous HSCT is considered a valuable alternative and may even be preferred in patients without minimal residual disease (MRD) after induction chemotherapy. Apart from MRD, the application of alloHSCT depends from a number of risk factors, that were validated individually or in composite risk scores. Collectively, a risk adapted approach has contributed to avoid excess treatment related mortality and morbidity in addition to improved supportive care measures. Currently, a major challenge in the application of alloHSCT in AML is the reduction of relapse post transplantation in poor-risk AML recipients. Multiple new approaches are being developed including early timing of transplantation and manipulation of post-transplant immunotherapy by donor lymphocyte infusions and epigenetic therapies. Different transplant strategies using either autologous or allogeneic stem cells in younger and older AML patients will be discussed and recent developments in the field of alternative donors and reduced will be highlighted.

Abstract Category: BSHT Biggs MacFarlane Plenary Lecture

Abstract No. 80

Abstract Title: Common challenges in the evaluation of inherited bleeding disorders: my personal reflections

Full Name: Catherine P.M. Hayward, MD PhD FRCPC.
Institution/Company: McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada

Abstract Details: Inherited bleeding disorders are common problems worldwide that can be challenging to assess.(Hayward 2012a) While coagulation disorders, von Willebrand disease and the rare syndromic forms of platelet disorders are now well characterized, the causes of the more common disorders that affect platelet function is only now emerging.(Leo, et al 2015, Nurden and Nurden 2015) Common bleeding disorders have been more challenging to diagnose and manage as some important diagnostic tests are only offered at specialized centers. Furthermore, there is need to consider how to combine testing for different common conditions for an efficient work up of a bleeding disorder.(Hayward and Moffat 2013, Hayward 2012b) I will share lessons learned from trying to improve the diagnostic assessment of more common bleeding disorders, including platelet function defects, in clinical and laboratory settings. The initial assessment of any bleeding problem involves an evaluation of the bleeding history. For some disorders, important new data has emerged from formal evaluation of the bleeding history using standardized assessment tools. Bleeding scores have been applied to a variety of conditions to quantify bleeding for research purposes. In the case of Quebec platelet disorder, a detailed comparison of the bleeding experiences of affected and unaffected family members helped defined the risks associated with inheriting this disorder, including the likelihood that an affected individual will experience different manifestations from menorrhagia to joint bleeds.(McKay, et al 2004) The challenge is now to quantify risks associated with the full spectrum of common bleeding disorders, so that risks can be assessed, with appropriate strategies for management, based on clinical evidence. We have been exploring the use of bleeding assessment tools to evaluate individuals with common but undefined defects in platelet function to gain similar insights on their bleeding risks and treatment outcomes. It is important for such assessments to address issues that are relevant to patients and evidence-based approaches to management.(Hayward 2013) There are important needs to improve laboratory testing for bleeding disorders, including making diagnostic tests for a variety of platelet disorders more accessible. We observed that with discovery of the genetic cause of
Quebec platelet disorder, it became possible to screen persons from many different regions of the globe with a history suspicious of the disorder, and to more readily test the relatives of affected individuals. (Paterson, et al 2010) With the rapid assessment of newborns of parents with this disorder by genetic testing of cord blood samples, it is now possible to intervene with appropriate therapy at an early age; this has changed the health burden of having this platelet disorder and relieved family members. (Hayward 2013) Moreover, insights on the molecular cause of Quebec platelet disorder has led us to investigate a key, unresolved issue with different methods: why inheriting one extra copy of PLAU (the urokinase plasminogen activator gene) in this disorder causes more than 100-fold increased PLAU expression selectively in megakaryocytes. In the last decade, there have been many efforts to standardize and improve the laboratory diagnosis of platelet disorders. In many regions of the world, the access to diagnostic tests for platelet function disorders is non-existent or quite limited. The variances in laboratory diagnostic practices are also problematic and stimulated the development of many guidelines. (Gresele et al 2014, Gresele and the Subcommittee on Platelet 2014, Harrison, et al 2011, Hayward, et al 2010) To help generate needed evidence for valid laboratory practice, we performed the first study on bleeding disorder investigations that assessed for non-inferiority and superiority of different laboratory approaches. (Castilloux, et al 2011) Our experiences with external quality assessment exercises for evaluating platelet function abnormalities indicate that laboratories greatly value efforts to improve their evaluation of platelet function disorders, including the post analytical phase of test interpretation. (Hayward, et al 2012, Hayward, et al 2009) As research generates important new knowledge on the causes and consequences of common bleeding disorders, it is important to translate discoveries in ways that improve the experiences and lives of persons living with these conditions.

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**Abstract Category:** BSHT/UKHDCO

**Abstract No. 81**

**Abstract Title:** Novel Protein Strategies for Hemophilia Treatment

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**Abstract Details:** Blood coagulation factors VIII and IX play a critical role in maintaining normal hemostasis by activating factor X. Deficiency of these proteins caused by mutations in the genes encoding FVIII or FIX leads to hemophilia A or B (HA and HB), respectively. (1) In each disease, there is impairment of the intrinsic pathway with inadequate thrombin generation and defective hemostasis. Protein replacement with plasma-derived or recombinant clotting factor is the standard or care. (2) Unfortunately, ~20-30% of patients with FVIII deficiency and ~3-5% of patients with FIX deficiency develop inhibitory antibodies to infused factor
replacement products. In these patients, hemostasis can be achieved using bypass therapies (e.g., aPCCs and rFVIIa) that enhance FXa production. However, these therapies have limitations that have prompted the research community to develop alternative strategies. These new approaches are in different phases of clinical development and include: a bispecific monoclonal antibody that mimics the action of FVIII; antibodies that target TFPI-an important anticoagulant that blocks FVIIa, FXa, and FV(a); and an siRNA that targets the anticoagulant antithrombin-α serpin that inhibits thrombin, FXa, and FIXa. While these therapies have their own limitations, a key feature of each approach are their long half-lives (weeks) and ability to be administered subcutaneously. Bypass therapies and the non-clotting factor therapeutic approaches function at the biochemical level by enhancing FXa production or by protecting FXa by reducing its natural inhibitor. In principle, direct infusion of FXa should bypass deficiencies in the intrinsic pathway; however it has limited utility since the infused FXa is rapidly inactivated by plasma inhibitors resulting in a very short half-life (<1-2 min). Our research group has recently characterized variants of FXa (e.g., FXa-I16L) which have “zymogen-like” properties that could circumvent these associated problems. For example we have found that i) these proteins have an incompletely formed active site, making them resistant to plasma protease inhibitors; ii) in the absence of FVα, the FXa variants are, in general, refractory to active site functions and thus do not have any appreciable activity; and iii) importantly, the variants are thermodynamically rescued by FVα; thus at the site of injury where FVα is present, prothrombinase rapidly forms generating a burst of thrombin. We have exploited these unique properties and evaluated whether these FXa variants could be effective and safe in enhancing hemostasis in a variety of clinical situations. Using hemophilia as a model, we found that defective clotting and Iαa generation could be restored in human HA, HB and inhibitor plasma/blood using our lead variant, FXa-I16L. Furthermore, the zymogen-like conformation protects FXa-I16L in plasma as it has a prolonged half-life (~2 hr) versus wt-FXa (<2 min). A study using hemophilic mice revealed that administration of FXa-I16L corrects the prolonged aPTT and was well tolerated at the efficacious dose as measured by markers of coagulation activation. Further, using three separate injury models, infusion of FXa-I16L, either before or after an injury, provided effective hemostasis. Several important questions remain however. Future work will need to focus on immunogenicity, safety to assess prothrombotic potential and whether the pharmacokinetic profile is desirable. Overall however, zymogen-like FXa offers a new approach to bypassing the intrinsic pathway in hemophilia and due to its strategic position in the coagulation cascade may be useful as a pro-hemostatic agent targeting a range of other bleeding conditions especially in the acute setting.

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Abstract No. 82

Abstract Title: Assessment of bleeding in anticoagulation

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Abstract Details: Oral anticoagulation is commonly administered to patients either following an acute thromboembolic event, to prevent recurrence, or as primary prevention, particularly in patients with atrial fibrillation (AF), at risk of thromboembolic stroke. Bleeding is the most relevant complication of treatment irrespective the type of (oral) anticoagulant that is administered. Major bleeding occurs in about 1-3% of patients, the most severe type, intracranial (ic) bleeding occurring in about 0.1-0.6% annually. Clinically relevant bleeding complications may occur up to about 10%, particularly in patients that use not only oral anticoagulants, but also platelet inhibitors; this double (or even triple) antithrombotic therapy is frequently seen in patients with AF undergoing a percutaneous coronary intervention for symptomatic coronary artery disease. Several risk factors for bleeding have been recognized; the HAS-BLED score (1) is one common example of a risk score that identifies elements that increase the risk of bleeding: hypertension, abnormal liver/renal function, stroke, history of bleeding, labile INR, elderly (>65 years), drugs/
alcohol; the sum of the points scored gives an estimate of bleeding risk while on oral anticoagulation (primarily vitamin K antagonists, VKA). As compared to other risk scores HAS-BLED may be superior in predicting bleeding (2). A HAS-BLED score $\geq 3$ indicates a high risk for bleeding and should trigger the physician to address the possible modifiable risk factors such as blood pressure, hepatic/renal function, stability of anticoagulation, avoiding antiplatelet agents and NSAI D’s, when possible (3). In practice, it is not the bleeding risk but the indication for anticoagulation which is leading and assessment of bleeding risk is a secondary element in the decision making process. With the current spectrum of anticoagulants, at least one can better take efficacy/risk elements into account. Many will favor a non vitamin K oral anticoagulant (NOAC) over a VKA, given the reduced risk of ic bleeding. In case VKA is preferred (for practical, financial, or other reasons), stability of INR is an important factor to take into consideration; sometimes a long-acting agent like fenprocoumon may be preferred (at least in countries where fenprocoumon is available); other measures include: improve adherence, reduce interactions, train more patients for self-management of VKA therapy. Optimal time-in-therapeutic range (TTR) is critically important and in a setting of excellent control like in Sweden, with TTR values of 76% in patients with AF on warfarin, even a very low rate of ic bleeding (comparable to NOAC in the clinical trials) can be achieved (4). Also, for NOAC, dose response effects related to bleeding have been reported, raising the issue of need for individual therapy optimization (discussed in 5,6). In order to achieve safe NOAC treatment, a careful choice of drug and dose also taking HAS-BLED factors into regard (except INR instability), is essential. Since routine laboratory monitoring is not required with NOAC treatment, guidance of patients by other means to maintain adherence and provide support in case of daily problems that occur during anticoagulation, is again critically important. The ESC has outlined recommendations for follow up of patients on NOAC, including assessment of adherence (7). Eventually, assessment of drug activity levels may be helpful, to further improve the benefit/risk ratio of NOAC therapy.

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Abstract Category: Waldenstrom Forum
Abstract No. 83
Abstract Title: Biology of Waldenström macroglobulinemia
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Abstract Details: Waldenström macroglobulinemia (WM) is a non-Hodgkin lymphoma characterized by the presence of a CD20+ lymphoplasmacytic infiltrate in the bone marrow and an elevated serum immunoglobulin M monoclonal protein.1 The lymphoplasmacytic cells present in WM commonly display high levels of surface CD19, CD20, and immunoglobulin light chain expression, but the malignant B-lymphocytes typically lack CD10 expression. The plasmacytic component expresses the same immunoglobulin light chain as the lymphocytic component, is positive for CD138, and shows diminished expression of B-cell–associated antigens such as CD19, CD20, and PAX5. Conventional cytogenetic analyses initially determined deletions of chromosome 6q to be the most common recurrent abnormality in WM, and this abnormality was identified in approximately half of the patients studied.2 Although the deletion of 6q is present in around 50% of WM patients, its presence cannot be used for diagnosis of the disease as the deletion is widely observed in other B-cell malignancies, such as marginal zone lymphoma, multiple myeloma and chronic lymphocytic leukemia. Recent data obtained from whole genome sequencing of WM patients reported a mutation in MYD88 in 90% of cases, which leads to a leucine to proline substitution in codon 265 (L265P).3 This MYD88 mutation has become a biomarker for differentiating WM from other related entities such as marginal zone lymphoma, where MYD88 L265P was detected in less than 10% of cases. Furthermore, a low prevalence of MYD88 mutations in IgM-MGUS suggests that the mutation is associated with disease progression or that there is more than one type of IgM-MGUS, with only certain types of IgM-MGUS progressing to WM. The second most common somatic alterations identified in WM are the C-X-C chemokine receptor type 4 (CXCR4) mutations.4,5 Somatic CXCR4
mutations in WM are similar to the germline CXCR4WTWHIM mutations described in the rare WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome. A WHIM mutation in CXCR4 results in the permanent activation by its ligand, stromal derived factor 1 alpha (SDF-1α/CXCL12), leading to activation of AKT and mitogen-activated protein kinase (MAPK) and promoting survival. Currently, three subpopulations of WM have been genomically defined and these groups respond differently to BTK inhibition. WM patients with mutated MYD88 and CXCR4WT benefit the most from ibrutinib exhibiting an overall response rate (ORR) of 100%, followed by those with mutated MYD88 and CXCR4WHIM (ORR 86%) and MYD88WT and CXCR4WT (ORR 60%). Gene expression profile (GEP) analysis of WM has also provided useful information about the transcriptional signature of the disease. A significant finding has been the high level of IL-6 transcript expression in WM when compared to multiple myeloma, CLL, and normal B cells. The increase in IL-6 expression in WM is suggestive of a functional relationship between IL-6, RANTES (CCL5), and IgM secretion that appears to be mediated through the JAK/STAT and PI3K pathways. Although the specific mechanisms of increased immunoglobulin secretion in WM are still not entirely understood, the pathogenic role of IL-6 and the JAK/STAT pathway in WM merits further study. A multitude of potentially effective therapies targeting cell-survival pathways are in development and offer a more precise approach for WM patients. One such agent, ibrutinib, a Bruton’s tyrosine kinase inhibitor, was recently granted approval in WM. A clearer understanding of WM biology will allow for optimal development and selection of therapies in the future.

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Abstract No. 84

Abstract Title: Bing Neel Syndrome

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Abstract Details: Bing Neel syndrome (BNS) is a rare disease in which malignant lymphoplasmacytic cells invade the central nervous system (CNS). (1) These cells may be detected in the cerebral spinal fluid, the meninges and/or the cerebral white matter. The clinical symptoms of BNS may be very diverse, and include headaches, dementia, paraplegia, and psychiatric symptoms. BNS is an extension of the disease spectrum of Waldenström's Macroglobulinemia (WM), and usually presents as a feature of relapsing disease although it may also occur at first diagnosis of WM. (2) It is very important to recognize that BNS can occur although the WM is in remission and the M-protein level is stable or not detectable. Hyperviscosity syndrome (HVS) can sometimes be confused with BNS, and should also be considered in the differential diagnosis of a WM patient presenting with CNS symptoms. While the gold standard for the diagnosis of BNS entails a direct biopsy of CNS or meningeal tissues to prove infiltration by clonal lymphoplasmacytic cells, alternative approaches including CSF examination and imaging are routinely employed. In the CSF besides morphology, also multi flow cytometry and protein electrophoresis to detect an IgM M protein can be helpful. Whole genome sequencing has shown mutations in MYD88 to be highly prevalent in WM. Using a highly sensitive real time quantitative PCR technique it has been demonstrated that MYD88 L265P can be detected in the CSF of BNS patients. Magnetic resonance imaging (MRI) of the brain and spinal cord is essential for the diagnosis and abnormalities can be found in the majority of patients. The MRI protocol must include fluid-attenuated inversion recovery and T1-weighted sequences before and after non-iodine gadolinium contrast injection. Although MRI is a very sensitive technique for the detection of malignant infiltration of the CNS, it cannot differentiate between the different histological entities of CNS lymphoma, nor does it obviate the need for CSF or tissue sampling. Treatment should be offered to symptomatic patients in whom a definitive
Cold agglutinin disease

Abstract Title: Cold agglutinin disease

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Abstract Details: Clonality, histopathology and pathogenesis Primary chronic cold agglutinin disease (CAD) is a clonal lymphoproliferative disease mediated by cold agglutinins (CA).1,2 The associated bone marrow disorder seemed strikingly heterogeneous within each of two previous studies.2,3 In a recent, comprehensive series of 54 patients with CAD, however, the findings were consistent with a surprisingly homogeneous disorder termed ‘primary CA-associated lymphoproliferative disease’ by the authors and distinct from other previously recognized entities.2 The MYD88 L265P mutation, found in most cases of lymphoplasmacytic lymphoma, could not be detected in CAD.4,5 In addition to IGHV gene sequence usage, IGLV usage is also highly restricted in CAD.6 The data suggest that subtle differences in light chain multiple binding sequences may contribute to differences in thermal amplitude and clinical phenotype.6 Following CA-binding to the I antigen at the erythrocyte surface, the antigen-antibody complex binds complement protein complex C1 and thereby triggers the classical complement pathway, resulting in predominantly extravascular, C3b-mediated hemolysis.7,8 Intravascular hemolysis mediated by the C5b6789 complex also occurs in some patients and situations.7,8 Clinical features and diagnostic workup CAD is defined by chronic hemolysis, positive direct antiglobulin test (DAT), monospecific DAT positive for C3d, and CA titer ≥ 64 (much higher in most cases).1,2 Approximately 90% of the patients have cold-induced circulatory symptoms.2 Median hemoglobin level has been estimated to 8.9 g/dL.2 In cold climates, a majority experiences seasonal variations with worsening of anemia and circulatory symptoms during winter or at low ambient temperatures. 70% of the patients have experienced exacerbations precipitated by febrile infection, major surgery or major trauma.2,10 15% or more have hemoglobinuria.3 50% of the patients have been considered transfusion dependent at some time during the course of the disease.2 A focused history and clinical examination is, therefore, an essential part of the diagnostic workup. Laboratory tests include full blood counts, microscopy of a blood smear, assessment of hemolysis (absolute reticulocyte count, LDH, bilirubin and haptoglobin), polyspecific and monospecific DAT, and CA titer. Results of serum electrophoresis with immunofixation, immunoglobulin class quantifications, C3/ C4 determinations and bone marrow examinations (biopsy and flow cytometry) are not part of the disease definition but should always be obtained.1,4 Of critical importance, serum for CA titration, electrophoresis and immunoglobulin assessments must be obtained from blood specimens kept at 37-38°C from sampling until serum has been removed from the clot.1 Management Pharmacologic therapy should be offered to patients with symptom-producing anemia or disabling circulatory symptoms.2,3 Corticosteroids are inefficient, and unacceptably high maintenance doses are usually required to maintain the remission in the few responders.1,3 Two prospective trials of rituximab monotherapy showed response rates of about 50%.11,12 Complete responses were rare. The median response duration was approximately one year. The safety and efficacy of combination therapy with fludarabine and rituximab was studied in 29 patients in a prospective trial.13 Twenty-two patients (76%) responded, six (21%) achieving complete response and 16 (55%) achieving partial response. An impressive estimated median response duration of more than 66 months was achieved. Short-time
hematologic toxicity was significant, with 12 patients (41%) experiencing grade 3 or 4 toxicity. Furthermore, the possibility of long-term toxicity may be a concern, in particular in younger patients. Future perspective Response to bendamustine-rituximab combination therapy has been reported,14 and a prospective study is ongoing. Therapy with bortezomib is also being prospectively explored. Favorable effect of the C5-inhibitor eculizumab has been described in a prospective trial.9 Since the hemolysis is predominantly C3b-mediated in most patients, complement blockade at a more proximal, classical pathway level might, in theory, be more successful.7,8 Preclinical studies with the anti-C1s monoclonal antibody, TNT003/009, have shown favorable results.7 If clinical documentation can be provided, complement modulation will probably still not replace clonally directed therapies, which are more causal and do not need to be continued infinitely. Complement-directed therapies seem very promising, however, in acute situations and in patients with severe CAD not responding to clonally directed immunochemotherapy.

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