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Approaches to augment the cell dose in cord blood to improve allogeneic haematopoietic stem cell transplantation outcomes in adults

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Abstract

Cord blood (CB) has been increasingly used as an alternative source of haematopoietic stem cells (HSCs) for allogeneic haematopoietic stem cell transplantation (HSCT) when a bone marrow (BM) or mobilised peripheral blood (PB) source from a suitable human leukocyte antigen (HLA)-matched related or unrelated donor is unavailable. The major disadvantage associated with the use of CB for transplantation in adults is the low cell dose contained in a single CB unit which has been reported to markedly delay engraftment of neutrophils and platelets, increase early transplant related mortality and decrease survival. Various approaches to augment the cell dose limitation in CB to improve HSCT outcomes in adults have been investigated including double CB transplant (DCBT), *ex vivo* expansion, co-transplantation with mobilised HSCs or mesenchymal stromal cells (MSCs), and intra BM injection. The experimental and clinical progress of these approaches will be the focus for this review.

**Keywords:** Cord blood, double cord blood transplant, *ex vivo* expansion, mobilised haematopoietic stem cells, mesenchymal stromal cells and intra bone marrow injection

Introduction

HSCT is an established treatment modality for a number of malignant and nonmalignant haematological disorders. Sources of HSCs available for allogeneic HSCT include BM, mobilised PB and CB. CB has been used increasingly as an alternative source of HSCs when a BM or mobilised PB source from a HLA-matched related or unrelated donor is unavailable. Early on, the safety and feasibility of using HLA-mismatched CB for transplantation in adults was demonstrated by Laughlin *et al* (2001). A major disadvantage highlighted by the investigators with the use of CB for transplantation in adults was the low cell dose contained in single CB units compared to BM grafts. When transplanting adults, the use of a single CB unit containing low cell dose was reported to markedly delay time to haematopoietic engraftment of neutrophils and platelets, increase early transplant related mortality and decrease survival (Laughlin *et al* 2001; Laughlin *et al* 2004). Conversely, the use of single CB units containing a higher total nucleated cell (TNC) dose (≥ 2.41 x 10^7/kg) was associated with faster and higher probability of neutrophil recovery (p= 0.003) and a higher CD34+ cell dose (≥ 1.2 x 10^5/kg) was associated with better event free survival (p= 0.05) (Laughlin *et al* 2001).

Despite over five hundred thousand HLA-typed CB units registered on the Bone Marrow Donor Worldwide...
Double cord blood transplant

The proof of principle that transplanting two CB units is a viable approach to augment the cell dose in CB was demonstrated in a non-obese diabetic/severe combined immunodeficient (NOD/SCID) mouse model by Nauta et al (2005). The investigators reported that engraftment of human CD34+ cells derived from a single CB unit containing 1 x 10^5 cells was not only significantly enhanced by the addition of a second unrelated CB unit containing 1 x 10^5 cells but comparable to engraftment from a single CB unit containing 2 x 10^5 cells. Also reported was a differing pattern of engraftment when two CB units were infused. The origin of the units was determined by flow cytometry using biotin labelled HLA class I allele specific monoclonal antibodies. In three of five experiments engraftment was dominated by a single unit whereas in two experiments both units contributed equally to engraftment.

Barker et al (2005) translated this principle to the clinical setting in a phase I/II study investigating the clinical safety and feasibility of DCBT in 23 patients with high risk haematological malignancy. In this study patients received two 4-6/6 HLA-matched CB units with a median cryopreserved TNC dose of 4.8 x 10^7/kg (range 1.6–7.0 x 10^7/kg) after myeloablative conditioning. The primary endpoint was neutrophil engraftment, defined as the first of three consecutive d after transplantation on which the absolute neutrophil count is > 0.5 x 10^9/L and secondary endpoints included cumulative incidence of platelet engraftment, acute and chronic GVHD and disease free survival. No major adverse infusion events were reported. All evaluable patients (n=21) demonstrated sustained donor neutrophil engraftment at a median of 23 d (range 15–41 d). By day 180 after transplantation, the cumulative incidence of platelet engraftment to > 50 x 10^9/L was 71%. The incidence of acute GVHD grade II – IV and III – IV were 65% and 13% respectively. The incidence of chronic GVHD was 23%. Disease free survival at 1 year was 57% and in patients who received transplants for acute leukaemia when in remission or chronic myeloid leukaemia, this percentage was even higher at 72%. The results from this study demonstrates a faster median time to neutrophil engraftment, relatively low transplant related mortality and better survival compared to single CB transplant outcomes previously published in the literature (Laughlin et al 2001). Therefore, the transplantation of two 4–6/6 HLA-matched CB units is safe, feasible and overcomes the cell dose limitation preventing the use of CB in adults and larger children.

More recently, in a retrospective study Brunstein et al (2010) investigated the efficacy of DCBT relative to conventional BM and mobilised PB transplants in 536 patients with haematological malignancy. In this study patients received BM or mobilised PB from 8/8 HLA-matched related donor (n=204), 8/8 HLA-matched unrelated donor (n=152), 7/8 HLA-matched unrelated donor (n=52) or two 4-6/6 HLA-matched CB units (n=128) after myeloablative conditioning. The primary endpoint was cumulative incidence of neutrophil recovery and the secondary endpoints included platelet recovery with complete donor chimerism, cumulative incidence of acute and chronic GVHD, relapse, cumulative incidence of non relapse mortality and leukaemia free survival. The investigators found that DCBT was associated with a marked reduction in relapse risk, a lower risk of acute and chronic GVHD and similar rates of leukaemia free survival compared to BM and mobilised PB transplants. However compared to BM and mobilised PB transplants, the delayed engraftment of neutrophils by more than a week was identified as the greatest barrier to successful use of DCBT and the most important contributor to early non relapse mortality with deaths mostly attributed to infection. The challenge now for investigators exploring other approaches to augment the cell dose in CB is to reduce the period of post transplant neutropenia and related early morbidity and mortality due to infection.

Interestingly, the DCBT approach is associated with the observation that despite the contributions of both units to short-term engraftment, long-term engraftment is usually accounted for by only one of the two CB units infused (Barker et al 2005; Brunstein et al 2010). Brunstein et al (2007) reported that neither infused TNC, CD34+ and CD3+ cell doses, HLA matching, TNC viability, ABO typing, gender match or order of infusion has consistently been able to predict which unit will eventually dominate. Barker et al (2005) reported similar findings with the exception of CD3+ cell dose. A larger CD3+ cell dose was found to be associated with unit dominance (p<0.01). This finding has been confirmed more recently by Scaradavou et al (2009), Avery et al (2011) and Eldjerou et al (2011).
Further support for an immune mediated basis to unit dominance arises from the work of Gutman et al (2010) in the investigation of 14 patients receiving myeloablative or reduced intensity conditioning and DCBT with either two unmanipulated CB units or one unmanipulated and one CD34+ selected and ex vivo expanded CB unit (without add back of T-cells). The phenotype of the T-cells present in 26 CB units after thaw and before infusion on the day of transplant were compared with the phenotype of T-cells present early after transplant (between d 14 and 28). The median CD4+/-CD8+ ratio in thawed CB units before infusion was 2.78 (range 1.82–5.56) compared to 0.38 (range 0.05–6.25) early after transplant and was evident in all patients regardless of conditioning regimen. The phenotype of the CD8+ T-cells present early after transplant predominately expressed CD45RO+/-CCR7-. At 28 d, dominant engraftment of a single unit occurred in 10 patients. An intracellular cytokine flow cytometry assay was used to analyse the reactivity of the engrafted T-cells against each of the CB units. In nine of these 10 patients, was used to analyse the reactivity of the engrafted T-cells to a significant subset of CD8+ T-cells derived from the engrafting unit. In three patients no significant interferon-γ augment the cell dose in CB has been demonstrated in a NOD/SCID mouse model by Piacibello et al (1999). The investigators reported that injection of > 2.0 x 10⁹ fresh or cryopreserved unmanipulated human CD34+ CB cells showed little if any sign of engraftment in a limited number of mice. However, cells that had been generated by the same number of initial CD34+ CB cells after 4 to 10 weeks expansion in stroma free liquid cultures containing a combination of early acting cytokines (fms-like tyrosine kinase/foetal liver kinase ligand, megakaryocyteocyte growth and development factor, stem cell factor and interleukin-6) showed engraftment in the vast majority of mice.

Following the encouraging results obtained by Piacibello et al (1999) in the mouse model, the safety and feasibility of ex vivo expanded cells to augment single CB transplants in 28 patients with malignant and non-malignant haematological disorders was investigated in a phase I/II clinical study by Jaroscak et al (2003). On day 0 patients were transplanted the majority of a single 3–6/6 HLA-matched unmanipulated CB unit with a median TNC dose of 2.05 x 10⁹/kg (range 1.10–5.55 x 10⁹/kg) and CD34+ cell dose of 0.78 x 10⁹/kg (range 0.02–15.99 x 10⁹/kg). The remaining cells (typically 1–2 x 10⁷ TNCs) were ex vivo expanded in the AastromReplicell System composed of a base medium containing Iscove modified Dulbecco medium, bovine serum, horse serum, hydrocortisone and glutamine. The base medium was supplemented with granulocyte macrophage colony stimulating factor, interleukin-3, fms-like tyrosine kinase ligand and erythropoietin. On day 12, patients were transplanted the ex vivo expanded cells with a median TNC dose of 2.05 x 10⁹/kg (range 0.06–10.19 x 10⁹/kg) and CD34+ cell dose of 0.10 x 10⁹/kg (range 0.01–1.66 x 10⁹/kg). The investigators reported that supplementing single CB transplants with ex vivo expanded cells was well tolerated by patients, however did not impact the median time to neutrophil engraftment (22 d, range 13–40 d) in evaluable patients when compared to the same DCBT outcomes reported in the literature (Barker et al 2005). Given that the ex vivo expanded cells were infused on day 12 and the median time to neutrophil engraftment was 22 d, the contribution of the ex vivo expanded cells to engraftment may have been masked. Perhaps a better way to understand the effects these ex vivo expanded CB cells have on engraftment is to simultaneously infuse both unmanipulated and expanded cells on day 0. Although the investigators demonstrated the feasibility of ex vivo expansion using the AastromReplicell System to augment the TNC cell dose, the CD34+ cell dose was decreased from that present in the original CB unit. Optimisation of the cytokine cocktail used for expansion may improve both the TNC and CD34+ cell dose.

A significant drawback to the expansion methodology by Jaroscak et al (2003) was the inability to generate an expanded population of committed haematopoietic progenitor cells without compromising the numbers of less differentiated progenitor cells (CD34+ CD38- or CD34+ Lin- cells) which are important functional

**Ex vivo expansion**

The feasibility of an ex vivo expansion approach to augment the cell dose in CB has been demonstrated in...
haematopoietic repopulating cells. In order to overcome this hurdle De Lima et al (2008) investigated the feasibility of expanding CB CD133+ cells using a cocktail of early acting cytokines (stem cell factor, fms-like tyrosine kinase ligand, interleukin-6, thrombopoietin) and the copper chelator tetraethylpenamine, a cellular differentiation inhibitor, which has been shown to preferentially expand primitive progenitor cells (Peled et al 2002). These ex vivo expanded cells were then used to augment single CB transplants in 10 patients with advanced haematological malignancy. Patients were transplanted with a single CB unit originally frozen in two fractions (80/20, 60/40 or 50/50). The smaller fraction was expanded for 21 d and transplanted 24 h after infusion of the larger unmanipulated fraction. The average fold expansion for TNCs was 219 (range 2–620) and a CD34+ cell mean increase of sixfold over the CD34+ cell content of the original unit. Despite the low cell dose infused (median TNCs 1.8 x 10^7/kg and CD34+ cells 1.5 x 10^6/kg) nine patients engrafted. The median time to neutrophil engraftment was 30 d (range 16–46 d). The investigators found that it was feasible to expand CB cells using a combination of early acting cytokines and the copper chelator tetraethylpenamine and that infusion of these ex vivo expanded cells is safe, however they found similarly to Jaroscak et al (2003) that neutrophil engraftment was not enhanced in evaluable patients.

The efforts to improve rates of neutrophil engraftment using the AastromReplicell System and the copper chelator tetraethylpenamine expansion methodologies have so far shown marginal to no clinical effect. Therefore Delaney et al (2010) in a preliminary phase I study investigated the feasibility of expanding CB CD34+ cells with a cocktail of early acting cytokines (stem cell factor, fms-like tyrosine kinase ligand, thrombopoietin, interleukin-6 and interleukin-3) in the presence of immobilised engineered Notch ligand (Delta1^1s4-lig"). Immobilised Notch ligand activation of endogenous Notch receptors has been shown in the mouse model to profoundly affect the growth and differentiation of progenitor cells with a multiple log increase in the number of precursor cells with short-term lymphoid and myeloid repopulating ability (Varnum-Finney et al 2003). These ex vivo expanded cells were then used to augment DCBTs in 10 patients with high risk leukaemia in morphologic remission. Patients were transplanted with one unmanipulated CB unit followed by a second CB unit expanded for 17–21 d. The infused CD34+ cell dose of the unmanipulated unit was 0.24 x 10^6/kg cells (range 0.06 – 0.54 x 10^6/kg) compared to 6 x 10^6/kg (range 0.93 – 13 x 10^6/kg) from the ex vivo expanded unit. The average fold expansion for CD34+ cells was 164 (± 48 standard error of the mean, range 41 – 471). In nine of 10 patients who engrafted the median time to neutrophil engraftment was 16 d (range 7–34 d). The results from this study demonstrates that Notch mediated ex vivo expansion is feasible, that infusion of these ex vivo expanded cells is safe and moreover enhances neutrophil engraftment (16 d versus 23 or 27 d) by more than a week when compared with the same DCBT

outcomes published in the literature (Barker et al 2005; Brunstein et al 2010). Notably, the expanded unit was the dominant contributor to early neutrophil engraftment in four patients and demonstrated long-term in vivo persistence in only two patients. In one of these patients, at day 240 post transplant, a portion (10-15%) of the donor CD14+, CD56+ and CD19+ cells were derived from the expanded unit, but by one year donor engraftment was 100% from the unmanipulated unit. In the second patient contribution to engraftment from the expanded unit ranged from 25% to 66% for CD33+, CD14+, CD56+ and CD19+ cells, however, the expanded unit did not contribute to CD3+ cell engraftment at day 180 post transplant.

Although Delaney et al (2010) has demonstrated that Notch mediated ex vivo expanded CB cells can provide rapid transient short-term engraftment, the concern that ex vivo expanded cells may lose pluripotency and the ability to contribute to long-term engraftment requires examination. Steiner et al (2009) addressed this concern by transducing human CD34+ CB cells with a lentiviral construct expressing luciferase to determine homing and engraftment patterns in vivo in a NOD/SCID/IL-2Rγ-/- (NSG) mouse model. Transduced cells were expanded in either minimum essential medium alpha or stem cell growth medium supplemented with gentamicin, stem cell factor, fms-like tyrosine kinase ligand, thrombopoietin and granulocyte colony stimulating factor. NSG mice were transplanted with 0.8 x 10^6 to 3.5 x 10^6 of either transduced unmanipulated cells or transduced 10 day expanded cells. Bioluminescent imaging was then used to assess the engraftment capabilities of the transduced cells. Mice that received the transduced expanded cells exhibited engraftment signals 2–5 d later than those that received the unmanipulated cells at day seven and nine, however, beyond day 20–25 there were few quantitative differences. The investigators reported that other than a mild delay at the onset of engraftment, there was no significant difference in long-term engraftment between expanded and unmanipulated CD34+ cells. At one year post transplant, the signal intensity of repopulated niche areas remained strong among mice transplanted with either expanded or unmanipulated CD34+ cells. The results from this study support the assertion that ex vivo expanded CB cells can contribute to long-term haematopoietic engraftment.

Co-transplantation

It has been postulated that co-transplantation of a certain number of mobilised HSCs from a third party donor could result in early engraftment and provide adequate haematological support to a patient while allowing time for a CB unit to engraft. The basis for this postulation arises from the known fast engraftment characteristics of mobilised PB and similarly the rapid engraftment and lack of GVHD observed in patients receiving mega doses of highly purified T-cell depleted mobilised HSCs from haploidentical donors (Aversa et al 1998). Bautista et al (2008) in a nonrandomised phase II study investigated the safety and feasibility of co-transplanting third party donor mobilised
HSCs with a single CB unit in 55 patients with high risk haematological malignancies. Patients received a single 4–6/6 HLA-matched CB unit with a median TNC and CD34+ cell dose of 2.39 x 10^6/kg (range 1.14–4.50 x 10^6/kg) and 1.1 x 10^6/kg (range 0.35–3.7 x 10^6/kg) respectively. The third party donor mobilised HSC CD34+ and/or CD133+ and CD3+ median cell dose was 2.4 x 10^5/kg (range 1.05–3.34 x 10^5/kg) and 3.2 x 10^6/kg (range 0.5–15.6 x 10^6/kg) respectively. The third party donor was haploidentical in 38 instances and in 17 instances the donor (related or unrelated) did not share a haplotype. The median time to neutrophil engraftment, to CB neutrophil engraftment and to full CB chimerism was 10, 21 and 44 d respectively. The five year overall survival and disease free survival were 56% and 47%. The results from this study demonstrates that co-transplanting third party donor mobilised HSCs with a single CB unit is feasible, that infusion of the third party donor mobilised HSCs is safe and validates the earlier hypothesis of a short-term engraftment advantage by third party donor mobilised HSCs resulting in prompt post transplant recovery and a final advantage for the CB graft to competitively achieve sustained engraftment. Further, this approach makes feasible the use of single CB units of lower cell content for transplantation in adults.

It has been postulated that co-transplantation of MSCs, defined as plastic adherent cells that express CD105, CD73, CD90, lack CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR and are able to differentiate to osteoblasts, adipocytes and chondroblasts (Dominica et al 2006) may assist in restoring the damaged BM microenvironment following conditioning regimens and thereby promote haematopoiesis. In addition MSCs have been shown to have immunomodulatory properties evident by reversal of therapy resistant acute GVHD (Ringden et al 2006). As such Gonzalo-Daganzo et al (2009) were prompted to evaluate the effects that co-transplanting third party donor MSCs and third party donor HSCs with a single CB unit may have on neutrophil engraftment, CB neutrophil engraftment and effectiveness for prevention of acute GVHD. Nine adult patients with high risk haematological malignancies received a single 3-6/6 HLA-matched CB unit with a median TNC and CD34+ cell dose of 2.35 x 10^6/kg (range 1.63–2.96 x 10^6/kg) and 1.2 x 10^6/kg (range 0.37–2.8 x 10^6/kg) respectively. This was followed by infusion of third party donor mobilised HSCs with a median CD34+ and/or CD133+ and CD3+ cell dose of 2.61 x 10^6/kg (range 2.40–3.31 x 10^6/kg), 3.6 x 10^6/kg (range 1.0–8.3 x 10^6/kg) and BM derived MSC from the same third party donor with a median 1.20 x 10^6/kg (range 0.35–3.7 x 10^6/kg) respectively. The third party donor was haploidentical in 38 instances and in 17 instances the donor (related or unrelated) did not share a haplotype. The median time to neutrophil engraftment, to CB neutrophil engraftment and to full CB chimerism was 10, 21 and 44 d respectively. The five year overall survival and disease free survival were 56% and 47%. The results from this study demonstrates that co-transplanting third party donor mobilised HSCs with a single CB unit is feasible, that infusion of the third party donor mobilised HSCs is safe and validates the earlier hypothesis of a short-term engraftment advantage by third party donor mobilised HSCs resulting in prompt post transplant recovery and a final advantage for the CB graft to competitively achieve sustained engraftment. Further, this approach makes feasible the use of single CB units of lower cell content for transplantation in adults.

Hiwase et al (2009) demonstrated the feasibility of co-transplanting MSCs with CB in the NOD/SCID mouse model using human CD34+ CB cells and human placental MSCs. Six individual experiments involving four cohorts of 24 NOD/SCID mice were evaluated. Cohort 1 received 5 x 10^6 CD34+ cells from unit one; cohort 2 received 5 x 10^6 CD34+ cells from unit one and 4 x 10^6 MSCs; cohort 3 received 2.5 x 10^6 CD34+ cells from unit one and 2.5 x 10^6 CD34+ cells from unit two; cohort 4 received 2.5 x 10^6 CD34+ cells from unit one, 2.5 x 10^4 CD34+ cells from unit two and 4 x 10^4 MSCs. Mice were considered to have engrafted if > 0.5% human CD45 cells were detected in the BM by flow cytometry. The investigators reported that MSC co-transplantation improved engraftment in both single CB transplants (48.7 ± 7.7% versus 17.5 ± 6.1%; p=0.07) and DCBT (51.75 ± 6.8% versus 14.86 ± 6.5%; p=0.04). In the DCBT approach, although single unit dominance was observed, MSC co-transplantation significantly reduced the degree of dominance (dominant to non-dominant unit ratio, 3.6:1 versus 1.6:1). In this scenario it is postulated that an immunomodulatory effect by MSC on the unit versus unit immune interaction allows the engraftment of both units. The results from this study demonstrates that MSC co-transplantation can enhance engraftment in both single and double CB transplants and also alleviate single donor dominance in the DCBT setting. Only with further clinical studies in adults will the exact value of the MSC co-transplantation approach be determined.

Intra bone marrow injection

The standard method for delivering HSCs for transplantation is by intravenous infusion. Cui et al (1999) demonstrated in the C57BL/6 mouse model that the seeding efficiency of intravenously infused cells to localise to the BM space is approximately 17% within 15 h in non myeloablated mice whereas a smaller proportion of cells (approximately 1–2%) localise to the BM in myeloablated mice. In addition, intravenously infused cells not reaching the BM are sequestered in the liver, spleen, muscle and other tissues. It has been hypothesised, therefore, that directly injecting HSCs into the BM may increase the seeding efficiency and thereby enhance engraftment. The feasibility of an intra BM injection approach has been demonstrated in a NOD/SCID mouse model by Castello et al (2004). Irradiated (320 cGy) mice were transplanted with 1 x 10^6 CB cells via intra BM injection or with 1x10^7 CB cells via intravenous injection. The investigators reported that the expansion of CD34+ cells was significantly higher (p <0.004) in the intra BM injection transplanted mice (210-, 360- and 275- times greater) than in the intravenously
matched CB units with a median TNC dose of 2.6 x 10^7/kg (range 1.2–3.0 x 10^7/kg) intravenously and 1.89 x 10^7/kg (range 1.4–3.4 x 10^7/kg) into the superior posterior iliac crest. The primary endpoint was neutrophil and platelet engraftment and secondary endpoints included the incidence of GVHD, relapse and overall survival. No local or general complications including pain, haemorrhage or infection as a result of injection were noted although the procedure was logistically and technically cumbersome. Of the 32 patients, 27 patients achieved complete haematological recovery. The median time to neutrophil engraftment was 23 d (range 14–44 d) and median time to platelet engraftment was remarkably rapid at 36 d (range 16–64 d). Chimerism was 100% donor from day 60 after transplantation in PB and BM CD3+ cells. Grade I acute GVHD was observed in two patients and grade II acute GVHD in four patients. No patients developed grade III-IV acute GVHD. Chronic GVHD was observed in five patients. Overall survival was 45% (95% CI 36–54%) at one year after transplant with median time to neutrophil engraftment of 23 d (range 14–49 d) and median time to platelet engraftment of 23 d (range 13–53 d). Chimerism was remarkably rapid at 36 d (range 14–80 d) at one year after transplant. The results from this study demonstrate that intra BM injection is safe, feasible, and more significantly platelets and lowered the incidence and severity of acute GVHD when compared to the same single CB transplant outcomes previously published in the literature (Laughlin et al 2001).

Brunstein et al (2009) further investigated the safety, feasibility and efficacy of intra BM injection in 10 patients with haematological malignancy in a phase I/II randomised study. Patients were infused two 4–6/6 HLA-matched CB units with a median TNC dose of 2.0 x 10^7/kg (range 1.4–4.2 x 10^7/kg) into the superior posterior iliac crest. The primary endpoint was neutrophil and platelet engraftment and secondary endpoints included platelet engraftment, incidence of GVHD, transplant related mortality and overall survival. No discernable adverse events including local pain, mass, erythema or increased skin temperature at 24 h and 7 d after the procedure were observed. Of 10 patients, nine patients engrafted. Complete chimerism with the intravenous unit was seen in five patients and four with the intra BM injection unit. The median time to neutrophil engraftment was 21 d (range 17–49 d) and platelet engraftment was 69 d (range 30–272 d). Grade II acute GVHD was noted in seven patients and two patients developed chronic GVHD. Overall survival was 47% (95% CI, 14–80%) at one year after transplant. The results from this study demonstrates that intra BM injection is safe, however, in contrast to Frassoni et al (2008) it did not alter the median time to engraftment of neutrophils or platelets and did not reduce the incidence of acute GVHD in evaluable patients when compared to the same DCBT outcomes previously published in the literature (Barker et al 2005). Furthermore, the intra BM injection unit was not afforded a repopulating advantage over the intravenously infused unit. As such while intra BM injection may have the potential to significantly modify the current practice of single CB transplants, in the DCBT setting this technically cumbersome and uncomfortable approach has shown no advantage over conventional DCBTs.

**Conclusion**

CB has become an important alternative source of HSCs for allogeneic HSCT when a suitable HLA-matched related or unrelated donor is unavailable. The low cell dose contained in a single CB unit is a major disadvantage when transplanting adults and larger children and may result in delayed engraftment, higher early transplantation related mortality and poor survival. Approaches that increase the cell dose, utilise accessory cells or enhance HSC homing have been investigated with varying experimental and clinical success. Of these approaches, DCBT is the most established although no clinical data exists to prove that in adults two CB units are better than one. Put simply, the use of two CB units extends the availability of HSCT to adults and larger children who would not otherwise be eligible because of insufficient cell dose in a single CB unit. It is anticipated that with time the DCBT, ex vivo expansion, co-transplantation and intra BM injection approaches will be refined to favourably alter HSCT outcomes in adults.

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**References**


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Algorithm for whole blood viscosity: implication for antiplatelet bleeding risk assessment

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Abstract

A series of evaluations on whole blood viscosity (WBV) issues tried to elucidate the sensitivity, specificity and usefulness of the laboratory parameter in clinical practice. The aim of this article is to postulate (1) how to use routine clinical laboratory tests to derive WBV, and (2) the usefulness of WBV in evidence-based practice for determination of the therapeutic risk of bleeding. The study used 10 years of archived clinical pathology data from South West Pathology. WBV was derived from calculations incorporating haematocrit and total protein and extrapolation chart and reference values were developed. Association of and/or changes in WBV level with acetylsalicylates, C-reactive protein (CRP), D-dimer, Erythrocyte Sedimentation Rate (ESR), Faecal Occult Blood (FOB), homocysteine, International Normalised Ratio (INR), leucocytosis, leukapheresis, and platelet levels were determined. Whether there are differences between grades of WBV levels in the laboratory indices of diabetes, dyslipidaemia and renal function test were also investigated. A comparison with diagnostic digital method was also performed. One possible false assumption is that WBV (akin to CRP and ESR) is too sensitive and not a specific marker for the diagnosis of a pathological condition. Our findings may refute this notion. Interestingly, lower WBV levels are significantly associated with higher INR and acetylsalicylate levels. The observations from this study also elucidate the potential of WBV for evidence-based pathology to support a decision of antiplatelet medication, akin to INR in anticoagulant therapy. The clinical laboratory method postulated here can be performed in any facility that performs routine biochemistry and haematology.

Keywords: antiplatelet therapy, bleeding risk, evidence-based pathology, whole blood viscosity

Introduction

Virchow’s triad has been an established concept of three broad factors that ultimately lead to, and/or result from thrombosis vis-à-vis cardiovascular complications (Bagot and Arya, 2008, Lowe, 2003). Each factor represents a subclinical vascular process, which in turn is indicated by a clinical pathology index (Table 1).

Table 1: Virchow’s triad, corresponding vascular process and pathology index

<table>
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<tr>
<th>Virchow’s triad</th>
<th>Vascular process</th>
<th>Pathology index</th>
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<tr>
<td>Atherothrombosis</td>
<td>Blood coagulability/ fibrinolysis</td>
<td>Plasma D-dimer</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td>Blood vessel injury or irritation</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Stasis</td>
<td>Blood flow changes</td>
<td>Blood viscosity</td>
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</table>

Antiplatelet therapy such as aspirin is known for its cardio-protective effects as well as its potential risk to cause bleeding complications. Hence, there are recommended guidelines for usage (Colwell and American Diabetes Association 2004, Bertrand 2008, U.S. Preventive Services Task Force 2002). One of the major confounding factors to the risk of bleeding is whole blood viscosity (WBV) (Mannini et al 2006, Cecchi et al 2009). Coloquially, antiplatelet agents are blood thinners (Weinberg 2011). Blood with a less than normal viscosity would bleed/flow faster compared to high viscosity blood (Berman et al 1994, Amir and Krauss 1973). Therefore, a logical contraindication for antiplatelet therapy, to avoid associated bleeding risk would be indicated by the WBV status.

The therapeutic assessment of the ‘risk of bleeding’ is possibly non-existent (Rodak et al 2012, Sabitha et al 2008). There have been various platelet function test (PFT) methods including bleeding time and platelet aggregometry. It has been acknowledged that clinical laboratories over the years have been performing PFT by different aggregometry methods with little or no standardization (Breddin, 2005). Hence, the Clinical and Laboratory Standards Institute recently developed a guideline to address this void (Christie et al 2009). However, it is pertinent to appreciate that the guideline is about standardizing aggregometry methods per se. The guideline does not recommend a particular method for diagnosis of platelet disorders or choice of a therapeutic agent (Christie et al 2009).

A critical review of the principles and utility of platelet aggregometry test will show that it is limited as a therapeutic
Figure 1. Chart for derivation of WBV level from haematocrit and serum protein (Nwose, 2010). Concomitant anemia and hypoproteinaemia translate to hypoviscosity, while concomitant hyperproteinaemia and polycythemia almost always translate to hyperviscosity. Critical hyperproteinaemia does not translate to hyperviscosity in the presence of anaemia, while polycythemia does not translate to hyperviscosity if there is hypoproteinaemia.
drug monitoring tool for investigating whether a patient is resistant, responsive or nonresponsive to therapy (Favaloro 2008, von Beckerath et al. 2010). Patients would have taken the medication prior to testing for resistance or responsiveness. This is quite different from testing prior to medication whether a patient would be at risk of bleeding. Therefore, there is still a void in PFT with reference to assessing bleeding risk or contraindication of antiplatelet therapy.

This technical note addresses a practical issue of evidence-based compliance to guidelines on the use of antiplatelet therapy in clinical practice. The objectives are to present (1) an algorithmic method for WBV testing; and (2) the value of the pathology test when appropriated.

Methods

This evaluation of de-identified data was approved by the HREC of South West Pathology Albury. The de-identified data pool for 1999–2008 were acquired as part of laboratory-based research agenda from the Auslab Laboratory Information System (Nwose et al. 2010). Using an arithmetic formula: ‘WBV (208 Sec-1) = 0.12 x HCT + 0.17(TP–2.07)’ (Tamariz et al. 2008), WBV at high shear stress was determined from various possible pairs of haematocrit and total proteins. Extrapolation chart and reference values were developed (Fig. 1), based on the formula, with HCT and TP being haematocrit (%) and serum total proteins (g/L) respectively (Nwose 2010). The results obtained from the extrapolation method were compared with a digital method (Nwose and Richards 2011).

To evaluate the specificity and sensitivity of WBV to associated pathophysilogies, the associations of WBV with several laboratory parameters were performed. Correlation with CRP and ESR was evaluated to determine whether WBV would be equally sensitive to similar clinical conditions. Changes in the level of WBV were compared with those patients on acetylsalicylate therapy and results of FOB to determine correlation and specificity for ‘risk of bleeding’ to aspirin. Also, changes in the level of WBV were compared with those of INR to determine specificity for ‘risk of bleeding’ associated with anticoagulants and antiplatelets.

Results

The result of the investigation of how WBV correlates with routine acute phase inflammation parameters showed that hyperviscosity was observed in 2.9% of increased CRP cases, and 2.7% of raised ESR results. The results show that hyperviscosity is not frequently observable in acute phase inflammation. The results also show that on average, normoviscosity is concordant with 85.3% of normal CRP and 93.8% of normal ESR reports. Further, the results indicate that there is more hyperviscosity, but less hypoviscosity, in elevated than in normal CRP and ESR subpopulations (Table 2).

On investigating whether WBV is associated with the INR and platelet count, it was observed that WBV is directly and inversely associated with platelet counts and INR respectively (p<0.002) (Fig. 2).

Since aspirin measured as acetyl-salicylate is used in the management of stasis, of which blood viscosity is an index, it was hypothesized and investigated whether WBV would be inversely related to the blood level of acetylsalicylate. The hypothesis was proven as it was observed that lower WBV is statistically significantly associated with higher acetylsalicylate level (p < 0.002; Table 3) (Nwose and Cann 2010).

When investigating the prevalence of hypoviscosity in diabetes, dyslipidaemia and renal failure with a view to determine the proportion of chronic disease patients who may not require antiplatelet therapy, it was observed that up to 97.5% of cases investigated for chronic diseases had a normal to high level of WBV, which could indicate patients may benefit from antiplatelet therapy (Fig. 3).
Discussion

The results from scientific research can quickly and erroneously be categorized as relevant or irrelevant. WBV falls into the latter category and attempts to discuss WBV most often turns out a waste of time (British Medical Journal blog: http://blogs.bmj.com/bmj/2009/04/24/richard-smith-on-countering-the-%E2%80%9Cwicked-problem%E2%80%9D-of-the-chronic-disease-pandemic/). Another reason for discussion or research on WBV not being given credence is the notion that WBV is too sensitive or non-specific. This is especially so considering the speculation of possible minor changes in blood viscosity without known physiologic consequence (Smith and La Celle 1982). However, the findings from this study show three distinct points as follows:

WBV is not too sensitive: WBV may not necessarily be too sensitive to related disease conditions. Acute inflammation can lead to stasis by normal physiological response. The cumulative prevalence of the different categories of WBV observed among sub-populations of normal and raised CRP and ESRs indicates that while normal WBV is most prevalent in the general population, hyperviscosity is not prevalent in acute phase inflammation (Table 2). The observations indicate that WBV is not arbitrarily as sensitive as CRP or ESR.

WBV is specific, not non-specific: The results indicate that salicylate medication (aspirin) reduces WBV level. Lower or no salicylate would mean relatively higher WBV level (Table 3). This observation proves the hypothesis.

Table 2: Prevalence of hyperviscosity in abnormal and normal sub-populations of CRP & ESR

<table>
<thead>
<tr>
<th>Year</th>
<th>CRP Normal</th>
<th>CRP Increased</th>
<th>ESR Normal</th>
<th>ESR Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>1270</td>
<td>3.6</td>
<td>3.9</td>
<td>92.5</td>
</tr>
<tr>
<td>2005</td>
<td>2507</td>
<td>4.2</td>
<td>3.8</td>
<td>92.0</td>
</tr>
<tr>
<td>2003</td>
<td>1672</td>
<td>4.7</td>
<td>2.8</td>
<td>92.5</td>
</tr>
<tr>
<td>2001</td>
<td>1226</td>
<td>6.7</td>
<td>3.1</td>
<td>90.2</td>
</tr>
<tr>
<td>1999</td>
<td>124</td>
<td>38.2</td>
<td>2.5</td>
<td>59.3</td>
</tr>
</tbody>
</table>

Table 3: WBV vs. acetylsalicylate statistics

<table>
<thead>
<tr>
<th>Analyses</th>
<th>Mean WBV levels</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topmost (n=30) vs. Lowest (n=30) Higher Sal*</td>
<td>16.11</td>
<td>18.19</td>
</tr>
<tr>
<td>4th vs. 1st</td>
<td>16.51</td>
<td>17.16</td>
</tr>
<tr>
<td>Top vs. Bottom halves</td>
<td>16.40</td>
<td>16.82</td>
</tr>
</tbody>
</table>

Keys: †Average = 2.9%; ‡Average = 2.7%; WBV = whole blood viscosity

WBV is not too sensitive: WBV may not necessarily be too sensitive to related disease conditions. Acute inflammation can lead to stasis by normal physiological response. The cumulative prevalence of the different categories of WBV observed among sub-populations of normal and raised CRP and ESRs indicates that while normal WBV is most prevalent in the general population, hyperviscosity is not prevalent in acute phase inflammation (Table 2). The observations indicate that WBV is not arbitrarily as sensitive as CRP or ESR.

WBV is specific, not non-specific: The results indicate that salicylate medication (aspirin) reduces WBV level. Lower or no salicylate would mean relatively higher WBV level (Table 3). This observation proves the hypothesis.
that antiplatelet prophylaxis or therapy is meant to reduce WBV. While this may have been implied or known (Higgins 2006), the issue is that INR is mainly used to measure certain haemostatic factors and to monitor anticoagulant therapy but is not assessed for chronic disease patients who merely require antiplatelet prophylaxis. Neither is WBV assessed on the chronic patients who are being managed with antiplatelet prophylaxis or therapy, nor is the risk of bleeding complication of less concern (Sabitha et al 2008).

WBV indicates antiplatelet prophylaxis is safe for most chronic disease patients: Another very positive finding is evidence-based pathology that most patients with chronic diseases would not be diagnosed with hyperviscosity or hypoviscosity i.e. the majority have normoviscosity (Fig. 3). It would be reasonable to presume that most patients attending pathology for routine creatinine, glucose, lipid profile monitoring could be on medication including antiplatelet prophylaxis or therapy. A study had reported that the prevalence of antiplatelet use was 54% overall, while another indicated 84% usage among a diabetic cohort (Miller et al 2005, Bulatova et al 2007), which would lower WBV in this population. Therefore, observations of normal to high blood viscosity in 97.5% of the patients is an indication of those who are benefiting from therapy without WBV falling to a level that predisposes to risk of bleeding.

Implications for clinical practice

Discussion in relation to practice: There is doubt over the evidence base for aspirin in chronic disease management (Walsh and Spurling 2008), which would benefit from the discussion on what Australia can do to increase Evidence based Pathology (The Royal College of Pathology 2010). It is known that WBV attenuates the efficacy of antiplatelet agents (Mannini et al 2006). That is, WBV is supposed to be duly assessed and monitored for those who going to be, or are being treated with this therapy (akin to INR monitoring of warfarin). Perhaps the limitation has been that test methodology is not readily available. It is therefore imperative to promote the availability of a algorithmic method to easily determine WBV.

Antiplatelet agents are recommended with emphasis that individuals with cardio-embolic or athero-thrombotic condition, stroke or TIA can receive an antiplatelet agent to reduce the risk of recurrent stroke on the condition of patient’s tolerance and no contraindication (Cucchiara and Messé 2011) and there are guidelines published from the American Heart Association/American Stroke Association (AHA/ASA) and the American College of Chest Physicians (Albers et al 2008, Furie et al 2011).

While there are platelet function tests (PFT) options to measure patient’s tolerance, the consideration for “no contraindication” has yet to be established. The original ‘bleeding time’ method is almost obsolete in modern day laboratory. Platelet aggregometry is becoming more common, but not without its limitations (Rodak et al 2012). One of the pre-analytical difficulties, and probably the most important in the quality assurance and control, is the accessibility, availability and transport of a fresh blood specimen containing functional platelets (Favaloro 2009).

There are issues relating to bleeding complications, non-response, resistance and treatment failure of antiplatelet therapy such as aspirin or clopidogrel (Hennekens et al 2011). Perhaps, it is pertinent to separate the first (bleeding complications) from the other three especially in terms of (i) medication prior to testing for resistance, responsiveness or treatment failure; versus (ii) testing prior to medication whether a patient would be at risk of bleeding. In the spirit of “what can Australasia do to increase evidence-based pathology” (The Royal College of Pathology 2010), this paper calls for consideration to integrate existing evidence for the underutilised test, WBV.

Implications for laboratory managers: Beside the benefit of WBV assessment to the patients who may be at risk of bleeding, a valuation of revenue accruable from such assessment indicated that the laboratory service would have generated AU$615,272.00 for a regional lab in a 3-year period, including AU$39,304.00 from the diabetes clients only (Nwose et al 2009). A brief cost analysis shows that revenue from a WBV test alone is far more than it costs to generate the result by the algorithmic method. This is beside the advantage of providing a service that has eluded remote communities.

Conclusion

This paper puts forward an extrapolation method for WBV test. The notion that WBV is too sensitive or non-specific marker is refuted and the issue of evidence base pathology for antiplatelet therapy is addressed. The concern for bleeding risk of antiplatelet therapy is also differentiated from the problems of responsiveness or resistance to therapy.

Acknowledgement

This study was done with material and moral support of the management of the South West Pathology Service, Albury.

References


A case of T lymphoblastic leukaemia in a four-year-old child

Gillian Rozenberg

South Eastern Sydney & Illawarra Area Health Service, Prince of Wales Hospital, New South Wales

The child in this update is the third and youngest of three children admitted to the Sydney Children's Hospital, Randwick, in the month of March 2013, with T lymphoblastic leukaemia. The child was a four-year-old male admitted with respiratory distress to the intensive care ward. He had a large mediastinal mass which was obstructing his airway. On examination, he was noted to have lymphadenopathy and hepatosplenomegaly. A full blood count was performed. The results were as follows:

<table>
<thead>
<tr>
<th>Table 1.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>102 RR 110-139 g/L</td>
</tr>
<tr>
<td>HCT</td>
<td>0.308 RR 0.37-0.60</td>
</tr>
<tr>
<td>MCV</td>
<td>79.8 RR 74-86 fl</td>
</tr>
<tr>
<td>MCH</td>
<td>26.4 RR 25.5-30.6 pg</td>
</tr>
<tr>
<td>WBC</td>
<td>347.8 RR 4.7-12.3 x 10^9/L</td>
</tr>
<tr>
<td>PLT</td>
<td>108 RR 205-457 x 10^9/L</td>
</tr>
</tbody>
</table>

The white cell differential showed 90% blast cells. Morphologically, the blood film demonstrated a monomorphic population of lymphoblasts. The blasts ranged from small to medium in size with a high N/C ratio, moderately condensed chromatin pattern and inconspicuous nucleoli. Many of the nuclei were folded and cleaved, a feature suggestive of a T lymphoblastic leukaemia.

The child was taken to theatre where a bone marrow aspirate was performed. Bone marrow aspirates on children are always performed under a general anaesthetic. A CSF specimen was also collected in theatre.

The bone marrow showed a heavy infiltrate of blast cells morphologically similar to those present in the peripheral blood. They were medium in size with cleaved and folded nuclei, immature chromatin and inconspicuous nucleoli. Many of the blasts demonstrated vacuolated cytoplasm.

Flow cytometry and cytogenetics were performed on the bone marrow aspirate. The flow cytometry results were as follows: CD45+, HLA-DR-, CD2+, CD3+, CD4+, CD5+, CD7+, CD8+, CD10+, CD1a, CD34+, TdT+.

These results were consistent with T lymphoblastic leukaemia. The cytogenetics showed a loss of chromosome 7. Abnormalities of chromosome 7 are common findings in T lymphoblastic leukaemia.

The CSF also showed a heavy infiltrate of lymphoblasts. The blasts were medium in size with a fine chromatin pattern and well defined nucleoli.
T lymphoblastic leukaemia occurs more commonly in adolescents than in young children. In comparison, B lymphoblastic leukaemia occurs in the younger child, usually under six years of age. Children with T lymphoblastic leukaemia frequently present with a mediastinal mass. The central nervous system (CNS) is often involved and less commonly the testis in males. T lymphoblastic leukaemia is considered a high risk disease. Patients usually relapse early into their treatment. An isolated relapse in the CNS and in the testis in males is not an infrequent occurrence.

![Figure 4. Fine needle biopsy of the testis (H&E) in a case of testicular relapse](image)

**Figure 4.** Fine needle biopsy of the testis (H&E) in a case of testicular relapse

**Figure 5.** Fine needle biopsy of the testis - touch preparation (Wright stain) demonstrating T lymphoblasts

This child is currently undergoing treatment however he will ultimately be given a stem cell or cord blood transplant.
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ABSOLUTE CONFIDENTIALITY OF RESULTS IS ASSURED

FOR ENROLMENT ENQUIRIES CONTACT
STEVE MACKAY  E-mail: aimsonqap@dspl.com.au
OBITUARY

David George Alexander Gibb
AIMLS Life Member
(1928-2012)

David George Alexander Gibb  AIMLT FRMS was born in Edinburgh on 5th August 1928 as could be discerned by the Scottish lilt to his softly-spoken voice throughout his long and productive life. His thorough training in medical technology began in the Department of Obstetrics and Gynaecology in the University of Edinburgh and in the Birmingham Accident Hospital (UK) from 1943 until he and his family migrated to Perth, Western Australia, in 1955.

His arrival proved fortunate for the development of academic medical technology in that State. In 1957 Perth’s Medical School was established with the newly appointed Foundation Professor of Pathology, R.E.J. ten Seldam, charged with directing the Department of Pathology at the Royal Perth Hospital where David Gibb was working as a Senior Laboratory Technician.

It was not long before ten Seldam recognised and appreciated David’s abilities, not only at the bench, but also as an able and efficient co-administrator and laboratory leader. He appointed him to his University Department (Staff File no.277) in 1957 as Senior Laboratory Technician with eventual promotion to Chief Laboratory Technologist in 1962.

The translocation of the academic pathology department from the Royal Perth Hospital to the Sir Charles Gairdner Hospital site at Nedlands required detailed and complex planning so that, in addition to his regular duties, David also helped in the multiplicity of tasks embracing the design of a large and diverse Service housed over three floors. In addition, he had to cope with a newly appointed Professor of Pathology who was charged with directing the diagnostic Hospital Laboratories as well as the academic and research components of the University Service. The Hospital’s Haematology Laboratory, not having an academic component, was also placed under his direction.

The combination of this leviathan was accomplished by the formation of the Hospital and University Pathology Services, and the day-to-day management of the different financial streams supporting it (State, University, and external research awards) fell to David Gibb. Nor did this organization remain static over successive years. Disciplines such as clinical immunology, exfoliative cytology, electron microscopy and molecular biology created new demands as did computerisation. The glue holding the entire structure as manageable and cooperative was David Gibb whose equanimity as the now Principal Technologist remained unruffled.

One would think that no time could possibly remain for him to pursue other activities. Not so. David retained an undying interest in the education of young technologists. As a member of the Australian Institute of Medical Scientists from 1955, he participated in their part-time training until the present full-time degree was established at Curtin University (formerly W.A.I.T.) and assisted in the efforts to introduce a National Registry as part of AIMS. He also was active in the formation of the University Salaried Officers Association and was its president from 1971 – 1979. For these endeavours he was made a Life Member of AIMS in 1994.

Apart from helping to forge the constructive and collegiate atmosphere that happily existed between technological and medical staff, David also managed to contribute as co-author to the research publications of some of his younger academic colleagues besides undertaking part-time studies in Arts at the University. He was also an Elder of the South Perth Presbyterian Church. On his retirement in August 1993 the University conferred on him the status of Honorary Consultant in Laboratory Management.

In his declining years David suffered failing vision and a tired heart; he passed away quietly on 16th December 2012 surrounded by his wife Moira and his children Kathryn, David and Peter.

Max N-I Walters
A personal reflection.

I first met Fenton in the mid 1960’s. Along with the late John Saal he was a National Councillor from Queensland and I a councillor from New South Wales. In those days state branches of the then Australian Institute of Medical Laboratory Technologists (AIMLT) now AIMS took responsibility for teaching the final two “professional” years of a Medical Technology cadetship of full time work and part time evening classes. Fenton took responsibility for teaching the Biochemistry component, often bringing reagents and “clinical specimens” to laboratories at the then Central Technical College at the end of George Street (a practice that probably would not pass today’s Health and Safety regulations!)

In addition to being a National Councillor Fenton had served as Secretary to both the Queensland Branch Committee and of the state Examining Council. Our National Council meetings at that time were centered on the release of the “Martin Report” that proposed the establishment of the Advanced education Sector and also called for state Institutes of Technology. With support from Fenton and others responsible for AIMLT Examining Council’s “professional components”, the Queensland Institute of Technology (QIT) assumed responsibility for the education of Medical Technologists from 1967.

My second period of interaction with Fenton followed my move to Queensland as a lecturer at QIT at the end of 1970. We served together on the Branch Committee and attended state and national conferences together.

In 1976 National Council resolved to establish a permanent staffed office for the Institute. At that time states could nominate a “Federal Executive” of President, Secretary and Treasurer for a three year term. All positions were honorary. The idea of a paid National Secretary was a major departure from past practice and required a person familiar with past history and committed to the establishment of a National Office. Fenton had not long retired from Queensland Medical Laboratories and readily agreed. Together with the late Stan Walsh as Treasurer, Fenton as Secretary and myself as President we were elected. QIT kindly provided space for the initial office in Q Block. Fenton’s initial responsibilities were centralising membership subscriptions and producing a National Newsletter. Treasurer Stan Walsh put forward cases for a steady increase in subscriptions to produce the income that allowed the Institute to lease office space in Toowong and hire a part time clerical assistant before Fenton’s retirement in 1982 the year he was also elected a Life Member. In retirement Fenton and his wife, Sue, moved to North Queensland, living in Cairns, and in recent times provided significant contributions to the team, led by Ian Stanger, compiling the history of our Institute.

AJ (Tony) Webber AM PhD FAIMS
Past President (1978-86)
In September 2013, the St John of God Healthcare Pathology Development Program assisted three Timorese laboratory staff to apply for AusAID supported scholarships to attend the 2013 Australian Institute of Medical Scientists (AIMS) National Scientific Meeting (NSM) in Darwin. All three were successful in their applications. The members of the touring party were Matias da Silva, Ibonia de Sousa and Evangelina Belo.

The NSM was a fantastic opportunity to meet fellow medical laboratory professionals, share knowledge and think about how the laboratories in Timor Leste could be improved. A visit to the Royal Darwin Hospital’s Pathology Laboratory, facilitated by manager Michael Lynch, was an eye opening afternoon as the Timorese staff were able to see and experience the large volume and variety of testing processed along with the high standards to which Australian laboratories adhere to.

Continue reading to hear about their experiences on their exciting trip to the 2012 AIMS NSM in Darwin, Australia.

Matias da Silva

I would like to thank the AIMS for giving me the opportunity to come to the 2012 NSM in Darwin. When I was told that I would be going to the meeting I was very excited for the chance to meet medical laboratory staff from Australia and other countries. It is very important for people from Timor to listen and learn from Australian scientists so we can share their knowledge and use it to improve pathology in Timor Leste.

It was interesting hearing from Dr Vip Viprakasit when he talked about haemoglobinopathies. In Timor Leste we do not yet have the knowledge or equipment that would let us test Hb electrophoresis or more advanced techniques. After having time to think, I feel that as the people of Timor Leste are from a number of different ethnic origins, testing for haemoglobinopathies needs to be considered. We have a very high number of births in Timor Leste with some of these babies born premature with very low haemoglobins. I learnt from this presentation that if a babies and children have a large liver and spleen with low haemoglobins, they could have a severe haemoglobinopathy. In the future I would suggest that the Ministry of Health in Timor Leste plan to have a maternal screening program that would include testing for Thalassemia and haemoglobinopathies. In the immediate future I will be working with my colleagues to reintroduce blood films to check on morphology which may help us to detect severe haemoglobin problems.

Ibonia De Sousa

The trip to Darwin in Australia was a fantastic experience and over the three days of the AIMS NSM I saw more than 10 presentations. I would like to thank AIMS and the organising people for giving me the opportunity to...
to come along, especially Ms Meredith Liddy. Everyone we met was really interested in Timor Leste and my work here. We have only been independent for a short time, so at the moment our laboratories are not as advanced as Australia. The people that I saw and listened to left me with some good ideas and suggestions that I can make to the leaders of pathology in Timor Leste.

Dengue is a major issue in Timor Leste. Along with the wet season, we have a dengue season, where the incidence of dengue increases around November/December and continues to stay high until February/March. A lot of my colleagues and their children have had dengue so I had a personal interest in the talk: Travel Medicine: Diagnosis and Management of Tropical Infections in Travellers and Expatriates given by Benjamin Burford and Stuart D Blacksell. It was mentioned that many countries from the SE Asian region use rapid tests to assist with diagnosis of infectious disease and I can say that this is true for Timor Leste. I learnt that testing for just IgM and IgG antibodies to dengue will not give acceptable detection rates as the body’s immune system can take up to 5-7 d to start making the antibodies. You need to use a rapid test which also has a strip for NS-1 antigen. NS-1 Antigen is from the dengue virus and will give positive results much earlier to allow for correct diagnosis and treatment. Given our high rate of dengue infection in Timor Leste, the one major recommendation I would like to make to my leaders is that we try and use a Dengue rapid test card that will detect the NS1 antigen.

Listening to the Thursday afternoon session of presentations on Malaria was very informative. Like dengue we have problems with malaria in Timor Leste. I was interested to hear about how platelets can help fight the infection. I will make sure to pass on information regarding the treatment of Malaria and making sure not to use aspirin for fever control and pain relief as it increases the chance of bleeding in the brain and permanent damage.

I really enjoyed dinner at the Darwin Yacht Club, where everyone was relaxed and dressed nicely. We met some really nice scientists from Adelaide who were making sure we had a good time.

Evangelina (Bella) Belo

Coming to Darwin in Australia for the AIMS NSM of 2012 was such an exciting event for me. It was the first time I had been to Australia and the night before we left Timor Leste I couldn’t sleep. The scholarship awarded to me was very much appreciated and I felt very lucky to be chosen. To all of the organisers and members of AIMS I would like to say thank you.

The display of scientific posters in the exhibition hall was informative and covered a lot of different topics. I was particularly interested in the poster titled; “Algorithm for the serological diagnosis of HIV – A comparison of three HIV point of care testing kits for second line testing,” by Nolene Wilson. In the community health centres of Timor Leste we also use a three test process similar to that which was analysed in this activity, to minimise the chance of false positive and false negative results. At the National Laboratory in Dili, when we have reagent available, we do confirmation testing on an Abbott AxSym for positive results.

The presentation by Stuart D Blacksell on Zoonotic Infections contained a lot of information that could be applicable in Timor Leste as we have a close relationship with our animals such as pigs and dogs. Unfortunately with limited resources, I think a lot of infections due to animal interaction could be misdiagnosed.

Like my colleagues, I really liked the experience of meeting with scientists from all over Australia and other countries. If possible, it would be great in the future for something similar to help organise a conference for all to the laboratory scientists of Timor Leste to attend. I also loved Darwin and taking a visit to the shopping centre and night markets on the beach.

Acknowledgment

We thank Nick Hayes for writing this brief article and editing the contribution of Matias da Silva, Ibonia De Sousa and Evangelina Belo. Nick Hayes also supported them in their applications for the AIMS scholarships.
Questions relating to ‘Approaches to augment the cell dose in cord blood to improve allogeneic haematopoietic stem cell transplantation outcomes in adults’, page 42 of this issue.

1. Cord blood is primarily used as an alternative source of HSCs when a BM or mobilised PB source from a human leukocyte antigen (HLA)-matched related or unrelated donor is unavailable.

2. A major disadvantage of using CB is the high cell dose contained in single CB units compared to BM grafts.

3. The primary criterion for CB unit selection is based on the cryopreserved CD34+ cell dose per kilogram recipient weight.

4. The best outcome for neutrophil and platelet engraftment, acute graft versus host disease (GVHD), transplant related mortality, treatment failure and overall mortality was associated with better HLA matching rather than the total nucleated cell dose used for the transplant.

5. There are over 2 million HLA-typed CB units registered on the Bone Marrow Donor Worldwide database (www.bmdw.org).

6. The concept of double cord blood transplants was introduced by investigators at the University of Minnesota.

7. In a double cord blood transplant it is usually only one of the grafts that contributes to the success of long term engraftment.

8. The efforts to improve rates of neutrophil engraftment using the AastromReplicell System and the copper chelator tetaethylenepentamine expansion methodologies have so far shown marginal to no clinical effect.

9. Direct injection of a cord blood graft into the marrow has been shown to be safe procedure although technically and logistically more difficult to perform.

10. Allogeneic haematopoietic stem cell transplantation (HSCT) is an established treatment modality for a number of malignant and non-malignant haematological disorders.

Name: _____________________________________________

Email: ____________________________________________

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Questions relating to ‘Algorithm for whole blood viscosity: implication for antiplatelet bleeding risk assessment’, page 50 of this issue.

1. The therapeutic assessment for the risk of bleeding is widely performed. True/False

2. WBV is not too specific or too sensitive a parameter to be useful. True/False

3. A study had reported that the prevalence of antiplatelet use was 54% overall. True/False

4. Blood with a less than normal viscosity would bleed slower compared to high viscosity blood. True/False

5. WBV is directly and inversely associated with platelet counts and INR respectively. True/False

6. Virchow’s triad is atherothrombosis, endothelial dysfunction and stasis. True/False

7. There is good quality assurance and controls available for platelet aggregometry testing. True/False

8. The majority of patients on antiplatelet prophylaxis have normal WBV. True/False

9. Hyperviscosity was observed in 2.9% of patients with increased CRP. True/False

10. Antiplatelet therapy such as aspirin does not give any cardio-protective effects. True/False

Full Name: ________________________________________________________________

Email: ________________________________________________________________

Please photocopy this page or print it from the electronic AJMS which is stored in the AIMS ‘Member centre’ under the heading ‘Journal’ at www.aims.org.au. Circle your answers then post, fax or scan and email to us by 31st August 2013 to:

AJMS APACE Questions, AIMS National Office, PO Box 1911, Milton Qld 4064. Facsimile: 61 7 3876 2999
Following is a list of books available for review by resource consultants and members of the Institute with particular expertise in the field. The reviewer is invited to retain the complimentary copy of the book once the review is received.

As per our agreement with the book publishing companies, complimentary books are submitted to the Institute provided that all reviews are published in the Australian Journal of Medical Science. These reviews must be of a high quality as buying decisions and the reputation of the book and author are important considerations.

Books not requested will be allocated at discretion of the Editors for the Australian Journal of Medical Science. Reviews should be 300 to 700 words depending on the volume of the book. Time limit for return of review is six weeks.

Unfortunately AIMS is unable to send books overseas.

Please send your request to: Australian Institute of Medical Scientists PO Box 1911 Milton Qld 4064
Tel: (07) 3876 2988 Fax: (07) 3876 2999 Email: aimsnat@aims.org.au

Latest additions:

1. Alzheimer’s Disease - Modernizing Concept, Biological Diagnosis and Therapy edited by H. Hampel & M.C. Carrillo. Karger. vi+194 pages


Alzheimer’s Disease - Modernizing Concept, Biological Diagnosis and Therapy
Edited by H. Hampel & M.C. Carrillo
Karger
Hard cover VI + 194 p
ISBN: 978-3-8055-9802-6
USD $79.00

In 1906 Dr Alois Alzheimer, a German neurologist described an aggressive form of dementia which was characterised by two forms of deposits: senile (amyloid) plaques and neurofibrillary tangles. This condition which became known as Alzheimer’s Disease (AD) is the most common type of age-related dementia.

The author’s claim that AD is now a world-wide epidemic with projected numbers of those affected ranging from 65.7 million by 2020 to 115.4 million by 2050. The greatest risk factor is an ageing population. The prevalence of the disease in America is estimated to be 1 in 8 over the age of 65 rising to 1 in 2 over the age of 85.

This book has two volume editors and 27 contributing authors. It is well-referenced with 977 references cited. Overall it seeks to address the history, genetics, social and financial implications, existing treatments and future directions of the disease.

Although written by experts in the field, the book is readable. Furthermore, it is suitable for those who require an up-to-date overview of AD as well as for those who need a more detailed knowledge of specific areas. To achieve this goal the authors provide a very good abstract at the beginning of each chapter.

Included in the book are nine figures, one in colour and 14 tables. These vary in complexity and are designed to supplement the text.

The current pharmacological treatments of AD are reviewed. Efficacy, adverse effects and controversies surrounding the use of these drugs is discussed. Currently the main drugs used are cholinesterase inhibitors, memanatine and Ginkgo biloba extract. It is claimed that no new drug has been approved for marketing since 2002/2003.

Although the use of vitamins and food supplements (neutraceuticals) is widespread, the authors find there is no scientific evidence to support their use in the prevention or treatment of AD.

The final chapter, Perspectives on Alzheimer’s Disease: Past, Present and Future contains sobering information on this serious brain disorder which has become a global challenge in health care. To obtain better outcomes, the cause of the disease needs to be determined and mechanisms established to enable early detection. Currently the disease is well-established by the time the first symptoms appear.

This book would be a welcome addition to a medical library.

Neville Tingle
Life Member of AIMS

Communicable Diseases a Global Perspective
By Roger Webber
CABI
Hard cover 328 pages
USD $75.00

Communicable Diseases a Global Perspective represents an excellent introduction to communicable disease theory and control.

The first two chapters are a crash course on communicable disease theory and the dynamics of disease spread. Chapters 3 and 4 build on the knowledge already presented, and introduce basic control principles and the importance of surveillance systems in monitoring the incidence of disease. Guidelines for the investigation of an outbreak are presented and briefly expanded upon. Regulations governing the notification of communicable disease are mentioned in chapter 5.

Chapters 6 through to 19 address the most common communicable diseases in the developing (and developed) world, grouped by means of transmission – poverty, faecal-oral diseases, foodborne diseases, soil-borne diseases, waterborne diseases, skin infections, airborne transmitted diseases, STIs and blood-borne diseases, Insect borne diseases, parasitic diseases, and other zoonotic diseases. Infectious diseases of particular importance during pregnancy and emerging diseases each earn themselves a chapter. Finally, a long table lists a myriad of communicable diseases, their clinical features, agent of transmission, and incubation period.

The author’s fundamental aim was to produce an affordable book of manageable size which can be used in developing countries. The result is a no frills, user-friendly
textbook of considerable quality. Figures, tables, maps and focus boxes are used expertly to elucidate the theory.

This text is suited perfectly to the undergraduate or graduate public health student. It is the perfect size (both physically and in terms of content) to serve as a quick reference; whether that be on a GP’s desk or in the backpack of a health worker in a developing country, as it is intended.

Anthony Draper MAIMS
Epidemiologist, Darwin NT

*From Kurmond Kid to Cancer Crusader: Pioneering Integrated Cancer Treatment*

**By Professor Fred Stephens**

Wakefield Press

Soft cover 208 pages


Professor Fred Stephens is a pioneer in the field of surgical oncology. He spent the latter parts of his distinguished career at Sydney University in conjunction with the historic Sydney Hospital.

The book starts with Stephens detailing his childhood in Kurmond (located northwest of Sydney) and his early decision to study medicine. He provides an insight into a simpler time and the obstacles for a country kid to access this career path.

He recalls stories of his early medical career in both Australia and overseas providing many entertaining anecdotes. Stephens spent time working on ocean liners and illustrates the difficulties experienced working as a ship’s surgeon and the wonderful perks available for a young doctor.

Stephens has written this book as an autobiography but also to highlight the need for a Chair of Surgical Oncology at Sydney University. He will donate the proceeds from the book to establishing such a chair.

Professor Fred Stephens details a frank but warm account of his time as a student, surgeon, father and husband. Stephens is an inspirational Australian who shares his personal account of his life and career openly and honestly.

Sophie Wylde MAIMS
Senior Scientific Officer (Biochemistry)
Curtin University

**Quantitative Real-time PCR in Applied Microbiology**

Edited by Martin Filion

Caister Academic Press

Hard cover x + 242 pages

ISBN: 978-1-908230-01-0

USD $319

This text is a hard cover, 2012 edition of 242 pages. There are 11 chapters distributed between three parts: part one covers Technical considerations, part II looks at qPCR for Quantifying Microorganisms and part III launches into RT-qPCR for Studying Microbial Gene Expression. Each chapter is written by an array of international experts in their field. Food and water microbiology are covered.

The text also compares various platforms and technologies used in the PCR field. How to assess, calibrate, develop control data and statistically analyse is covered in this text. There is a required level of previous knowledge before encountering this text as it is very technical and only suited to the regular user of these techniques. The text is not recommended for students as a first text on PCR technology but would be useful for research students.

The compilation of chapters by various experts is a good concept for a text as it renders the users of these technologies wise to the good the bad and the ugly of various methodologies. This text also enlightens readers on what happens in many specimen-in result-out platforms, giving the background information and knowledge required to understand these technologies.

To this end I would recommend this text to anyone involved in the purchase of equipment for diagnostic or research use.

Noelene Wilson MAIMS
Hospital Scientist
Hunter Area Pathology Service

**Bile acids as Metabolic Integrators and Therapeutics**

Editor by D. Häussinger, U. Beuers, A. Stiehl & M. Trauner.

Karger

Soft cover 123 pages

ISBN: 978-3-8055-9804-0

USD $64.00

Bile acids as Metabolic Integrators and Therapeutics is a collection of reprints from Digestive diseases Vol 29 (1), (2011) that were presented at the 175th Falk Symposium and 21st International Bile Acid Meeting held in October 2010 in Freiburg.
The contents of the conference proceedings are broadly categorised into sections describing bile acid metabolism and transport, receptor regulation, pleiotropic actions, the influence of genetic variants and therapeutic potential. The importance of the last category, implicit in the title, is disappointingly underdeveloped.

The contents are a series of scientific papers and are presented in a format expected of the primary scientific literature. Papers describing signalling and stimulation mechanisms for bile acids, Organic Solute Transporter and the bile acid export pump in regulating bile acid concentrations. In functional design of therapeutics, some attention is given to BA receptors, notably TGR5, that may also be targeted by other steroid substrates and related compounds.

The maternal-foetal BA relationship is discussed with respect to the impact maternal cholestasis has on raising foetal BA and the consequent risk to the foetus. The resistance of cholangiocytes to BA damage is also discussed as is the mechanisms triggering pruritus. Some weight is given to the BA activation of nuclear receptors and thus touches on understanding liver disease and potential target sites for the development of new therapies. Ursodeoxycholic acid is discussed with respect to PBC and the treatment of fatty liver disease but, disappointingly, not its influence on metabolism or the distribution of acids in the bile.

Bile acids as Metabolic Integrators and Therapeutics is not a textbook or a cohesive treatise on the development of one or more therapeutic substances. It is therefore a difficult work to review. Bile acids are undoubtedly important metabolic regulators and imbalances in their metabolism or distribution can lead to significant physiological consequences. That said, this volume does not specifically address the therapeutic potential of bile acids or their importance in regulating other metabolic pathways. Many researchers involved in the investigation of hepatic disease will either subscribe already to this journal or better source specific items through their searches of the primary literature. The volume is less relevant to those involved in rational design of new therapeutics.

Dr Paul Wynne
Toxicologist and Analytical Chemist

Dr Paul Wynne is a Toxicologist and Analytical Chemist with interests in metabolomics modifiers of both endogenous and exogenous substances.
AIMS NSM 2013
"Tackling Science, Kicking Goals"

2nd - 4th SEPTEMBER 2013 | Grand Hyatt, Melbourne Victoria

PROGRAM

EARLY BIRD REGISTRATION CLOSES: 19th July 2013

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<tr>
<th>Time</th>
<th>Session</th>
</tr>
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<tbody>
<tr>
<td>8:40</td>
<td>Official Opening</td>
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<tr>
<td>9:00</td>
<td>Keynote Address, Prof Fiona Wood, Burns Service Western Australia &amp; Fiona Wood Foundation, The Quest for Scarless Healing</td>
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<tr>
<td>10:00</td>
<td>Saal-Foley Lecture, Prof Denise Jackson, RMIT University, Developing the Careers of Medical Scientists in Australia</td>
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<tr>
<td>10:45</td>
<td>Morning Tea</td>
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<tr>
<td>11:15</td>
<td>Plenary 1, Prof Stephen Fox, Peter MacCallum Cancer Centre, Molecular Pathology: Evolution or Revolution in Tumour Classification and Therapeutics, Dr Dominic Wall, Peter MacCallum Cancer Centre, Cell Therapies - Translation to the Clinic</td>
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<tr>
<td>12:45</td>
<td>Lunch</td>
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<tr>
<td>13:00</td>
<td>Breakout Session 1 - Biochemistry, George Streitberg, Impact of Technology on Service Provision in Core and Biochemistry Labs, Dr Hans Schneider - Natriuretic Peptide testing in Heart Failure</td>
</tr>
<tr>
<td>13:30</td>
<td>Breakout Session 1 - Microbiology, Danielle Sevier - MALDI TOF, Dr Peter Ward - Gram Negative Resistance and Phenotype Testing, Mick Huysmans - Transition to EUCAST, Patricia White - Gonorrhoea and Antimicrobial Resistance</td>
</tr>
<tr>
<td>13:30</td>
<td>Breakout Session 1 - Haematology/Coagulation/Transfusion, Dr Erica Wood - Platelet Transfusions - Why, When and How, Anthony Bell - Transitioning Molecular Haematology to Next Gen Sequencing (NGS), Dr John Rowell - Haemophilia Genetic Testing</td>
</tr>
<tr>
<td>13:30</td>
<td>Breakout Session 1 - Histology, Dr Michael Christie - Molecular Testing of Colorectal Cancer Samples, Beena Kumar - IHC - Does it have a Role in Targeted Therapy</td>
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<tr>
<td>13:30</td>
<td>Breakout Session 1 - Pathology, Funding &amp; E-Health, Ed Wilson - Pathology Under Medicare, The Need for a New Approach to Funding, Jenny Sikorski - E-health in Pathology</td>
</tr>
<tr>
<td>15:00</td>
<td>Breakout Session 2 - Biochemistry, David Faulkner - Clinical Chemistry of Multiple Myeloma, Dr Ken Sikaris - Tumour Marker Presentation</td>
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<tr>
<td>15:30</td>
<td>Breakout Session 2 - Microbiology, 6 x Microbiology Case Study Presentations, Patricia Szczurek, Amy Batey, Geremie Ganino</td>
</tr>
<tr>
<td>15:30</td>
<td>Breakout Session 2 - Haematology/Coagulation/Transfusion, Dr Emmanuel Favalaro - Futility of Testing for Thrombophilia, Kylie Rushford - Blood Transfusion Practice in Thalassemia, Joe Manitta - Malaria Incidence, Diagnosis &amp; Therapy</td>
</tr>
<tr>
<td>15:30</td>
<td>Breakout Session 2 - Molecular Pathology and Somatic Mutations, A/Prof Elizabeth Algar - Cancer Molecular Pathology: Lessons Learned from Paediatric Cancer, Dr Ben Solomon - Topic TBC</td>
</tr>
<tr>
<td>15:30</td>
<td>Breakout Session 2 - Regulatory Session, Michelle McNiven - TGA &amp; IVD Regulation Presentation, Andy Griffin - Updates from NATA</td>
</tr>
</tbody>
</table>
# Program Day 2

**Day 2 | Transplantation and Immunisation | Tuesday 3rd September 2013**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>7:30</td>
<td>Breakfast Master Class - Molecular Pathology</td>
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<tr>
<td>7:40</td>
<td>Anthony Bell &amp; Dr Victoria Beshay - From DNA to Life Changing Decisions</td>
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<tr>
<td>7:50</td>
<td>Breakfast Master Class - Coagulation</td>
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<tr>
<td>8:00</td>
<td>Robert Bird - The Clinical Utility of Thrombophilia Screening</td>
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<tr>
<td>8:10</td>
<td>Murray Adams - QC of Lupus Testing</td>
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<tr>
<td>8:20</td>
<td>Breakfast Master Class - Flow Cytometry</td>
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<tr>
<td>8:30</td>
<td>Ralph Rossi - Introduction to Physics Flow Cytometry</td>
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<tr>
<td>8:40</td>
<td>Vuong Nguyen &amp; Gosia Gorniak - Clinical Flow Cytometry Case Studies</td>
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<tr>
<td>9:00</td>
<td>Plenary 2</td>
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<tr>
<td>9:10</td>
<td>Dr Helen Opdam, Donatellife</td>
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<td>9:20</td>
<td>Organ donation - What's New and Changing</td>
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<td>9:30</td>
<td>A/Prof David Ritchie, Royal Melbourne Hospital</td>
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<tr>
<td>9:40</td>
<td>Haematopoietic Stem Cell Transplantation; The Power and the Promise</td>
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<td>10:00</td>
<td>Morning Tea</td>
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<tr>
<td>11:00</td>
<td>Plenary 3</td>
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<tr>
<td>11:10</td>
<td>Prof Monica Slavin, Peter MacCallum Cancer Centre</td>
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<tr>
<td>11:20</td>
<td>Infections in the Immunocompromised</td>
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<td>11:30</td>
<td>Dr Solomon Cohney, University of Melbourne &amp; Monash University</td>
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<tr>
<td>11:40</td>
<td>ABO Incompatible Solid Organ Transplantation</td>
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<tr>
<td>12:00</td>
<td>Lunch (including Poster Session)</td>
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<td>12:30</td>
<td>Afternoon Tea</td>
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<tr>
<td>14:00</td>
<td>Preferred Papers</td>
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<tr>
<td>14:10</td>
<td>Margaret May Baekalia - Assessing Vaginal Smears from Solomon Islands for Bacterial Vaginosis by Nugent Score Method</td>
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<tr>
<td>14:20</td>
<td>Helen Bardsey - Transfusion in HELLP</td>
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<tr>
<td>14:30</td>
<td>Rebecca Donkin - Utilising Virtual Microscopy to Teach Haematology in a Regional University</td>
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<tr>
<td>14:40</td>
<td>Pranav Dorwal - Flow Cytometric Cross Match (FCXM): A sensitive tool to detect Donor Specific Antibodies (DSA)</td>
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<tr>
<td>14:50</td>
<td>Dennis Mok - ISO 15189:2012 implementation: an applied change management approach</td>
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<tr>
<td>15:00</td>
<td>Leanne Sinclair - Case study of adult MLL-rearranged B-precursor acute lymphoblastic leukaemia</td>
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<td>15:30</td>
<td>Afternoon Tea</td>
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<tr>
<td>16:00</td>
<td>Breakout Session 3 - Microbiology</td>
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<tr>
<td>16:10</td>
<td>Dr Jason Trubiano - Faecal Transplantation for C. difficile</td>
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<td>16:20</td>
<td>Prof Heath Kelly - Influenza Vaccination Trends and Issues</td>
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<td>16:30</td>
<td>Christopher Maher - Polio Eradication Program and Progress Versus Issues Faced</td>
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<tr>
<td>16:40</td>
<td>Breakout Session 3 - Haematology/Coagulation/Transfusion</td>
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<td>16:50</td>
<td>Geoff Magrin - Blood Transfusion Requirements in Transplantation</td>
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<td>17:00</td>
<td>Dr Kate Burbury - Haemostasis in Massive Transfusion</td>
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<td>17:10</td>
<td>Peter Gambell - CD34 Testing for Transplantation Planning: What's New?</td>
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<td>17:20</td>
<td>Breakout Session 3 - Histology</td>
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<td>17:30</td>
<td>Prof Greg Snell - Lung Transplantation: Interfacing Clinical Medicine and Basic Science</td>
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<td>17:40</td>
<td>Dr Donna Rudd - Preservative Solutions for Solid Organs</td>
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<td>17:50</td>
<td>Breakout Session 3 - Biochemistry</td>
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<tr>
<td>18:00</td>
<td>Sabrina Kortziger - Monitoring Your Method Using the RCPAQAP</td>
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<td>18:10</td>
<td>Marion Black - Immunosuppressant Drug Testing</td>
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<td>18:20</td>
<td>Breakout Session 3 - POC &amp; Automation</td>
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<tr>
<td>18:30</td>
<td>Tony O'Neill - POC Presentation</td>
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<tr>
<td>18:40</td>
<td>Ray Dauer - Challenges for Medical Scientists in an Automated World</td>
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<tr>
<td>18:50</td>
<td>Robyn Woodburn-Dennis - Update on Automation Platforms</td>
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<tr>
<td>Time</td>
<td>Session</td>
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<tr>
<td>9:00</td>
<td>Plenary 4</td>
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</table>
| 10:30  | Dr Catrina Goebel, Australian Sports Drug Testing Laboratory  
The Australian Sports Drug Testing Laboratory  
Dr Peter Larkins, Epworth Sports & Exercise Medicine Group  
An Historical Perspective of Drugs & Doping in Sport – and Where to Next? |
| 10:30  | Morning Tea                                  |
| 11:00  | Plenary 5                                    |
| 12:30  | Levinia Crookes, Australasian Society for HIV Medicine  
Status and Latest Developments in POCT for HIV in Australia  
Prof Andrew Grigg, Austin Health  
Advances and Road Blocks in the Management of Haematological Malignancy |
| 13:30  | Lunch and AGM                                |
| 13:30  | Joint Session - Multidisciplinary Topics     |
| 15:00  | Dr Ross Brown - Blood Boosting               |
| 15:00  | Dr Jim Vadolas - Development of New Treatments for Haemoglobin Disorders |
| 15:00  | Carolyn George - Surviving AML - A Patient’s Perspective |
| 15:30  | Afternoon Tea                                |
| 15:30  | Joint Session - Multidisciplinary Topics     |
| 15:30  | Dr Ross Brown - Ethics of the In Vitro Diagnostic Industry |
| 15:30  | Prof Lindsay Grayson - Use and Abuse of Antimicrobials and Antibiotic Stewardship |
| 17:00  | Meeting Closed                              |

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"Tackling Science, Kicking Goals"
2nd - 4th SEPTEMBER 2013 | Grand Hyatt, Melbourne Victoria

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JULY 20 - 21
APaN Conference
Brisbane  QLD  AUSTRALIA

AUGUST 20 - 23
New Zealand Institute of Medical Laboratory Science
Annual Scientific Meeting 2013 "Bridging Science and Education"
Claudelands Conference & Exhibition Centre
Hamilton  NEW ZEALAND

AUGUST 25 - 28
International Council on Alcohol Drugs and Traffic Safety Conference
Brisbane Convention and Exhibition Centre
Brisbane  QLD  AUSTRALIA

SEPTEMBER 2 - 4
AIMS National Scientific Meeting
Grand Hyatt
Melbourne  VIC  AUSTRALIA

SEPTEMBER 16 - 19
AACB 51st Annual Scientific Conference
Evidence Based Laboratory Medicine
Gold Coast Convention & Exhibition Centre
Gold Coast  QLD  AUSTRALIA

OCTOBER 6 - 9
Asia-Pacific Federation for Clinical Biochemistry and Laboratory Medicine Congress
Bali Nusa Due Convention Centre
Bali  INDONESIA

OCTOBER 20 - 23
HAA Meeting
Gold Coast  QLD  AUSTRALIA

NOVEMBER 1 - 3
AIMS NSW North Coast Division Annual Conference
Darlington Beach Resort
Arrawarra  NSW  AUSTRALIA

DECEMBER 2 - 5
43rd Annual Scientific Meeting
Australasian Society for Immunology
The Michael Fowler Centre
Wellington  NEW ZEALAND
http://cmnzl05.eventcms.co.nz/page/63/home
The following instructions are based on the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals”, also known as the Declaration of Vancouver, and on the Australian Government Style manual: for authors, editors and printers, 6th edition, 2002. URLs were correct on September 29th, 2008.

Manuscripts that do not fully comply with the following ‘Instructions to Authors’ may be returned for revision before they are considered for publication.

The Australian Journal of Medical Science (AJMS) will consider for publication any paper relevant to the field of Medical Science. Disciplines include blood banking, clinical biochemistry, haematology, histopathology, immunology, microbiology and molecular biology. Areas of general interest to medical laboratory scientists, including toxicology, epidemiology, public and community health, and professional and management issues will also be considered.

Papers published in the AJMS are in the form of:
- Review Articles
- Original Articles
- Brief Communications
- Technical Notes
- Case Studies
- Letters to the Editor
- Book Reviews

Articles submitted for publication are understood to be offered only to the AJMS and those accepted become the property of the AJMS.

All individuals listed as authors must have made a substantial contribution to the conception and design of the study, the acquisition of data or the analysis and interpretation of data; the drafting of the article or revising it critically for important intellectual content; and final approval of the version to be published. The corresponding author must take responsibility for obtaining permission from all the authors for the submission of any version of the manuscript and for any changes in authorship.

When the manuscript is submitted the authors must disclose any potential conflict of interest and/or commercial support.

**Title page**

The title of the article should not exceed three lines (40 characters per line), including punctuation and spacing. All authors must be identified on the title page (e.g., William Smith, Susan Yeo, …”). Where applicable, the title page should also include the name of the institution with which each author is affiliated and to which the work should be attributed. In the case of multiple authors, the name, postal address, email address, telephone and facsimile number of the author responsible for correspondence relating to the manuscript should be indicated.

**Abstract & keywords**

The abstract should be approximately 150 words and should make sense when read alone or in conjunction with the article. The abstract should be a concise overview that describes the important details of the article including the purpose of the study/investigation, basic procedures (study subjects/experimental animals/observational and analytic methods) and the results and principal conclusions. New and important aspects of the work and its implications may also be included. References should not be included.

Three to ten keywords may be listed. Authors are advised to comply with the terms from the Medical Subject Headings (MeSH) list from Index Medicus (see http://www.nlm.nih.gov/mesh/). Keywords should be given below the Abstract.

**Text**

The style of writing should conform to acceptable English usage. Do not use slang, medical jargon or unnecessary abbreviations. Accepted spelling is the first choice given in the latest edition of the Macquarie Dictionary.

Wherever possible observational or experimental articles should be divided into sections headed:
- Acknowledgements
- References
- Tables - each table, complete with title and footnotes, on a separate page
- Legends for illustrations.

Authors should ensure that their manuscript communicates their ideas and concepts simply and clearly so that the article is easily read and understood. Authors are strongly recommended to refer to the recommendations on reporting standards as outlined in the statements and checklists of the CONSORT group (see: http://www.consort-statement.org/) and similar groups such as STARD (see: http://www.stard-statement.org/). The principles outlined in these standards may be used as general guidelines and not just as applied to clinical trials and diagnostic studies.
• Discussion
• References

For other types of articles such as commentaries, reports and reviews, use an appropriate format or consult the Editors for guidance.

Introduction

Clearly state the purpose of the article leading the reader from the known to the unknown. Summarise the rationale for the study and state the question to be answered as appropriate. Give only strictly pertinent references, and do not review the subject extensively.

Materials & methods

Present the materials and methods in a logical sequence. Describe the selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Notification of ethics approval must be given where relevant. Identify the methods, apparatus and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods. Adequately describe new or substantially modified methods. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not identify patients or hospitals without consent.

Results

Present the results in the same sequence as given in the Materials and methods; use tables and illustrations where these will help the reader understand the work being presented. Do not repeat in the text all the data in the tables or illustrations.

Discussion

Indicate the new and important aspects of the study and emphasise the conclusions that follow. Do not repeat in detail data given in the Results section and do not add new data. Include in the Discussion the implications of the findings and their limitations and compare the observations to other relevant studies. Recommendations may be included if appropriate. Link the conclusions with the goals of the study and answer the experimental question stated in the Introduction. However, avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such.

Acknowledgements

Acknowledge individuals who have made substantial contributions to the study including technical work and financial support. Authors are responsible for obtaining consent from all the individuals acknowledged by name as inclusion may be interpreted as an endorsement of the article's contents.

References

The AJMS uses a modified Harvard System (author-date system).

Throughout the body of the manuscript cite the author/s name and the publication year in parentheses as in the following examples:

(i) Research in this area (Jones 1999) …
(ii) It has been successfully demonstrated that (Smith and Brown 1981; Auteur 1995; Scienziato et al 2007).
(iii) Following further investigation, Wetenschapper (2002) highlighted the difficulties inherent in…

Where there are three or more authors, acknowledge only the first author, e.g., (Smith et al 2007). For two authors the following style should be used: (Smith and Brown 2007).

The reference list should be in the format described below. Journal titles should be abbreviated in Index Medicus format (see: ftp://nlmpubs.nlm.nih.gov/online/journals/ljiweb.pdf) using standard abbreviations from the ISSN List of Title Word Abbreviations (see: http://www.isss.org/en/node/344) All authors should be given in the reference list.

Do not use abstracts as references. “Unpublished observations” and “personal communications” may not be used as references, although references to written, not verbal, communications may be cited (in parentheses) in the text. Include in the references manuscripts accepted but not yet published, designate the journal followed by “in press” (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as “unpublished observations” (in parentheses).

Examples of the correct form for references are given below:

i) Journal Reference:

ii) Personal Author(s) of a book:

iii) Editor, Compiler, Chairman as Author:

iv) Chapter in Book:

v) Online documents:

Tables

Number tables consecutively with Arabic numerals and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in headings. Explain in footnotes all non-standard abbreviations used in each table.

For footnotes, use the following symbols in this sequence:

* † ‡ § ¶ ** ††
In preparing tables, consideration should be given to the page width of the Australian Journal of Medical Science. All tables should be prepared for publication vertically. In the text, cite each table in consecutive order, and mark in the margin of the text its approximate location.

If data from another published or unpublished source is used, written permission must be obtained and a copy must accompany the manuscript.

Illustrations
Colour illustrations may be submitted on a CD. Images should be scanned at a minimum of 300 dpi.

When plotting points, the following symbols are preferred:

* O, ●, ▲, ▼, □, ■

In most instances, figures will be reduced to one column in width. All letters and numbers should be drawn to be at least 1.5 mm high after reduction, symbols at least 1.0 mm. Titles for illustrations belong in the legends for illustrations and not on the illustrations themselves.

Photomicrographs must have internal scale markers and the magnification must be stated. Symbols, arrows, or letters used in the photomicrographs should contrast with the background.

Cite each figure in the text in consecutive order, e.g., “Figure 1 illustrates …” or “… as shown (fig. 2)”. If a figure has been published, acknowledge the original source and submit with the manuscript written permission from the copyright holder to reproduce the material. Permission is required, regardless of authorship or publisher, except for documents in the public domain.

Legends for illustrations
When symbols, arrows, numbers, or letters are used to identify parts of illustrations, identify and explain each one in the legends. The figure legend must contain a boldface (a) name (“Figure” + arabic figure number) and (b) substantive title.

Abbreviations
Use only standard abbreviations (see list of commonly used abbreviations, below).

Avoid abbreviations in the title. The full term for which an abbreviation stands must precede its first use in the text unless it is a standard abbreviation for a unit of measurement.

Report measurements in the units in which the measurements were made. In most countries the International System of Units (SI) is standard.

Commonly used abbreviations

<table>
<thead>
<tr>
<th>Abbreviation or Symbol</th>
<th>Standard Units of Measurement</th>
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<tr>
<td>g</td>
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Additional information
The following are useful sources of information. The first two publications are used by the AJMS as standard references.


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