Haematology Research Review™

Making Education Easy

Issue 29 - 2018

In this issue:

Abbreviations used in this issue
CV = cardiovascular
DOAC = direct oral anticoagulant
GI = gastrointestinal
ITP = immune thrombocytopenia
IVIG = intravenous immunoglobulin
JAK = Janus kinase
LMWH = low-molecular-weight heparin
VTE = venous thromboembolism

Welcome to issue 29 of Haematology Research Review.

This issue begins with a prospective multicentre French cohort study that set out to identify risk factors for thrombotic complications among outpatients with cancer. We have also included the recommended guidance from the SSC of the ISTH on the management of cancer-associated VTE, with focus on the use of DOACs. There is also NZ research published in JAMA included, reporting estimates of annual major bleeding and nonfatal major bleeding risks in primary-care patients not receiving antiplatelet therapy, to help inform population-level guidelines for primary CV disease prevention. The authors of the final paper included in this issue have provided a comprehensive analysis comparing the different phenotypic and clinical aspects of the various genetic types of hereditary haemochromatosis.

We hope you enjoy this latest issue of Haematology Research Review, and we welcome your comments and feedback.

Kind regards,

Dr Paul Ockelford
paulockelford@researchreview.co.nz

Dr Laura Young
laurayoung@researchreview.co.nz

Cancer-associated thrombosis in patients with implanted ports

Authors: Decousus H et al.

Summary: The French ONCOCIP study prospectively followed 3032 consecutive adults with breast, lung or colorectal tumours and an implanted port to identify risk factors for catheter-related thrombosis and non-catheter-related VTE; 97.1% of the patients had received chemotherapy. The 12-month catheter-related thrombosis rate was 3.8% and the 12-month non-catheter thrombosis rate was 9.6%. Use of the cephalic vein for catheter insertion was found to be predictive for, and ongoing antiplatelet therapy protected against, catheter-related thrombosis. Factors predictive of non-catheter-related VTE were advanced age, prior VTE, cancer site and low haemoglobin level or increased leucocyte count prior to chemotherapy.

Comment (PO): Current management guidelines do not recommend primary prophylaxis in ambulatory patients with malignancy, including those with central-vein catheters. Thromboprophylaxis trials have been inconclusive or showed a small absolute benefit. The primary objective of this study was to identify risk factors for thrombotic events including catheter-related thrombosis. Cancers were 78% adenocarcinoma (breast, lung, colorectal), metastatic in 43%, undergoing chemotherapy. Thromboembolic incidence at 12 months was 13.8% with a median time to event of <3 months. Most were non-catheter-related, but 29% involved an indwelling catheter. The only independent catheter-related risk factor was cephalic vein insertion, with ongoing antiplatelet therapy apparently reducing this risk (hazard ratio 0.44). The risk factors for non-catheter-related episodes were different: age >60 years, previous VTE, certain cancer sites, anaemia and leucocytosis prior to chemotherapy. An effective risk assessment model for cancer outpatients most likely to benefit from thromboprophylaxis is still needed, and may be different for preventing catheter-associated events.

Reference: Blood 2018;132:707–16
Abstract

For more information, please go to http://www.medsafe.govt.nz

Intravenous immunoglobulin versus observation in childhood immune thrombocytopenia

Authors: Heitink-Pollé KMJ et al., for the TIKI Investigators

Summary: Children aged 3 months to 16 years with newly diagnosed ITP (platelet count ≤20×10^9 cells/L) and mild-to-moderate bleeding were randomised to receive either a single infusion of IVIG 0.8 g/kg (n=102) or careful observation (n=104) in this trial. Compared with observation, IVIG was associated with a trend for a lower rate of chronic ITP as defined at the start of the study (platelet count <150×10^9 cells/L at 6 months; primary outcome; 18.6% vs. 28.9%; relative risk 0.64 [95% CI 0.38, 1.08]), but not as defined at the time of reporting (platelet count <100×10^9 cells/L at 12 months; 10% vs. 12%; 0.83 [0.38, 1.84]). IVIG recipients had a higher 3-month complete response rate; IgG- Fc receptor IIb genetic variations were associated with early complete response in both groups. The IVIG and observation groups had grade 4–5 bleeding rates of 1% and 9%, respectively.

Comment (PO): Childhood ITP, isolated thrombocytopenia in the absence of other causes, usually presents with acute-onset purpura and bruising after a mild infection, with a platelet count <20×10^9/L. Most recover within 3–12 months. Chronic ITP is defined as persisting thrombocytopenia <100×10^9 cells/L at 12 months. Most patients are managed expectantly, independent of the platelet count, in the absence of severe bleeding. The latter occurs in approximately 3–5% of cases and is an indication for active treatment. IVIG is safe and effective as a single dose (ASH guideline 0.8–1.0 g/kg). A platelet response occurs in 70–80% within 48 hours. This randomised trial reports a lower rate of chronic ITP (11%) in this condition than previously suggested by observational studies (20–25%). Although IVIG improves recovery time, and is associated with fewer postinfusion bleeding events, it does not reduce the rate of chronic ITP.

Reference: Blood 2018;132:883–91
Abstract

Reduced-dose direct oral anticoagulants in the extended treatment of venous thromboembolism

Authors: Vasanthamohan L et al.

Summary: This systematic review and meta-analysis included two trials comparing reduced-dose DOACs with full-dose DOACs and aspirin or placebo for the extended phase treatment of VTE; 5847 participants were analysed for efficacy outcomes and 5842 were analysed for safety outcomes. Reduced-dose and full-dose DOACs were similarly effective for preventing VTE recurrence at 1 year (risk ratio 1.12 [95% CI 0.67, 1.87]) and reduced-dose DOACs were more effective than aspirin/placebo (0.26 [0.14, 0.46]) with similar major or clinically relevant nonmajor bleeding event rates (1.19 [0.81, 1.77]); there was a trend for less bleeding with reduced-dose versus full-dose DOACs (0.74 [0.52, 1.05]).

Comment (PO): Dose-reduced long-term DOAC therapy is an option for patients in whom there is equipoise in the decision to discontinue anticoagulation. Evidence is based on two studies, respectively using apixaban and rivaroxaban. It is still unclear if the benefit is a class effect that can be generalised to other DOACs. Reducing to low 'prophylactic' dosing after the acute treatment phase is not associated with increased thrombosis recurrence, and major bleeding is similar to aspirin or no anticoagulant treatment. The strategy of using low-dose DOACs indefinitely is attractive, but the safety and efficacy beyond 1 year remains unknown. A further caution is that very few patients weighed >120kg in the studies. Expert opinion currently suggests that DOACs should be avoided in those with a very high body mass index.

Reference: J Thromb Haemost 2018;16:1288–95
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**

Independent commentary by Dr Laura Young, a haematologist specialising in thrombosis and haemostasis at Auckland Hospital as part of the Thrombosis Unit and Haemophilia Centre. She also has a part-time lecturing position in the Department of Molecular Medicine and Pathology at the University School of Medicine. **For full bio CLICK HERE.**

Independent commentary by Dr Paul Ockelford, a haematologist and Clinical Associate Professor at the University of Auckland School of Medicine and Director of both the Adult Haemophilia Centre and Thrombosis Unit at Auckland City Hospital. He serves on the Medical Advisory panel of the New Zealand Haemophilia Foundation and the National Haemophilia Management Group. **For full bio CLICK HERE.**

Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism

Authors: Khorana AA et al

Summary: This paper presents guidance from the SSC (Scientific and Standardization Committee) of the ISTH for the management of patients with cancer-associated VTE. The authors reviewed evidence from randomised controlled trials and clinical practice studies, and considered patient preferences and values, limitations and precautions, to come up with the following recommendations: i) treatment regimens should be individualised after shared decision-making with patients; ii) use of specific DOACs for patients with acute VTE and a low bleeding risk bleeding provided there are no drug-drug interactions with current systemic therapy, with LMWHs as an acceptable alternative; and iii) use of LMWHs for patients with acute VTE who have a high bleeding risk, with specific DOACs as acceptable alternatives provided there are no drug-drug interactions with current systemic therapy.

Comment (PO): The role of DOACs in the treatment of cancer-related VTE is topical with the recent publication of two clot in cancer studies using oral direct Xa inhibitors (edoxaban and rivaroxaban). This SSC publication from the ISTH provides some guidance. Shared decision making with patients is recommended. Specific DOACs (e.g. rivaroxaban) are suggested for those with acute VTE, a low bleeding risk and no potential drug interactions with other systemic therapy, provided they are able to successfully manage oral anticoagulation. LMWHs (e.g. enoxaparin [Clexane®]) are still favoured where the bleeding risk is high. This includes those with luminal GI tract cancers and an intact primary, genitourinary malignancy and active GI mucosal abnormalities (gastric ulcers, colitis, etc). Initial LMWH and delayed introduction of the DOAC (weeks–months) may be an option in this situation. The optimal duration of anticoagulation is not addressed and remains unresolved.

Reference: J Thromb Haemost; Published online June 29, 2018
Abstract

A randomized trial of early endovenous ablation in venous ulceration

Authors: Gohel MS et al., for the EVRA Trial Investigators

Summary: Patients with venous leg ulcers (n=450) were randomised to receive compression therapy with or without early endovenous ablation of superficial venous reflux within 2 weeks; in the control group, consideration of endovenous ablation was deferred until after the ulcer had healed or until 6 months after randomisation if the ulcer was unhealed. Compared with the control group, early endovenous ablation was associated with a shorter median time to ulcer healing (primary outcome; 56 vs. 82 days), a greater likelihood of ulcer healing (hazard ratio 1.38 [95% CI 1.13, 1.68]), a higher 24-week ulcer healing rate (85.6% vs. 76.3%) and a longer median ulcer-free duration during the first year (306 vs. 278 days [p=0.002]). Pain and deep vein thrombosis were the most common complications associated with endovenous ablation.

Comment (PO): Varicose veins with superficial venous reflux can be treated with various endovenous interventions including ultrasound-guided foam sclerotherapy and laser or nonthermal ablation. Faster ulcer healing was achieved by early endovenous intervention in this 'pragmatic' multicentre study. The advantage was demonstrated despite high-quality compression therapy, only achievable in a clinical trial, which potentially explains the high healing rates in both treatment groups. In the real world, endovenous ablation is usually a one-off procedure, so is less dependent on patient compliance with compression stockings. Ablation was also beneficial in patients with concomitant deep venous reflux, but the best method and the extent to which ablation therapy prevents long-term ulcer recurrence remain unclear. Perhaps surprisingly despite faster ulcer healing in the early intervention group, the quality of life scores were similar in the two groups.

Reference: N Engl J Med 2018;378:2105–14
Abstract

Annual risk of major bleeding among persons without cardiovascular disease not receiving antiplatelet therapy

Authors: Selak V et al.

Summary: This NZ study assessed the risk of major bleeding in a prospective cohort of 359,166 primary-care patients aged 30–79 years who had undergone CV disease risk assessments and were not receiving antiplatelet therapy. Repeat analyses were performed after excluding individuals with medical conditions associated with increased bleeding risk (non-high-risk cohort; n=305,057) and after further excluding those receiving other medications associated with increased bleeding risk (nonmedication cohort; n=240,254). In the baseline cohort, 3976 patients experienced a major bleeding event during 1,281,896 person-years of follow-up. Almost three-quarters of these events were GI, and 7% were fatal; 153 of the 274 fatal bleeds were intracerebral. The respective incidences of nonfatal GI bleeding events in the baseline, non-high-risk and nonmedication cohorts were 2.19, 1.77 and 1.61 per 1000 person-years, and the respective fatality rates associated with GI bleeding were 3.4%, 4.0% and 4.6%.

Comment (LY): The use of aspirin as primary prophylaxis to prevent vascular events is contentious; another large randomised cohort suggesting minimal benefit has recently been published (Lancet 2018). Estimates of benefit versus risk depend on accurate, age-adjusted absolute risks of bleeding. This large cohort from NZ primary care of patients without antiplatelet therapy extracted via the use of a CV risk assessment online tool provides these data, showing a clear increase in the risk of bleeding and case fatality with age (notably GI bleeding). As expected, intracerebral bleeding was rare, but with a high case fatality.

Reference: JAMA 2018;319:2507–20
Abstract

CLICK HERE to read previous issues of Haematology Research Review

Aggressive B-cell lymphomas in patients with myelofibrosis receiving JAK1/2 inhibitor therapy

Authors: Porpaczy E et al.

Summary: These researchers reported lymphoma development in patients with myeloproliferative neoplasms. Compared with patients who received conventional treatment (n=557), a greater proportion of those with myelofibrosis treated with JAK1/2 inhibitors (n=69) developed B-cell lymphomas (5.8% vs. 0.36%); a similar 15-fold greater rate was seen in an independent cohort of 929 patients with myeloproliferative neoplasms. When only patients with primary myelofibrosis were considered (n=216), 9.7% of inhibitor-treated patients developed lymphoma, compared with 0.54% of control patients. Lymphomas were of aggressive B-cell type, extranodal or leukaemic with high MYC expression, without *JAK2* V617F or other myeloproliferative neoplasm-associated mutations. Lymphomas were diagnosed in a median of 25 months after starting inhibitor therapy, at which time clonal immunoglobulin gene rearrangements had already been detected in the bone marrow during myelofibrosis in 16.3%. Among all of the three patients tested, lymphoma development during JAK1/2 inhibitor treatment was preceded by a pre-existing B-cell clone; clonal identity was verified on sequencing in two patients. Studies in 24 *Stat1*$^{-/-}$ mice revealed that 16 developed spontaneous myeloid hyperplasia with concomitant aberrant B-cell presence, and bone marrow transplantations from diseased mice showed outgrowth of a malignant B-cell clone evolving into aggressive B-cell leukaemia-lymphoma.

Comment (LY): It has been recognised historically that clonal B-cell populations can be identified in a small subset of myeloproliferative neoplasm patients. However, the association between JAK2 inhibition in myelofibrosis patients and a 16-fold increase in the risk of aggressive B-cell lymphoma is an example of unintended effects of inhibition of JAK. Ruxolitinib does not conclusively improve overall survival in myelofibrosis (Blood 2017), so postmarketing extended studies to ensure that potential risks are adequately identified are important. These B-cell clones can be isolated prior to JAK inhibition with PCR, which is likely to be required prior to therapy in the future.

Reference: Blood 2018;132:694–706
Abstract

GPIbα is required for platelet-mediated hepatic thrombopoietin generation

Authors: Xu M et al.

Summary: This research revealed that compared with wild-type control mice, GPIbα$^{-/-}$ mice had 2–3 times lower circulating thrombopoietin levels, which the authors noted is consistent with GPIbα-deficient Bernard-Soulier syndrome in humans. They showed that such decreases in thrombopoietin levels were due to decreased hepatic thrombopoietin mRNA transcription and production, and not increased thrombopoietin clearance by GPIbα$^{-/-}$ platelets. Hepatic thrombopoietin mRNA and circulating thrombopoietin levels were restored by wild-type, but not GPIbα$^{-/-}$, platelet transfusions in GPIbα$^{-/-}$ mice. Disruption of the platelet-mediated hepatic generation of thrombopoietin in the absence of GPIbα was confirmed in hepatocyte cocultures with platelets or GPIbα-coupled beads *in vitro*. Significant desialylation was seen when GPIbα$^{-/-}$ platelets were treated with neuraminidase, but impaired hepatic thrombopoietin production was not restored with desialylated GPIbα$^{-/-}$ platelets *in vivo* or *in vitro*, suggesting that hepatic thrombopoietin generation requires GPIbα independently of platelet desialylation. Furthermore, impaired hepatic thrombopoietin production was confirmed in an IL-4/GPIbα-transgenic mouse model, and also using antibodies targeting the extracellular portion of GPIbα, showing that the GPIbα N-terminus is necessary for platelet-mediated hepatic thrombopoietin generation.

Comment (LY): It has been recognised for many years that thrombopoietin produced in the liver binds to the MPL receptor on megakaryocytes to stimulate platelet production. However, this did not explain how ITP patients could respond to thrombopoietin receptor agonists, as logically thrombopoietin levels should already be high with low platelet numbers. This group also showed a lower thrombopoietin level in patients with Bernard-Soulier syndrome, a rare severe platelet disorder with both dysfunctional and low numbers of platelets. The link to GPIbα (the receptor that interacts with von Willebrand factor) is elegantly shown in this work. In ITP, it is likely that anti-GP1bα antibodies explain the lower thrombopoietin levels and disease sensitivity to thrombopoietin agonists. The mechanisms controlling thrombopoietin levels are complex and multifactorial.

Reference: Blood 2018;132:622–34
Abstract

Hemostatic efficacy of pathogen-inactivated vs untreated platelets

Authors: van der Meer PF et al.

Summary: Patients with haematological malignancies and thrombocytopenia were randomised to receive pathogen-inactivated platelets using riboflavin and ultraviolet B illumination technology (intervention; n=284) or standard plasma-stored platelets (control; n=283) for haemorrhage prevention in this noninferiority trial. In an intent-to-treat analysis, the grade ≥2 bleeding rates (primary outcome) in the respective intervention and control arms were 54% and 51% (p=0.012 for noninferiority), but significance for noninferiority was lost in a per-protocol analysis (52% and 44% [p=0.19 for noninferiority]). The intervention arm was also associated with ~50% lower transfusion increment parameters. The proportions of participants developing HLA class I alloantibodies did not differ significantly between the trial arms.

Comment (LY): Infection from blood products, both immediate bacterial contamination and longer term viral or unexpected novel infection, remains an important consideration in transfusion practice. Animal studies also suggested that pathogen inactivation reduces the risk of alloimmunisation, which is another important complication in heavily transfused patients. This large multicentre study explored the use of two methods that appeared promising. Unfortunately though, as demonstrated in other trials, the efficacy of the platelets numerically and in terms of function is probably affected by the treatment, meaning more transfusions are likely to be required. This remains an important area of transfusion research, but the optimal solution has not been found yet.

Reference: Blood 2018;132:223–31
Abstract

Phenotypic analysis of hemochromatosis subtypes reveals variations in severity of iron overload and clinical disease

Authors: Sandhu K et al.

Summary: Phenotypic and clinical presentations of hepcidin-deficient forms of hereditary haemochromatosis were compared for 156 patients with non-HFE hereditary haemochromatosis extracted from 53 publications, compared with 984 patients with *HFE*-p.C282Y homozygous hereditary haemochromatosis from a haemochromatosis database. Compared with HFE hereditary haemochromatosis, non-HFE hereditary haemochromatosis was found to have an earlier age of onset and a more severe clinical course. HJV and HAMP hereditary haemochromatosis were phenotypically and clinically very similar and had the most severe presentation, which in particular included cardiomyopathy and hypogonadism. The age of onset and severity of TFR2 hereditary haemochromatosis was found to be more intermediate. All clinical outcomes analysed were more prevalent in the juvenile forms of hereditary haemochromatosis, except for arthritis and arthropathy, which were more common in HFE hereditary haemochromatosis.

Comment (LY): HFE haemochromatosis is a well-recognised recessive genetic disorder, which is common in Caucasian populations. The mechanism is now known to relate to the absence of hepcidin, so that iron is always absorbed and transported even when stored in excess. Interestingly, there is marked phenotypic variation for the same genetic diagnosis. It is helpful to remember that there are other rare hepcidin deficient causes of haemochromatosis that may be diagnosed more frequently with next-generation sequencing techniques. This paper summarises the published cases to look for common features. Interestingly, these are also phenotypically variable, although in general more severe at diagnosis. While patients were younger, they were still diagnosed in adulthood with a greater frequency of all the described clinical features of iron overload.

Reference: Blood 2018;132:101–10
Abstract