Haematology Research Review™

Making Education Easy

Issue 26 - 2017

In this issue:

Abbreviations used in this issue
DOAC = direct oral anticoagulant
FVL = factor V Leiden
HIT = heparin-induced thrombocytopenia
ITP = immune thrombocytopenia
VTE = venous thromboembolism

Welcome to issue 26 of Haematology Research Review.

The first paper selected for this issue has identified contributory factors for bleeding that remains a significant problem for thrombocytopenic haematology/oncology patients even after receiving platelet transfusions. A Sweden-based team of researchers has reported on the use of prothrombin complex concentrates for managing rivaroxaban- or apixaban-associated major bleeding events. Continuing on the topic of DOACs, Canadian researchers have reported their experience using this class of anticoagulants for treating HIT. To conclude Haematology Research Review for 2017, a propensity-matched study describes the therapeutic profiles for hydroxycarbamide (hydroxyurea) and phlebotomy treatments for managing polycythaemia vera.

We hope you have been finding the selected papers and commentaries useful in your everyday practice. We look forward to bringing you more interesting updates in haematology research next year.

Kind regards,

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Laboratory predictors of bleeding and the effect of platelet and RBC transfusions on bleeding outcomes in the PLADO trial

Authors: Uhl L et al.

Summary: These researchers sought to identify contributory factors for bleeding on or after a first platelet transfusion over 16,320 participant-days in 1077 adults enrolled in the PLADO trial. Compared with platelet counts ≥81×10^9/L, platelet counts ≤5×10^9/L were associated with a greater likelihood of bleeding (odds ratio 3.1 [95% CI 2.0, 4.8]); the risk was somewhat increased with platelet counts 6–80×10^9/L in participants treated with allogeneic stem-cell transplantation or chemotherapy, but not those undergoing autologous stem-cell transplantation. Bleeding was also significantly predicted by haematocrit ≤25% (odds ratio 1.29 [95% CI 1.11, 1.49]), activated partial thromboplastin times 30–50 and >50 seconds (1.40 [1.08, 1.81] and 2.34 [1.54, 3.56], respectively), and international normalised ratios 1.2–1.5 and >1.5 (1.46 [1.17, 1.83] and 2.05 [1.43, 2.95], respectively).

Comment (LY): For those involved with care of inpatients undergoing acute myeloid leukaemia chemotherapy and also transplantation, this is an interesting subanalysis of a major trial that confirmed the importance of prophylactic platelet transfusion in allogeneic transplantation with less benefit for autologous transplantation. In this paper, other factors such as haematocrit and activated partial thromboplastin time/international normalised ratio were shown to be significant. It is important to note that the testing of coagulation results coincided with bleeding, so the correlation may reflect clinical concern rather than the laboratory test itself. However, in these days of restrictive transfusion policies, the correlation with lower haematocrit is interesting, although as noted in the Blood editorial, meta-analyses of such studies have not shown more bleeding with lower haemoglobin levels, and other factors not included here, such as fever, are also relevant. This work shows that studies looking at risk factors for bleeding in these patients are valuable.

Reference: Blood 2017;130(10):1247–58
Abstract

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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.**

Comparison of risk prediction scores for venous thromboembolism in cancer patients

Authors: van Es N et al.

Summary: The performance of the Khorana, Vienna, PROTECHT and CONKO scores for predicting which patients with cancer are at increased risk of VTE was investigated in a prospective cohort of 876 patients with advanced cancer who were due to start (n=260) or within the prior 3 months had started chemotherapy. VTE occurred in 6.1% of the patients over 6 months of follow-up, and the c-statistics of the four scores were 0.50–0.57. The scores classified 13–34% of the participants as high risk when the conventional positivity threshold of 3 points was applied; the respective 6-month VTE incidence ranged from 6.5% for the Khorana score to 9.6% for the PROTECHT score. When the Vienna and PROTECHT scores were used, participants classified as high risk were at significantly increased risk of VTE (respective subhazard ratios 1.7 [95% CI 1.0, 3.1] and 2.1 [1.2, 3.6]).

Comment (LY): The question of VTE prophylaxis in cancer outpatients is a difficult one. Large trials show that low-molecular-weight heparin halves the VTE risk; however, a baseline risk of 4–5% implies a number needed to treat of around 40–50 with associated inconvenience of injections, cost and bleeding risk. Selecting those at highest risk is therefore appealing, but suggested prediction scores lack external validation. Unfortunately in this relatively large prospective cohort with a VTE incidence of 6% in the first 6 months of therapy, none of the scores showed satisfactory discriminatory ability. This illustrates the importance of confirming such predictive tools in multinational studies before adoption. The question of prophylaxis remains largely unanswered, other than in specific groups such as immunomodulatory drug/steroid-treated myeloma patients and possibly those with pancreatic cancer.

Reference: Haematologica 2017;102(9):1494–501
Abstract

Outcomes of restrictive versus liberal transfusion strategies in older adults from nine randomised controlled trials

Authors: Simon GI et al.

Summary: To help determine if special guidelines are warranted for older surgical patients, these authors conducted a systematic review and meta-analysis of 13 papers covering a total of nine randomised controlled trials (five in orthopaedic surgery, three in cardiac surgery and one in oncology surgery; n=5780) comparing restrictive and liberal transfusion strategies, focussing on participants aged ≥65 years. Compared with a liberal transfusion strategy, a restrictive strategy was associated with a higher risk of death within 30 days and within 90 days in these older participants (respective risk ratios 1.36 [95% CI 1.05, 1.74] and 1.45 [1.05, 1.98]).

Comment (LY): In general clinical trials of restrictive transfusions, policies have demonstrated less transfusion requirement and at worst noninferiority of outcome since the landmark TRICC study more than 15 years ago, resulting in widespread change in hospital practice to a lower haemoglobin level threshold in stable anaemic patients. This meta-analysis challenges this, suggesting higher mortality for patients aged over 65 years with restrictive transfusion thresholds. However, only 10% of the trials included were specifically conducted in older patients, and the editorial in Lancet Haematol suggests that other papers that should have been included were not, and of course a meta-analysis is only as good as the methodology. Nevertheless this does raise questions for further study, particularly in the elderly with cardiac disease.

Reference: Lancet Haematol 2017;4(10):e465–74
Abstract

Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide

Authors: Harrison CN et al.

Summary: This paper reported findings from the phase 2 MAJIC-ET trial in a modified intent-to-treat population of 58 and 52 participants with essential thrombocythaemia resistant or intolerant to hydroxycarbamide who were randomised to receive ruxolitinib (n=58) or best available therapy (n=52). No significant difference was seen between the ruxolitinib versus best available therapy arm for complete response within 1 year (46.6% vs. 44.2% [p=0.40]) or for the 2-year thrombosis, haemorrhage or transformation rate, although there were improvements in some disease-related symptoms with ruxolitinib. There were only two complete molecular responses and one partial molecular response in *CALR*-positive ruxolitinib-treated patients, with one participant who achieved a complete molecular response transforming to myelofibrosis. There were higher rates of grade 3 anaemia and grade 3 thrombocytopenia in the ruxolitinib versus best available therapy arm (19% vs. 0% and 5.2% vs. 0%, respectively); grade 4 anaemia did not occur in either arm and grade 4 thrombocytopenia occurred in 1.7% of ruxolitinib recipients and 0% in the best available therapy arm. There was no significant between-group difference for discontinuations or treatment switching.

Comment (LY): Essential thrombocythaemia is the myeloproliferative neoplasm with the most indolent course in terms of overall outcome, but significant risks of thrombosis and bleeding. Around half of cases are related to the *JAK2* V617F mutation, and the majority of the others are due to *CALR* or *MPL* mutations, which do upregulate JAK signalling. This UK study independent of pharma funding was phase 2 and explored the use of a JAK2 inhibitor, ruxolitinib, in high-risk patients in whom hydroxycarbamide was not adequate for control either due to intolerance or resistance. While there was some symptom improvement (which is relevant given the significant impairment of quality of life in these patients), the disease response and rates of transformation did not differ in this study, which was powered for a signal of benefit. The best available care group was quite heterogeneous and included some hydroxycarbamide use. This study does not exclude a longer term benefit with reduced transformation in these patients with ruxolitinib, but given the side effects and cost, it is certainly not encouraging.

Reference: Blood 2017;130(17):1889–97
Abstract

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

Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates

Authors: Majeed A et al.

Summary: This cohort study included 84 patients who received prothrombin complex concentrates 1500–2000IU following a major bleeding event associated with rivaroxaban or apixaban use; the most bleeding events requiring reversal were intracerebral haemorrhages (70.2%) followed by GI bleeds (15.5%). Effectiveness of prothrombin complex concentrates, assessed using the International Society of Thrombosis and Hemostasis Scientific and Standardization Subcommittee's criteria, was reported for 69.1% of the participants; 61.5% of participants for whom it was ineffective had intracerebral haemorrhage. Ischaemic strokes occurred in two participants in 5 or 10 days after receiving prothrombin complex concentrates. The mortality rate within 30 days of the major bleeding event was 32%.

Comment (LY): The reversal of DOACs has been hotly contentious. The question is answered for dabigatran with idarucizumab; however, for the Xa inhibitors, the antidote (andexanet) has a higher rate of thrombotic complications and remains in phase 3 trials currently. The use of prothrombin complex concentrates is currently recommended for Xa inhibitors but is based on very limited clinical data. This large Swedish cohort of patients reversed with four-factor prothrombin complex concentrates appears to demonstrate some benefit, although the heterogeneity of the cases illustrates the difficulty with clinical endpoints showing improvement. In NZ we have a three-factor product, therefore the results cannot be directly extrapolated, although it is hard to imagine theoretically that the absence of factor VII would make much difference to the reversal of Xa inhibition. Presently the use of prothrombinex is a reasonable standard of care; however, the efficacy cannot be guaranteed.

Reference: Blood 2017;130(15):1706–12
Abstract

Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag

Authors: Wong RSM et al.

Summary: This paper reported outcomes from the open-label EXTEND (Eltrombopag eXTENded Dosing) study, in which 302 adults with ITP who had completed eltrombopag treatment in a previous study received the agent for a median of 2.37 years. By week 2, the median platelet count had increased to ≥50×10^9/L, and the increase was sustained throughout treatment, with 85.8% of participants achieving response (defined as ≥1 platelet count measurement of ≥50×10^9/L in the absence of rescue) and 52% achieving response for ≥25 weeks. Response was decreased in participants with baseline platelet count <15×10^9/L, those who had received more prior therapies and splenectomised participants. Among participants receiving concomitant pharmacotherapy for ITP (n=101), 34% discontinued ≥1 medication. The WHO grades 1–4 bleeding rate decreased from 57% at baseline to 16% at 1 year among evaluable participants. The adverse event-related withdrawal rate was 14%. There was no increase in thromboembolic event rate (6%) or hepatobiliary adverse event rate (15%) with treatment duration >1 year.

Comment (PO): EXTEND is a phase 3 open-label long-term study of the safety, tolerability and efficacy of eltrombopag in chronic (>6–12 months) ITP. The 3 years follow-up has been previously reported (Blood 2013). Now after continuous surveillance for up to 8 years this final report confirms safety, tolerability and efficacy in all patient subgroups. Those responding less well predictably are splenectomised and heavily pretreated patients, those with very low baseline platelet counts and needing concomitant ITP therapy. There is a low frequency of serious adverse events, thromboembolic episodes and bone marrow fibrosis. Dosing requirements do fluctuate on therapy necessitating regular platelet monitoring, even in apparently stable patients, together with liver function testing. The revised ASH guidelines for treating ITP are due for publication by the end of this year. It will be interesting to see where TPO receptor agonist therapy fits into treatment recommendations in view of the lack of comparative evidence with other treatments.

Reference: Blood; Published online Oct 17, 2017
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**

Acquired hemophilia A: updated review of evidence and treatment guidance

Authors: Kruse-Jarres R et al.

Summary: These authors note that it is likely that acquired haemophilia A is underdiagnosed and misdiagnosed in real-world clinical practice. They report an update to existing guidelines that was compiled by a panel of experts on acquired haemophilia A from around the globe who analysed key questions, reviewed the literature, weighed the evidence and formed a consensus. Based on available data integrated with the clinical experience of the panel's participants, this paper summarises the recommendations for acquired haemophilia A management.

Comment (PO): Acquired haemophilia is rare, so consensus guidelines based on the available clinical trial and registry data are helpful as a guide to treatment. This critical review is from an international expert panel convened in 2015. It has been endorsed by the Hemostasis and Thrombosis Research Society of North America and is a useful reference for managing this condition. The incidence, determined by registries in Australia (n=25) and UK (n=172), approximates 1.2–1.48 per million cases per year. We might therefore expect 5–6 cases in NZ annually. Approximately half will be idiopathic. The review tabulates options for first-line haemostatic therapy and immunosuppression, usually with steroids and cyclophosphamide, as well as thromboembolic risks with bypassing agents (approximately 5%). Fortunately around 30% of patients do not need haemostatic therapy, but it is important to recognise that clinically significant bleeding can occur despite only modest reductions in factor VIII activity.

Reference: Am J Hematol 2017;92(7):695–705
Abstract

Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review

Authors: Warkentin TE et al.

Summary: These Canadian authors reported their experience using rivaroxaban for serologically confirmed HIT, and reviewed the literature on treating HIT with DOACs, focussing on DOACs for primary versus secondary therapy. All ten of their patients who received rivaroxaban for acute HIT recovered without new, progressive or recurrent thrombosis. Data from the literature plus their data determined that the thrombosis rate was 2.2% in patients who received rivaroxaban during acute HIT as primary (n=25) or secondary (n=21) therapy; no major haemorrhagic events were reported among these 46 patients. Outcomes were similar for 12 patients treated with apixaban and 11 with dabigatran.

Comment (PO): The thrombotic rate with acute HIT (platelets count $<150\times10^9$/L meeting serological and clinical diagnostic criteria) is estimated as 5% per day, reducing with platelet recovery (defined as subacute HIT). The most common treatment in the acute phase worldwide is fondaparinux. The usual approach when more extended anticoagulation is needed is to transition to warfarin after platelet recovery ($>150\times10^9$/L) to avoid warfarin-induced thrombosis during the acute phase. The DOACs have been identified as alternative treatment options for HIT as they do not react immunologically with HIT antibodies, have a rapid onset of action and can be commenced before platelet recovery. To date only small numbers of patients have been treated, but DOACs seem to be consistently effective. An additional 12 patients have been reported since this publication (Davis *et al.* Eur J Haematol 3 July 2017). In total, most have received rivaroxaban (n=49) and apixaban (n=21). Only 11 patient reports have used dabigatran.

Reference: Blood 2017;130(9):1104–13
Abstract

Pregnancy, thrombophilia, and the risk of a first venous thrombosis

Authors: Croles FN et al.

Summary: This systematic review and Bayesian meta-analysis included 36 studies reporting first VTEs for pregnant women with thrombophilia and without anticoagulant exposure. The probabilities of pregnancy-associated VTE were ≥91% for all thrombophilias. Thrombophilias with the greatest absolute risks for antepartum and postpartum pregnancy-associated VTE were antithrombin deficiency (7.3% and 11.1%, respectively), protein C deficiency (3.2% and 5.4%), protein S deficiency (0.9% and 4.2%) and homozygous FVL (2.8% and 2.8%). The absolute combined antepartum and postpartum risks for heterozygous FVL, heterozygous prothrombin G20210A mutations or compound heterozygous FVL and prothrombin G20210A mutations were <3%.

Comment (PO): Guidelines for the management of pregnant women with an inherited thrombophilic marker and no previous VTE event differ because of the limited data on which to base recommendations on risk assessment. The threshold risk for using prophylaxis has also varied, but recently this has been accepted as 3% in both the antepartum and postpartum periods. Previous guidelines are based on a limited number of cohort studies, with estimates of baseline VTE incidence multiplied by reported odds ratios. This systematic analysis confirms that all women with an inherited thrombotic marker have an increased risk of pregnancy-associated VTE. It challenges the current 2012 ACCP recommendations noting the impact of family history on risk. Both antepartum and postpartum prophylaxis are suggested for antithrombin deficiency, protein C deficiency and homozygous FVL, but only postpartum for protein S deficiency and a family history. Risk estimates do not support routine prophylaxis for FVL and prothrombin mutation heterozygotes, or compound FVL/prothrombin heterozygosity.

Reference: BMJ 2017;359:j4452
Abstract

A reappraisal of the benefit-risk profile of hydroxyurea in polycythemia vera

Authors: Barbui T et al.

Summary: Outcomes were reported for a cohort of 681 participants with polycythaemia vera from the European Collaborative Low-dose Aspirin study treated with hydroxycarbamide only and 342 propensity matched participants treated with phlebotomy only for maintenance of haematocrit at <45%; the follow-up periods for these participant groups were 34.7 months and 29.9 months, respectively. Compared with the phlebotomy group, hydroxycarbamide recipients had a significantly lower incidence of fatal/nonfatal CV events (3.0 vs. 5.8 per 100 person-years [p=0.002]), and myelofibrosis transformation was seen only in the phlebotomy group. Evolution to acute leukaemia was recorded for one hydroxycarbamide recipient and one participant from the phlebotomy group. High-risk participants from the phlebotomy group accounted for the excess mortality and CV events in their group; mortality and CV events were also significantly increased in participants from the phlebotomy versus hydroxycarbamide group who failed to reach the haematocrit target.

Comment (PO): Better haematocrit (packed cell volume <45%) control, and control of leucocytosis, is achieved in patients with myeloproliferative polycythaemia vera receiving hydroxycarbamide than in those treated with venesections alone. This may explain the lower incidence of fatal and nonfatal thrombosis in hydroxycarbamide-treated patients. As well as reducing CV mortality, hydroxycarbamide also reduces disease evolution into myelofibrosis without increasing leukaemic transformation. These advantages are confined to high-risk patients, defined by age >60 years and a prior thrombosis history. Hydroxycarbamide is not recommended for younger patients for whom venesection and aspirin is used, although it has not been studied in a prospective controlled trial. The CV event rate is still high at 1.9% (controls 0.7%) in this 'low-risk' group who might also benefit from better packed cell volume and white blood cell control. Interferon is currently being studied in this population (NCT03003325).

Reference: Am J Hematol 2017;92(11):1131–6
Abstract