



Estcourt, L. J., Birchall, J., Allard, S., Basse, S. J., Hersey, P., Kerr, J. P., Mumford, A. D., Stanworth, S. J., Tinegate, H., & British Committee for Standards in Haematology (2016). Guidelines for the use of platelet transfusions. *British Journal of Haematology*.
<https://doi.org/10.1111/bjh.14423>

Peer reviewed version

Link to published version (if available):
[10.1111/bjh.14423](https://doi.org/10.1111/bjh.14423)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Wiley at <http://onlinelibrary.wiley.com/doi/10.1111/bjh.14423/abstract>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Guidelines for the Use of Platelet Transfusions A British Society for Haematology Guideline

Lise J Estcourt¹, Janet Birchall (Writing Group Chair)², Shubha Allard (BCSH Task Force Member)³, Stephen J Bassey⁴, Peter Hersey⁵, J Paul Kerr⁶, Andrew D Mumford⁷, Simon J Stanworth⁸, Hazel Tinegate⁹ on behalf of the British Committee for Standards in Haematology.

¹NHSBT and Radcliffe Department of Medicine, University of Oxford, Oxford,

²NHSBT and Department of Haematology, North Bristol NHS Trust, Bristol,

³NHSBT and Department of Haematology, Royal London Hospital, London,

⁴Department of Haematology, Royal Cornwall Hospital Trust, ⁵Department of Critical Care Medicine & Anaesthesia, City Hospitals Sunderland NHS

Foundation Trust, ⁶Department of Haematology, Royal Devon & Exeter NHS

Foundation Trust, Exeter, ⁷School of Cellular and Molecular Medicine,

University of Bristol, Bristol, ⁸NHSBT and Department of Haematology, John

Radcliffe Hospital Oxford, ⁹NHSBT Newcastle upon Tyne,.

Correspondence: BSH Administrator, British Society for Haematology, 100 White Lion Street, London N1 9PF, UK. E-mail: bshguidelines@b-s-h.org.uk

Introduction

The demand for platelets in England was stable at around 220,000 adult therapeutic doses (ATD) per year until 2007/8 at which point demand has increased year on year to 275,000 ATD in 2014/15, an increase of 25%. Similar rises in demand have been seen in Australia and the United States. A recent review which considered causes for this dramatic rise identified that an ageing population and an increase in the incidence of haematological malignancies (with increased treatment intensity, duration and survival) accounted for most of this change (Estcourt 2014). In 2012 the population aged over 70 in the UK was 7.5 million. By 2046 this number is expected to reach 15 million (Office of National Statistics (ONS) 2013). In addition, since 1990, the number of haematopoietic stem cell transplants performed in Europe has risen from 4,200 to over 30,000 annually (Passweg, *et al* 2012).

Although a national audit of platelet use in haematology identified that 28% of transfusions were outside of guidelines (Estcourt, *et al* 2012b) these findings demonstrate less inappropriate use than a previous audit (Qureshi, *et al* 2007). An increase in the proportion of inappropriate use is therefore unlikely to have contributed significantly to recent changes in demand (Estcourt 2014). Currently up to 67% of all platelets are used in the management of patients with haematological malignancies (Cameron, *et al* 2007, Charlton, *et al* 2014, Greeno, *et al* 2007, Jones, *et al* 2013, Pendry and Davies 2011). Much of the remainder are used in cardiac surgery (7-10%) and in intensive care (5-9%). In contrast to platelet demand, the donor base is steadily dropping with a 35% reduction in active donors from 1.893 million in 2000 to 1.231 million in 2015 (NHS Blood & Transplant data). As the majority of platelets in the UK are collected from approximately 14,000 registered platelet donors (apheresis platelets), and whole blood donors give blood on average 1.7 times a year this could have a significant impact on the future supply (European Blood Alliance 2015, European Committee (Partial Agreement) on Blood Transfusion CD-P-TS 2016).

SCOPE

This guideline aims to provide practical advice on platelet transfusions to help clinicians to decide when support is expected to be beneficial and to reduce inappropriate use. If the reason for thrombocytopenia is unclear, further investigation is required as this is likely to influence management. This document will cover practice in adults relevant to the UK and replace the 2003 BCSH platelet use guideline. A one page summary document is available in appendix 1. The indications for platelet transfusion in children and neonates and more general specifications such as cytomegalovirus (CMV) status and irradiation are not included, and can be found elsewhere (New, *et al* 2016, SaBTO 2012, Treleaven, *et al* 2011).

Methodology

The classification of platelet transfusion into either 'therapeutic' to treat bleeding or 'prophylactic' to prevent bleeding was based on the modified WHO bleeding score (Table I) (Stanworth, *et al* 2013a). Recommendations for prophylactic transfusion relate to patients with bleeding scores of 0 or 1 and therapeutic transfusion to patients with bleeding scores of 2 or higher.

For each indication, the recommendations include a threshold or target platelet count and a suggested dose, when relevant.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are specified on the BCSH website

(http://www.bcsguidelines.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html) and the GRADE working group website (<http://www.gradeworkinggroup.org>).

Literature review details

A search of published literature was undertaken using the evidence from several systematic reviews that are either currently being undertaken by members of the writing group (Estcourt, *et al* 2014a, Estcourt, *et al* 2014b, Estcourt, *et al* 2014c), or that have been recently published (Crighton, *et al* 2015, Hedges, *et al* 2007, Kumar, *et al* 2014, Lieberman, *et al* 2013, Nahirniak, *et al* 2015, Pavenski, *et al* 2013, van Veen, *et al* 2010, Vassallo, *et al* 2014, Wardrop, *et al* 2013). This was supplemented by searching PubMed and the UKBTS/SRI Transfusion Evidence Library (www.transfusionevidencelibrary.com) up to November 2014 using specific search terms relevant to each section of the guidelines.

Working Group Membership

The guideline group was selected to be representative of UK based medical (anaesthetics, benign and malignant haematology, haemostasis, transfusion) and laboratory experts with practical experience in platelet transfusion.

Review

Given the breadth of application, the draft guideline was provided to sounding board members of the Haemato-oncology, General Haematology, Haemostasis and Thrombosis, and Transfusion Task Forces of BCSH for comment and subsequent revision.

SUMMARY OF KEY RECOMMENDATIONS

- **If the reason for thrombocytopenia is unclear, further investigation is required to determine appropriate management (1A)**

Recommendations for Prophylactic Transfusion of Platelets to Patients with Thrombocytopenia Because Of Reversible Bone Marrow Failure Where Recovery Is Anticipated

- **Give prophylactic platelet transfusions (platelet transfusions to patients who do not have clinically significant bleeding [WHO grade 0 or 1] and do not require a procedure) to patients with reversible bone marrow failure receiving intensive chemotherapy or undergoing allogeneic HSCT to maintain a platelet count at or above $10 \times 10^9/L$ (1B)**
- **Use only one adult dose (one unit) routinely for prophylactic platelet transfusions (1A)**
- **Consider not giving prophylactic platelet transfusions to well patients with no evidence of bleeding who have had an autologous stem cell transplant (2B)**
- **Consider increasing the threshold for prophylactic platelet transfusion to between 10 and $20 \times 10^9/L$ in patients judged to have additional risk factors for bleeding. Individual review is required. (2C)**

Recommendations for Prophylactic Transfusion of Platelets to Patients with Thrombocytopenia Because Of Chronic Bone Marrow Failure, Where Recovery Is Not Anticipated

- **Use a ‘no prophylactic platelet transfusion’ strategy for asymptomatic patients with chronic bone marrow failure (including those taking low dose oral chemotherapy or azacitidine) (2B)**
- **Give prophylactic platelet transfusions to patients with chronic bone marrow failure receiving intensive treatment (1B)**
- **Manage patients with chronic bleeding of WHO grade 2 or above individually, according to the severity of their symptoms and signs. Consider a strategy of prophylaxis (e.g. twice a week) (2C)**

Recommendations for Prophylactic Transfusion of Platelets to Other Patient Groups

- **Use the platelet count thresholds for reversible bone marrow failure as a general guide for prophylactic platelet transfusion in patients with critical illness in the absence of bleeding or planned procedures. (2C)**

Recommendations for Prophylactic Platelet Transfusion Prior To Procedures or Surgery

- **Whenever possible use a procedure/equipment associated with the lowest bleeding risk. Apply local measures, such as compression, to reduce the risk of bleeding post-procedure. (1C)**
- **Do not give platelet transfusions routinely prior to:**
 - **bone marrow aspirate or trephine biopsy (1B)**
 - **peripherally inserted central catheters (PICCs) (2C)**
 - **traction removal of tunnelled CVCs (2C)**
 - **cataract surgery (2C)**
- **Consider performing the following procedures above the platelet count threshold indicated –**

- venous central lines (both tunnelled and un-tunnelled), inserted by experienced staff using ultrasound guidance techniques, when the platelet count is $> 20 \times 10^9/L$. (1B)
 - lumbar puncture when the platelet count is $\geq 40 \times 10^9/L$. (2C)
 - insertion/removal of epidural catheter when the platelet count is $\geq 80 \times 10^9/L$. (2C)
 - major surgery - when the platelet count is $> 50 \times 10^9/L$ (1C)
 - neurosurgery or ophthalmic surgery involving the posterior segment of the eye when the platelet count is $> 100 \times 10^9/L$ (1C)
 - percutaneous liver biopsy when the platelet count is $> 50 \times 10^9/L$ (2B). Consider trans-jugular biopsy if the platelet count is below this level (2B)
- Prior to renal biopsy ensure potential risk factors for bleeding are corrected: anaemia (iron and erythropoietin), uraemia (dialysis) (1B). If renal biopsy is urgent consider desmopressin (DDAVP) pre-procedure (1B) or oestrogen if time allows (2B)
 - Avoid platelet transfusion in renal failure since infused platelets will acquire a dysfunction similar to the patients' own platelets and platelet transfusion may result in alloimmunisation (1B)

Recommendations for Therapeutic Platelet Transfusions

- In severe bleeding, maintain the platelet count above $50 \times 10^9/L$. Consider empirical use for the initial management of major haemorrhage (1C).
- In patients with multiple trauma, traumatic brain injury or spontaneous intracerebral haemorrhage maintain the platelet count above $100 \times 10^9/L$ (2C)
- In patients with bleeding that is not considered severe or life-threatening, consider platelet transfusion if the platelet count is below $30 \times 10^9/L$ (2C)

Recommendations for Platelet Function Disorders (Congenital)

- **For first line treatment or prevention of bleeding, consider recombinant factor VIIa (rFVIIa) in Glanzmann thrombasthenia and tranexamic acid (TXA) plus desmopressin in other congenital platelet function disorders (2B)**
- **If pharmaceutical therapies are contraindicated, ineffective or if there is high risk of bleeding, consider transfusion of platelets. In Glanzmann thrombasthenia, consider HLA-matched platelets. (2C)**

Recommendations for Platelet Function Disorders (Acquired)

- **Do not use platelet transfusion pre-procedure when antiplatelet agents have not been discontinued (2C)**
- **Use general haemostatic measures to treat bleeding in patients during treatment with aspirin, P2Y₁₂ antagonists or GPIIa/IIIb inhibitors. If necessary, consider drug cessation and reversal of the effect of co-prescribed anticoagulants (2C).**
- **Use TXA to counteract the effect of anti-platelet agents when a risk/benefit assessment would support this (1B)**
- **Consider the use of platelet transfusion as an additional measure to those suggested above for critical bleeding (2C).**
- **Consider platelet transfusion to prevent bleeding in severe thrombocytopenia (platelet count < 10 x 10⁹/l) caused by abciximab (2C).**

Recommendations for Immune Thrombocytopenia

- **Do not use prophylactic platelet transfusions in patients with autoimmune thrombocytopenia ('ITP') (1C)**
- **Only use platelet transfusion prior to a procedure or surgery when other treatment has failed and/or the intervention is urgent. Usual threshold counts may be unachievable or unnecessary and individual case review is required (1C)**
- **Give therapeutic platelet transfusions (more than one dose) to treat serious bleeding (1C). In ITP consider co-administration of**

intravenous immunoglobulin in addition to the platelet transfusion (2C). In post-transfusion purpura (PTP) intravenous immunoglobulin is the treatment of choice (1C)

Contraindications to Platelet Transfusions

- **In patients with thrombotic microangiopathies only use platelet transfusions to treat life-threatening bleeding (1C)**

Risks from Platelet Transfusions

- **Hospitals should establish a strategy to maximise the transfusion of ABO compatible platelets especially to patients who require regular platelet support (2B).**
- **It is acceptable to use ABO incompatible platelets to reduce wastage. Platelets tested and negative for high titre haemagglutinins and non group O platelets are associated with a lower risk of haemolysis. Pooled platelets suspended in PAS would also be expected to reduce this risk. (1B).**
- **RhD negative girls or women of childbearing potential should receive RhD negative platelets. If unavailable RhD positive platelets can be given with anti-D prophylaxis. (1B).**
- **For RhD negative boys under 18 years of age, those who already have anti-D antibodies, and transfusion-dependant adults, the platelets of choice are RhD negative. RhD positive platelets should be given if RhD negative platelets are unavailable or to prevent wastage of RhD positive components. Anti-D prophylaxis is not required (1B).**
- **In patients with a history of allergic transfusion reactions, apart from mild, use platelets suspended in PAS. If reactions continue or are severe, washed platelets (resuspended in 100% PAS) may be required (1B).**
- **All clinical areas where platelet transfusions are administered should have access to guidance on the investigation and management of acute transfusion reactions to blood and blood**

components. We recommend that these are based on BCSH guidance (Tinegate, *et al* 2012) (1A).

Recommendations for Platelet Refractoriness

- **ABO matched platelets should be used when available to maximise increments (2C)**
- **Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions solely due to non-immune factors should not receive HLA-selected platelet transfusion (2C)**
- **Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions and have class I HLA antibodies should receive class I HLA-selected platelet transfusion (2C)**
- **Patients with hypoproliferative thrombocytopenia who continue to be refractory to HLA-selected platelet transfusions and have HPA antibodies should receive HPA-selected platelet transfusion (2C)**
- **Patients with hypoproliferative thrombocytopenia who are not refractory to platelet transfusion should not receive HLA-selected or HPA-selected platelets (2C).**

Recommendations for Other Alternatives or Additions to Platelet Transfusion

- **Administer TXA early in trauma patients who are bleeding/at risk of bleeding (1A)**
- **Use TXA in surgical patients expected to have greater than a 500 ml blood loss, unless contraindications exist (1A)**
- **Consider TXA as an alternative or in addition to therapeutic platelet transfusion, in patients with chronic thrombocytopenia caused by bone marrow failure (2B)**
- **In severe perioperative bleeding/bleeding associated with major trauma give fibrinogen (concentrate or cryoprecipitate) if plasma fibrinogen concentration is < 1.5 g/L or if signs of a functional fibrinogen deficit are seen on near patient testing (1C).**

- **Use thrombopoietin receptor agonists in ITP according to international guidelines. At present there is insufficient evidence to recommend these agents in other patient categories (1A).**

PROPHYLACTIC TRANSFUSION OF PLATELETS TO PATIENTS WITH THROMBOCYTOPENIA BECAUSE OF REVERSIBLE BONE MARROW FAILURE WHERE RECOVERY IS ANTICIPATED

The evidence for these recommendations is based on studies in patients with haematological malignancy causing thrombocytopenia due to the disease or its treatment. Other patient populations are considered separately.

Should Prophylactic Platelet Transfusions Be Given Routinely?

A systematic review identified six randomised-controlled trials (RCTs) that compared a prophylactic versus therapeutic platelet transfusion strategy (Crichton, *et al* 2015). Four of the included studies were conducted at least 30 years ago and used outdated methods of platelet component production and patient supportive care. Two included studies were recent large RCTs (Stanworth, *et al* 2013a, Wandt, *et al* 2012). Both of these recent studies showed that prophylactic platelet transfusions reduced the risk of bleeding when all patients with haematological malignancies receiving treatment (e.g. chemotherapy or transplantation) were considered (Crichton, *et al* 2015), but this effect was not seen in a pre-specified sub-group – patients receiving autologous haematopoietic stem cell transplants (HSCT) (Table II) (Stanworth, *et al* 2014). This finding indicates that prophylactic transfusion should continue to be the standard of care in patients receiving intensive chemotherapy or allogeneic transplantation but may not be appropriate in low risk groups with short periods of thrombocytopenia.

What Platelet Transfusion Threshold Should Be Used?

A systematic review identified three RCTs that compared different platelet transfusion thresholds (Estcourt, *et al* 2012a). Two compared a threshold of

20 x 10⁹/L vs. 10 x 10⁹/L, whereas the third compared a threshold of 30 x 10⁹/L vs. 10 x 10⁹/L. A fourth RCT excluded from the systematic review compared a threshold of 20 x 10⁹/L vs. 10 x 10⁹/L (Zumberg, *et al* 2002). A meta-analysis of all four studies (658 patients) showed that the 10 x 10⁹/L threshold was not associated with increased bleeding in comparison with a higher threshold and also showed a significant reduction in the number of platelet transfusions given (Estcourt, *et al* 2011). However, this meta-analysis may not be sufficiently powered to detect an increased bleeding risk in this lower threshold arm of less than 50% (Estcourt, *et al* 2011).

The use of other transfusion thresholds, such as platelet mass, absolute immature platelet numbers and immature platelet fraction have been considered as alternatives to a platelet count threshold but there have been no randomised studies in adult patients. (Briggs, *et al* 2006, Eldor, *et al* 1982, Gerday, *et al* 2009, Zisk, *et al* 2013).

What Platelet Transfusion Dose Should Be Used?

A systematic review identified six RCTs that compared different platelet transfusion doses. Four of these studies assessed clinically significant bleeding as an outcome measure (usually defined as WHO grade 2 or above). There was no evidence of a difference in the risk of bleeding between low dose (1.1 x 10¹¹/m²) and standard dose (2.2 x 10¹¹/m²) and between standard dose and high dose platelet transfusions (4.4 x 10¹¹/m²). Low dose transfusions decreased the total amount of platelets patients received, but at the expense of a higher number of transfusions episodes. Increasing the dose from a standard to a high dose did not increase the transfusion interval (median 5 days for both regimens). The mean UK adult platelet dose (one unit of platelets) is around 3 x 10¹¹ platelets, equivalent to between the low and standard doses defined above, although there is evidence of considerable variation (Pietersz, *et al* 2012).

Additional Risk Factors for Bleeding

Numerous clinical factors have been reported to be associated with an increased risk of bleeding (Table III). However, the majority of these postulated risk factors are based on low level evidence, such as expert opinion or retrospective analysis of patient databases. Inflammation has been shown to be associated with an increased risk of bleeding in mice (Goerge, *et al* 2008). Although studies have differed in their opinion of whether fever increases the risk of bleeding in humans (Table III), currently, the platelet transfusion threshold is commonly raised to $20 \times 10^9/L$ when patients have an infection or fever (Estcourt, *et al* 2012b). Further studies are required to identify clearly which factors should prompt an increase in the transfusion threshold, and what this threshold should be.

Recommendations

- **Give prophylactic platelet transfusions (platelet transfusions to patients who do not have clinically significant bleeding [WHO grade 0 or 1] and do not require a procedure) to patients with reversible bone marrow failure receiving intensive chemotherapy or undergoing allogeneic HSCT to maintain a platelet count at or above $10 \times 10^9/L$ (1B)**
- **Use only one adult dose (one unit) routinely for prophylactic platelet transfusions (1A)**
- **Consider not giving prophylactic platelet transfusions to well patients with no evidence of bleeding who have had an autologous stem cell transplant (2B)**
- **Consider increasing the threshold for prophylactic platelet transfusion to between 10 to $20 \times 10^9/L$ in patients judged to have additional risk factors for bleeding. Individual review is required. (2C)**

PROPHYLACTIC TRANSFUSION OF PLATELETS TO PATIENTS WITH THROMBOCYTOPENIA BECAUSE OF CHRONIC BONE MARROW FAILURE, WHERE RECOVERY IS NOT ANTICIPATED

There is little evidence to inform practice. A retrospective study considered platelet transfusion in outpatients with stable chronic severe aplastic anaemia (AA) (Sagmeister, *et al* 1999). Prophylactic platelets were given if the count was $5 \times 10^9/l$ or less. In total 55,239 patient days were reviewed with 18,706 days when the platelet count was $10 \times 10^9/l$ or less. All deaths from haemorrhage were associated with alloimmunisation or withdrawal from treatment. Three non-fatal major bleeding episodes occurred. The authors concluded that this restrictive policy, with a median transfusion interval of 7 days, was feasible, safe and economical.

International guidelines that consider patients with chronic thrombocytopenia recommend either a 'no prophylaxis' strategy (Kaufman, *et al* 2015, Liunbruno, *et al* 2009, Schiffer, *et al* 2001) or prophylaxis below a count of $5 \times 10^9/l$ (The Board of the German Medical Association on the Recommendation of the Scientific Advisory Board 2009).

A major concern in using a threshold of $5 \times 10^9/l$ is the reported inaccuracy of current automated counters when the platelet count is very low (De la Salle, *et al* 2012, Segal, *et al* 2005).

A policy of prophylaxis has an impact on resources and on patient quality of life.

Recent BCSH guidelines for the diagnosis and management of adult AA and for the diagnosis and management of adult myelodysplastic syndromes (Killick, *et al* 2015, Killick, *et al* 2014) advise a no prophylaxis strategy for patients who are not receiving active treatment with the latter including patients taking low dose oral chemotherapy or azacitidine (Killick, *et al* 2014).

Recommendations

- **A no prophylaxis platelet transfusion strategy should be used for patients with asymptomatic chronic bone marrow failure (including those taking low dose oral chemotherapy or azacitidine) (2B)**

- **Prophylactic platelet transfusion should be given to patients with chronic bone marrow failure receiving intensive treatment (1B)**
- **Patients with chronic bleeding of WHO grade 2 or above require individual management according to the severity of their symptoms and signs. A strategy of prophylaxis (e.g. twice a week) should be considered (2C)**

PROPHYLACTIC TRANSFUSION OF PLATELETS TO OTHER PATIENT GROUPS

Platelet function defects, immune-mediated thrombocytopenia and thrombotic thrombocytopenic purpura are considered in later sections. There is little evidence to guide practice in other patient populations. One patient group who are significant users of prophylactic platelet transfusions are those in critical care. A large observational study of critically ill patients showed that 9% (169/1923) of all critically ill patients received platelet transfusions and 55% (296/534 units) of these were given on days when no significant bleeding occurred (Stanworth, *et al* 2013b). The optimal platelet transfusion management of these patients (Lieberman, *et al* 2013) may differ depending upon the underlying clinical diagnosis (Assir, *et al* 2013).

As the evidence base in non-haematological patients is sparse we have extrapolated the evidence from studies in haematology patients to this population as a basis for our recommendation until further evidence is available.

Recommendation

- **Platelet count thresholds used for reversible bone marrow may be used as a general guide for prophylactic platelet transfusion in patients with critical illness in the absence of bleeding or planned procedures (2C)**

PROPHYLACTIC PLATELET TRANSFUSION PRIOR TO PROCEDURES OR SURGERY

Bone Marrow Aspirates and Trephine Biopsies

According to the confidential registry of complications after bone marrow aspirates and trephines the risk of significant bleeding is very low (less than 1 in 1,000), and the majority of patients with bleeding did not have significant thrombocytopenia (Table IV). Maintaining pressure on the biopsy site until bleeding has stopped is advised.

Central Venous Catheters

Seventeen observational studies have reported bleeding outcomes in thrombocytopenic patients after insertion of central venous catheters (CVCs) (Table V). Only one case of severe bleeding (Hb drop >15 g/L) was reported throughout all of these studies (Weigand, et al 2009). Three studies reported on risk factors, in addition to thrombocytopenia, associated with bleeding. In two of these studies ultrasound guidance was not used and on multivariable analysis the risk of bleeding was significantly increased by the number of attempts, site of insertion (jugular vs. subclavian) and failed guide-wire insertion (Barrera, et al 1996, Fisher and Mutimer 1999). In the third study where ultrasound guidance was used no such correlation was identified (Zeidler, et al 2011). Systematic reviews of complications of CVC placement (Hind, et al 2003, Randolph, et al 1996) and a more recent small study (Tomoyose, et al 2013) found that ultrasound guidance significantly reduced failure and complication rates.

The study by Zeidler looked at the risk of bleeding according to platelet count thresholds with multivariable analysis. All CVCs were un-tunnelled and inserted by experienced individuals and the analysis was controlled for sex, type of leukaemia, insertion site and use of prophylactic platelet transfusions. The risk of bleeding only increased when the platelet count was less than $20 \times 10^9/L$ (OR 2.88, 95% CI 1.23 to 6.75, $p = 0.015$) (Zeidler, et al 2011). In a large study by Haas tunnelled CVCs were installed and all bleeding episodes were effectively controlled by simple pressure at the site of insertion. The platelet count threshold for insertion was $25 \times 10^9/L$ (Haas, et al 2010).

One additional prospective study assessed insertion of peripherally inserted central catheters (PICCs) without prophylactic platelet transfusions. Among the 50 patients who had a line inserted with a platelet count less than $20 \times 10^9/L$, only one bleeding episode occurred (minor oozing) (Potet, *et al* 2013).

One prospective non-randomised study assessed the risk of bleeding after traction removal of tunnelled cuffed CVCs in patients with abnormal platelet counts or an increased International Normalised Ratio (INR) (Stecker, *et al* 2007). 14 of the 179 patients enrolled in the study had a time to haemostasis of over 5 minutes and only one of these patients had a platelet count $< 100 \times 10^9/L$.

Lumbar Punctures and Neuraxial Anaesthesia

A wide-ranging review of the literature has been performed to assess the risk of spinal haematoma following lumbar puncture and spinal and epidural anaesthesia. The evidence was based on case series, case reports, and expert opinion. There was insufficient information to consider epidural and spinal anaesthesia separately (van Veen, *et al* 2010).

The authors recommend that providing the platelet count is stable and no additional coagulopathy or platelet function defect is present a platelet count of $\geq 80 \times 10^9/L$ should be used for placing/removing an epidural catheter or performing spinal anaesthesia and a count of $\geq 40 \times 10^9/L$ for lumbar puncture. As the technique for spinal anaesthesia is comparable to that of a lumbar puncture, a count of $\geq 40 \times 10^9/L$ for both of these procedures and a separate threshold of $80 \times 10^9/L$ for epidural anaesthesia would be more logical.

We are aware of no new studies that have contributed to the literature since this review.

Liver Biopsy

2,740 percutaneous liver biopsies were conducted in the HALT-C trial (Seeff, *et al* 2010); only 16 patients (0.6%) had a serious adverse event due to bleeding. Percutaneous liver biopsies are considered safe when the platelet

count is at least 50 to 60 x 10⁹/L (British Society of Gastroenterologists (BSG) 2004, Rockey, *et al* 2009). Below this level transjugular liver biopsy (TJLB) should be considered. This procedure has been shown to be safe in patients with low platelet counts and with modern techniques can produce comparable histological samples to those from a percutaneous route (Kalambokis, *et al* 2007, Mammen, *et al* 2008, Wallace, *et al* 2003).

Renal Biopsy

Patients with uraemia have a platelet dysfunction which is thought to be associated with von Willebrand factor (Hedges, *et al* 2007). Uncontrolled hypertension, high serum creatinine, anaemia, older age and female sex have been shown to be risk factors for bleeding following renal biopsy and to prolong the bleeding time (Manno, *et al* 2004, Torres Munoz, *et al* 2011, Whittier 2004, Zhu, *et al* 2014). Reversal of these problems by treatment of hypertension (Zhu, *et al* 2014), dialysis (Hedges, *et al* 2007, Mannucci 2012), the use of desmopressin (Hedges, *et al* 2007, Manno, *et al* 2011, Mannucci, *et al* 1983) or conjugated oestrogens (Mannucci 2012) and the correction of anaemia (Hedges, *et al* 2007) have all been reported to reduce the risk of bleeding in non-RCTs . Although treatment of anaemia with recombinant human EPO can take many weeks a more rapid effect on haemostasis has been noted. This may be through improved platelet adhesion and aggregation (Cases, *et al* 1992, Zwaginga, *et al* 1991) and an increase in the number of reticulated platelets within 7 days (Tàssies, *et al* 1998).

Transjugular renal biopsy has been used in patients in whom percutaneous renal biopsy has failed or been contraindicated and has produced a similar diagnostic yield and safety profile (Cluzel, *et al* 2000). Platelet transfusion is likely to be ineffective or at best very short lived as the same dysfunction affecting the patient's own platelets will be acquired. The transfusion may also be harmful in patients who progress to renal transplant, because of the risk of alloimmunisation (Scornik, *et al* 2013).

Dental Extraction

One recent small RCT (23 patients requiring 35 procedures and 84 teeth removed) has shown a low rate of bleeding complications without blood product support, in patients prior to liver transplantation (Perdigão, *et al* 2012). Patients had platelet counts $\geq 30 \times 10^9/L$, an INR ≤ 3.0 and were randomised to the presence or absence of tranexamic acid on gauze used to apply local pressure. A third of patients had a platelet count $< 50 \times 10^9/L$. Only one patient in the control arm had post-operative bleeding which was controlled with local pressure. Further research is required before a recommendation can be made to use local haemostatic measures alone.

Surgery

There remains a lack of evidence to guide the prophylactic use of platelet transfusions before major surgery. Guidelines from around the world suggest a threshold of $50 \times 10^9/l$ before major surgery (BCSH 2003, Liunbruno, *et al* 2011, Miller, *et al* 2007, Samama, *et al* 2006), and a threshold of $100 \times 10^9/l$ prior to neurosurgery or ophthalmic surgery involving the posterior segment of the eye, because of the critical sites involved (BCSH 2003, Liunbruno, *et al* 2011, Miller, *et al* 2007, Samama, *et al* 2006). Cataract surgery is an avascular procedure and therefore platelet transfusions are not routinely required. Measurement of the platelet count increment following platelet transfusion pre-procedure is desirable, but may be limited by the circumstances.

Recommendations

- **Whenever possible use a procedure/equipment associated with the lowest bleeding risk. Apply local measures, such as compression, to reduce the risk of bleeding post procedure. (1C)**
- **Do not give platelet transfusions routinely prior to:**
 - **bone marrow aspirate or trephine biopsy (1B)**
 - **peripherally inserted central catheters (PICCs) (2C)**
 - **traction removal of tunnelled CVCs (2C)**
 - **cataract surgery (2C)**

- **The following procedures may be performed above the platelet count threshold indicated –**
 - **venous central lines (both tunnelled and un-tunnelled), inserted by experienced staff using ultrasound guidance techniques, when the platelet count is $> 20 \times 10^9/L$ (1B)**
 - **lumbar puncture when the platelet count is $\geq 40 \times 10^9/L$ (2C)**
 - **insertion/removal of epidural catheter when the platelet count is $\geq 80 \times 10^9/L$ (2C)**
 - **major surgery - when the platelet count is $> 50 \times 10^9/L$ (1C)**
 - **neurosurgery or ophthalmic surgery involving the posterior segment of the eye when the platelet count is $> 100 \times 10^9/L$ (1C)**
 - **percutaneous liver biopsy when the platelet count is $> 50 \times 10^9/L$ (2B). Consider trans-jugular biopsy if the platelet count is below this level (2B)**
- **Prior to renal biopsy ensure potential risk factors for bleeding are corrected: anaemia (iron and EPO) uraemia (dialysis) (1B). If renal biopsy is urgent consider DDAVP pre-procedure (1B) or oestrogen if time allows (2B)**
- **In renal failure platelet transfusion should be avoided as infused platelets will acquire a dysfunction similar to the patient's own platelets and may result in alloimmunisation (1B)**

THERAPEUTIC PLATELET TRANSFUSIONS

There is little evidence for the effectiveness of platelet transfusions or the optimal dose when a patient with thrombocytopenia is actively bleeding i.e. WHO grade 2 or above (Estcourt, *et al* 2013). This may reflect the challenges involved in conducting trials in these often complex clinical settings and also the fact that platelet dysfunction may develop with major exsanguinating bleeding which is not captured by measuring the platelet count (Wohlauer, *et al* 2012). One recent large national audit reported the resolution of bleeding after a therapeutic platelet transfusion in 58% of cases with clinically significant bleeding (WHO grade 2 or above) (Estcourt, *et al* 2012b).

Current recommendations are based on consensus guidelines from around the world (BCSH 2003, Liunbruno, *et al* 2011, Miller, *et al* 2007, National Blood Authority 2011, Rossaint, *et al* 2010, Samama, *et al* 2006, Spahn, *et al* 2013) and recently revised BCSH guidelines for major haemorrhage (Hunt, *et al* 2015).

Recommendations

- **Severe bleeding, maintain the platelet count above $50 \times 10^9/l$. Consider empirical use for the initial management of major haemorrhage (1C).**
- **In patients with multiple trauma, traumatic brain injury or spontaneous intracerebral haemorrhage maintain the platelet count above $100 \times 10^9/l$ (2C)**
- **In patients with bleeding that is not considered severe or life-threatening, consider platelet transfusion if the platelet count is below $30 \times 10^9/l$ (2C)**

PLATELET FUNCTION DISORDERS (CONGENITAL)

Glanzmann Thrombasthenia (GT) is usually a severe bleeding disorder in which many patients do not express $\alpha IIb\beta_3$ integrin on the platelet surface. This increases the risk of alloimmunisation to platelet antigens and refractoriness to platelet transfusion, which may prevent the effective treatment of bleeding (Bakdash, *et al* 2008, Hayward, *et al* 2006). Recombinant Factor VIIa (rFVIIa; NovoSeven, Novo Nordisk Limited) is licensed as a pro-haemostatic treatment in GT patients with anti-platelet antibodies and platelet refractoriness.

However, most UK experts also advocate rFVIIa first line for the treatment or prevention of bleeding in GT, and that rFVIIa plus platelet transfusion should be considered for refractory bleeding or before high bleeding-risk surgery (Bolton-Maggs, *et al* 2006). In less severe heritable platelet function disorders, including Bernard-Soulier syndrome, TXA and desmopressin may be sufficient for haemostasis.

Recommendations

- **For first line treatment or prevention of bleeding, consider rFVIIa in Glanzmann thrombasthenia and TXA plus desmopressin in other congenital platelet function disorders (2B)**
- **If pharmaceutical therapies are contraindicated, ineffective or if there is high risk of bleeding, consider transfusion of platelets. In Glanzmann thrombasthenia, consider HLA matched platelets. (2C)**

PLATELET FUNCTION DISORDERS (ACQUIRED)

Anti-Platelet Agents

If a patient has recently ingested an anti-platelet agent any platelets transfused prior to or during the onset of action of the drug will acquire the same defect as the patients' own platelets (Makris, *et al* 2013) (Table VI). The effect of platelet transfusion to control bleeding outside of this critical period is unclear. A recent randomised controlled trial of 190 adults taking anti-platelet agents with spontaneous intracranial haemorrhage found no evidence to support the use of platelet transfusions (Baharoglu, *et al* 2016). This confirms the findings of two systematic reviews examining the treatment of adults on anti-platelet agents with spontaneous or traumatic intracranial haemorrhage which found no evidence of a benefit, however all included studies were of low or very low quality (Batchelor and Grayson 2012, Nishijima, *et al* 2012). In vitro experiments and a case report suggest that platelet dysfunction caused by aspirin is much easier to correct with platelet transfusion than treatment with clopidogrel or ticagrelor (Godier, *et al* 2015, Hansson, *et al* 2014, Li, *et al* 2012, Vilahur, *et al* 2007). A pilot study in 14 healthy volunteers supported these in vitro findings as two units of platelets was shown to overcome clopidogrel-induced low platelet reactivity but there was no improvement in ADP-induced platelet aggregation (Pruller, *et al* 2011).

Platelet transfusion to reverse the effects of aspirin is usually unnecessary as although it increases the risk of surgical bleeding 1.5-fold, it does not increase bleeding severity for most procedures (Makris, *et al* 2013).

In addition to concerns regarding efficacy of platelet transfusion for anti-platelet agents other than aspirin, many patients who are prescribed these drugs are at high risk of arterial thrombosis and a platelet transfusion may increase this risk (Makris, *et al* 2013). In the randomised controlled trial of spontaneous intracranial haemorrhage in patients on anti-platelet agents by Baharogluas, identified above, as well as no evidence of benefit the odds of death or disability at 3 months were higher in those who received platelet transfusion compared to those who received standard care.

In a pilot study of 14 patients administered two units of platelets 1 to 2 hours prior to urgent surgery to “transiently reverse” the effects of aspirin and clopidogrel, one patient developed acute coronary syndrome 4 days after surgery (aspirin and clopidogrel had been started 6 and 24 hours after surgery, respectively) (Thiele, *et al* 2012).

In contrast TXA has been used in three randomised controlled trials in patients taking clopidogrel (with or without aspirin) before coronary artery bypass grafting (total 766 patients) and significantly reduced blood transfusion requirements (Ahn, *et al* 2012, Shi, *et al* 2013a, Shi, *et al* 2013b). No difference in adverse events were reported between the groups however the authors advised caution regarding the small numbers and limited follow up (in the two largest studies follow up was for one year).

Uraemia

Management of the acquired anti-platelet effect of uraemia is discussed in the section above on Platelet transfusion prior to procedures and surgery under ‘Renal biopsy’.

Recommendations

- **Do not use platelet transfusion pre-procedure when antiplatelet agents have not been discontinued (2C)**
- **Use general haemostatic measures to treat bleeding in patients during treatment with aspirin, P2Y₁₂ antagonists or GPIIa/IIIb**

inhibitors. If necessary, consider drug cessation and reversal of the effect of co-prescribed anticoagulants (2C).

- **Use TXA to counteract the effect of anti-platelet agents when a risk/benefit assessment would support this (1B)**
- **Consider the use of platelet transfusion as an additional measure to those suggested above for critical bleeding (2C).**
- **Consider platelet transfusion to prevent bleeding in severe thrombocytopenia ($<10 \times 10^9/l$) caused by abciximab (2C).**

IMMUNE THROMBOCYTOPENIA

Primary Immune Thrombocytopenia (ITP)

ITP is an acquired immune-mediated disorder characterised by isolated thrombocytopenia (platelet count $<100 \times 10^9/L$), in the absence of any obvious underlying cause (Provan, *et al* 2010). Signs and symptoms vary widely; some patients have little or no bleeding, whereas others can experience life-threatening/fatal haemorrhage. Platelet transfusions are not recommended as prophylaxis (Provan, *et al* 2010). The Obstetric Anaesthetists' Association advise that for ITP and gestational thrombocytopenia, if the patient and platelet count are stable and coagulation screen normal, neuroaxial blockade can be done when the count is $>50 \times 10^9/L$ when performed by a skilled and experienced anaesthetist (Lyons and Hunt 2010). Platelets have been used, often in association with other treatments, to treat major bleeding (Neunert, *et al* 2011). There are no RCTs, and publications consist of case reports, observational studies, and uncontrolled interventional studies.

A review of these studies (Table VII) shows that high-dose or high-frequency platelet transfusions have been effective at stopping bleeding, even if the platelet count has not been affected. A platelet count rise appears to be more sustained if platelet transfusions and intravenous immune globulin are administered together (Baumann, *et al* 1986, Spahr and Rodgers 2008), and one study suggests this combination is more effective clinically (Spahr and Rodgers 2008).

Heparin-Induced Thrombocytopenia (HIT)

Guidelines on the diagnosis and management of HIT have been published (Watson, *et al* 2012). It has been widely stated that giving a platelet transfusion may increase the risk of thrombosis (Hopkins and Goldfinger 2008, Linkins, *et al* 2012, Warkentin 2011). However, the evidence for this is poor and based on two case series from the 1970s (16 patients in total) (Babcock, *et al* 1976, Cimo, *et al* 1979). Two more recent case series (forty-one patients in total) have reported no association with thrombosis (Hopkins and Goldfinger 2008, Refaai, *et al* 2010).

Post-Transfusion Purpura (PTP)

This is a rare condition associated with severe thrombocytopenia following blood transfusion and caused by antibodies against platelet specific antigens. Bleeding can be serious and fatal. The incidence has reduced since universal leucodepletion. Multiparous women are the main at risk group (Bolton-Maggs, *et al* 2014). Management is based on individual case reports and case series (Murphy 2013). Current practice is to transfuse high dose intravenous immunoglobulin without waiting for the results of laboratory investigations with random donor platelets reserved to control severe bleeding.

Recommendations

- **Do not use prophylactic platelet transfusions in patients with immune mediated thrombocytopenia (1C)**
- **Only use platelet transfusion prior to a procedure or surgery when other treatment has failed and/or the intervention is urgent. Usual threshold counts may be unachievable or unnecessary and individual case review is required (1C)**
- **Give therapeutic platelet transfusions (more than one dose) to treat serious bleeding (1C). In ITP consider co-administration of intravenous immunoglobulin in addition to the platelet transfusion (2C). In PTP intravenous immunoglobulin is the treatment of choice (1C)**

CONTRAINDICATIONS TO PLATELET TRANSFUSIONS

Thrombotic Thrombocytopenic Purpura (TTP)

Guidelines on the diagnosis and management of TTP and other thrombotic microangiopathies have been published (Scully, *et al* 2012). Evaluation of the effect of platelet transfusions in patients with TTP between different studies are affected by differing definitions of TTP and study inclusion and exclusion criteria, therefore the evidence base is poor (Estcourt, *et al* 2013) Table VIII. Despite this, data from these studies suggest a significant increase in mortality in patients who have received a platelet transfusion (Estcourt, *et al* 2013, Peigne, *et al* 2012). This may be because platelet transfusions precipitate further thrombotic events (Scully, *et al* 2012). One study has suggested an association between a recent platelet transfusion and an increased risk of cardiac failure (Gami, *et al* 2005).

Recommendations

- **In patients with thrombotic microangiopathies only use platelet transfusions to treat life-threatening bleeding (1C)**

RISKS FROM PLATELET TRANSFUSIONS

Platelet transfusions have been associated with all blood transfusion reaction types (Bolton-Maggs *et al* 2014). Table IX. Management of these reactions has been described in previous BCSH guidance (Tinegate, *et al* 2012). Acute transfusion reaction (ATR) is the most frequently reported category and largely consists of either allergic or febrile non-haemolytic reactions. These are three times more frequent with platelet than with red cell transfusion, (Bolton-Maggs, *et al* 2014).

Interventions such as leucodepletion, the use of male donor plasma, irradiation and bacterial screening have significantly reduced the risk of harm from platelet transfusions. Haemagglutinin testing has reduced the risk of haemolysis from the use of minor ABO mismatched units (Berseus, *et al* 2013). To further reduce this risk group A platelets rather than group O platelets are held as stock (Bolton-Maggs, *et al* 2014). A recent review and a laboratory study have questioned the wisdom of this strategy providing evidence of

potential harm from infusion of mismatched platelet components, particularly in patients who are regularly transfused (Blumberg, *et al* 2015, Zaffuto, *et al* 2015). ABO matching of all platelet transfusions would eliminate this risk however would have significant resource implications because of the increased stock required and associated wastage. Currently ABO matching is achieved in around 55% of platelet transfusions (Dunbar, *et al* 2015). The introduction of an artificial platelet additive solution (PAS) to replace plasma has lagged behind use in red cells but is now available and has the potential to reduce the risk of plasma associated problems. Studies assessing the impact of PAS on allergic reactions, a relatively common plasma associated reaction of up to 3% if mild reactions are included (Tinegate, *et al* 2012), report a significant reduction (Cazenave, *et al* 2011, Cohn, *et al* 2014, Tobian, *et al* 2014, Yanagisawa, *et al* 2013). This may also be cost effective (Kacker, *et al* 2013).

Although there is little risk of an acute reaction following transfusion of RhD positive platelets to an RhD negative recipient, alloimmunisation can occur from red cell contamination (Cid, *et al* 2015, Kitazawa, *et al* 2011, Moncharmont, *et al* 2014). The largest study investigating this risk has recently been published and anti-D developed in only 1.44% of patients. This was not associated with the type of platelet component transfused or whether the patient was immunosuppressed (Cid, *et al* 2015). Current BCSH guidelines recommend that for RhD negative patients RhD negative red cells should always be given to women of childbearing potential, patients under 18 years, those who already have anti-D and transfusion dependant adults (Milkins, *et al* 2013). Prophylactic anti-D is only recommended following transfusion of RhD positive platelets to girls and women of childbearing capacity but not to females without childbearing capacity or males (Qureshi, *et al* 2014).

Transfusion related acute lung injury (TRALI), was previously more commonly reported with plasma-rich components than with red cells. Following the introduction of universal leucodepletion and the use of male donor plasma this situation is no longer the case with no recorded cases, where concordant

antibodies were identified, due to platelets in recent years (Bolton-Maggs *et al* 2015).

To date 33 /40 cases of bacterial transfusion transmitted infection (TTI) (overall mortality 28%) reported to SHOT have been associated with platelet transfusion. Since the introduction of bacterial screening in 2010 no proven cases of TTI have been described (Bolton-Maggs *et al* 2015). However, as bacterial contamination of platelets is known to occur despite negative screening results (Bolton-Maggs *et al* 2015) and TTI carries a high mortality, investigation and recall of associated components should be considered for all moderate or severe febrile reactions (Tinegate, *et al* 2012).

Recommendations

- **Hospitals should establish a strategy to maximise the transfusion of ABO compatible platelets especially to patients who require regular platelet support (2B).**
- **It is acceptable to use ABO incompatible platelets to reduce wastage. Units tested and negative for high titre haemagglutinins and non group O platelets are associated with a lower risk of haemolysis. Pooled platelets suspended in PAS would also be expected to reduce this risk. (1B).**
- **RhD negative girls or women of childbearing potential should receive RhD negative platelets. If unavailable RhD positive platelets can be given with anti-D prophylaxis. (1B).**
- **For RhD negative boys under 18 years of age, those who already have anti-D antibodies, and transfusion-dependant adults, the platelets of choice are RhD negative. RhD positive platelets should be given if RhD negative platelets are unavailable or to prevent wastage of RhD positive components. Anti-D prophylaxis is not required (1B).**
- **In patients with a history of allergic transfusion reactions, apart from mild, use platelets suspended in PAS. If reactions continue or are severe, washed platelets (resuspended in 100% PAS) may be required (1B).**

- **All clinical areas where platelet transfusions are administered should have access to guidance on the investigation and management of acute transfusion reactions to blood and blood components. We recommend these are based on BCSH guidance (Tinegate, *et al* 2012) (1A).**

PLATELET REFRACTORINESS

Refractoriness to platelet transfusion has been studied in a recent review by an international panel using two systematic search strategies (Pavenski, *et al* 2013, Vassallo, *et al* 2014) and standardised methods to develop recommendations (Nahirniak, *et al* 2015). Non-immune conditions such as consumptive coagulopathy, sepsis and splenomegaly are recognised as the most common cause of platelet refractoriness, accounting for approximately 80% of cases (Doughty, *et al* 1994, Legler, *et al* 1997). Alloimmune refractoriness in a patient with thrombocytopenia due to bone marrow failure was defined as a 10 minute to one hour increment of less than $5 \times 10^9/l$ on 2 consecutive occasions, using ABO-identical platelets and in the absence of predominantly non-immunological factors. The trials available to address ABO matching and refractoriness due to alloimmunisation were of overall low quality. There were 30 studies including 1 RTC which considered HLA matching and 29 studies with no RCTs which considered cross-matched platelets.

Recommendations

- **ABO matched platelets should be used when available to maximise increments (2C)**
- **Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions solely due to non-immune factors should not receive HLA-selected platelet transfusion (2C)**
- **Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions and have class I HLA antibodies should receive class I HLA-selected platelet transfusion (2C)**

- **Patients with hypoproliferative thrombocytopenia who continue to be refractory to HLA-selected platelet transfusions and have HPA antibodies should receive HPA-selected platelet transfusion (2C)**
- **Patients with hypoproliferative thrombocytopenia who are not refractory to platelet transfusion should not receive HLA-selected or HPA-selected platelets (2C).**

OTHER ALTERNATIVES OR ADDITIONS TO PLATELET TRANSFUSION

Antifibrinolytic Agents

The antifibrinolytic agent TXA reduces mortality in trauma without increasing vascular events (Shakur, *et al* 2010), and reduces blood loss and transfusion requirements during surgery (Ker, *et al* 2012, Poeran, *et al* 2014). Recent NICE guidance contains a strong recommendation for the use of TXA in adults undergoing surgery when blood loss is expected to be greater than 500ml (NICE 2015). A Cochrane review (Wardrop, *et al* 2013) examined antifibrinolytic agents and prophylactic platelet transfusion in patients with thrombocytopenia due to bone marrow failure. Of the three eligible studies, all noted a reduction in bleeding and platelet transfusion with antifibrinolytic usage; the review concluded that an appropriately powered RCT was required.

BCSH guidelines recommend short term TXA in thrombocytopenic patients with MDS with mucous membrane bleeding, advising caution in patients with ischaemic heart disease or haematuria (BCSH 2003, Killick, *et al* 2014).

Desmopressin

Desmopressin promotes coagulation by stimulating factor VIII release from endothelial stores and increasing vWF activity. Two recent European guidelines regarding bleeding in trauma (Spahn, *et al* 2013) and perioperative bleeding (Kozek-Langenecker, *et al* 2013) advocate desmopressin to improve platelet function. In trauma this is recommended for patients receiving aspirin and in the perioperative setting in patients with uraemia or inherited platelet defects.

Fibrinogen

Fibrinogen concentrate is currently only licenced in the UK for congenital deficiency. It has been used to treat bleeding in surgical patients and was associated with reduced bleeding and blood product usage in a recent systematic review; however the included studies were small and at high risk of bias, thus more evidence is required (Wikkelsø, *et al* 2013). Two recent European guidelines (Kozek-Langenecker, *et al* 2013, Spahn, *et al* 2013) recommend using fibrinogen for haemorrhage where there is evidence of fibrinogen deficiency.

Thrombopoietin Receptor Agonists and Other Therapies

Initial studies of Romiplostim for thrombocytopenia secondary to MDS/NHL showed encouraging platelet count improvements (Greenberg, *et al* 2012, Sekeres, *et al* 2011, Wang, *et al* 2012); however, in 2011 a larger placebo controlled trial in low/intermediate 1 risk MDS patients was discontinued due to transient blast cell count increases (Giagounidis and Kantarjian 2014, Kantarjian, *et al* 2012).

Eltrombopag has also been used in small non-randomised studies in patients with advanced MDS/AML and severe AA (Olnes, *et al* 2012); further studies are needed to assess the benefits/risks including clonal progression. In elderly patients with aplastic anaemia, BCSH guidelines suggest consideration of use of eltrombopag where all other treatment modalities have been explored (Killick, *et al* 2015).

A large randomised-controlled study using Eltrombopag pre-procedure in patients with chronic liver disease was terminated early because of an increased incidence of portal vein thrombosis (Afdhal, *et al* 2012).

Both Romiplostim and Eltrombopag are licenced and NICE approved for treatment in ITP. In a recent retrospective observational study a sustained response was achieved in at least 29% after temporary use of these agents with a median follow up of more than a year. (Mahévas, *et al* 2014).

Erythropoietin (EPO) has been observed to reduce both red cell and platelet transfusion requirements in patients following HSCT and iron chelation has

been reported to improve haematopoiesis in patients with iron overload (Michallet, *et al* 2013).

Recommendations

- **Administer TXA early in trauma patients who are bleeding/at risk of bleeding (1A)**
- **Use TXA in surgical patients expected to have greater than a 500 ml blood loss, unless contraindications exist (1A)**
- **Consider TXA as an alternative or in addition to therapeutic platelet transfusion in patients with chronic thrombocytopenia caused by bone marrow failure (2B)**
- **In severe perioperative bleeding/bleeding associated with major trauma give fibrinogen (concentrate or cryoprecipitate) if plasma fibrinogen concentration is < 1.5 g/L or if signs of a functional fibrinogen deficit are seen on near patient testing (1C).**
- **Use thrombopoietin receptor agonists according to international guidelines in ITP. At present there is insufficient evidence to recommend these agents in other patient categories (1A).**

PLATELET TRANSFUSION IN TIMES OF SHORTAGE

Table X provides general guidance for the use of platelet transfusions in the context of reduced availability. Category 1 patients are those with the greatest clinical need for platelet support and therefore should be given priority when considering allocation. Category 3 patients are the lowest priority and should be the first to have platelet transfusions withheld. Patients who have had an autologous stem cell transplant have been included in category 3 based on evidence from two large RCTs (Stanworth, *et al* 2013a, Wandt, *et al* 2012) (Table II) and from consideration of the risks associated with platelet transfusions (described earlier).

ACKNOWLEDGMENT

We would like to thank Professor Mike Murphy, Consultant Haematologist for his review and revision of this document.

AUTHOR CONTRIBUTIONS

LE, JB, SS, AM and HT performed literature reviews and wrote initial draft sections of the text. All of the authors were involved in formulation, writing and approval of the final version of the manuscript.

The authors would like to thank BCSH sounding board members of the Haemato-oncology, General Haematology, Haemostasis and Thrombosis, and Transfusion Task Forces for their comments and subsequent revision of these guidelines.

DECLARATION OF INTERESTS

All authors have made a declaration of interests to the BCSH and Task Force Chairs which may be viewed on request. In summary none of the authors have any conflicts of interest to declare.

REVIEW PROCESS

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BCSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BCSH guidelines website (web link). If minor changes are required due to changes in level of evidence or significant additional evidence supporting current recommendations becomes available a new version of the current guidance will be issued on the BCSH website.

DISCLAIMER

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the British Committee for Standard in Haematology, nor the publishers accept any legal responsibility for the content of this guidance.

REFERENCES

- Afdhal, N.H., Giannini, E.G., Tayyab, G., Mohsin, A., Lee, J.W., Andriulli, A., Jeffers, L., McHutchison, J., Chen, P.J., Han, K.H., Campbell, F., Hyde, D., Brainsky, A., Theodore, D. & Group, E.S. (2012) Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. *N Engl J Med*, **367**, 716-724.
- Ahn, S.W., Shim, J.K., Youn, Y.N., Song, J.W., Yang, S.Y., Chung, S.C. & Kwak, Y.L. (2012) Effect of Tranexamic Acid on Transfusion Requirement in Dual Antiplatelet-Treated Anemic Patients Undergoing Off-Pump Coronary Artery Bypass Graft Surgery. *Circulation Journal*, **76**, 96-101.
- Assir, M.Z.K., Kamran, U., Ahmad, H.I., Bashir, S., Mansoor, H., Anees, S.B. & Akram, J. (2013) Effectiveness of platelet transfusion in dengue fever: A randomized controlled trial. *Transfusion Medicine and Hemotherapy*, **40**, 362-368.
- Babcock, R.B., Dumper, C.W. & Scharfman, W.B. (1976) Heparin-induced immune thrombocytopenia. *N Engl J Med*, **295**, 237-241.
- Baharoglu, M.I., Cordonnier, C., Salman, R.A.-S., de Gans, K., Koopman, M.M., Brand, A., Majoie, C.B., Beenen, L.F., Marquering, H.A., Vermeulen, M., Nederkoorn, P.J., de Haan, R.J. & Roos, Y.B. (2016) Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *The Lancet*.
- Bain, B. (2003) Bone marrow biopsy morbidity and mortality. *British Journal of Haematology*, **121**, 949-951.
- Bain, B.J. (2004) Bone marrow biopsy morbidity and mortality: 2002 data. *Clin Lab Haem*, **26**, 315-318.
- Bain, B.J. (2005) Bone marrow biopsy morbidity: review of 2003. *J Clin Pathol*, **58**, 406-408.
- Bain, B.J. (2006) Morbidity associated with bone marrow aspiration and trephine biopsy - a review of UK data for 2004. *Haematologica*, **91**, 1293-1294.
- Bakdash, S., Lyons, J.M., Bastacky, S.I., Pezzone, M.A., McGee, J.B., Schoen, R.E., Regueiro, M., Lee, K.K. & Bontempo, F.A. (2008) Management of persistent gastric bleeding in a patient with Glanzmann's thrombasthenia. *American Journal of Hematology*, **83**, 411-415.
- Barrera, R., Mina, B., Huang, Y. & Groeger, J.S. (1996) Acute complications of central line placement in profoundly thrombocytopenic cancer patients. *Cancer*, **78**, 2025-2030.
- Batchelor, J.S. & Grayson, A. (2012) A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet medication-associated intracranial haemorrhage. *BMJ Open*, **2**, e000588.
- Baumann, M., Menitove, J., Aster, R. & Anderson, T. (1986) Urgent treatment of idiopathic thrombocytopenic purpura with single-dose gammaglobulin infusion followed by platelet transfusion. *Ann Intern Med*, **104**, 808-809.

- BCSH (2003) British Committee for Standards in Haematology: Guidelines for the use of platelet transfusions. *British Journal of Haematology*, **122**, 10-23.
- Berseus, O., Boman, K., Nessen, S.C. & Westerberg, L.A. (2013) Risks of hemolysis due to anti-A and anti-B caused by the transfusion of blood or blood components containing ABO-incompatible plasma. *Transfusion*, **53 Suppl 1**, 114S-123S.
- Bleggi-Torres, L.F., Werner, B., Gasparetto, E.L., de Medeiros, B.C., Pasquini, R. & de Medeiros, C.R. (2002) Intracranial hemorrhage following bone marrow transplantation: an autopsy study of 58 patients. *Bone Marrow Transplant*, **29**, 29-32.
- Blumberg, N., Refaai, M. & Heal, J. (2015) ABO matching of platelet transfusions - "Start Making Sense". "As we get older, and stop making sense..." - The Talking Heads (1984). *Blood Transfus*, **13**, 347-350.
- Bolton-Maggs, P., Chalmers, E., Collins, P., P, H., Kitchen, S., Liesner, R., Minford, A., Mumford, A., Parapia, L., Perry, D., Watson, S., Wilde, J. & Williams, M. (2006) A review of inherited platelet disorders with guidelines for their management on behalf of UKHCDO. *British Journal of Haematology*, **135**, 603-633.
- Bolton-Maggs, P.E., Poles, D., Watt, A., Thomas, D. & on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group (2014) The 2013 Annual SHOT Report.
- Briggs, C., Hart, D., Kunka, S., Oguni, S. & Machin, S.J. (2006) Immature platelet fraction measurement: a future guide to platelet transfusion requirement after haematopoietic stem cell transplantation. *Transfus Med*, **16**, 101-109.
- British Society of Gastroenterologists (BSG) (2004) Guidelines on the use of Liver Biopsy in Clinical Practice.
- Byrnes, J.J. (1981) Plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *Semin Thromb Hemost*, **7**, 9-14.
- Cameron, B., Rock, G., Olberg, B. & Neurath, D. (2007) Evaluation of platelet transfusion triggers in a tertiary-care hospital. *Transfusion*, **47**, 206-211.
- Carr, E., Jayabose, S., Stringel, G., Slim, M., Ozkaynak, M.F., Tugal, O. & Sandoval, C. (2006) The safety of central line placement prior to treatment of pediatric acute lymphoblastic leukemia. *Pediatric Blood & Cancer*, **47**, 886-888.
- Carr, J.M., Kruskall, M.S., Kaye, J.A. & Robinson, S.H. (1986) Efficacy of platelet transfusions in immune thrombocytopenia. *The American Journal of Medicine*, **80**, 1051-1054.
- Cases, A., Escolar, G., Reverter, J.C., Ordinas, A., Lopez-Pedret, J., Revert, L. & Castillo, R. (1992) Recombinant human erythropoietin treatment improves platelet function in uremic patients. *Kidney Int*, **42**, 668-672.
- Cavanna, L., Civardi, G., Vallisa, D., Di Nunzio, C., Cappucciati, L., Berte, R., Cordani, M.R., Lazzaro, A., Cremona, G., Biasini, C., Muroni, M., Mordenti, P., Gorgni, S., Zaffignani, E., Ambroggi, M., Bidin, L., Palladino, M.A., Rodino, C. & Tibaldi, L. (2010) Ultrasound-guided central venous

- catheterization in cancer patients improves the success rate of cannulation and reduces mechanical complications: a prospective observational study of 1,978 consecutive catheterizations. *World J Surg Oncol*, **8**, 91.
- Cazenave, J.P., Isola, H., Waller, C., Mendel, I., Kientz, D., Laforet, M., Raidot, J.P., Kandel, G., Wiesel, M.L. & Corash, L. (2011) Use of additive solutions and pathogen inactivation treatment of platelet components in a regional blood center: impact on patient outcomes and component utilization during a 3-year period. *Transfusion*, **51**, 622-629.
- Chandramouli, N.B. & Rodgers, G.M. (2000) Prolonged immunoglobulin and platelet infusion for treatment of immune thrombocytopenia. *Am J Hematol*, **65**, 85-86.
- Charlton, A., Wallis, J., Robertson, J., Watson, D., Iqbal, A. & Tinegate, H. (2014) Where did platelets go in 2012? A survey of platelet transfusion practice in the north of England. *Transfusion Medicine*, **24**, 213-218.
- Chen, C.Y., Tai, C.H., Tsay, W., Chen, P.Y. & Tien, H.F. (2009) Prediction of fatal intracranial hemorrhage in patients with acute myeloid leukemia. *Annals of Oncology*, **20**, 1100-1104.
- Cid, J., Lozano, M., Ziman, A., West, K.A., O'Brien, K.L., Murphy, M.F., Wendel, S., Vazquez, A., Ortin, X., Hervig, T.A., Delaney, M., Flegel, W.A., Yazer, M.H. & Biomedical Excellence for Safer Transfusion, c. (2015) Low frequency of anti-D alloimmunization following D+ platelet transfusion: the Anti-D Alloimmunization after D-incompatible Platelet Transfusions (ADAPT) study. *Br J Haematol*, **168**, 598-603.
- Cimo, P.L., Moake, J.L., Weinger, R.S., Ben-Menachem, Y.B. & Khalil, K.G. (1979) Heparin-induced thrombocytopenia: association with a platelet aggregating factor and arterial thromboses. *Am J Hematol*, **6**, 125-133.
- Cluzel, P., Martinez, F., Bellin, M.F., Michalik, Y., Beaufile, H., Jouanneau, C., Lucidarme, O., Deray, G. & Grenier, P.A. (2000) Transjugular versus percutaneous renal biopsy for the diagnosis of parenchymal disease: comparison of sampling effectiveness and complications. *Radiology*, **215**, 689-693.
- Cohn, C.S., Stubbs, J., Schwartz, J., Francis, R., Goss, C., Cushing, M., Shaz, B., Mair, D., Brantigan, B. & Heaton, W.A. (2014) A comparison of adverse reaction rates for PAS C versus plasma platelet units. *Transfusion*, **54**, 1927-1934.
- Coppo, P., Bussel, A., Charrier, S., Adrie, C., Galicier, L., Boulanger, E., Veyradier, A., Leblanc, T., Alberti, C., Azoulay, E., Le Gall, J.-R. & Schlemmer, B. (2003) High-Dose Plasma Infusion versus Plasma Exchange as Early Treatment of Thrombotic Thrombocytopenic Purpura/Hemolytic-Uremic Syndrome. *Medicine*, **82**, 27-38.
- Crighton, G., Estcourt, L., Wood, E., Stanworth, S., Trivella, M., Doree, C., Timmouth, A. & Murphy, M. (2015) A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. *Cochrane Database of Systematic Reviews*, [In press].

- De la Salle, B.J., McTaggart, P.N., Briggs, C., Harrison, P., Doré, C.J., Longair, I., Machin, S.J. & Hyde, K. (2012) The Accuracy of Platelet Counting in Thrombocytopenic Blood Samples Distributed by the UK National External Quality Assessment Scheme for General Haematology. *American Journal of Clinical Pathology*, **137**, 65-74.
- De la Serna, J., Montesinos, P., Vellenga, E., Rayon, C., Parody, R., Leon, A., Esteve, J., Bergua, J.M., Milone, G., Deben, G., Rivas, C., Gonzalez, M., Tormo, M., az-Mediavilla, J., Gonzalez, J.D., Negri, S., Amutio, E., Brunet, S., Lowenberg, B. & Sanz, M.A. (2008) Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. *Blood*, **111**, 3395-3402.
- Della Vigna, P., Monfardini, L., Bonomo, G., Curigliano, G., Agazzi, A., Bellomi, M. & Orsi, F. (2009) Coagulation disorders in patients with cancer: nontunneled central venous catheter placement with US guidance--a single-institution retrospective analysis. *Radiology*, **253**, 249-252.
- Devalia, V. (2013) Annual British Society for Haematology confidential survey of bone marrow examination associated adverse events 2011. *British Journal of Haematology*, **161**, 22-23.
- Doerfler, M.E., Kaufman, B. & Goldenberg, A.S. (1996) Central venous catheter placement in patients with disorders of hemostasis. *Chest*, **110**, 185-188.
- Doughty, H., Murphy, M., Metcalfe, P., Rohatiner, A., Lister, T. & Waters, A. (1994) Relative importance of immune and non-immune causes of platelet refractoriness. *Vox Sanguinis*, **66**, 200-205.
- Duffy, S.M. & Coyle, T.E. (2013) Platelet transfusions and bleeding complications associated with plasma exchange catheter placement in patients with presumed thrombotic thrombocytopenic purpura. *J Clin Apher.*
- Dunbar, N.M., Katus, M.C., Freeman, C.M. & Szczepiorkowski, Z.M. (2015) Easier said than done: ABO compatibility and D matching in apheresis platelet transfusions. *Transfusion*, **55**, 1882-1888.
- Egerman, R.S., Witlin, A.G., Friedman, S.A. & Sibai, B.M. (1996) Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome in pregnancy: review of 11 cases. *Am J Obstet Gynecol*, **175**, 950-956.
- Eldor, A., Avitzour, M., Or, R., Hanna, R. & Penchas, S. (1982) Prediction of haemorrhagic diathesis in thrombocytopenia by mean platelet volume. *Br Med J (Clin Res Ed)*, **285**, 397-400.
- Estcourt, L. (2014) Why has demand for platelet components increased? A review. [Review]. *Transfusion Medicine*, **24**, 260-268.
- Estcourt, L., Gregg, R., Stanworth, S., Doree, C., Trivella, M., Murphy, M. & Tinmouth, A. (2014a) Alternative agents versus prophylactic platelet transfusion for preventing bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation (protocol). *Cochrane database of systematic reviews (Online)*, **2014**, CD010982.
- Estcourt, L., Stanworth, S., Doree, C., Hopewell, S., Murphy, M.F., Tinmouth, A. & Heddle, N. (2012a) Prophylactic platelet transfusion for prevention of bleeding in patients with haematological

- disorders after chemotherapy and stem cell transplantation. *Cochrane database of systematic reviews (Online)*, CD004269.
- Estcourt, L., Stanworth, S., Doree, C., Trivella, M., Hopewell, S., Murphy, M. & Tinmouth, A. (2014b) Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation (protocol). *Cochrane database of systematic reviews (Online)*, **2014**, CD010983.
- Estcourt, L., Stanworth, S., Doree, C., Trivella, M., Hopewell, S., Murphy, M. & Tinmouth, A. (2014c) Different doses of prophylactic platelet transfusion for preventing bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation. *Cochrane database of systematic reviews (Online)*, **2014**, CD010984.
- Estcourt, L.J., Birchall, J., Lowe, D., Grant-Casey, J., Rowley, M. & Murphy, M.F. (2012b) Platelet transfusions in haematology patients: are we using them appropriately? *Vox Sanguinis*, **103**, 284-293.
- Estcourt, L.J., Curry, N.S., Simons, G.N., Jairath, V., Butler, C., Harrison, P., Stanworth, S.J. & Murphy, M.F. (2013) Platelet transfusion for the actively bleeding patient. In: *Platelet transfusion therapy* (ed. by Sweeney, J. & Lozano, M.), pp. 271-320. AABB.
- Estcourt, L.J., Stanworth, S.J. & Murphy, M.F. (2011) Platelet transfusions for patients with haematological malignancies: who needs them? *British Journal of Haematology*, **154**, 425-440.
- European Blood Alliance (2015) European Blood Alliance Annual Report 2015.
- European Committee (Partial Agreement) on Blood Transfusion CD-P-TS (2016) The collection, testing and use of blood and blood components in Europe, EDQM 2013 report.
- Fisher, N. & Mutimer, D. (1999) Central venous cannulation in patients with liver disease and coagulopathy - a prospective audit. *Intensive Care Medicine*, **25**, 481-485.
- Foster, P.F., Moore, L.R., Sankary, H.N., Hart, M.E., Ashmann, M.K. & Williams, J.W. (1992) Central venous catheterization in patients with coagulopathy. *Arch Surg*, **127**, 273-275.
- Friedmann, A.M., Sengul, H., Lehmann, H., Schwartz, C. & Goodman, S. (2002) Do basic laboratory tests or clinical observations predict bleeding in thrombocytopenic oncology patients? A reevaluation of prophylactic platelet transfusions. *Transfusion Medicine Reviews*, **16**, 34-45.
- Gami, A.S., Hayman, S.R., Grande, J.P. & Garovic, V.D. (2005) Incidence and prognosis of acute heart failure in the thrombotic microangiopathies. *The American Journal of Medicine*, **118**, 544-547.
- Gerber, D.E., Segal, J.B., Levy, M.Y., Kane, J., Jones, R.J. & Streiff, M.B. (2008) The incidence of and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation: implications for VTE prevention. *Blood*, **112**, 504-510.

- Gerday, E., Baer, V.L., Lambert, D.K., Paul, D.A., Sola-Visner, M.C., Pysher, T.J. & Christensen, R.D. (2009) Testing platelet mass versus platelet count to guide platelet transfusions in the neonatal intensive care unit. *Transfusion*, **49**, 2034-2039.
- Giagounidis, A.M.G.J.F.P.S.M.A.S.J.P.U.K.A.G.G.W.-J.W.H.K.W.P. & Kantarjian, H.M. (2014) Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. *Cancer*, **120**, 1838-1846.
- Godier, A., Taylor, G. & Gaussem, P. (2015) Inefficacy of platelet transfusion to reverse ticagrelor. *N Engl J Med*, **372**, 196-197.
- Goerge, T., Ho-Tin-Noe, B., Carbo, C., Benarafa, C., Remold-O'Donnell, E., Zhao, B.Q., Cifuni, S.M. & Wagner, D.D. (2008) Inflammation induces hemorrhage in thrombocytopenia. *Blood*, **111**, 4958-4964.
- Goodnough, L.T., Strasburg, D., Verbrugge, D. & Fisher, C. (1994) Morbidity and mortality in adults with "idiopathic" thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. *Journal of Intensive Care Medicine*, **9**, 167-171.
- Gordon, L.I., Kwaan, H.C. & Rossi, E.C. (1987) Deleterious effects of platelet transfusions and recovery thrombocytosis in patients with thrombotic microangiopathy. *Semin Hematol*, **24**, 194-201.
- Gottschall, J.L., Pisciotta, A.V., Darin, J., Hussey, C.V. & Aster, R.H. (1981) Thrombotic thrombocytopenic purpura: experience with whole blood exchange transfusion. *Semin Thromb Hemost*, **7**, 25-32.
- Greenberg, P.L., Garcia-Manero, G., Moore, M., Damon, L., Roboz, G., Hu, K., Yang, A.S. & Franklin, J. (2012) A randomized controlled trial of romiplostim in patients with low- or intermediate-risk myelodysplastic syndrome (MDS) receiving decitabine. *Leukemia & Lymphoma*, **0**, 1-21.
- Greeno, E., McCullough, J. & Weisdorf, D. (2007) Platelet utilization and the transfusion trigger: a prospective analysis. *Transfusion*, **47**, 201-205.
- Haas, B., Chittams, J.L. & Trerotola, S.O. (2010) Large-bore Tunneled Central Venous Catheter Insertion in Patients with Coagulopathy. *Journal of vascular and interventional radiology*, **21**, 212-217.
- Hansson, E.C., Shams Hakimi, C., Astrom-Olsson, K., Hesse, C., Wallen, H., Dellborg, M., Albertsson, P. & Jeppsson, A. (2014) Effects of ex vivo platelet supplementation on platelet aggregability in blood samples from patients treated with acetylsalicylic acid, clopidogrel, or ticagrelor. *Br J Anaesth*, **112**, 570-575.
- Harris, A., Atterbury, C., Chaffe, B., Elliott, C., Hawkins, T., Hennem, S., Howell, C., Jones, J., Murray, S., New, H., Norfolk, D., Pirie, L., Russell, J. & Taylor, C. (2009) Guideline on the Administration of Blood Components.
- Hayward, C.P.M., Rao, A.K. & Cattaneo, M. (2006) Congenital platelet disorders: overview of their mechanisms, diagnostic evaluation and treatment. *Haemophilia*, **12**, 128-136.

- Hedges, S.J., Dehoney, S.B., Hooper, J.S., Amanzadeh, J. & Busti, A.J. (2007) Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol*, **3**, 138-153.
- Hind, D., Calvert, N., McWilliams, R., Davidson, A., Paisley, S., Beverley, C. & Thomas, S. (2003) Ultrasonic locating devices for central venous cannulation: meta-analysis. *BMJ*, **327**, 361.
- Hong Pheng Loh, A. & Hon Chui, C. (2007) Port-A-Cath insertions in acute leukemia: does thrombocytopenia affect morbidity? *Journal of Pediatric Surgery*, **42**, 1180-1184.
- Hopkins, C.K. & Goldfinger, D. (2008) Platelet transfusions in heparin-induced thrombocytopenia: a report of four cases and review of the literature. *Transfusion*, **48**, 2128-2132.
- Jones, A., Birchall, J., Roberts, P., Davies, L., Webb, M., Cooke, S.J., Mead, K., MacRate, E., Thompson, P. & McMahan, J. (2013) A survey of where and why platelets are used in hospitals in the South West region of England. *Transfusion Medicine*, **23**, PO34.
- Kacker, S., Ness, P.M., Savage, W.J., Frick, K.D., McCullough, J., King, K.E. & Tobian, A.A. (2013) The cost-effectiveness of platelet additive solution to prevent allergic transfusion reactions. *Transfusion*, **53**, 2609-2618.
- Kalambokis, G., Manousou, P., Vibhakorn, S., Marelli, L., Cholongitas, E., Senzolo, M., Patch, D. & Burroughs, A.K. (2007) Transjugular liver biopsy – Indications, adequacy, quality of specimens, and complications – A systematic review. *Journal of Hepatology*, **47**, 284-294.
- Kantarjian, H.M., Mufti, G.J., Fenaux, P., Sekeres, M.A., Szer, J., Platzbecker, U., Kuendgen, A., Gaidano, G., Wiktor-Jedrzejczak, W., Bennett, J.M., Meibohm, A., Yang, A.S. & Giagounidis, A. (2012) Treatment with the thrombopoietin (TPO)-receptor agonist romiplostim in thrombocytopenic patients (PTS) with low or intermediate-1 (INT-1) risk myelodysplastic syndrome (MDS): Follow-up aml and survival results of a randomized, double-blind, placebo (PBO)-controlled study. *Blood*, **120**, Various.
- Kaufman, R.M., Djulbegovic, B., Gernsheimer, T., Kleinman, S., Tinmouth, A.T., Capocelli, K.E., Cipolle, M.D., Cohn, C.S., Fung, M.K., Grossman, B.J., Mintz, P.D., O'Malley, B.A., Sesok-Pizzini, D.A., Shander, A., Stack, G.E., Webert, K.E., Weinstein, R., Welch, B.G., Whitman, G.J., Wong, E.C. & Tobian, A.A. (2015) Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*, **162**, 205-213.
- Ker, K., Edwards, P., Perel, P., Shakur, H. & Roberts, I. (2012) Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ*, **344**, e3054.
- Killick, S., Carter, C., Culligan, D., Dalley, C., Das-Gupta, E., Drummond, M., Enright, H., Jones, G., Kell, J., Mills, J., Mufti, G., Parker, J., Raj, K., Sternberg, A., Vyas, P. & Bowen, D. (2014) Guidelines for the diagnosis and management of adult myelodysplastic syndromes. *British Journal of Haematology*, **164**, 503-525.
- Killick, S.B., Bown, N., Cavenagh, J., Dokal, I., Foukaneli, T., Hill, A., Hillmen, P., Ireland, R., Kulasekararaj, A., Mufti, G., Snowden, J.A., Samarasinghe, S., Wood, A., Marsh, J.C. & British

- Society for Standards in, H. (2015) Guidelines for the diagnosis and management of adult aplastic anaemia. *Br J Haematol*.
- Kim, H., Lee, J.H., Choi, S.J., Kim, W.K., Lee, J.S. & Lee, K.H. (2004) Analysis of fatal intracranial hemorrhage in 792 acute leukemia patients. *Haematologica*, **89**, 622-624.
- Kitazawa, J., Nollet, K., Morioka, H., Tanaka, K., Inomata, M., Kubuki, Y. & Ohto, H. (2011) Non-D Rh antibodies appearing after apheresis platelet transfusion: stimulation by red cells or microparticles? *Vox Sanguinis*, **100**, 395-400.
- Kozek-Langenecker, S.A., Afshari, A., Albaladejo, P., Santullano, C.A., De Robertis, E., Filipescu, D.C., Fries, D., Gorlinger, K., Haas, T., Imberger, G., Jacob, M., Lance, M., Llau, J., Mallett, S., Meier, J., Rahe-Meyer, N., Samama, C.M., Smith, A., Solomon, C., Van der Linden, P., Wikkelso, A.J., Wouters, P. & Wyffels, P. (2013) Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*, **30**, 270-382.
- Kumar, A., Mhaskar, R., Grossman, B.J., Kaufman, R.M., Tobian, A.A., Kleinman, S., Gernsheimer, T., Tinmouth, A.T., Djulbegovic, B. & Panel, A.P.T.G. (2014) Platelet transfusion: a systematic review of the clinical evidence. *Transfusion*.
- Lawrence, J., Yomtovian, R., Hammons, T., Masarik, S., Chongkolwatana, V., Cregar, R. & al, e. (2001) Lowering the prophylactic platelet transfusion threshold: a prospective analysis. *Leukemia & Lymphoma*, **41**, 67-76.
- Legler, T., Fischer, I., Dittmann, J., Simson, G., Lynen, R., Humpe, A., Riggert, J., Schleyer, E., Kern, W., Hiddemann, W. & Köhler, M. (1997) Frequency and causes of refractoriness in multiply transfused patients. *Annals of Hematology*, **74**, 185-189.
- Li, C., Hirsh, J., Xie, C., Johnston, M.A. & Eikelboom, J.W. (2012) Reversal of the anti-platelet effects of aspirin and clopidogrel. *J Thromb Haemost*, **10**, 521-528.
- Lieberman, L., Sholapur, N.S., Bercovitz, R.S., Heddle, N., Stanworth, S. & Arnold, D.M. (2013) Platelet transfusions in critically ill patients with thrombocytopenia: An evidence-based review. *Blood*.
- Linkins, L.A., Dans, A.L., Moores, L.K., Bona, R., Davidson, B.L., Schulman, S. & Crowther, M. (2012) Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, **141**, e495S-530S.
- Liu, E.T., Linker, C.A. & Shuman, M.A. (1986) Management of treatment failures in thrombotic thrombocytopenic purpura. *American Journal of Hematology*, **23**, 347-361.
- Liumbruno, G., Bennardello, F., Lattanzio, A., Piccoli, P. & Rossetti, G. (2009) Recommendations for the transfusion of plasma and platelets. *Blood Transfus*, **7**, 132-150.
- Liumbruno, G.M., Bennardello, F., Lattanzio, A., Piccoli, P., Rossetti, G., Italian Society of Transfusion, M. & Immunohaematology Working, P. (2011) Recommendations for the transfusion management of patients in the peri-operative period. I. The pre-operative period. *Blood Transfus*, **9**, 19-40.

- Lyons, G. & Hunt, B. (2010) Platelet counts and Obstetric Analgesia & Anaesthesia. Obstetric Anaesthetists Association www.oaa-anaes.ac.uk.
- Mahévas, M., Fain, O., Ebbo, M., Roudot-Thoraval, F., Limal, N., Khellaf, M., Schleinitz, N., Bierling, P., Languille, L., Godeau, B. & Michel, M. (2014) The temporary use of thrombopoietin-receptor agonists may induce a prolonged remission in adult chronic immune thrombocytopenia. Results of a French observational study. *British Journal of Haematology*, **165**, 865-869.
- Makris, M., Van Veen, J.J., Tait, C.R., Mumford, A.D., Laffan, M. & British Committee for Standards in H. (2013) Guideline on the management of bleeding in patients on antithrombotic agents. *Br J Haematol*, **160**, 35-46.
- Mammen, T., Keshava, S.N., Eapen, C.E., Raghuram, L., Moses, V., Gopi, K., Babu, N.S., Ramachandran, J. & Kurien, G. (2008) Transjugular Liver Biopsy: A Retrospective Analysis of 601 Cases. *Journal of vascular and interventional radiology*, **19**, 351-358.
- Manno, C., Bonifati, C., Torres, D.D., Campobasso, N. & Schena, F.P. (2011) Desmopressin Acetate in Percutaneous Ultrasound-Guided Kidney Biopsy: A Randomized Controlled Trial. *American Journal of Kidney Diseases*, **57**, 850-855.
- Manno, C., Strippoli, G.F.M., Arnesano, L., Bonifati, C., Campobasso, N., Gesualdo, L. & Schena, F.P. (2004) Predictors of bleeding complications in percutaneous ultrasound-guided renal biopsy. *Kidney Int*, **66**, 1570-1577.
- Mannucci, P.M. (2012) Desmopressin (DDAVP) in the treatment of bleeding disorders. *Treatment of Hemophilia*, 1-9.
- Mannucci, P.M., Remuzzi, G., Pusineri, F., Lombardi, R., Valsecchi, C., Mecca, G. & Zimmerman, T.S. (1983) Deamino-8-D-Arginine Vasopressin Shortens the Bleeding Time in Uremia. *New England Journal of Medicine*, **308**, 8-12.
- McCarthy, L.J., Danielson, C.F.M., Graves, V., Jackson, L., Axelrod, F., Greist, A., Cornetta, K. & Gabig, T. (1994) Do platelet transfusions to patients with TTP influence their survival? *Blood*, **84**, 669a.
- Michallet, M., Goldet, K., Sobh, M., Morisset, S., Chelghoum, Y., Thomas, X., Barraco, F., Ducastelle, S., Labussiere, H., Renzullo, C., Paillet, C., Pivot, C., Straaten, P.B., Denis, A., Termoz, A., Detrait, M., Nicolini, F.E. & Jaisson-Hot, I. (2013) Prospective study of erythropoietin use on quality of life and cost effectiveness in acute myeloid leukemia and allogeneic hematopoietic stem cell transplantation patients. *Cancer*, **119**, 107-114.
- Milkins, C., Berryman, J., Cantwell, C., Elliott, C., Haggas, R., Jones, J., Rowley, M., Williams, M., Win, N. & British Committee for Standards in Haematology (2013) Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories. British Committee for Standards in Haematology. *Transfus Med*, **23**, 3-35.
- Miller, Y., Bachowski, G., Benjamin, R., Eklund, D.K., Hibbards, A.J., Lightfoot, T., Meena-Leist, C., Quaraishy, N., Sapatnekar, S., Squires, J., Strupp, A., Vassallo, R. & Weiss, J. (2007) Practice

- Guidelines for Blood Transfusion. In: *A Compilation from Recent Peer-Reviewed Literature* (ed. by American National Red Cross). American National Red Cross.
- Monchamont, P., Barday, G. & Meyer, F. (2014) Red blood cell alloimmunisation after platelet transfusion: a 5-year study. *Blood Transfusion*, **12**, s147-s148.
- Mumtaz, H., Williams, V., Hauer-Jensen, M., Rowe, M., Henry-Tillman, R.S., Heaton, K., Mancino, A.T., Muldoon, R.L., Klimberg, V.S., Broadwater, J.R., Westbrook, K.C. & Lang, N.P. (2000) Central venous catheter placement in patients with disorders of hemostasis. *The American Journal of Surgery*, **180**, 503-506.
- Murphy, M. (2013) Post-transfusion purpura. In: *Practical Transfusion Medicine* (ed. by Murphy, M., Pamphilon, D. & Heddle, N.), pp. 127-130. Wiley-Blackwell.
- Nahirniak, S., Slichter, S.J., Tanael, S., Rebullia, P., Pavenski, K., Vassallo, R., Fung, M., Duquesnoy, R., Saw, C.-L., Stanworth, S., Tinmouth, A., Hume, H., Ponnampalam, A., Moltzan, C., Berry, B. & Shehata, N. (2015) Guidance on Platelet Transfusion for Patients With Hypoproliferative Thrombocytopenia. *Transfusion Medicine Reviews*.
- Najima, Y., Ohashi, K., Miyazawa, M., Nakano, M., Kobayashi, T., Yamashita, T., Akiyama, H. & Sakamaki, H. (2009) Intracranial hemorrhage following allogeneic hematopoietic stem cell transplantation. *American Journal of Hematology*, **84**, 298-301.
- Napolitano, M., Malato, A., Raffaele, F., Palazzolo, M., Iacono, G.L., Pinna, R., Geraci, G., Modica, G., Saccullo, G., Siragusa, S. & Cajozzo, M. (2013) Ultrasonography-guided central venous catheterisation in haematological patients with severe thrombocytopenia. *Blood Transfusion*, 1-5.
- National Blood Authority (2011) The National Blood Authority's Patient Blood Management Guideline: Module 1 – Critical Bleeding/Massive Transfusion.
- Neunert, C., Lim, W., Crowther, M., Cohen, A., Solberg, L. & Crowther, M.A. (2011) The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*, **117**, 4190-4207.
- Nevo, S., Fuller, A.K., Hartley, E., Borinsky, M.E. & Vogelsang, G.B. (2007) Acute bleeding complications in patients after hematopoietic stem cell transplantation with prophylactic platelet transfusion triggers of 10×10^9 and 20×10^9 per L. *Transfusion*, **47**, 801-812.
- New, H.V., Berryman, J., Bolton-Maggs, P.H.B., Cantwell, C., Chalmers, E.A., Davies, T., Gottstein, R., Andrea Kelleher, A., Kumar, S., Morley, S.L., Stanworth, S.J. & on behalf of the British Committee for Standards in Haematology (2016) Guidelines on transfusion for fetuses, neonates and older children.
- NICE (2015) Blood transfusion NG24. (ed. by National Institute for Health and Clinical Excellence).
- Nishijima, D.K., Zehtabchi, M., Berrong, J. & Legome, E. (2012) Utility of platelet transfusion in adult patients with traumatic intracranial hemorrhage and preinjury antiplatelet use: a systematic review. *J Trauma Acute Care Surg*, **72**, 1658-1663.

- Office of National Statistics (ONS) (2013) 2012-based national population projections. (ed. by Statistics, O.o.N.).
- Olnes, M.J., Scheinberg, P., Calvo, K.R., Desmond, R., Tang, Y., Dumitriu, B., Parikh, A.R., Soto, S., Biancotto, A., Feng, X., Lozier, J., Wu, C.O., Young, N.S. & Dunbar, C.E. (2012) Eltrombopag and improved hematopoiesis in refractory aplastic anemia. *New England Journal of Medicine*, **367**, 11-19.
- Passweg, J.R., Baldomero, H., Gratwohl, A., Bregni, M., Cesaro, S., Dreger, P., de Witte, T., Farge-Bancel, D., Gaspar, B., Marsh, J., Mohty, M., Peters, C., Tichelli, A., Velardi, A., de Elvira, C.R., Falkenburg, F., Sureda, A., Madrigal, A., European Group for, B. & Marrow, T. (2012) The EBMT activity survey: 1990-2010. *Bone Marrow Transplant*, **47**, 906-923.
- Pavenski, K., Rebullá, P., Duquesnoy, R., Saw, C.L., Slichter, S.J., Tanael, S., Shehata, N. & International Collaboration for Guideline Development, I.E.f.T.T., Collaborators (2013) Efficacy of HLA-matched platelet transfusions for patients with hypoproliferative thrombocytopenia: a systematic review. *Transfusion*, **53**, 2230-2242.
- Peigne, V., Perez, P., Resche Rigon, M., Mariotte, E., Canet, E., Mira, J.-P., Coppo, P., Veyradier, A. & Azoulay, E. (2012) Causes and risk factors of death in patients with thrombotic microangiopathies. *Intensive Care Medicine*, **38**, 1810-1817.
- Pendry, K. & Davies, T. (2011) An audit of the use and wastage in the North West of England and North Wales - where have all the platelets gone? *Blood and Transfusion Matters*, **34**, 17-19.
- Perdigão, J.P.V., de Almeida, P.C., Rocha, T.D.S., Mota, M.R.L., Soares, E.C.S., Alves, A.P.N.N. & Sousa, F.B. (2012) Postoperative Bleeding After Dental Extraction in Liver Pretransplant Patients. *Journal of Oral and Maxillofacial Surgery*, **70**, e177-e184.
- Pietersz, R.N.I., Reesink, H.W., Panzer, S., Gilbertson, M.P., Borosak, M.E., Wood, E.M., Leitner, G.C., Rabitsch, W., Ay, C., Lambermont, M., Deneys, V., Sondag, D., Compennolle, V., Legrand, D., Francois, A., Tardivel, R., Garban, F., Sawant, R.B., Rebullá, P., Handa, M., Ohto, H., Kerkhoffs, J.L.H., Brand, A., Zhiburt, E., Cid, J., Escolar, G., Lozano, M., Puig, L., Knutson, F., Hallbook, H., Lubenow, N., Estcourt, L., Stanworth, S., Murphy, M.F., Williams, L., Mraz, D.L., Ross, R.L. & Snyder, E. (2012) Prophylactic platelet transfusions. *Vox Sanguinis*, **103**, 159-176.
- Poeran, J., Rasul, R., Suzuki, S., Danninger, T., Mazumdar, M., Opperer, M., Boettner, F. & Memtsoudis, S.G. (2014) Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ*, **349**, g4829.
- Potet, J., Thome, A., Curis, E., Arnaud, F.X., Weber-Donat, G., Valbousquet, L., Peroux, E., Flor, E., Dody, C., Konopacki, J., Malfuson, J.V., Cartry, C., Lahutte, M., de Revel, T., Baccialone, J. & Teriitehau, C.A. (2013) Peripherally inserted central catheter placement in cancer patients with profound thrombocytopenia: a prospective analysis. *Eur Radiol*.

- Provan, D., Stasi, R., Newland, A.C., Blanchette, V.S., Bolton-Maggs, P., Bussel, J.B., Chong, B.H., Cines, D.B., Gernsheimer, T.B., Godeau, B., Grainger, J., Greer, I., Hunt, B.J., Imbach, P.A., Lyons, G., McMillan, R., Rodeghiero, F., Sanz, M.A., Tarantino, M., Watson, S., Young, J. & Kuter, D.J. (2010) International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*, **115**, 168-186.
- Puller, F., Drexler, C., Archan, S., Macher, S., Raggam, R.B. & Mahla, E. (2011) Low platelet reactivity is recovered by transfusion of stored platelets: a healthy volunteer in vivo study. *J Thromb Haemost*, **9**, 1670-1673.
- Qureshi, H., Lowe, D., Dobson, P., Grant-Casey, J., Parris, E., Dalton, D., Hickling, K., Waller, F., Howell, C. & Murphy, M. (2007) National comparative audit of the use of platelet transfusions in the UK. *Transfusion Clinique et Biologique*, **14**, 509-513.
- Qureshi, H., Massey, E., Kirwan, D., Davies, T., Robson, S., White, J., Jones, J. & Allard, S. (2014) BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. *Transfusion Medicine*, **24**, 8-20.
- Randolph, A.G., Cook, D.J., Gonzales, C.A. & Pribble, C.G. (1996) Ultrasound guidance for placement of central venous catheters: A meta-analysis of the literature. *Critical Care Medicine*, **24**, 2053-2058.
- Ray, C.E. & Shenoy, S.S. (1997) Patients with thrombocytopenia: outcome of radiologic placement of central venous access devices. *Radiology*, **204**, 97-99.
- Refaai, M.A., Chuang, C., Menegus, M., Blumberg, N. & Francis, C.W. (2010) Outcomes after platelet transfusion in patients with heparin-induced thrombocytopenia. *J Thromb Haemost*, **8**, 1419-1421.
- Rockey, D.C., Caldwell, S.H., Goodman, Z.D., Nelson, R.C., Smith, A.D. & American Association for the Study of Liver, D. (2009) Liver biopsy. *Hepatology*, **49**, 1017-1044.
- Rose, M. & Eldor, A. (1987) High incidence of relapses in thrombotic thrombocytopenic purpura: Clinical Study of 38 Patients. *The American Journal of Medicine*, **83**, 437-444.
- Rossaint, R., Bouillon, B., Cerny, V., Coats, T.J., Duranteau, J., Fernandez-Mondejar, E., Hunt, B.J., Komadina, R., Nardi, G., Neugebauer, E., Ozier, Y., Riddez, L., Schultz, A., Stahel, P.F., Vincent, J.L. & Spahn, D.R. (2010) Management of bleeding following major trauma: an updated European guideline. *Crit Care*, **14**, R52.
- Rutkow, I. (1978) Thrombotic Thrombocytopenic Purpura (TTP) and splenectomy: a current appraisal. *Ann Surg*, **188**, 701-705.
- SaBTO (2012) SaBTO report of the Cytomegalovirus Steering Group. Vol. 2015.
- Sagmeister, M., Oec, L. & Gmur, J. (1999) A restrictive platelet transfusion policy allowing long-term support of outpatients with severe aplastic anemia. *Blood*, **93**, 3124-3126.

- Salama, A., Kiesewetter, H., Kalus, U., Movassaghi, K. & Meyer, O. (2008) Massive platelet transfusion is a rapidly effective emergency treatment in patients with refractory autoimmune thrombocytopenia. *Thrombosis and Haemostasis*, **100**.
- Samama, C.M., Djoudi, R., Lecompte, T., Nathan, N. & Schved, J.-F. (2006) Perioperative platelet transfusion Recommendations of the French Health Products Safety Agency (AFSSAPS) 2003. *Minerva Anestesiologica*, **72**, 447-452.
- Sarode, R., Gottschall, J.L., Aster, R.H. & McFarland, J.G. (1997) Thrombotic thrombocytopenic purpura: Early and late responders. *American Journal of Hematology*, **54**, 102-107.
- Schiffer, C.A., Anderson, K.C., Bennett, C.L., Bernstein, S., Elting, L.S., Goldsmith, M., Goldstein, M., Hume, H., McCullough, J.J., McIntyre, R.E., Powell, B.L., Rainey, J.M., Rowley, S.D., Rebull, P., Troner, M.B. & Wagnon, A.H. (2001) Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *Journal of Clinical Oncology*, **19**, 1519-1538.
- Scornik, J.C., Bromberg, J.S., Norman, D.J., Bhandari, M., Gitlin, M. & Petersen, J. (2013) An update on the impact of pre-transplant transfusions and allosensitization on time to renal transplant and on allograft survival. *BMC Nephrology*, **14**.
- Scully, M., Hunt, B.J., Benjamin, S., Liesner, R., Rose, P., Peyvandi, F., Cheung, B., Machin, S.J. & on behalf of British Committee for Standards in, H. (2012) Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *British Journal of Haematology*, **158**, 323-335.
- Seeff, L.B., Everson, G.T., Morgan, T.R., Curto, T.M., Lee, W.M., Ghany, M.G., Shiffman, M.L., Fontana, R.J., Di Bisceglie, A.M., Bonkovsky, H.L., Dienstag, J.L. & Group, H.-C.T. (2010) Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol*, **8**, 877-883.
- Segal, H.C., Briggs, C., Kunka, S., Casbard, A., Harrison, P., Machin, S.J. & Murphy, M.F. (2005) Accuracy of platelet counting haematology analysers in severe thrombocytopenia and potential impact on platelet transfusion. *British Journal of Haematology*, **128**, 520-525.
- Sekeres, M.A., Kantarjian, H., Fenaux, P., Becker, P., Boruchov, A., Guerci-Bresler, A., Hu, K., Franklin, J., Wang, Y.M. & Berger, D. (2011) Subcutaneous or intravenous administration of romiplostim in thrombocytopenic patients with lower risk myelodysplastic syndromes. *Cancer*, **117**, 992-1000.
- Shakur, H., Roberts, I., Bautista, R., Caballero, J., Coats, T., Dewan, Y., El-Sayed, H., Gogichaishvili, T., Gupta, S., Herrera, J., Hunt, B., Iribhogbe, P., Izurieta, M., Khamis, H., Komolafe, E., Marrero, M.A., Mejia-Mantilla, J., Miranda, J., Morales, C., Olaomi, O., Ollidashi, F., Perel, P., Peto, R., Ramana, P.V., Ravi, R.R. & Yutthakasemsunt, S. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*, **376**, 23-32.

- Shamseddine, A., Saliba, T., Aoun, E., Chahal, A., El-Saghir, N., Salem, Z., Bazarbachi, A., Khalil, M. & Taher, A. (2004) Thrombotic thrombocytopenic purpura: 24 years of experience at the American University of Beirut Medical Center. *Journal of Clinical Apheresis*, **19**, 119-124.
- Shi, J., Ji, H., Ren, F., Wang, G., Xu, M., Xue, Y., Chen, M., Qi, J. & Li, L. (2013a) Protective effects of tranexamic acid on clopidogrel before coronary artery bypass grafting: a multicenter randomized trial. *JAMA Surg*, **148**, 538-547.
- Shi, J., Wang, G., Lv, H., Yuan, S., Wang, Y., Ji, H. & Li, L. (2013b) Tranexamic Acid in on-pump coronary artery bypass grafting without clopidogrel and aspirin cessation: randomized trial and 1-year follow-up. *Ann Thorac Surg*, **95**, 795-802.
- Spahn, D.R., Bouillon, B., Cerny, V., Coats, T.J., Duranteau, J., Fernandez-Mondejar, E., Filipescu, D., Hunt, B.J., Komadina, R., Nardi, G., Neugebauer, E., Ozier, Y., Riddez, L., Schultz, A., Vincent, J.L. & Rossaint, R. (2013) Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care*, **17**, R76.
- Spahr, J.E. & Rodgers, G.M. (2008) Treatment of immune-mediated thrombocytopenia purpura with concurrent intravenous immunoglobulin and platelet transfusion: A retrospective review of 40 patients. *American Journal of Hematology*, **83**, 122-125.
- Stanworth, S., Estcourt, L.J., Llewelyn, C., Murphy, M.F., Wood, E.M. & for the TOPPS study investigators (2014) Impact of prophylactic platelet transfusions on bleeding events in patients with hematologic malignancies: a sub-group analysis of a randomized trial. *Transfusion*, **54**, 2385–2393.
- Stanworth, S.J., Estcourt, L.J., Powter, G., Kahan, B., Dyer, C., Choo, L., Bakrania, L., Llewelyn, C., Littlewood, T., Soutar, R., Norfolk, D., Coppleson, A., Smith, N., Kerr, P., Jones, G., Raj, K., Westerman, D., Szer, J., Jackson, N., Bardy, P., Plews, D., Lyons, S., Bielby, L., Wood, E.M. & Murphy, M. (2013a) A no-prophylaxis platelet transfusion strategy for hematologic cancers. *New England Journal of Medicine*, **368**, 1771-1780.
- Stanworth, S.J., Hudson, C.L., Estcourt, L.J., Johnson, R.J. & Wood, E.M. (2015) Risk of bleeding and use of platelet transfusions in patients with hematological malignancies: recurrent event analysis. *Haematologica*.
- Stanworth, S.J., Walsh, T.S., Prescott, R.J., Lee, R.J., Watson, D.M. & Wyncoll, D.L. (2013b) Thrombocytopenia and platelet transfusion in UK critical care: a multicenter observational study. *Transfusion*, **53**, 1050-1058.
- Stecker, M.S., Johnson, M.S., Ying, J., McLennan, G., Agarwal, D.M., Namyslowski, J., Ahmad, I., Shah, H., Butty, S. & Casciani, T. (2007) Time to hemostasis after traction removal of tunneled cuffed central venous catheters. *J Vasc Interv Radiol*, **18**, 1232-1239; quiz 1240.
- Swisher, K.K., Terrell, D.R., Vesely, S.K., Kremer Hovinga, J.A., Lämmle, B. & George, J.N. (2009) Clinical outcomes after platelet transfusions in patients with thrombotic thrombocytopenic purpura. *Transfusion*, **49**, 873-887.

- Taft, E. (1979) Thrombotic thrombocytopenic purpura and dose of plasma exchange. *Blood*, **54**, 842-849.
- Tàssies, D., Reverter, J.C., Cases, A., Calls, J., Escolar, G. & Ordinas, A. (1998) Effect of recombinant human erythropoietin treatment on circulating reticulated platelets in uremic patients: Association with early improvement in platelet function. *American Journal of Hematology*, **59**, 105-109.
- Tercan, F., Ozkan, U. & Oguzkurt, L. (2008) US-guided placement of central vein catheters in patients with disorders of hemostasis. *Eur J Radiol*, **65**, 253-256.
- The Board of the German Medical Association on the Recommendation of the Scientific Advisory Board (2009) Platelet Concentrates. Cross-sectional guidelines for therapy with blood components and plasma derivatives. *Transfusion Medicine and Hemotherapy*, **36**, 372-382.
- Thiele, T., Sumnig, A., Hron, G., Muller, C., Althaus, K., Schroeder, H.W. & Greinacher, A. (2012) Platelet transfusion for reversal of dual antiplatelet therapy in patients requiring urgent surgery: a pilot study. *J Thromb Haemost*, **10**, 968-971.
- Tingate, H., Birchall, J., Gray, A., Haggas, R., Massey, E., Norfolk, D., Pinchon, D., Sewell, C., Wells, A., Allard, S. & Force, B.B.T.T. (2012) Guideline on the investigation and management of acute transfusion reactions. Prepared by the BCSH Blood Transfusion Task Force. *Br J Haematol*, **159**, 143-153.
- Tobian, A.A., Fuller, A.K., Uglich, K., Tisch, D.J., Borge, P.D., Benjamin, R.J., Ness, P.M. & King, K.E. (2014) The impact of platelet additive solution apheresis platelets on allergic transfusion reactions and corrected count increment (CME). *Transfusion*, **54**, 1523-1529; quiz 1522.
- Tomoyose, T., Ohama, M., Yamanoha, A., Masuzaki, H., Okudaira, T. & Tokumine, J. (2013) Real-time ultrasound-guided central venous catheterization reduces the need for prophylactic platelet transfusion in thrombocytopenic patients with hematological malignancy. *Transfusion and Apheresis Science*, **49**, 367-369.
- Torres Munoz, A., Valdez-Ortiz, R., Gonzalez-Parra, C., Espinoza-Davila, E., Morales-Buenrostro, L.E. & Correa-Rotter, R. (2011) Percutaneous renal biopsy of native kidneys: efficiency, safety and risk factors associated with major complications. *Arch Med Sci*, **7**, 823-831.
- Treleaven, J., Gennery, A., Marsh, J., Norfolk, D., Page, L., Parker, A., Saran, F., Thurston, J. & Webb, D. (2011) Guidelines on the use of irradiated blood components prepared by the British Committee for Standards in Haematology blood transfusion task force. *British Journal of Haematology*, **152**, 35-51.
- van Veen, J.J., Nokes, T.J. & Makris, M. (2010) The risk of spinal haematoma following neuraxial anaesthesia or lumbar puncture in thrombocytopenic individuals. *British Journal of Haematology*, **148**, 15-25.
- Vassallo, R.R., Fung, M., Rebullà, P., Duquesnoy, R., Saw, C.L., Slichter, S.J., Tanael, S., Shehata, N., International Collaboration for Guideline Development, I. & Evaluation for Transfusion

- Therapies, C. (2014) Utility of cross-matched platelet transfusions in patients with hypoproliferative thrombocytopenia: a systematic review. *Transfusion*, **54**, 1180-1191.
- Vilahur, G., Choi, B., Zafar, M., Viles-Gonzalez, J., Vorchheimer, D., Fuster, V. & Badimon, J. (2007) Normalization of platelet reactivity in clopidogrel-treated subjects. *Journal of Thrombosis & Haemostasis*, **5**, 82-90.
- Wallace, M.J., Narvios, A., Lichtiger, B., Ahrar, K., Morello, F.A., Gupta, S., Madoff, D.C. & Hicks, M.E. (2003) Transjugular Liver Biopsy in Patients with Hematologic Malignancy and Severe Thrombocytopenia. *Journal of vascular and interventional radiology*, **14**, 323-327.
- Wandt, H., Schaefer-Eckart, K., Wendelin, K., Pilz, B., Wilhelm, M., Thalheimer, M., Mahlknecht, U., Ho, A., Schaich, M., Kramer, M., Kaufmann, M., Leimer, L., Schwerdtfeger, R., Conradi, R., Dolken, G., Klenner, A., Hanel, M., Herbst, R., Junghanss, C. & Ehninger, G. (2012) Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet*, **380**, 1309-1316.
- Wang, E.S., Lyons, R.M., Larson, R.A., Gandhi, S., Liu, D., Matei, C., Scott, B., Hu, K. & Yang, A.S. (2012) A randomized, double-blind, placebo-controlled phase 2 study evaluating the efficacy and safety of romiplostim treatment of patients with low or intermediate-1 risk myelodysplastic syndrome receiving lenalidomide. *Journal of Hematology & Oncology*, **5**.
- Wardrop, D., Estcourt, L.J., Brunskill, S.J., Doree, C., Trivella, M., Stanworth, S. & Murphy, M.F. (2013) Antifibrinolytics (lysine analogues) for the prevention of bleeding in patients with haematological disorders. [Review]. *Cochrane Database of Systematic Reviews*. 7:CD009733, 2013.
- Warkentin, T.E. (2011) How I Diagnose and Manage HIT. *ASH Education Program Book*, **2011**, 143-149.
- Watson, H., Davidson, S. & Keeling, D. (2012) Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. *British Journal of Haematology*, **159**, 528-540.
- Webert, K., Cook, R.J., Sigouin, C.S., Rebutta, P. & Heddle, N.M. (2006) The risk of bleeding in thrombocytopenic patients with acute myeloid leukemia. *Haematologica*, **91**, 1530-1537.
- Weigand, K., Encke, J., Meyer, F.J., Hinkel, U.P., Munder, M., Stremmel, W. & Zahn, A. (2009) Low levels of prothrombin time (INR) and platelets do not increase the risk of significant bleeding when placing central venous catheters. *Med Klin (Munich)*, **104**, 331-335.
- Whittier, W.L. (2004) Timing of Complications in Percutaneous Renal Biopsy. *Journal of the American Society of Nephrology*, **15**, 142-147.
- Wikkelsø, A., Lunde, J., Johansen, M., Stensballe, J., Wetterslev, J., Møller, A.M. & Afshari, A. (2013) Fibrinogen concentrate in bleeding patients. *Cochrane database of systematic reviews (Online)*, **2013**, CD008864.
- Wohlauer, M.V., Moore, E.E., Thomas, S., Sauaia, A., Evans, E., Harr, J., Silliman, C.C., Ploplis, V., Castellino, F.J. & Walsh, M. (2012) Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. *J Am Coll Surg*, **214**, 739-746.

- Yanagisawa, R., Shimodaira, S., Kojima, S., Nakasone, N., Ishikawa, S., Momose, K., Honda, T., Yoshikawa, K., Saito, S., Tanaka, M., Nakazawa, Y., Sakashita, K., Shiohara, M., Akino, M., Hirayama, J., Azuma, H. & Koike, K. (2013) Replaced platelet concentrates containing a new additive solution, M-sol: safety and efficacy for pediatric patients. *Transfusion*, **53**, 2053-2060.
- Zaffuto, B.J., Conley, G.W., Connolly, G.C., Henrichs, K.F., Francis, C.W., Heal, J.M., Blumberg, N. & Refaai, M.A. (2015) ABO-immune complex formation and impact on platelet function, red cell structural integrity and haemostasis: an in vitro model of ABO non-identical transfusion. *Vox Sang.*
- Zeidler, K., Arn, K., Senn, O., Schanz, U. & Stussi, G. (2011) Optimal preprocedural platelet transfusion threshold for central venous catheter insertions in patients with thrombocytopenia. *Transfusion*, **51**, 2269-2276.
- Zhu, M.S., Chen, J.Z. & Xu, A.P. (2014) Factors that can minimize bleeding complications after renal biopsy. *Int Urol Nephrol*, **46**, 1969-1975.
- Zisk, J.L., Mackley, A., Clearly, G., Chang, E., Christensen, R.D. & Paul, D.A. (2013) Transfusing neonates based on platelet count vs. platelet mass: A randomized feasibility-pilot study. *Platelets*.
- Zumberg, M.S., del Rosario, M.L., Nejame, C.F., Pollock, B.H., Garzarella, L., Kao, K.J., Lottenberg, R. & Wingard, J.R. (2002) A prospective randomized trial of prophylactic platelet transfusion and bleeding incidence in hematopoietic stem cell transplant recipients: 10,000/ μ L versus 20,000/ μ L trigger. *Biology of Blood and Marrow Transplantation*, **8**, 569-576.
- Zwaginga, J., IJsseldijk, M., de Groot, P., Kooistra, M., Vos, J., van Es, A., Koomans, H., Struyvenberg, A. & Sixma, J. (1991) Treatment of uremic anemia with recombinant erythropoietin also reduces the defects in platelet adhesion and aggregation caused by uremic plasma. *Thromb Haemost*, **66**, 638-647.

1 **TABLES**

2

3 **Table 1: Modified WHO bleeding score (Stanworth *et al*, 2013a)**

Grade	Type of bleeding
Grade 1	<ul style="list-style-type: none"> • Petechiae/purpura that is localized to 1 or 2 dependent sites, or is sparse/non-confluent • Oropharyngeal bleeding, epistaxis <30 minutes duration
Grade 2	<ul style="list-style-type: none"> • Melaena, haematemesis, haemoptysis, fresh blood in stool, musculoskeletal bleeding, or soft tissue bleeding not requiring red cell transfusion within 24 hours of onset and without haemodynamic instability • Profuse epistaxis or oropharyngeal bleeding >30 minutes • Symptomatic oral blood blisters, i.e. bleeding or causing major discomfort • Multiple bruises, each >2 cm or any one >10 cm • Petechiae/purpura that is diffuse • Visible blood in urine • Abnormal bleeding from invasive or procedure sites • Unexpected vaginal bleeding saturating more than 2 pads with blood in a 24 hr period • Bleeding in cavity fluids evident macroscopically • Retinal hemorrhage without visual impairment

Grade 3	<ul style="list-style-type: none"> • Bleeding requiring red cell transfusion specifically for support of bleeding within 24 hours of onset and without hemodynamic instability • Bleeding in body cavity fluids grossly visible • Cerebral bleeding noted on computerized tomography (CT) without neurological signs and symptoms
Grade 4	<ul style="list-style-type: none"> • Debilitating bleeding including retinal bleeding and visual impairment* • Non-fatal cerebral bleeding with neurological signs and symptoms • Bleeding associated with haemodynamic instability (hypotension, >30 mmHg change in systolic or diastolic BP) • Fatal bleeding from any source

4 * visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmological
5 consultation

6 **Table II: Data from (Stanworth *et al*, 2013a) and (Stanworth *et al*, 2014)**

Patient Group	Difference in proportion of patients who bled (therapeutic versus prophylactic)		Number of patients needed to be treated with prophylactic platelet transfusions to prevent 1 patient from bleeding within a 30 day period	
		95% CI		95% CI
All patients	8.4	0.3 to 16.5	12	6 to 333
Autologous stem cell transplant patients	2.3	-7.2 to 11.9	43	Not estimable as no significant difference between treatment arms
Chemotherapy/allogeneic stem cell transplant patients	20.0	5.6 to 34.5	5	3 to 18

7

8 **Table III: Examples of bleeding risks in haematology patients noted in both randomised controlled trials (RCTs) and**
9 **observational studies. (Data from RCTs on a specific bleeding risk have been placed before data from**
10 **retrospective studies.) Table updated from original (Estcourt, *et al* 2011)**
11

Haemorrhagic Risk	Study	Type of Study	No. of patients in study	Analysis	OR/ HR/ RR/ P value	Statistically significant
Baseline Characteristics – Female Sex	(Stanworth, <i>et al</i> 2015)	RCT	589	M	HR 1.33 (95% CI 1.10 to 1.61)	Y
	(Kim, <i>et al</i> 2004)	Retrospective, observational	792	M	RR 5.23 (95% CI 2.13to 12.89)	Y
	(De la Serna, <i>et al</i> 2008)	Prospective, observational	732	M	P = 0.16	N
Baseline Characteristics -Poor risk disease	(Nevo, <i>et al</i> 2007)	Retrospective, observational	480	M	OR 1.84 (95% CI 1.05 to 3.22)	Y
Baseline Characteristics – APL vs. other acute leukaemia	(Kim, <i>et al</i> 2004)	Retrospective, observational	792	M	RR 4.06 (95% CI 1.63 to 10.13)	Y
	(Chen, <i>et al</i> 2009)	Retrospective, observational	790	U	P = 0.001	Y

Treatment – BM HSCT within 100 d	(Friedmann, <i>et al</i> 2002)	Retrospective, observational	2942	M	OR 1.32 (95% CI 1.22 to 1.43)	Y
Treatment – Blood & BM HSCT	(Lawrence, <i>et al</i> 2001)	Prospective, interventional	141	M	r = 0.174 (major haemorrhage) P < 0.001 r = 0.054 (minor haemorrhage) P < 0.001	Y
Treatment – Allogeneic HSCT or chemotherapy vs. autologous HSCT	(Stanworth, <i>et al</i> 2015)	RCT	589	M	HR 1.43 (95% CI 1.19 to 1.72)	Y
Treatment - HSCT (Allogeneic vs. Autologous)	(Zumberg, <i>et al</i> 2002)	RCT	159	U	OR 2.8 (95% CI 1.1 to 7.7)	Y
	(Nevo, <i>et al</i> 2007)	Retrospective, observational	480	M	OR 2.29 (95% CI 1.11 to 4.77)	Y
	(Gerber, <i>et al</i> 2008)	Retrospective, observational	1514	M	OR 2.17 (95% CI 1.56 to 3.03)	Y
Infection - bacteraemia	(Friedmann, <i>et al</i> 2002)	Retrospective, observational	2942	M	OR 1.01 (95% CI 0.81 to 1.26)	N

Infection – clinical	(Webert, <i>et al</i> 2006)	Retrospective analysis of RCT*	255	M	RR 1.98 (95% CI 1.0 to 3.92)	Y
Infection – systemic	(Najima, <i>et al</i> 2009)	Retrospective, observational	622	M	HR 1.52 (95% CI 0.57 to 4.03)	N
Infection – sepsis	(Lawrence, <i>et al</i> 2001)	Prospective, interventional	141	M	$r = 0.024$; $P = 0.036^{\textcircled{a}}$	Y
Fever $\geq 38^{\circ}\text{C}$	(Stanworth, <i>et al</i> 2015)	RCT	469	M	HR 1.7 (95% CI 1.3 to 2.4)	Y
Fever – per 1°C rise in temp	(Friedmann, <i>et al</i> 2002)	Retrospective, observational	2942	M	OR 1.02 (95% CI 0.94 to 1.1)	N
Fever – not specified	(Lawrence, <i>et al</i> 2001)	Prospective, Interventional	141	M	$r = 0.072$; $P < 0.001^{\textcircled{a}}$	Y
Fever $> 38.5^{\circ}\text{C}$	(Webert, <i>et al</i> 2006)	Retrospective analysis of RCT*	255	M	RR 3.95 (95% CI 1.90 to 8.20)	Y
Fever associated with WHO grade 3&4 haemorrhage only					RR 1.62 (95% CI 0.44 to 5.91)	N

Medication – semi-synthetic penicillin	(Lawrence, <i>et al</i> 2001)	Prospective, Interventional	141	M	$r = 0.032$; $P = 0.014^{\textcircled{a}}$	Y
	(Friedmann, <i>et al</i> 2002)	Retrospective, Observational	2942	M	OR 0.94 (95% CI 0.80 to 1.09)	N
Medication – anti-fungal medication	(Webert, <i>et al</i> 2006)	Retrospective analysis of RCT*	255	M	RR 0.59 (95% CI 0.39 to 0.9)	Y
Medication - amphotericin	(Zumberg, <i>et al</i> 2002)	RCT	159	M	$P < 0.0001$	Y
	(Lawrence, <i>et al</i> 2001)	Prospective, Interventional	141	M	$r = 0.064$ (major haemorrhage) $P < 0.001$ $r = 0.114$ (minor haemorrhage) $P < 0.001$	Y
	(Friedmann, <i>et al</i> 2002)	Retrospective, Observational	2942	M	OR 0.97 (95% CI 0.84 to 1.13)	N
Medication - anticoagulants	(Gerber, <i>et al</i> 2008)	Retrospective, Observational	1514	M	OR 3.1 (95% CI 1.8 to 5.5)	Y
	(Friedmann, <i>et al</i> 2002)	Retrospective, Observational	2942	M	OR 0.94 (95% CI 0.09 to 10.12)	N

Laboratory parameters -Uraemia (urea > 17.9mmol/l)	(Friedmann, <i>et al</i> 2002)	Retrospective, Observational	2942	M	OR 1.64 (95% CI 1.40 to 1.92)	Y
Laboratory parameters – platelet count	(Lawrence, <i>et al</i> 2001)	Prospective, Interventional	141	M	r = -0.101 (major haemorrhage) P < 0.001 r = -0.144 (minor haemorrhage) P < 0.001	Y
Laboratory parameters - for every 1x10 ⁹ /L increase in platelet count	(Webert, <i>et al</i> 2006)	Retrospective analysis of RCT*	255	M	RR 0.96 (95% C.I. 0.93 to 0.98)	Y
Laboratory parameters – Platelet count 0 to 9x10 ⁹ /l vs. 40 to 49x10 ⁹ /l	(Friedmann, <i>et al</i> 2002)	Retrospective, Observational	2942	M	OR 1.14 (95% C.I. 0.89 to 1.46) (not transfused) OR 0.98 (95% C.I. 0.69 to 1.39) (transfused)	N

14

15

Other co-morbidities - Acute Graft vs Host Disease	(Zumberg, <i>et al</i> 2002)	RCT	159	M	P < 0.049	Y
	(Bleggi-Torres, <i>et al</i> 2002)	Retrospective, Observational	180	U	OR 0.86 (95% CI (0.45 to 1.62)	N
	(Gerber, <i>et al</i> 2008)	Retrospective, Observational	1514	M	OR 2.4 (95% CI 1.8 to 3.3)	Y
	(Najima, <i>et al</i> 2009)	Retrospective, Observational	622	M	HR 1.41 (95% CI 1.01 to 1.97)	Y
Other co-morbidities – Veno-occlusive disease	(Zumberg, <i>et al</i> 2002)	RCT	159	M	P < 0.033	Y
	(Gerber, <i>et al</i> 2008)	Retrospective, Observational	1514	M	OR 2.2 (95% CI 1.4 to 3.6)	Y
	(Najima, <i>et al</i> 2009)	Retrospective, Observational	622	M	HR 2.63 (95% CI 0.77 to 9.00)	N
Other co-morbidities Splénomegaly	(Lawrence, <i>et al</i> 2001)	Prospective, Interventional	141	M	r = 0.055; P < 0.001 [@]	Y

16

17

Other co-morbidities Recent history of severe haemorrhage (≤5d)	(Friedmann, <i>et al</i> 2002)	Retrospective, Observational	2942	M	OR 6.72 (95% CI 5.53 to 8.18)	Y
--	-----------------------------------	---------------------------------	------	---	-------------------------------	---

18 APL, acute promyelocytic leukaemia; BM = bone marrow; CI = confidence interval; HR = hazards ratio; HSCT = haemopoietic stem
19 cell transplantation; M = multivariate analysis; N = no; OR = odds ratio; RCT = randomised controlled trial; RR = relative risk; U =
20 univariate analysis; Y = yes

21 * Data from Rebullà et al, 1997

22 @Minor haemorrhage. No association with major haemorrhage

23

24

25 **Table IV: Bone Marrow Aspirate and/or Trepine Biopsy. Adverse bleeding events reported in UK confidential**
 26 **morbidity/mortality reports**

Study	Study period	No. of hospitals	No. of procedures	No. of haemorrhages	Risk Factors for haemorrhage									
					Thrombocytopenia (< 50x 10 ⁹ /l)	Aspirin	Heparin	Warfarin	DIC	Other	Obesity	Renal Impairment	MDS	MPN
(Bain 2003)	1995 to 2000	34	39,264	14	1	3	0	1	2	0	2	NR	2	9
	2001	60	19,332											
(Bain 2004)	2002	53	13,506	10	3	4	1	1	0	0	1	2	1	5
(Bain 2005)	2003	63	19,259	11	2	3	0	1	0	1*	1	0	1	5
(Bain 2006)	2004	120	20,323	9	0	3	0	0	0	1†	0	0	1	3
Devalia**	2006	49	15,388	8	1	3	0	1	0	0	3	0	0	4
Devalia**	2007	NR	NR	8	1	0	0	1	1	1†	0	0	0	1
Devalia**	2008	NR	NR	11	3	4	0	1	1	1†	3	0	1	2
(Devalia 2013)	2011	45	9,295	9	6	0	0	0	0	1‡	1	0	2	0

27 DIC = disseminated intravascular coagulation; MDS = myelodysplastic syndromes; MPN = myeloproliferative neoplasm; No. = number; NR =
 28 not reported

- 29 * Patient had von Willebrand disease
- 30 † Patient had deranged coagulation associated with myeloma
- 31 ‡ Patient had alcohol related problems
- 32 ** personal communication with Dr Vinod Devalia
- 33

34 **Table V: Observational studies reporting bleeding outcomes after insertion of venous central line insertions**

35

Study	Study duration	Type of study	Number of participants (procedures)	Type of patient	Definition of thrombocytopenia	Number of procedures with thrombocytopenia	Definition of coagulopathy	Number of procedures with thrombocytopenia and/or coagulopathy	Number of procedures with bleeding	Number of procedures with major bleeding	Number of procedures with thrombocytopenia and major bleeding (major bleeding)
(Carr, <i>et al</i> 2006)	Jan'93 to Jun'03	Observational Retrospective	115 (NR)	Acute leukaemia	NR	NR*	NR	NR	0	0	0 (0)
(Mumtaz, <i>et al</i> 2000)	Sep'97 to Aug'99	Observational Retrospective	1,825 (2,010)	Haematological malignancy; solid tumours; ICU; renal failure	< 150	NR	INR > 1.3 aPTT > 37s	88	4	0	3 (0)
(Foster, <i>et al</i> 1992)	Jan'88 to Dec'88	Observational Retrospective	40 (259)	Liver disease	< 80	122	PT < 40% aPTT ≥ 77s	122	0	0	0 (0)
(Barrera, <i>et al</i> 1996)	Jul'90 to Sep'93	Observational Prospective	115 (115)	Haematological malignancy; solid tumours	≤ 50	108	Prolonged PT and aPTT	8	23	0	20 (0)

(Cavanna, <i>et al</i> 2010)	Dec'00 to Jan'09	Observational Prospective	1,660 (1,978)	Haematological malignancy; solid tumours	≤ 50	116	NR	NR	4†	0	NR
(Della Vigna, <i>et al</i> 2009)	Sep'01 to Aug'08	Observational Retrospective	157 (239)	Haematological malignancy; solid tumours	≤ 50	NR	PT or aPTT > 2.2 x normal	45	1	0	0 (0)

36

37

(Doerfler, <i>et al</i> 1996)	Oct'92 to Oct'93	Observational	76 (104)	Haematological malignancy; solid tumours; liver transplant; other	≤ 50	41	PT or aPTT > 1.5 x normal	76	7	0	7 (0)
(Fisher and Mutimer 1999)	Jan'96 to Sep'97	Observational Prospective	283 (658)	Liver disease	≤ 50	146	INR > 1.5	NR	62	1	19 (0)
(Haas, <i>et al</i> 2010)	Jul'01 to Jul'08	Observational Retrospective	2,514 (3,170)	Haematological malignancy; renal failure; other	≤ 50	344	INR ≥ 1.5	626	3**	1	0 (0)
(Hong Pheng Loh and Hon Chui 2007)	Jan'02 to Dec'04	Observational Retrospective	80 (80)	Acute leukaemia	< 50	22	NR	NR	2	0	0 (0)
(Ray and Shenoy 1997)	Oct'95 to Sep'96	Observational Prospective	105 (112)	NR	< 50	37	NR	NR	4	1	0 (0)
(Tercan, <i>et al</i> 2008)	Apr'02 to Jul'06	Observational	133 (133)	NR	≤ 50	38	INR ≥ 1.5 or aPTT $\geq 50s$	90	8	0	NR (0)

(Tomoyose, <i>et al</i> 2013)	Jan'03 to Feb'09	Observational Retrospective	72 (108)	Haematological malignancies	≤ 50	67	NR	NR	5	0	4 (0)
(Weigand, <i>et al</i> 2009)	Oct'05 To Apr'07	Observational Prospective	196 (NR)	Liver disease; ICU; renal failure; haematological malignancy	≤ 50	19	INR > 1.5	51	NR	34	NR (1)
(Zeidler, <i>et al</i> 2011)	'01 to '07	Observational Retrospective	193 (604)	Acute leukaemia	≤ 50	173	INR > 1.4	NR	8**	0	5 (0)

38

(Duffy and Coyle 2013)	Jan'99 to Jul'11	Observational Retrospective	55 (57)	TTP	≤ 30	29	NR	NR	17	0	10 (0)
(Napolitano, <i>et al</i> 2013)	Jan'99 to Jun'09	Observational Retrospective	431	Haematological disorders	< 30	39	NR	NR	8	0	1 (0)

39 aPTT = activated partial thromboplastin time; ICU = intensive care unit; INR = international normalised ratio; NR = not reported; PT = prothrombin time; TTP = thrombotic thrombocytopenic purpura

40 * Median platelet count $72 \times 10^9/l$, range 10 to 347

41 † Patients all had puncture of artery causing a haematoma

42 **Bleeding in this study is defined as bleeding that required at least pressure at the insertion site to stop bleeding

43 Major bleeding defined as requiring a red cell transfusion to treat bleeding; haemothorax; significant fall in haemoglobin concentration

44

45 **Table VI: Onset of action and half-life of anti-platelet agents**

Anti-platelet agent	Onset of action after oral administration	Plasma half-life of active drug or metabolite	Time from drug administration when any platelet transfusion given will have reduced efficacy (active drug or metabolite still present in plasma at >25% peak drug levels)	Time to normal platelet function/coagulation activity after discontinuation of drug
Abciximab	Not applicable	30 minutes	1 hour	24 to 48 hours
Aspirin	< 1 hour 3 to 4 hours with enteric-coated preparations	15 to 20 minutes	2 hours 4 to 5 hours with enteric-coated preparations	5 to 7 days
Clopidogrel	4 to 8 hours	30 minutes	12 hours	5 to 7 days

Dipyridamole	1.25 hours	2 to 3 hours	5 to 7 hours	24 hours
Eptifbatide	Not applicable	2.5 hours	4 hours	4 to 8 hours
Ibuprofen	45 minutes to 2 hours	2 hours	6 hours	24 hours
Prasugrel	2 to 4 hours	7 hours	16 to 18 hours	5 to 7 days
Ticagrelor	1.5 hours	8 to 12 hours	18 to 26 hours	3 to 5 days
Tirofiban	Not applicable	1.5 hours	4 hours	4 to 8 hours

47 **Table VII: Studies that assessed the use of platelet transfusions in patients with autoimmune or drug-induced immune**
 48 **thrombocytopenia**

49

Study	Study Period	No. of Pts	Sex	Type	Median Age (Range)	Bleeding	Corticosteroids at Time of Plt Tx	Treatment	Post-Rx Platelet Count	Clinical Response
Prospective, interventional, Uncontrolled										
(Baumann, et al 1986)	NR	6	M (2) F (4)	Idiopathic (2 previous Rx with steroids)	56.5 (32 to 85)	1 pt had menorrhagia	1	8 units plt tx Then 400 mg/kg IVIG + 8 units plt tx	Plt increment after IVIG + plt tx (median: $68 \times 10^9/L$; range: 20-130); time to baseline >60 hrs Plt tx alone (median: 31; range: 18-33) Median time to baseline: 6hrs	1 pt: menorrhagia responded to IVIG + plt tx, not plt tx alone
(Salama, et al 2008)	NR	10	M (3) F (7)	Chronic, refractory	48 (24 to 79)	Severe bleeding (5) GI bleed (2)	4	1 unit every 30 min	Plt count increased to $>80 \times 10^9/L$ in all cases; returned to	Bleeding stopped in all cases

								3 to 7 apheresis units (2.7×10^{11} plts per unit)	baseline in 7/10 by 48 hrs	
--	--	--	--	--	--	--	--	--	-------------------------------	--

50

51

Retrospective, Observational										
(Carr, et al 1986)	Jan 1981 - Jul 1984	11	M (4) F (7)	Idiopathic (6) Quinidine induced (5)	71 (25 to 88)	CNS (2) Epistaxis (6) Upper GI (2) Petechiae alone (1)	Idiopathic (6) Quinidine (1)	Plt Tx. Median/pt 2 (Range 1 to 6) Pooled (28 plt tx) Apheresis (3 plt tx)	7/11 (13/31 tx) received "successful tx" = increment $\geq 20 \times 10^9/L$ within 5 hrs of tx; 5/31 tx plt count still higher at 24 hrs	Idiopathic (1) bleeding improved despite poor plt increment Quinidine (2) bleeding decreased or stopped
(Chandramouli and Rodgers 2000)	NR	2	F (2)	Autoimmune associated	NR (20 to 71)	Large retroperitoneal bleed (1)	2	IVIg continuous 24-hr infusion + concomitant apheresis plt tx (1/2 pheresis pack every 4 hrs)	Plt count $>100 \times 10^9$	NR
(Spahr and Rodgers 2008)	Jan 2000 - Dec 2005	40	M (23) F (17)	Idiopathic (9 previously refractory to IVIG alone)	52 (19 to 87)	33 pts	38 (usually 1 mg/kg/day)	IVIg (1 g/kg) continuous infusion over 24 hrs	51% achieved plt count $>50 \times 10^9/L$ by 24 hrs	Bleeding controlled initially in all pts regardless of plt count

								Plt apheresis unit (1 unit every 8 hrs)		
--	--	--	--	--	--	--	--	---	--	--

52

53 CNS = central nervous system; F = female; GI = gastrointestinal; IVIG = intravenous immune globulin; ITP = autoimmune thrombocytopenia; M = male; NR =

54 not reported; plt = platelet; pt = patient; pts = patients; Rx = treatment; tx = transfusion.

55

56

57 **Table VIII: Studies that reported the use of platelet transfusions in patients with thrombotic thrombocytopenic purpura**
 58 **and mortality in those receiving or not receiving platelet transfusion**
 59

Study	Type of Study	Study Period	No. of centres	Country	Number of Patients	Number Received Plasma Therapy	Number Received Platelet Tx	Mortality§ Plt Tx	Thrombosis Plt Tx	Mortality§ Non-Plt Tx	Thrombosis Non-Plt Tx	Definition of TTP
(Rutkow 1978)	Unclear from the text that only one of the patients received platelet transfusions. One patient received plt Tx and survived.											
(Taft 1979)	Unclear	NR	Single centre	USA	4	4 TPE	3	1	NR	0	NR	NR
(Gottschall, et al 1981)	Observational; Retrospective	1974 to 1979	Single centre	USA	11	11 WBE 3 TPE	8 (inc 4 FWB)	3	NR	0	NR	CNS abnormalities MAHA
(Byrnes 1981)	Observational; retrospective	NR	Multicentre (NR)	USA, S. America	18	18 TPE	1	0	NR	5	NR	MAHA
(Liu, et al 1986)	Observational; Retrospective	NR	Single centre	USA	8	8 TPE	7	0	NR	1	NR	CNS abnormalities, MAHA, thrombocytopenia
(Gordon, et al 1987)					15		2	1		3		

(Rose and Eldor 1987)*	Observational; Retrospective	1977 to 1985	Multicentre (15)	Israel & USA	38	37	14	5	NR	1	NR	Plt count < 100 x 10 ⁹ /l, MAHA, neurology (major criteria) Fever, renal abnormalities supportive
(McCarthy, et al 1994)	Observational; Retrospective	1973 to 1994	Single centre	USA	55	55 TPE	25	13	NR	2	NR	NR
(Goodnough, et al 1994)	Observational; Retrospective	NR§	Single centre	USA	39	39	22	10	NR	3	NR	Plt count < 150 x 10 ⁹ /l, MAHA

60

(Egerman, et al 1996)	Observational; Retrospective	Jan 1988 to Feb 1996	Single centre	USA	11	8 TPE 3 HPI	5	1	NR	1	NR	Plt count < 100 x 10 ⁹ /l, MAHA
(Sarode, et al 1997)	Observational; Retrospective	Jan 1985 to Jun 1995	Single centre	USA	70	68 TPE	4	0	NR	10 (2 died before TPE)	NR	Plt count < 100 x 10 ⁹ /l, MAHA, neurological symptoms and/or renal impairment

(Coppo, <i>et al</i> 2003) *†	Observational; Retrospective	1989 to 2001	Single centre	France	37	19 HPI 18 TPE	8	1	NR	4	NR	Plt count < 100 x 10 ⁹ /l & MAHA with no known cause
(Shamseddine, <i>et al</i> 2004)*	Observational; Retrospective	1980 to 2003	Single centre	Lebanon	47	40 TPE 7 HPI	4	2	NR	7	NR	Plt count < 100 x 10 ⁹ /l & MAHA with no known cause
(Swisher, <i>et al</i> 2009)* ‡	Observational; Retrospective	Nov 1995 to Dec 2007	Single centre	USA	54	49 TPE	33	8 (2 died before TPE)	5 died	5 (3 died before TPE)	4 died	Plt count < 100 x 10 ⁹ /l, MAHA

61

62

63 **Table IX: Data from SHOT Annual Report 2013 (Bolton-Maggs, *et al* 2014)**

64

Adverse Event	Estimated Risk per Unit of Platelets in the UK
Febrile non-haemolytic transfusion reaction (excluding mild)	1 in 6,000
Allergic (excluding mild)	1 in 6,000
Bacterial sepsis	Rare since introduction of bacterial screening 2010
Transfusion-related acute lung injury (TRALI)	Less than 1 in 1,000,000
Haemolysis from ABO incompatible plasma	1 in 600,000
Hepatitis B infection	1 in 1,000,000
Hepatitis C infection	1 in 30,000,000
Human immunodeficiency (HIV) infection	1 in 7,000,000

65

66

67

68 **Table X: Platelet transfusion in times of shortage**

69

Category 1	Category 2	Category 3
<p>Massive haemorrhage & Critical care</p> <p>Massive transfusion for any condition including obstetrics, emergency surgery and trauma, with on-going bleeding, maintain platelet count > 50 x 10⁹/L. Aim for platelet count >100 x 10⁹/L if multiple trauma or CNS trauma</p> <p>Bleeding in the presence of acute DIC, maintain >50x 10⁹/L.</p>	<p>Critical care</p> <p>Patients resuscitated following massive transfusion with no on-going active bleeding, maintain platelet count > 50 x 10⁹/L</p> <p>Surgery Urgent but not emergency surgery for a patient requiring platelet support</p> <p>Transfusion triggers for invasive procedures</p> <p>According to BCSH guideline</p>	<p>Surgery</p> <p>Elective, non-urgent surgery likely to require platelet support for thrombocytopenia or congenital/ acquired platelet defects</p>
<p>Bone marrow failure</p> <p>Active bleeding associated with severe thrombocytopenia or functional platelet defects</p> <p>Immune thrombocytopenia if serious/life-threatening bleeding</p>	<p>Bone marrow failure</p> <p>All other indications except those in category 1 or 3</p>	<p>Bone marrow failure</p> <p>Prophylactic transfusion of stable patients following autologous stem cell transplant.</p>

<p>Neonates For neonatal alloimmune thrombocytopenia or severe thrombocytopenia in an otherwise well neonate, platelet transfusions are required when the platelet count falls to between 20 –30 x 10⁹/L. Higher target levels should be maintained if extremely low birth weight or unwell/bleeding or Intra-cranial haemorrhage suspected/confirmed.</p>		
--	--	--

70 DIC, disseminated intravascular coagulation; CNS = central nervous system

71 **Platelet transfusion: principles, risks, alternatives and best practice**

72

73 Platelet transfusions are an essential component in the management of selected patients with
74 thrombocytopenia. However they need to be used judiciously as they are a limited resource and are not risk
75 free.

76

77 **Classification of conditions which may require platelet transfusion**

78 • Bone marrow failure (BMF). Reversible associated with treatable disease and/or chemotherapy and
79 occasionally chronic (irreversible) BMF e.g. myelodysplastic syndromes

80 • Thrombocytopenia in critical care

81 • Peripheral platelet consumption/destruction e.g. disseminated intravascular coagulation and immune
82 thrombocytopenia

83 • Abnormal platelet function. Inherited or acquired disorders e.g. anti-platelet agents, uraemia

84 •

85 **Principles of platelet transfusion**

86

87 Platelets are used in 3 distinct situations –

88 - **Prophylactic (WHO bleeding grade 0 or 1)** to prevent bleeding

89 o Routine use in non-bleeding patients

90 o In the presence of additional risk factors for bleeding e.g. sepsis or abnormalities of haemostasis

91 - **Pre-procedure** to prevent bleeding expected to occur during surgery/invasive procedure

92 - **Therapeutic (WHO bleeding grade ≥ 2)** to treat active bleeding

93 **Contraindications to platelet transfusion unless life-threatening haemorrhage**

94 • Thrombotic Thrombocytopenic Purpura (TTP)

95 **Risks associated with platelet transfusion**

96

Reduced effectiveness of future platelet transfusion

Alloimmunisation

Adverse effects

Febrile non-haemolytic transfusion reactions (FNHTR) and allergic reactions (including mild), reported incidence up to 3%. May require investigation to exclude other causes and prolong hospital stay.

Estimated risk of moderate/severe reactions and infection transmission

FNHTR	1 in 6,000
Allergic	1 in 6,000
Haemolysis	1 in 600,000
Bacterial sepsis	Rare since bacterial screening 2010
Transfusion Related Acute Lung Injury	Less than 1 in 1,000,000
Hepatitis B infection	1 in 1,000,000

Hepatitis C infection	1 in 30,000,000
HIV infection	1 in 7,000,000

97 **Possible alternatives to platelet transfusion**

Apply surface pressure after superficial procedures and correct surgical causes for bleeding

Surgical patients expected to have at least a 500 ml blood loss, use tranexamic acid (TXA) unless contraindicated

Trauma patients who are bleeding/ at risk of bleeding, early use of TXA

Severe bleeding replace fibrinogen if plasma concentration less than 1.5 g/L

Anti-platelet agents - discontinue or if urgent procedure/bleeding use TXA if risk/benefit would support

Uraemia with bleeding or preprocedure – dialyse, correct anaemia, consider desmopressin

Inherited platelet function disorders - specialist haematology advice required. Consider desmopressin

Chronic BMF with bleeding – consider TXA

98 **Prior to prescribing a platelet transfusion consider –**

- 99 • What are the indications for transfusion in this patient?
- 100 • Are there alternatives which could be used in preference to platelet transfusion?
- 101 • Has the indication been documented in the patients' record and on the transfusion request form?
- 102 • Has the patient consented to receive a platelet transfusion?

Indications for use of platelet transfusion in adults

Indication	Transfusion indicated (threshold)/not indicated
<p>Prophylactic use (No bleeding or WHO grade 1)</p> <p>One adult dose required</p> <ul style="list-style-type: none"> - Reversible bone marrow failure (BMF) including allogeneic stem cell transplant - Reversible BMF with autologous stem cell transplant (consider no prophylaxis) - Critical illness - Chronic BMF receiving intensive therapy - Chronic BMF to prevent persistent bleeding of grade ≥ 2 	<p>10 x 10⁹/L</p> <p>10 x 10⁹/L</p> <p>10 x 10⁹/L</p> <p>10 x 10⁹/L</p> <p>Count variable</p>
<ul style="list-style-type: none"> - Chronic stable BMF, abnormal platelet function, platelet consumption/ destruction (e.g. DIC, TTP) or immune thrombocytopenia (ITP, HIT, PTP) 	Not indicated
<p>Prophylactic use in the presence of risk factors for bleeding (e.g. sepsis, antibiotic treatment, abnormalities of haemostasis)</p> <ul style="list-style-type: none"> - Reversible/chronic bone marrow failure/critical care 	10 to 20 x 10 ⁹ /L
<ul style="list-style-type: none"> - Abnormal platelet function, platelet consumption/destruction, immune thrombocytopenia 	Not indicated
<p>Platelet transfusion preprocedure</p> <ul style="list-style-type: none"> - Central venous catheter (CVC) excluding PICC line - Lumbar puncture - Percutaneous liver biopsy - Major surgery - Epidural anaesthesia, insertion & removal - Neurosurgery or ophthalmic surgery involving the posterior segment of the eye 	<p>20 x 10⁹/l</p> <p>40 x 10⁹/l</p> <p>50 x 10⁹/l</p> <p>50 x 10⁹/l</p> <p>80 x 10⁹/l</p> <p>100 x 10⁹/l</p>
<ul style="list-style-type: none"> Bone marrow aspirate or trephine biopsies, PICC line insertion, traction removal of central venous catheters (CVCs), cataract surgery 	Not indicated
Specific clinical conditions – see below for indications	
<p>Therapeutic use (Bleeding WHO grade 2 or above)</p> <ul style="list-style-type: none"> - Severe bleeding - Multiple trauma, brain or eye injury, spontaneous intracerebral haemorrhage - Bleeding (WHO grade ≥ 2) but not severe 	<p>50 x 10⁹/L</p> <p>100 x 10⁹/L</p> <p>30 x 10⁹/L</p>
<ul style="list-style-type: none"> - Bleeding in specific clinical conditions – see below for indications 	

Specific clinical conditions

Platelet function defect

Count variable

- *Congenital* – Preprocedure or therapeutic use. When alternative therapy contraindicated or ineffective. Directed by specialist in haemostasis.

- *Acquired* (anti-platelet agents, uraemia)- only indicated for severe bleeding

Disseminated intravascular bleeding Preprocedure or therapeutic use. Consider threshold counts above but may not be achievable and individual case review required.

Use preprocedure / therapeutic threshold as guide

Thrombotic thrombocytopenic purpura Platelet transfusion contraindicated unless *life-threatening bleeding*

Count variable

Immune thrombocytopenia (ITP, HIT, PTP). Pre-procedure when other therapy ineffective/procedure urgent or to treat severe bleeding. Consider threshold counts above but may be unachievable or unnecessary and individual case review required.

Use preprocedure / therapeutic threshold as guide

104

105 Disseminated intravascular coagulation (DIC), peripherally inserted central catheter (PICC),
106 thrombotic thrombocytopenic purpura (TTP), primary immune thrombocytopenia (ITP), heparin-
107 induced thrombocytopenia (HIT), post-transfusion purpura (PTP)

108

109