

Guidelines for the Use of Platelet Transfusions

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,.

Corresponding Author:

Dr Janet Birchall: c/o BCSH Secretary, British Society for Haematology, 100

White Lion Street, London N1 9PF, UK. E-mail: bcsh@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).

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52 **SCOPE**

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

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64 **Methodology**

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

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

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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 (Crichton, *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**

- 149 • **Whenever possible use a procedure/equipment associated with the**
150 **lowest bleeding risk. Apply local measures, such as compression, to**
151 **reduce the risk of bleeding post-procedure. (1C)**
- 152 • **Do not give platelet transfusions routinely prior to:**
 - 153 ○ **bone marrow aspirate or trephine biopsy (1B)**
 - 154 ○ **peripherally inserted central catheters (PICCs) (2C)**
 - 155 ○ **traction removal of tunnelled CVCs (2C)**
 - 156 ○ **cataract surgery (2C)**
- 157 • **Consider performing the following procedures above the platelet**
158 **count threshold indicated –**
 - 159 ○ **venous central lines (both tunnelled and un-tunnelled),**
160 **inserted by experienced staff using ultrasound guidance**
161 **techniques, when the platelet count is > 20x10⁹/L. (1B)**
 - 162 ○ **lumbar puncture when the platelet count is ≥ 40x10⁹/L. (2C)**
 - 163 ○ **insertion/removal of epidural catheter when the platelet**
164 **count is ≥80x10⁹/L. (2C)**
 - 165 ○ **major surgery - when the platelet count is > 50x10⁹/L (1C)**
 - 166 ○ **neurosurgery or ophthalmic surgery involving the posterior**
167 **segment of the eye when the platelet count is > 100x10⁹/L**
168 **(1C)**
 - 169 ○ **percutaneous liver biopsy when the platelet count is > 50 x**
170 **10⁹/L (2B). Consider trans-jugular biopsy if the platelet count**
171 **is below this level (2B)**
- 172 • **Prior to renal biopsy ensure potential risk factors for bleeding are**
173 **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.

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300 **Should Prophylactic Platelet Transfusions Be Given Routinely?**

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

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318 **What Platelet Transfusion Threshold Should Be Used?**

319 A systematic review identified three RCTs that compared different platelet
 320 transfusion thresholds (Estcourt, *et al* 2012a). Two compared a threshold of
 321 $20 \times 10^9/L$ vs. $10 \times 10^9/L$, whereas the third compared a threshold of $30 \times 10^9/L$
 322 vs. $10 \times 10^9/L$. A fourth RCT excluded from the systematic review compared a
 323 threshold of $20 \times 10^9/L$ vs. $10 \times 10^9/L$ (Zumberg, *et al* 2002). A meta-analysis of

all four studies (658 patients) showed that the $10 \times 10^9/L$ 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 ($1.1 \times 10^{11}/m^2$) and standard dose ($2.2 \times 10^{11}/m^2$) and between standard dose and high dose platelet transfusions ($4.4 \times 10^{11}/m^2$). 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 3×10^{11} 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).

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

403

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

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

412

413 **Recommendations**

- 414 • **A no prophylaxis platelet transfusion strategy should be used for**
415 **patients with asymptomatic chronic bone marrow failure (including**
416 **those taking low dose oral chemotherapy or azacitidine) (2B)**
- 417 • **Prophylactic platelet transfusion should be given to patients with**
418 **chronic bone marrow failure receiving intensive treatment (1B)**
- 419 • **Patients with chronic bleeding of WHO grade 2 or above require**
420 **individual management according to the severity of their symptoms**
421 **and signs. A strategy of prophylaxis (e.g. twice a week) should be**
422 **considered (2C)**

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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 $60 \times 10^9/L$ (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, Liumbruno, *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 (Olmes, *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).

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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.

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1646

1647 **TABLES**

1648 **Table I: Modified WHO bleeding score (Stanworth *et al*, 2013a)**

1649

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

1650 * visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmological
1651 consultation

1652 **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

1653

1654 **Table III: Examples of bleeding risks in haematology patients noted in both randomised controlled trials (RCTs) and**
 1655 **observational studies. (Data from RCTs on a specific bleeding risk have been placed before data from**
 1656 **retrospective studies.) Table updated from original (Estcourt, *et al* 2011)**
 1657

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 –	(Kim, <i>et al</i> 2004)	Retrospective, observational	792	M	RR 4.06 (95% CI 1.63 to 10.13)	Y

APL vs. other acute leukaemia	(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

1658

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 [@]	Y
Fever ≥ 38°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 [@]	Y
Fever > 38.5°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

1659

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 $1 \times 10^9/L$ 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 $9 \times 10^9/l$ vs. 40 to $49 \times 10^9/l$	(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

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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 Splenomegaly	(Lawrence, <i>et al</i> 2001)	Prospective, Interventional	141	M	r = 0.055; P < 0.001 [@]	Y

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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
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1664 APL, acute promyelocytic leukaemia; BM = bone marrow; CI = confidence interval; HR = hazards ratio; HSCT = haemopoietic stem
 1665 cell transplantation; M = multivariate analysis; N = no; OR = odds ratio; RCT = randomised controlled trial; RR = relative risk; U =
 1666 univariate analysis; Y = yes
 1667 * Data from Rebulla et al, 1997
 1668 @Minor haemorrhage. No association with major haemorrhage
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1671 **Table IV: Bone Marrow Aspirate and/or Trepine Biopsy. Adverse bleeding events reported in UK confidential**
 1672 **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

1673 DIC = disseminated intravascular coagulation; MDS = myelodysplastic syndromes; MPN = myeloproliferative neoplasm; No. = number; NR =

1674 not reported

1675 * Patient had von Willebrand disease

1676 † Patient had deranged coagulation associated with myeloma

1677 ‡ Patient had alcohol related problems

1678 ** personal communication with Dr Vinod Devalia

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1680 **Table V: Observational studies reporting bleeding outcomes after insertion of venous central line insertions**

1681

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 thrombocytopenic 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)

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(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 ≥ 50 s	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)

(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)

1685 aPTT = activated partial thromboplastin time; ICU = intensive care unit; INR = international normalised ratio; NR = not reported; PT = prothrombin time; TTP = thrombotic thrombocytopenic purpura

1686 * Median platelet count $72 \times 10^9/l$, range 10 to 347

1687 † Patients all had puncture of artery causing a haematoma

1688 **Bleeding in this study is defined as bleeding that required at least pressure at the insertion site to stop bleeding

1689 Major bleeding defined as requiring a red cell transfusion to treat bleeding; haemothorax; significant fall in haemoglobin concentration

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1691 **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
Eptifibatide	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

1692	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

1693 **Table VII: Studies that assessed the use of platelet transfusions in patients with autoimmune or drug-induced immune**
 1694 **thrombocytopenia**

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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 3 to 7 apheresis units (2.7×10^{11} plts per unit)	Plt count increased to $>80 \times 10^9/L$ in all cases; returned to baseline in 7/10 by 48 hrs	Bleeding stopped in all cases

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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 Plt apheresis unit (1 unit every 8 hrs)	51% achieved plt count $>50 \times 10^9/L$ by 24 hrs	Bleeding controlled initially in all pts regardless of plt count

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CNS = central nervous system; F = female; GI = gastrointestinal; IVIG = intravenous immune globulin; ITP = autoimmune thrombocytopenia; M = male; NR = not reported; plt = platelet; pt = patient; pts = patients; Rx = treatment; tx = transfusion.

1703 **Table VIII: Studies that reported the use of platelet transfusions in patients with thrombotic thrombocytopenic purpura**
 1704 **and mortality in those receiving or not receiving platelet transfusion**
 1705

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

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(Egerman, <i>et al</i> 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, <i>et al</i> 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

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1709 **Table IX: Data from SHOT Annual Report 2013 (Bolton-Maggs, *et al* 2014)**

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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

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1714 **Table X: Platelet transfusion in times of shortage**

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Category 1	Category 2	Category 3
<p>Massive haemorrhage & Critical care Massive transfusion for any condition including obstetrics, emergency surgery and trauma, with on-going bleeding, maintain platelet count $> 50 \times 10^9/L$. Aim for platelet count $> 100 \times 10^9/L$ if multiple trauma or CNS trauma</p> <p>Bleeding in the presence of acute DIC, maintain $> 50 \times 10^9/L$.</p>	<p>Critical care Patients resuscitated following massive transfusion with no on-going active bleeding, maintain platelet count $> 50 \times 10^9/L$</p> <p>Surgery Urgent but not emergency surgery for a patient requiring platelet support</p> <p>Transfusion triggers for invasive procedures According to BCSH guideline</p>	<p>Surgery Elective, non-urgent surgery likely to require platelet support for thrombocytopenia or congenital/ acquired platelet defects</p>
<p>Bone marrow failure Active bleeding associated with severe thrombocytopenia or functional platelet defects</p> <p>Immune thrombocytopenia if serious/life-threatening bleeding</p>	<p>Bone marrow failure All other indications except those in category 1 or 3</p>	<p>Bone marrow failure 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 $20 - 30 \times 10^9/L$. Higher target levels should be maintained if extremely low birth weight or unwell/bleeding or Intra-cranial haemorrhage suspected/confirmed.</p>		

1716 DIC, disseminated intravascular coagulation; CNS = central nervous system

Platelet transfusion: principles, risks, alternatives and best practice

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

Classification of conditions which may require platelet transfusion

- Bone marrow failure (BMF). Reversible associated with treatable disease and/or chemotherapy and occasionally chronic (irreversible) BMF e.g. myelodysplastic syndromes
- Thrombocytopenia in critical care
- Peripheral platelet consumption/destruction e.g. disseminated intravascular coagulation and immune thrombocytopenia
- Abnormal platelet function. Inherited or acquired disorders e.g. anti-platelet agents, uraemia
-

Principles of platelet transfusion

Platelets are used in 3 distinct situations –

- **Prophylactic (WHO bleeding grade 0 or 1)** to prevent bleeding
 - o Routine use in non-bleeding patients
 - o In the presence of additional risk factors for bleeding e.g. sepsis or abnormalities of haemostasis
- **Pre-procedure** to prevent bleeding expected to occur during surgery/invasive procedure
- **Therapeutic (WHO bleeding grade ≥ 2)** to treat active bleeding

Contraindications to platelet transfusion unless life-threatening haemorrhage

- Thrombotic Thrombocytopenic Purpura (TTP)

Risks associated with platelet transfusion

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

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

Prior to prescribing a platelet transfusion consider –

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

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Indications for use of platelet transfusion in adults

Indication	Transfusion indicated (threshold)/not indicated
Prophylactic use (No bleeding or WHO grade 1) One adult dose required <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 	10 x 10 ⁹ /L 10 x 10 ⁹ /L 10 x 10 ⁹ /L 10 x 10 ⁹ /L Count variable
<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
Prophylactic use in the presence of risk factors for bleeding (e.g. sepsis, antibiotic treatment, abnormalities of haemostasis) <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
Platelet transfusion preprocedure <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 	20 x 10 ⁹ /l 40 x 10 ⁹ /l 50 x 10 ⁹ /l 50 x 10 ⁹ /l 80 x 10 ⁹ /l 100 x 10 ⁹ /l
<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	
Therapeutic use (Bleeding WHO grade 2 or above) <ul style="list-style-type: none"> - Severe bleeding - Multiple trauma, brain or eye injury, spontaneous intracerebral haemorrhage - Bleeding (WHO grade ≥ 2) but not severe 	50 x 10 ⁹ /L 100 x 10 ⁹ /L 30 x 10 ⁹ /L
<ul style="list-style-type: none"> - Bleeding in specific clinical conditions – see below for indications 	

Specific clinical conditionsPlatelet function defect

- *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.

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

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.

Count variable

Use preprocedure / therapeutic threshold as guide

Count variable

Use preprocedure / therapeutic threshold as guide

1750

1751 Disseminated intravascular coagulation (DIC), peripherally inserted central catheter (PICC),
1752 thrombotic thrombocytopenic purpura (TTP), primary immune thrombocytopenia (ITP), heparin-
1753 induced thrombocytopenia (HIT), post-transfusion purpura (PTP)

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