bjh guideline

Guidelines for the use of platelet transfusions

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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 in the UK aged over 70 years 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 4200 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*, 2012a), 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; Greeno *et al*, 2007; Pendry & Davies, 2011; Jones *et al*, 2013; Charlton *et al*, 2014). 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with a 35% reduction in active donors from 1·893 million in 2000 to 1·231 million in 2015 (NHS Blood & Transplant, unpublished data).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 British Committee for Standards in Haematology (BCSH) platelet use guideline (British Committee for Standards in Haematology Blood Transfusion Task Force 2003). 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; Advisory Committee on the Safety of Blood, Tissues and Organs (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 World Health Organization

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(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 [Audit tool (Appendix S1)] 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.bcshguidelines.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,b,c), or that have been recently published (Hedges *et al*, 2007; van Veen *et al*, 2010; Lieberman *et al*, 2013; Pavenski *et al*, 2013; Wardrop *et al*, 2013; Kumar *et al*, 2014; Vassallo *et al*, 2014; Crighton *et al*, 2015; Nahirniak *et al*, 2015). This was supplemented by searching PubMed and the United Kingdom Blood Transfusion Services (UKBTS)/Systematic Review Initiative (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 the 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 [World Health Organization (WHO) grade 0 or 1] and do not require a procedure) to patients with reversible bone marrow failure receiving intensive**

Table I. Modified World Health Organization bleeding score (Stanworth *et al*, 2013a).

Grade	Type of bleeding
Grade 1	• Petechiae/purpura that is localized to 1 or 2 dependent sites, or is sparse/non-confluent • Oropharyngeal bleeding, epistaxis <30 min duration
Grade 2	• Melaena, haematemesis, haemoptysis, fresh blood in stool, musculoskeletal bleeding, or soft tissue bleeding not requiring red cell transfusion within 24 h of onset and without haemodynamic instability • Profuse epistaxis or oropharyngeal bleeding >30 min • 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-h period • Bleeding in cavity fluids evident macroscopically • Retinal hemorrhage without visual impairment
Grade 3	• Bleeding requiring red cell transfusion specifically for support of bleeding within 24 h of onset and without haemodynamic instability • Bleeding in body cavity fluids grossly visible • Cerebral bleeding noted on computed tomography (CT) without neurological signs and symptoms
Grade 4	• 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 blood pressure) • Fatal bleeding from any source

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

chemotherapy or undergoing allogeneic haematopoietic stem cell transplantation (HSCT) to maintain a platelet count at or above 10 × 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 × 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 × 10^9/l. (1B)
  - lumbar puncture when the platelet count is ≥40 × 10^9/l. (2C)
  - insertion/removal of epidural catheter when the platelet count is ≥80 × 10^9/l. (2C)
  - major surgery – when the platelet count is >50 × 10^9/l (1C)
  - neurosurgery or ophthalmic surgery involving the posterior segment of the eye when the platelet count is >100 × 10^9/l (1C)
  - percutaneous liver biopsy when the platelet count is >50 × 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 because 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 × 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 × 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 × 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 human leucocyte antigen (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, $P2Y_{12}$ antagonists or glycoprotein IIa/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 $< 1 \times 10^9$/l) caused by abciximab (2C).**

Recommendations for Immune Thrombocytopenia (ITP):

- **Do not use prophylactic platelet transfusions in patients with autoimmune 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 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 Platelet Additive Solution (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 (Harris *et al*, 2009) (2C)**
- **Patients with hypoproliferative thrombocytopenia who continue to be refractory to HLA-selected platelet transfusions and have human platelet antigen (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 (Crighton *et al*, 2015). Four of the included studies were conducted at least 30 years ago and used out-dated methods of platelet component production and patient supportive care. Two of the included studies were recent large RCTs (Wandt *et al*, 2012; Stanworth *et al*, 2013a), both of which 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 (Crighton *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*, 2012b). Two compared a threshold of 20×10^9/l vs. 10×10^9/l, whereas the third compared a threshold of 30×10^9/l vs. 10×10^9/l. A fourth RCT excluded from the systematic review compared a threshold of 20×10^9/l vs. 10×10^9/l (Zumberg *et al*, 2002). A meta-analysis of all four studies (658 patients) showed that the 10×10^9/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. (*Eldor et al, 1982*; *Briggs et al, 2006*; 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 (Estcourt *et al*, 2015). 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 ($1{\cdot}1 \times 10^{11}/m^2$) and standard dose ($2{\cdot}2 \times 10^{11}/m^2$) and between standard dose and high dose platelet transfusions ($4{\cdot}4 \times 10^{11}/m^2$). 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 20×10^9/l when patients have an infection or fever (Estcourt *et al*, 2012a). Further studies are required to clearly identify which factors should prompt an increase in the transfusion threshold, and what this threshold should be.

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

	Difference in proportion of patients who bled (therapeutic versus prophylactic) (%)		Number of patients who needed treatment with prophylactic platelet transfusions to prevent 1 patient from bleeding within a 30-day period	
Patient group		95% CI	*n*	95% CI
All patients	8·4	0·3–16·5	12	6–333
Autologous stem cell transplant patients	2·3	−7·2–11·9	43	Not estimable as no significant difference between treatment arms
Chemotherapy/allogeneic stem cell transplant patients	20·0	5·6–34·5	5	3–18

95% CI, 95% confidence interval.

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

Haemorrhagic risk	Study	Type of study	Patients in study (*n*)	Analysis	OR/HR/RR/P value	Statistically significant
Baseline characteristics – female sex	Stanworth *et al* (2015)	RCT	589	M	HR 1·33 (95% CI 1·10–1·61)	Y
	Kim *et al* (2004)	Retrospective, observational	792	M	RR 5·23 (95% CI 2·13–12·89)	Y
	De la Serna *et al* (2008)	Prospective, observational	732	M	$P = 0·16$	N
Baseline characteristics – poor risk disease	Nevo *et al* (2007)	Retrospective, observational	480	M	OR 1·84 (95% CI 1·05–3·22)	Y
Baseline characteristics – APL vs. other acute leukaemia	Kim *et al* (2004)	Retrospective, observational	792	M	RR 4·06 (95% CI 1·63–10·13)	Y
	Chen *et al* (2009)	Retrospective, observational	790	U	$P = 0·001$	Y
Treatment – BM HSCT within 100 days	Friedmann *et al* (2002)	Retrospective, observational	2942	M	OR 1·32 (95% CI 1·22–1·43)	Y
Treatment – blood & BM HSCT	Lawrence *et al* (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 *et al* (2015)	RCT	589	M	HR 1·43 (95% CI 1·19–1·72)	Y
Treatment – HSCT (Allogeneic vs. Autologous)	Zumberg *et al* (2002)	RCT	159	U	OR 2·8 (95% CI 1·1–7·7)	Y
	Nevo *et al* (2007)	Retrospective, observational	480	M	OR 2·29 (95% CI 1·11–4·77)	Y
	Gerber *et al* (2008)	Retrospective, observational	1514	M	OR 2·17 (95% CI 1·56–3·03)	Y
Infection – bacteraemia	Friedmann *et al* (2002)	Retrospective, observational	2942	M	OR 1·01 (95% CI 0·81–1·26)	N
Infection – clinical	Webert *et al* (2006)	Retrospective analysis of RCT*	255	M	RR 1·98 (95% CI 1·0–3·92)	Y
Infection – systemic	Najima *et al* (2009)	Retrospective, observational	622	M	HR 1·52 (95% CI 0·57–4·03)	N
Infection – sepsis	Lawrence *et al* (2001)	Prospective, interventional	141	M	$r = 0·024$; $P = 0·036^{\dagger}$	Y
Fever ≥38°C	Stanworth *et al* (2015)	RCT	469	M	HR 1·7 (95% CI 1·3–2·4)	Y
Fever – per 1°C rise in temp	Friedmann *et al* (2002)	Retrospective, observational	2942	M	OR 1·02 (95% CI 0·94–1·1)	N
Fever – not specified	Lawrence *et al* (2001)	Prospective, Interventional	141	M	$r = 0·072$; $P < 0·001^{\dagger}$	Y
Fever >38·5°C	Webert *et al* (2006)	Retrospective analysis of RCT*	255	M	RR 3·95 (95% CI 1·90–8·20)	Y
Fever associated with WHO grade 3&4 haemorrhage only					RR 1·62 (95% CI 0·44–5·91)	N
Medication – semi-synthetic penicillin	Lawrence *et al* (2001)	Prospective, Interventional	141	M	$r = 0·032$; $P = 0·014$†	Y
	Friedmann *et al* (2002)	Retrospective, Observational	2942	M	OR 0·94 (95% CI 0·80–1·09)	N

Table III. (*Continued*)

Haemorrhagic risk	Study	Type of study	Patients in study (*n*)	Analysis	OR/HR/RR/P value	Statistically significant
Medication – anti-fungal medication	Webert *et al* (2006)	Retrospective analysis of RCT*	255	M	RR 0·59 (95% CI 0·39–0·9)	Y
Medication–amphotericin	Zumberg *et al* (2002)	RCT	159	M	$P < 0·0001$	Y
	Lawrence *et al* (2001)	Prospective, Interventional	141	M	$r = 0·064$ (major haemorrhage) $P < 0·001$ $r = 0·114$ (minor haemorrhage) $P < 0·001$	Y
	Friedmann *et al* (2002)	Retrospective, Observational	2942	M	OR 0·97 (95% CI 0·84–1·13)	N
Medication–anticoagulants	Gerber *et al* (2008)	Retrospective, Observational	1514	M	OR 3·1 (95% CI 1·8–5·5)	Y
	Friedmann *et al* (2002)	Retrospective, Observational	2942	M	OR 0·94 (95% CI 0·09–10·12)	N
Laboratory parameters - Uraemia (urea >17·9 mmol/l)	Friedmann *et al* (2002)	Retrospective, Observational	2942	M	OR 1·64 (95% CI 1·40–1·92)	Y
Laboratory parameters – platelet count	Lawrence *et al* (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 1×10^9/l increase in platelet count	Webert *et al* (2006)	Retrospective analysis of RCT*	255	M	RR 0·96 (95% C.I. 0·93–0·98)	Y
Laboratory parameters – Platelet count $0 - 9 \times 10^9$/l vs. $40–49 \times 10^9$/l	Friedmann *et al* (2002)	Retrospective, Observational	2942	M	OR 1·14 (95% C.I. 0·89–1·46) (not transfused) OR 0·98 (95% C.I. 0·69–1·39) (transfused)	N
Other co-morbidities–acute graft vs host disease	Zumberg *et al* (2002)	RCT	159	M	$P < 0·049$	Y
	Bleggi-Torres *et al* (2002)	Retrospective, Observational	180	U	OR 0·86 (95% CI (0·45–1·62)	N
	Gerber *et al* (2008)	Retrospective, Observational	1514	M	OR 2·4 (95% CI 1·8–3·3)	Y
	Najima *et al* (2009)	Retrospective, Observational	622	M	HR 1·41 (95% CI 1·01–1·97)	Y
Other co-morbidities – veno-occlusive disease	Zumberg *et al* (2002)	RCT	159	M	$P < 0·033$	Y
	Gerber *et al* (2008)	Retrospective, Observational	1514	M	OR 2·2 (95% CI 1·4–3·6)	Y
	Najima *et al* (2009)	Retrospective, Observational	622	M	HR 2·63 (95% CI 0·77–9·00)	N

Table III. (*Continued*)

Haemorrhagic risk	Study	Type of study	Patients in study (*n*)	Analysis	OR/HR/RR/P value	Statistically significant
Other co-morbidities Splenomegaly	Lawrence *et al* (2001)	Prospective, Interventional	141	M	$r = 0{\cdot}055$; $P < 0{\cdot}001$†	Y
Other co-morbidities Recent history of severe haemorrhage (≤5 days)	Friedmann *et al* (2002)	Retrospective, Observational	2942	M	OR 6·72 (95% CI 5·53–8·18)	Y

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

*Data from Rebulla *et al*, 1997

†Minor haemorrhage. No association with major haemorrhage.

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 10×10^9/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 5×10^9/l or less. In total, 55 239 patient days were reviewed of which there were 18 706 days when the platelet count was 10×10^9/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 (Schiffer *et al*, 2001; Liumbruno *et al*, 2009; Kaufman *et al*, 2015) or prophylaxis below a count of 5×10^9/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 5×10^9/l is the reported inaccuracy of current automated counters when the platelet count is very low (Segal *et al*, 2005; De la Salle *et al*, 2012).

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*, 2014, 2015) 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 1000), 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.

Table IV. Bone marrow aspirate and/or trephine biopsy. Adverse bleeding events reported in UK confidential morbidity/mortality reports.

					Risk factors for haemorrhage								
Study	Study period	Hospitals (*n*)	Procedures (*n*)	Haemorrhages (*n*)	Thrombocytopenia (<50 × 10^9/l)	Aspirin	Heparin	Warfarin	DIC	Other	Obesity	Renal Impairment	MDS	MPN
Bain (2003)	1995–2000	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	9295	9	6	0	0	0	0	1‡	1	0	2	0

DIC, disseminated intravascular coagulation; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasm; NR, not reported

*Patient had von Willebrand disease

†Patient had deranged coagulation associated with myeloma

‡Patient had alcohol related problems

§Personal communication with Dr Vinod Devalia, Consultant Haematologist, Princess of Wales Hospital, Abertawe Bro Morgannwg University Health Board, Wales

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 multivariate analysis, the risk of bleeding was significantly increased by the number of attempts, site of insertion (jugular versus subclavian) and failed guidewire insertion (Barrera *et al*, 1996; Fisher & 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 (*Randolph et al, 1996*; *Hind et al, 2003*) and a more recent small study (Tomoyose *et al*, 2013) found that ultrasound guidance significantly reduced failure and complication rates.

Zeidler *et al* (2011) looked at the risk of bleeding according to platelet count thresholds with multivariate 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 20×10^9/l (Odds ratio 2·88, 95% confidence interval 1·23–6·75, $P = 0{\cdot}015$) (Zeidler *et al*, 2011). In a large study by Haas *et al* (2010), 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 25×10^9/l (Haas *et al*, 2010).

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

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). Of the 179 patients enrolled in the study, 14 had a time to haemostasis of over 5 min 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 (van Veen *et al*, 2010). 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 80×10^9/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

A total of 2740 percutaneous liver biopsies were conducted in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (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 $50–60 \times 10^9$/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 (Wallace *et al*, 2003; Kalambokis *et al*, 2007; Mammen *et al*, 2008).

Renal biopsy

Patients with uraemia have a platelet dysfunction that 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; Whittier, 2004; Torres Munoz *et al*, 2011; 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 (Mannucci *et al*, 1983; Hedges *et al*, 2007; Manno *et al*, 2011) 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 erythropoietin can take many weeks a more rapid effect on haemostasis has been noted. This may be through improved platelet adhesion and aggregation (Zwaginga *et al*, 1991; Cases *et al*, 1992) 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

Table V. Observational studies reporting bleeding outcomes after insertion of venous central line insertions.

Study	Study duration	Type of study	Number of participants (procedures)	Type of patient	Definition of thrombocytopenia ($\times 10^9$/l)	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 participants bleeding (major bleeding)
Carr *et al* (2006)	Jan'93 to Jun'03	Observational Retrospective	115 (NR)	Acute leukaemia	NR	NR*	NR	NR	0	0	0 (0)
Mumtaz *et al* (2000)	Sep'97 to Aug'99	Observational Retrospective	1825 (2010)	Haematological malignancy; solid tumours; ICU; renal failure	<150	NR	INR > 1·3 aPTT > 37 s	88	4	0	3 (0)
Foster *et al* (1992)	Jan'88 to Dec'88	Observational Retrospective	40 (259)	Liver disease	<80	122	PT <40% aPTT ≥ 77 s	122	0	0	0 (0)
Barrera *et al* (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 *et al* (2010)	Dec'00 to Jan'09	Observational Prospective	1660 (1978)	Haematological malignancy; solid tumours	≤50	116	NR	NR	4†	0	NR
Della Vigna *et al* (2009)	Sep'01 to Aug'08	Observational Retrospective	157 (239)	Haematological malignancy; solid tumours	≤50	NR	PT or aPTT > 2·2 × normal	45	1	0	0 (0)
Doerfler *et al* (1996)	Oct'92 to Oct'93	Observational	76 (104)	Haematological malignancy; solid tumours; liver transplant; other	≤50	41	PT or aPTT > 1·5 × 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 *et al* (2010)	Jul'01 to Jul'08	Observational Retrospective	2514 (3170)	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 *et al* (2008)	Apr'02 to Jul'06	Observational	133 (133)	NR	≤50	38	INR ≥ 1·5 or aPTT ≥ 50 s	90	8	0	NR (0)

Table V. (*Continued*)

Study	Study duration	Type of study	Number of participants (procedures)	Type of patient	Definition of thrombocytopenia ($\times 10^9$/l)	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 participants bleeding (major bleeding)
Tomoyose *et al* (2013)	Jan'03 to Feb'09	Observational Retrospective	72 (108)	Haematological malignancies	≤50	67	NR	NR	5	0	4 (0)
Weigand *et al* (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 *et al* (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 *et al* (2013)	Jan'99 to Jun'09	Observational Retrospective	431	Haematological disorders	<30	39	NR	NR	8	0	1 (0)

Major bleeding defined as requiring a red cell transfusion to treat bleeding; haemothorax; significant fall in haemoglobin concentration. aPTT, activated partial thromboplastin time; ICU, intensive care unit; INR, international normalised ratio; NR, not reported; PT, prothrombin time; TTP, thrombotic thrombocytopenic purpura

*Median platelet count 72 × 10^9/l, range 10–347

†Patients all had puncture of artery causing a haematoma

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

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 $\leq 3{\cdot}0$ and were randomised to the presence or absence of TXA 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 postoperative 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 50×10^9/l before major surgery (British Committee for Standards in Haematology Blood Transfusion Task Force 2003, Samama *et al*, 2006; Liumbruno *et al*, 2011; Vassallo *et al*, 2013), and a threshold of 100×10^9/l prior to neurosurgery or ophthalmic surgery involving the posterior segment of the eye, because of the critical sites involved (British Committee for Standards in Haematology Blood Transfusion Task Force 2003, Samama *et al*, 2006; Liumbruno *et al*, 2011; Vassallo *et al*, 2013). 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 erythropoietin) uraemia (dialysis) (1B). If renal biopsy is urgent consider desmopressin 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 that 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*, 2012a).

Current recommendations are based on consensus guidelines from around the world (British Committee for Standards in Haematology Blood Transfusion Task Force 2003, Samama *et al*, 2006; Rossaint *et al*, 2010; Liumbruno *et al*, 2011, National Blood Authority 2011; Spahn *et al*, 2013; Vassallo *et al*, 2013) and recently revised BCSH guidelines for major haemorrhage (Hunt *et al*, 2015).

Recommendations

- **Severe bleeding, maintain the platelet count above 50×10^9/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 100×10^9/l (2C)**

- **In patients with bleeding that is not considered severe or life-threatening, consider platelet transfusion if the platelet count is below 30 × 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 (Hayward *et al*, 2006; Bakdash *et al*, 2008). Recombinant Factor VIIa (rFVIIa; NovoSeven, Novo Nordisk Limited, Bagsværd, Denmark) 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 RCT 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 & 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 (Vilahur *et al*, 2007; Li *et al*, 2012; Hansson *et al*, 2014; Godier *et al*, 2015). 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

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 min	1 h	24–48 h
Aspirin	<1 h 3–4 h with enteric-coated preparations	15–20 min	2 h 4–5 h with enteric-coated preparations	5–7 days
Clopidogrel	4–8 h	30 min	12 h	5–7 days
Dipyridamole	1·25 h	2–3 h	5–7 h	24 h
Eptifbatide	Not applicable	2·5 h	4 h	4–8 h
Ibuprofen	45 min–2 h	2 h	6 h	24 h
Prasugrel	2–4 h	7 h	16–18 h	5–7 days
Ticagrelor	1·5 h	8–12 h	18–26 h	3–5 days
Tirofiban	Not applicable	1·5 h	4 h	4–8 h

this risk (Makris *et al*, 2013). In the RCT of spontaneous intracranial haemorrhage in patients on anti-platelet agents (Baharoglu *et al*, 2016), 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 1–2 h 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 h after surgery, respectively) (Thiele *et al*, 2012).

In contrast, TXA has been used in three RCTs 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,b). No differences 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 1 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, $P2Y_{12}$ antagonists or glycoprotein IIa/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 the 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 & Hunt, 2010). Platelets have been used, often in association with other treatments, to treat major bleeding (Neunert *et al*, 2011). There are no RCTs; 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 immunoglobulin are administered together (Baumann *et al*, 1986; Spahr & Rodgers, 2008), and one study suggests this combination is more effective clinically (Spahr & 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 & Goldfinger, 2008; Warkentin, 2011; Linkins *et al*, 2012). 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 (41 patients in total) have reported no association with thrombosis (Hopkins & 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 the introduction of 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**

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

Study	Study period	Pts (*n*)	Sex	Type	Median age, years (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 (32–85)	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: 68×10^9/l; range: 20–130); time to baseline >60 h Plt tx alone (median: 31; range: 18–33) Median time to baseline: 6 h	1 pt: menorrhagia responded to IVIG + plt tx, but not plt tx alone
Salama *et al* (2008)	NR	10	M (3) F (7)	Chronic, refractory	48 (24–79)	Severe bleeding (5) GI bleed (2)	4	1 unit every 30 min 3–7 apheresis units ($2{\cdot}7 \times 10^{11}$ plts per unit)	Plt count increased to $>80 \times 10^9$/l in all cases; returned to baseline in 7/10 by 48 h	Bleeding stopped in all cases
Retrospective, Observational										
Carr *et al* (1986)	Jan 1981 –Jul 1984	11	M (4) F (7)	Idiopathic (6) Quinidine-induced (5)	71 (25–88)	CNS (2) Epistaxis (6) Upper GI (2) Petechiae alone (1)	Idiopathic (6) Quinidine (1)	Plt Tx. Median/pt 2 (Range 1–6) 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 h of tx; 5/31 tx plt count still higher at 24 h	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 (20–71)	Large retroperitoneal bleed (1)	2	IVIG continuous 24-h infusion + concomitant apheresis plt tx (1/2 pheresis pack every 4 h)	Plt count $>100 \times 10^9$/l	NR
Spahr and Rodgers (2008)	Jan 2000–Dec 2005	40	M (23) F (17)	Idiopathic (9 previously refractory to IVIG alone)	52 (19–87)	33 pts	38 (usually 1 mg/kg/day)	IVIG (1 g/kg) continuous infusion over 24 h Plt apheresis unit (1 unit every 8 h)	51% achieved plt count $>50 \times 10^9$/l by 24 h	Bleeding controlled initially in all pts regardless of plt count

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

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 (Peigne *et al*, 2012; Estcourt *et al*, 2013). 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 types of blood transfusion reactions (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 transfusion 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, but 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 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; Yanagisawa *et al*, 2013; Cohn *et al*, 2014; Tobian *et al*, 2014). 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 (Kitazawa *et al*, 2011; Moncharmont *et al*, 2014; Cid *et al*, 2015). The largest study investigating this risk has recently been published and reported that anti-D developed in only 1·44% of patients (Cid *et al*, 2015). 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. This situation is no longer the case following the introduction of universal leucodepletion and the use of male donor plasma, 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 the Serious Hazards of Transfusion (SHOT) team 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).**

Table VIII. Studies that reported the use of platelet transfusions in patients with thrombotic thrombocytopenic purpura and mortality in those receiving or not receiving platelet transfusion.

Study	Type of study	Study period	Centres involved	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	1974–1979	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)	Retrospective observational	1982–1986	Single centre	USA	15	15 TPE	2	1	NR	3	NR	Thrombocytopenia, MAHA, neurology OR fever and renal abnormalities
Rose and Eldor (1987)*	Observational; Retrospective	1977–1985	Multicentre (15)	Israel & USA	38	37	14	5	NR	1	NR	Plt count <100 × 10^9/l, MAHA, neurology (major criteria) Fever, renal abnormalities supportive
McCarthy *et al* (1994)	Observational; Retrospective	1973–1994	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 × 10^9/l, MAHA
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 × 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 × 10^9/l, MAHA, neurological symptoms and/or renal impairment
Coppo *et al* (2003) *†	Observational; Retrospective	1989–2001	Single centre	France	37	19 HPI 18 TPE	8	1	NR	4	NR	Plt count <100 × 10^9/l & MAHA with no known cause

Table VIII. (*Continued*)

Study	Type of study	Study period	Centres involved	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
Shamseddine *et al* (2004)*,†	Observational; Retrospective	1980–2003	Single centre	Lebanon	47	40 TPE 7 HPI	4	2	NR	7	NR	Plt count <100 × 10^9/l & MAHA with no known cause
Swisher *et al* (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 × 10^9/l, MAHA

CNS, central nervous system; FWB, fresh whole blood; MAHA, microangiopathic haemolytic anaemia; NR, not reported; PI, plasma infusion; plt, platelet; TPE, total plasma exchange; TTP, thrombotic thrombocytopenic purpura; tx, transfusion; WBE; §Deaths reported that occurred when patients were not in complete remission.

*Reported for initial course of treatment until complete remission (as defined by the study), not for relapses or exacerbations.

†Excluded patients with TTP/HUS associated with stem cell transplantation, HIV, or metastatic cancer.

‡Excluded patients <10 years old (10); or at relapse; or with TTP associated with stem cell transplantation (15), cancer chemotherapy (12), or autoimmune disorders (35); or with ADAMTS13 level ≥10% (if measured; 95).

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

Adverse event	Estimated risk per unit of platelets in the UK
Febrile non-haemolytic transfusion reaction (excluding mild)	1 in 6000
Allergic (excluding mild)	1 in 6000
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

- **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 (re-suspended 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-min to 1-h increment of less than 5×10^9/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 RCT that considered HLA matching and 29 studies with no RCTs that 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 National Institute for Health and Clinical Excellence (NICE) guidance contains a strong recommendation for the use of TXA in adults undergoing surgery when blood loss is expected to be greater than 500 ml (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 mucus membrane bleeding, advising caution in patients with ischaemic heart disease or haematuria (British Committee for Standards in

Table X. Platelet transfusion in times of shortage.

Category 1	Category 2	Category 3
Massive haemorrhage and 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 Bleeding in the presence of acute DIC, maintain >50 $\times$ 10^9/l.	*Critical care* Patients resuscitated following massive transfusion with no on-going active bleeding, maintain platelet count >50 $\times$ 10^9/l ***Surgery*** Urgent but not emergency surgery for a patient requiring platelet support *Transfusion triggers for invasive procedures* According to current BCSH guidelines	*Surgery* Elective, non-urgent surgery likely to require platelet support for thrombocytopenia or congenital/acquired platelet defects
Bone marrow failure Active bleeding associated with severe thrombocytopenia or functional platelet defects ***Immune thrombocytopenia*** if serious/life-threatening bleeding ***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 and 30 $\times$ 10^9/l. Higher target levels should be maintained if extremely low birth weight or unwell/bleeding or intracranial haemorrhage suspected/confirmed.	*Bone marrow failure* All other indications except those in category 1 or 3	*Bone marrow failure* Prophylactic transfusion of stable patients following autologous stem cell transplant.

DIC, disseminated intravascular coagulation; CNS, central nervous system

Haematology Blood Transfusion Task Force, 2003; Killick *et al*, 2014).

Desmopressin

Desmopressin promotes coagulation by stimulating factor VIII release from endothelial stores and increasing von Willebrand factor 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 myelodysplastic syndrome (MDS)/non-Hodgkin lymphoma showed encouraging platelet count improvements (Sekeres *et al*, 2011; Greenberg *et al*, 2012; 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 (Kantarjian *et al*, 2012; Giagounidis *et al*, 2014).

Eltrombopag has also been used in small non-randomised studies in patients with advanced MDS/acute myeloid leukaemia 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 the use of eltrombopag should be considered when 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. A recent retrospective observational study a reported that a sustained response was achieved in at least 29% of cases after temporary use of these agents with a median follow-up of more than a year. (Mahévas *et al*, 2014).

Erythropoietin 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 (Wandt *et al*, 2012; Stanworth *et al*, 2013a) (Table II) and from consideration of the risks associated with platelet transfusions (described earlier).

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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

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Declaration of interests

All authors have made a declaration of interests to the BCSH and Task Force Chairs and 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 (http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html). 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.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Haematology audit template.

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Appendix 1

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 that 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 [World Health organization (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 6000	1 in 6,000
Allergic 1 in 6000	1 in 6,000
Haemolysis 1 in 600 000	1 in 600,000
Bacterial sepsis	Rare since bacterial screening introduced in 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 that 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?

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	
Reversible BMF including allogeneic stem cell transplantation	10×10^9/l
Reversible BMF with autologous stem cell transplantation (consider no prophylaxis)	10×10^9/l
Critical illness	10×10^9/l
Chronic BMF receiving intensive therapy	10×10^9/l
Chronic BMF to prevent persistent bleeding of grade ≥2	Count variable
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)	
Reversible/chronic bone marrow failure/critical care	10–20 $\times 10^9$/l

Indication	Transfusion indicated (threshold)/not indicated
Abnormal platelet function, platelet consumption/destruction, immune thrombocytopenia	Not indicated
Platelet transfusion pre-procedure	
Central venous catheter (CVC) excluding PICC line	20×10^9/l
Lumbar puncture	40×10^9/l
Percutaneous liver biopsy	50×10^9/l
Major surgery	50×10^9/l
Epidural anaesthesia, insertion & removal	80×10^9/l
Neurosurgery or ophthalmic surgery involving the posterior segment of the eye	100×10^9/l
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)	
Severe bleeding	50×10^9/l
Multiple trauma, brain or eye injury, spontaneous intracerebral haemorrhage	100×10^9/l
Bleeding (WHO grade ≥2) but not severe	30×10^9/l
Bleeding in specific clinical conditions – see below for indications	
Specific clinical conditions	
Platelet function defect	Count variable
Congenital – Pre-procedure 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 Pre-procedure or therapeutic use. Consider threshold counts above but may not be achievable and individual case review required.	Use pre-procedure/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 pre-procedure/therapeutic threshold as guide

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