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Platelet transfusion: Alloimmunization and refractoriness

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ABSTRACT

The transfusion of platelets for both prophylaxis and treatment of bleeding is relevant to all areas of medicine and surgery. Historically, guidance regarding platelet transfusion has been limited by a lack of good quality clinical trials and so has been based largely on expert opinion. In recent years however there has been renewed interest in methods to prevent and treat hemorrhage, and the field has benefited from a number of large clinical trials. Some studies, such as platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH) and platelets for neonatal transfusion Study 2 (PLANET-2), have reported an increased risk of harm with platelet transfusion in specific patient groups. These studies suggest a wider role of platelets beyond hemostasis, and highlight the need for further clinical trials to better understand the risks and benefits of platelet transfusions.

This review evaluates the indications for platelet transfusion, both prophylactic and therapeutic, in the light of recent studies and clinical trials. It highlights new developments in the fields of platelet storage and platelet substitutes, and novel ways to avoid complications associated with platelet transfusions. Lastly, it reviews initiatives designed to reduce inappropriate use of platelet transfusions and to preserve this valuable resource for situations where there is evidence for their beneficial effect.

Introduction

"To those who are concerned with the in-depth study of the blood of humans, the study of these granules in human blood is enthusiastically recommended." [1]

W.W. Duke first demonstrated a clear clinical benefit of transfusing platelets (as fresh whole blood) in patients with significant hemorrhage over a century ago [2]. However it was not until the 1960s that platelet concentrates were developed in response to the recognition that thrombocytopenic bleeding was a major cause of death in patients with hematological malignancies treated with chemotherapy. There followed a rapid increase in the use of platelet transfusions and new techniques for their collection, storage and administration were developed [3].

Platelet transfusions have undoubtedly reduced morbidity and mortality from severe hemorrhage and allowed for the development and use of intensive chemotherapy regimens and hematopoietic stem cell transplantation in patients with hematological and other cancers. In recent years, platelet transfusion research has focused on refining the indications for platelet transfusion and minimising complications such as bacterial transmission.

Indications for their use

Prophylactic platelet transfusions

Prophylactic platelet transfusions constitute the majority of platelet transfusions [4]. They are mainly used in patients receiving chemotherapy or after hematopoietic stem cell transplantation, which result in bone marrow suppression and subsequent thrombocytopenia, and in patients with bone marrow disease or bone marrow infiltration which limits platelet production. Well defined thresholds have been established by various organisations (Table 1).

The platelet count threshold of 10×10^9/L for prophylactic transfusions was established by a landmark study where it was found to be as safe as the historical threshold of 20×10^9/L and was associated with a 21.5% reduction in platelet use [5]. There is no evidence that using a higher platelet dose for prophylac-

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Table 1
Indications for platelet use.

Indication	Platelet threshold	Recommending body	Level of evidence
Reversible bone marrow failure following chemotherapy or allogeneic bone marrow transplantation	$<10 \times 10^9$/L $<20 \times 10^9$/L when there is ongoing infection or additional risk factor for bleeding	BSH, ASCO, NICE, AABB	1B 2C
Reversible bone marrow failure following autologous bone marrow transplantation	No platelet transfusion is indicated Transfuse at the first sign of bleeding	BSH, ASCO	2B
Chronic bone marrow failure	No platelet transfusion is indicated Reserve platelet transfusions for bleeding episodes	BSH, NICE, ASCO	2B
Nonsevere or life threatening bleeding	$>30 \times 10^9$/L	BSH, NICE	2C
Severe bleeding	$>50 \times 10^9$/L Or empirically according to Major haemorrhage protocol	BSH	1C
CNS bleeding	$>100 \times 10^9$/L	BSH, NICE	2C
Bone marrow aspiration or trephine biopsy	No transfusion is indicated	BSH	1B
Central line insertion (US guided)	$>20 \times 10^9$/L	BSH, AABB	1B
Peripherally inserted central catheters (PICC) and traction removal of tunnelled lines	No transfusion is indicated	BSH	2C
Lumbar puncture	$>40 \times 10^9$/L $>50 \times 10^9$/L	BSH AABB	2C
Liver biopsy	$>50 \times 10^9$/L	BSH	2B
Kidney biopsy	Avoid platelet transfusion Consider use of desmopressin	BSH	1B
Major surgery	$>50 \times 10^9$/L	BSH, NICE, AABB	1C
CNS or ophthalmic surgery of the posterior segment of the eye	$>100 \times 10^9$/L	BSH, NICE, AABB	1C
Abciximab related thrombocytopenia	$<10 \times 10^9$/L	BSH	2C
Immune thrombocytopenic purpura (ITP)	Use platelet transfusions only in serious bleeding or prior to a procedure or surgery when other measures have failed Consider concomitant use of IVIG	BSH	2C
Thrombotic microangiopathies (TTP, HIT)	Consider platelet transfusions only in life-threatening bleeding	BSH, NICE	2C

AABB = American Association of Blood Banks [82]; ASCO = American Society of Clinical Oncology [20]; BSH = British Society of Haematology [10]; NICE = The National Institute for Health and Care Excellence [81].
Levels of evidence. 1A: Systematic reviews of randomised controlled trials, 1B: Randomised controlled trials, 1C: intervention or no intervention randomized controlled trials, 2A: Systematic reviews of cohort studies, 2B: Cohort study or low-quality randomised control trial, 2C: Ecological studies [83].

tic transfusions decreases the risk of bleeding [6]. There have subsequently been 2 large randomized controlled trials which investigated the safety of a no prophylaxis strategy that is only therapeutic platelet transfusions to treat hemorrhage. Both trials found a reduced bleeding risk with prophylactic platelets, but the effect size was small, and many patients continued to experience bleeding events despite a policy of prophylaxis [7,8]. There was no evidence of a benefit to reduce bleeding in patients undergoing autologous hematopoietic stem cell transplantation.

Recommendations for the use of prophylactic platelet transfusions in bone marrow failure cannot be extrapolated to patients with platelet consumption disorders. There is little evidence that prophylactic platelet transfusion provides clinical benefit even in severe thrombocytopenia in patients with thrombotic thrombocytopenic purpura (TTP), idiopathic thrombocytopenic purpura, and heparin-induced thrombocytopenia (HIT). In TTP and HIT prophylactic platelet transfusion is associated with a greater risk of arterial thrombosis and all-cause mortality [9]. Prophylactic platelet use is only recommended in serious bleeding in idiopathic thrombocytopenic purpura where it should be used alongside other therapies such as intravenous immunoglobulin. In thrombotic microangiopathies such as TTP and HIT, it is recommended for use only in life-threatening bleeding [10].

In updated guidelines for the management of sepsis and septic shock, platelet transfusion is recommended when the platelet count drops to $<10 \times 10^9$/L, or $<20 \times 10^9$/L if there is risk of bleeding or $<50 \times 10^9$/L when there is active bleeding, impeding surgery or invasive procedure [11].

In critical care patients, thrombocytopenia is common, and it can be a result of a plethora of pathophysiological mechanisms. Platelet transfusion should only be used when a patient is bleeding and thrombocytopenia is the most likely cause of the hemorrhage. This approach is based on empirical clinical practice without strong evidence that platelet transfusions decrease mortality, while there is weak evidence that platelet transfusion precipitate arterial thrombosis. A recent review on critically ill patients with thrombocytopenia concluded that a platelet transfusion should be given only in life threatening situations [12].

Thromboelastography may play an increasingly important role in guiding the hemostatic management of these patients and dictating the need of platelet transfusions [13,14].

A clinical trial comparing prophylactic platelet transfusion with no prophylaxis in patients with Dengue fever, where severe thrombocytopenia and hemorrhagic fever can complicate the clinical course and result in significant morbidity and mortality, showed no difference between the 2 study arms. There were however many adverse events noted in the transfusion arm, including anaphylaxis, transfusion-associated lung injury (TRALI), and transfusion-associated circulatory overload (TACO) [15].

Similarly there is little evidence to support particular thresholds for platelet transfusion in neonates and children. The PLANET-2 randomised controlled trial has provided strong evidence against a higher threshold of 50×10^9/L in neonates as the group that received transfusions at 25×10^9/L had significant lower death and bleeding rates [16] Thresholds for children have previously been set mainly by consensus and are similar to the thresholds for adults [17]. The PLANET trial team hypothesised that platelet transfusion may lead to harm by several mechanisms including, infection and transfusion reactions.

Preprocedure platelet transfusions

Bone marrow aspiration and biopsy

Although hemorrhage is the most serious complication in this group of patients, its incidence is very low [10]. Only 14 patients in

a review of 54,890 aspirations and biopsies developed hemorrhage and only 3 of these patients were thrombocytopenic [18].

Central venous catheters

A platelet count above 20×10^9/L is currently considered a safe threshold[19,20], but there is only weak evidence that such an approach leads to reduced bleeding rates and all-cause mortality [21,22]. With ultrasound guidance now being used routinely to insert central lines there has been a reduction in the associated bleeding rate, making prophylactic platelet transfusion a more appropriate option only for patients with additional identified risk factors for bleeding [23]. Randomized trials are required to determine a platelet threshold or to indicate that universal prophylactic platelet transfusions for central venous catheter insertion should be abandoned [19]. The Prophylactic Platelet Transfusion Prior to Central Venous Catheter Placement in Patients with Thrombocytopenia (PACER) trial will aim to settle this issue by randomizing patients with platelet counts between 10 and 50×10^9/L to either a single prophylactic platelet transfusion or no prophylactic transfusion. It will be a prospective, multicenter, noninferiority trial with a primary endpoint of bleeding [24]

Lumbar Puncture and neuraxial anesthesia

There is very low quality evidence about the value of platelet transfusions in patients undergoing lumbar puncture and neuraxial anesthesia at present and this is unlikely to change as a trial would be required to include at least 47,030 cases to be able to demonstrate a difference between a prophylactic and nonprophylactic approach due to the rarity of bleeding following a lumbar puncture [25]. British Society for Haematology guidelines recognise the absence of any strong evidence and recommend a platelet threshold of 40×10^9/L for lumbar puncture and spinal anesthesia and $>80 \times 10^9$/L for epidural anesthesia. American Association of Blood Banks recommend a slightly higher threshold of 50×10^9/L for lumbar puncture (Table 1).

There is very little evidence in terms of the benefit of platelet transfusions perioperatively or before biopsies. In most cases, local consensus guidelines have been developed. A common issue here is defining stepwise changes in need for platelet transfusion by level of platelet count, which is likely to be surrogate marker of bleeding risk, and does not, for example, provide information on platelet dysfunction.

Therapeutic platelet transfusions

Platelet transfusions are part of major hemorrhage protocols. A multicenter randomized trial, the PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial, concluded that there was no difference between the 1:1:1 and 1:1:2 ratios (Platelets: Fresh Frozen Plasma: Red Blood Cells) in terms of mortality at 24 hours and at 30 days [26]. However, a substudy of the PROPPR trial found that early platelet administration was associated with an improvement in hemostasis and reduced mortality in severely injured and bleeding patients [27]. However, the clinical implications of this trial remain uncertain.

Harmful effects

The platelet transfusion vs standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH) trial demonstrated that platelet transfusions may be harmful in patients with intracranial hemorrhage who are taking antiplatelet therapy. It was a multicenter, open-label, masked-endpoint, randomized trial at 60 hospitals in the Netherlands, UK, and France, and it demonstrated that platelet transfusion was inferior to standard of care in this group of patients [28]. This unexpected result raises questions about the current practice of transfusing platelets to reverse the action of antiplatelet drugs and also highlights that platelets may play a significant role beyond hemostasis in human physiology. Based on this trial, a recommendation to transfuse platelets in intracranial hemorrhage can no longer be made. The PATCH trial team hypothesized that platelet transfusion may lead to thrombosis of collateral vessels leading to worsening brain ischemia. Larger studies will be required to confirm this unexpected result.

New developments in platelet storage

Cold stored platelets

Standard clinical practice is to store platelets at 22°C with continuous gentle agitation. Platelets can be stored for up to 7 days when measures are taken to minimize the risk of bacterial transmission (see below). The idea of storing platelets at lower temperatures is not new, but was abandoned in the 1970s due to concerns that cold stored platelets were cleared more rapidly from the circulation than platelets stored at room temperature. However, the concept of cold storage continues to appeal. In particular, the bacteriostatic effect of a lower temperature would reduce the risk of bacterial infection and the potential for septic reactions.

Recently the argument for cold storage of platelets has been reignited by new studies suggesting that cold stored platelets may have superior hemostatic qualities when compared to room temperature stored platelets [29], and that in the treatment of hemorrhage platelet activity is likely to be more important than count recovery and survival. In 2015 the US Food and Drug Administration (FDA) announced their approval of cold stored apheresis platelets for resuscitation of actively bleeding trauma patients. Their agreement allows storage of apheresis platelets for 3 days at 1°C-6°C, without the need for agitation [30] Initial feedback shows a high discard rate due to the short storage period and the formation of clots in plasma rich cold stored platelets. In the future, use of a platelet additive solution may prove to be a practical solution to reduce storage related clots.

Cryopreserved platelets

Whilst the use of cold-stored platelets addresses the problem of transfusion-transmitted infections, the issue of the short shelf life of platelet concentrates remains. Cryopreserved platelets, which have a shelf life of at least 2 years, offer a potential solution, in particular, to improve platelet availability at remote locations and far forward military medical facilities close to conflict zones. In addition, cryopreserved platelets could be stockpiled for use in times of shortage and to create a bank of rare Human Leucocyte Antigen (HLA-) and Human Platelet Antigens- types.

Much of what is known today about cryopreserved platelets comes from studies conducted in the 1970s. These studies demonstrated that cryopreserved platelets underwent multiple structural and functional changes compared to platelets that were preserved conventionally at room temperature, but nonetheless seemed to remain hemostatically effective [31].

The recent military conflicts in Iraq and Afghanistan have propelled this research into changes in practice. In 2001 the Netherlands Military Blood Bank was the first to implement the use of cryopreserved platelets. Results to date seem to confirm that cryopreserved platelets stem bleeding, and cause no increase in thrombotic or other serious adverse events [32]. Nonetheless, the evidence base for the safety and efficacy of cryopreserved platelets is still very limited compared to conventional platelet products.

Lyophilized, or freeze-dried platelets

Lyophilized, or freeze-dried platelets have been under development for over 40 years since Brinkhous and Read experimented with formaldehyde-fixed human platelets [33]. Since then animal studies have demonstrated correction or reduction of bleeding times with freeze-dried platelets in a number of different scenarios, including in a thrombocytopenic rabbit model, a canine cardiopulmonary bypass model of open-heart surgery, and a porcine trauma model. It has also been shown that the process of freeze-drying kills viruses and bacteria spiked into the platelet solutions. However, there are concerns regarding the safety of this product, particularly regarding thrombotic complications, following trials using a porcine liver injury model [34].

In 2018 the first clinical, dose escalation trial to evaluate the safety and immunogenicity of autologous lyophilized platelet was conducted. Ten healthy, nonbleeding subjects received autologous Thrombosomes prepared from their apheresis platelets, and no serious adverse events were reported [35]. Whilst this is encouraging, the study size was very small and the subjects were not bleeding. Further larger trials are required to determine the safety and efficacy of the product.

Pathogen-reduced platelets

In 2016 the FDA approved the INTERCEPT blood system for pathogen inactivation of apheresis platelets stored in plasma and platelet additive solution; other pathogen-reduction processes are available but they have not yet been FDA approved. The INTERCEPT system uses a chemical agent, amotosalen, that is activated by ultraviolet A light to bind nucleic acids so that DNA, and therefore cells, cannot replicate, so-called "photochemical inactivation". The process is effective against cells with nucleic acids, including viruses, bacteria, parasites, protozoa, and lymphocytes. Red cells and platelets are not affected. It is hoped that this technology will allow an extension of platelet shelf life, and because of its action against lymphocytes eliminate the need for irradiation to prevent transfusion-associated graft-versus-host disease. A Cochrane review, first published in 2013 and updated in 2017, assessed the effectiveness of pathogen-reduced platelets for the prevention of bleeding and demonstrated no differences in mortality, clinically significant bleeding, or severe bleeding between patient groups receiving INTERCEPT platelets and those receiving standard platelets. It did however find that pathogen-reduced platelet transfusions increased the risk of platelet refractoriness and the platelet transfusion requirement [36] The eventual use of pathogen-reduced platelets is still uncertain, and will likely depend on the ability of blood services to increase supply at a cost that hospitals find acceptable. This in turn may be dependent on the acceptance by regulators that some current requirements for infectious disease testing and irradiation of blood products may be dropped, and the same or similarly effective pathogen reduction processes are available for red blood cell concentrates.

Alternatives to platelet transfusions

Before considering alternatives to platelet transfusions, a key question is whether platelet transfusion is necessary at all. A systemic review of 6 randomized control trials of prophylactic platelet transfusion vs therapeutic only platelet transfusion for patients undergoing myelosuppressive chemotherapy or stem cell transplantation found that patients who received therapeutic only platelets had more days with a WHO grade 2 or above bleed, and a shorter time to first bleed [37] However there are particular groups of patients, for example recipients of autologous stem cell transplantation and nonbleeding patients with chronic bone marrow failure, in whom current evidence suggests no difference in bleeding between the 2 different platelet transfusion strategies [38,39] In TTP and HIT platelet transfusion is likely to be harmful [9].

Tranexamic acid reduces fibrinolysis by inhibiting the conversion of plasmin to plasminogen. It is inexpensive, safe, and can be given orally or intravenously. The clinical randomisation of an antifibrinolytic in significant haemorrhage (CRASH-2) trial of more than 20,000 people showed that patients who received tranexamic acid within 3 hours of trauma had significantly less mortality without an increase in thromboembolic events [40]. The World Maternal Antifibrinolytic (WOMAN) trial, reported in the Lancet in 2017, showed that tranexamic acid reduces death due to bleeding in women with postpartum hemorrhage with no adverse effects. Studies have also shown that in surgery tranexamic acid reduces both the risk of requiring a blood transfusion and the need for further surgery due to rebleeding. The trial to evaluate tranexamic acid therapy in thrombocytopenia (TREATT) trial, due to complete in 2020, is a double-blind, randomized controlled trial evaluating the safety and efficacy of tranexamic acid in patients with hematological malignancies [41].

Recombinant activated Factor VII (rFVIIa) bypasses other clotting pathways to directly activate clot formation at site of exposed tissue factor in damaged blood vessels. It is licensed for treatment of bleeding in patients with hemophilia A and B and inhibitors. However, the majority of its use is off label in patients with major hemorrhage. In this setting it has not been shown to reduce mortality and can cause serious thromboembolic complications. A systemic review of 35 randomized control trials including 4468 subjects found that treatment with rFVIIa was associated with an increased risk of arterial but not venous thromboembolic events, especially amongst the elderly [42].

Desmopressin causes release of Factor VIII and von Willebrand Factor from endothelial cells and is traditionally used in patients with von Willebrand disease and hemophilia A. More recently it has been shown to improve bleeding time in platelet dysfunction associated with uremia [43].

Various forms of artificial platelets have been developed to the preclinical stage or to the point of use in animal models. For example, synthetic hemostatic particles displaying fibrinogen have been designed to augment platelet aggregation. Infusible H12 peptide-coated liposomes that encapsulate adenosine diphosphate have been created by research groups in Japan with the aim of enhancing platelet activation [44] Microvesicles of platelet membranes, known as infusible platelet membranes, have similar hemostatic properties to intact platelets and have the advantage of being prepared from outdated platelet concentrates that might otherwise be discarded. Infusible platelet membranes have been successfully administrated to normal human volunteers and thrombocytopenic patients in phase I and II clinical trials, however further development has been limited by difficulties in demonstrating the efficacy of this product [45].

A future strategy in development is the generation of platelets from stem cells. If successful, manipulating megakaryocytes to produce platelets ex vivo might ensure that platelet supply meets demand without compromising platelet function through longer storage times. Moreau et al demonstrated that ectopic expression of transcription factors GATA, FLI1, and TAL1 in human pluripotent stem cells, along with chemically defined conditions induces them to differentiate into megakaryocytes that can be expanded, banked, and used to generate functional platelets [46]. Stem cells could also be manipulated to create HLA-compatible or HLA-silent platelets for use in patients with HLA antibodies. The major issue with this has been that yield is very low and the technique labor intensive. Whilst this approach has considerable promise the technology to generate functional platelets ex vivo on an industrial scale remains in its infancy.

Risk and avoidance of complications

Bacterial contamination

Bacterial contamination of platelets resulting in clinically significant posttransfusion infection is one of the biggest challenges in platelet transfusion. Initial implementation of bacterial cultures of platelet concentrates reduced the rate of sepsis secondary to contaminated platelets by 82.6% [47]. Culture techniques, like the BACT/Alert system, are able to detect Gram-negative bacteremia, but this measure has failed to detect Gram-positive bacteria early enough, resulting in a breakthrough rate of 50% [48]. Although Gram-positive infected platelet pools are more common, the clinical manifestation of this type of infection is less severe [49]. By implementing early bacterial culture the overall rate of bacteria contamination has been reduced from 1 in 2000-3000 [50,51] to 1 in 5399; a reduction of around 50% [49]. A most impressive reduction in bacterial contamination has taken place in the UK where the shelf-life is 7 days. NHS Blood and Transplant has implemented the use of BACT/alert protocol which reduced the rate of bacterial contamination by a quoted 90% [52].

False negative results are also problematic [53,54]. The main source of Gram positive bacteria is the donor's skin and better techniques of acquiring blood from donors could further decrease this rate [55] The implementation of culturing methods has led to questioning of the rationale for shortening of platelet lifespan to 5 days. However, the landmark study called Post Approval Surveillance Study of Platelet Outcomes Release Tested (PASSPORT) supported the 5-day shelf life strategy [56] At the moment, use of 6- and 7-day apheresis platelets is allowed by FDA with extra testing for bacterial contamination and new storage containers [57].

Alloimmunization and Platelet Refractoriness

Platelet refractoriness remains a clinical challenge and it is associated with worse clinical outcomes [58] It is generally under recognised by clinicians, with some studies suggesting that from 27% up to 44% of patients have unsatisfactory responses to platelet transfusions [59–61] Although there are some mathematical formulas that clinicians can use [62,63], a diagnosis of refractoriness can most simply be established by observing a failure to increment following at least 2 platelet transfusions [64] (Fig. 1). Nonimmune refractoriness is the most common cause of poor responses to platelet transfusions; the underlying clinical associations are infection, high fever, splenomegaly, disseminated intravascular coagulation, certain drugs, and bleeding [65].

Alloimmunization against platelets leading to platelet refractoriness is an important challenge in the practice of platelet transfusion. The commonest causative antibodies are against HLA class 1 antigens developed due to previous exposure to HLA antigens either through pregnancy or blood transfusions. Antibodies can also be developed against Human Platelet Antigens, but they are a rare cause of platelet refractoriness and usually associated with concomitant presence of anti-HLA antibodies [66]. It is important to note that the presence of anti-HLA antibodies does not necessarily translate into platelet refractoriness [67].

Other reactions

Reactions to platelet transfusions are a common occurrence. According to the Serious Hazards of Transfusion (SHOT) report of 2017, there were 90 reactions following a platelet transfusion out of 284 reported reactions to blood products [68] Out of these 90 reactions, 33 were allergic, 22 anaphylaxis type, 21 febrile, 12 mixed allergic/febrile, and 2 hypotensive. It is very likely that many reactions are still underreported.

Febrile reactions are usually benign and require no treatment other than antipyretics and cessation of the transfusion. However, it will often be appropriate to investigate for alternative more serious causes for the fever as well. Premedications offer no benefit in preventing those reactions as demonstrated by randomized trials [69]. However, they are still widely used around the world [70,71]

A plethora of mechanisms have been proposed to explain the pathophysiology of allergic reactions to platelet transfusions but a clear answer remains elusive. A type 1 hypersensitivity reaction to platelet proteins could trigger histamine release from basophils [72] The destruction of the platelets can also release mitochondrial damage associated molecular patterns that could act as proinflammatory mediators [73] A case of passive salmon and peanut allergy following platelet transfusion is also described in the literature [74]. A similar case of passive peanut allergy transfer following blood transfusion is also described [75] but the incidence of this type of reactions is limited in a few case reports. Acute haemolysis following platelet transfusion is extremely rare [76]. Most cases involve transfusion of group O door platelets to group A recipients.

Issues with current practice including data from studies and audits and how to improve platelet transfusion practice

In recent years there has been a coordinated drive to change the approach to the clinical use of platelet transfusions. It is now widely accepted that transfusion of all blood components, including platelets, is not without significant risks, particularly if they are used incorrectly. The value of platelet transfusions is both monetary, for example the National Health Service in England spent £260.7 million on blood components in 2017-2018 [77] and ethical, recognizing that platelet donation is a more demanding process for a donor than red cell donation as well as carrying risks for the recipient as described above.

The 2017 National Comparative Audit of Platelet Use in haematology patients in the UK found that 39% of prophylactic and 11% of therapeutic platelet transfusions fell outside of national guidelines and that 6% of prophylactic platelet transfusions were double-dose transfusions. Many initiatives exist to improve the appropriateness of platelet transfusion as part of a drive for Patient Blood Management. These include the publication of practice guidelines (Table 1), "Don't Give 2 when 1 Will Do," and the Choosing Wisely campaign. The latter is an international campaign; it lists tests and treatments across all specialties that are unlikely to benefit patients and encourages dialogue between doctors and patients about the risks and benefits of interventions and possible safer alternative options. With regards to platelet transfusion its key recommendation is to only consider transfusing platelets for patients with chemotherapy-induced thrombocytopenia where the platelet count is $<10 \times 10^9$/L, except when the patient has clinically significant bleeding or will be undergoing a procedure with a high risk of bleeding [78]

In addition to national audits and international initiatives, blood services and hospitals are increasingly harnessing technology to help regulate and educate platelet transfusion practice. Clinical decision support systems have been implemented to improve safety, help transfusion decision making and alert prescribers when they might be deviating from guidelines. In 2013 the Oxford University Hospitals introduced an end-to-end electronic blood transfusion system [79] This included an electronic blood ordering and decision support tool in which the prescriber was required to identify the patient's diagnostic group and indication for transfusion. If the transfusion was not justified an alert would appear prompting the prescriber to check the intended blood product prescription. Three years later Oxford University Hospitals found that compliance with agreed platelet transfusion triggers had improved from 54% to 99%, equating to an annual saving of £139,635 (unpublished data).

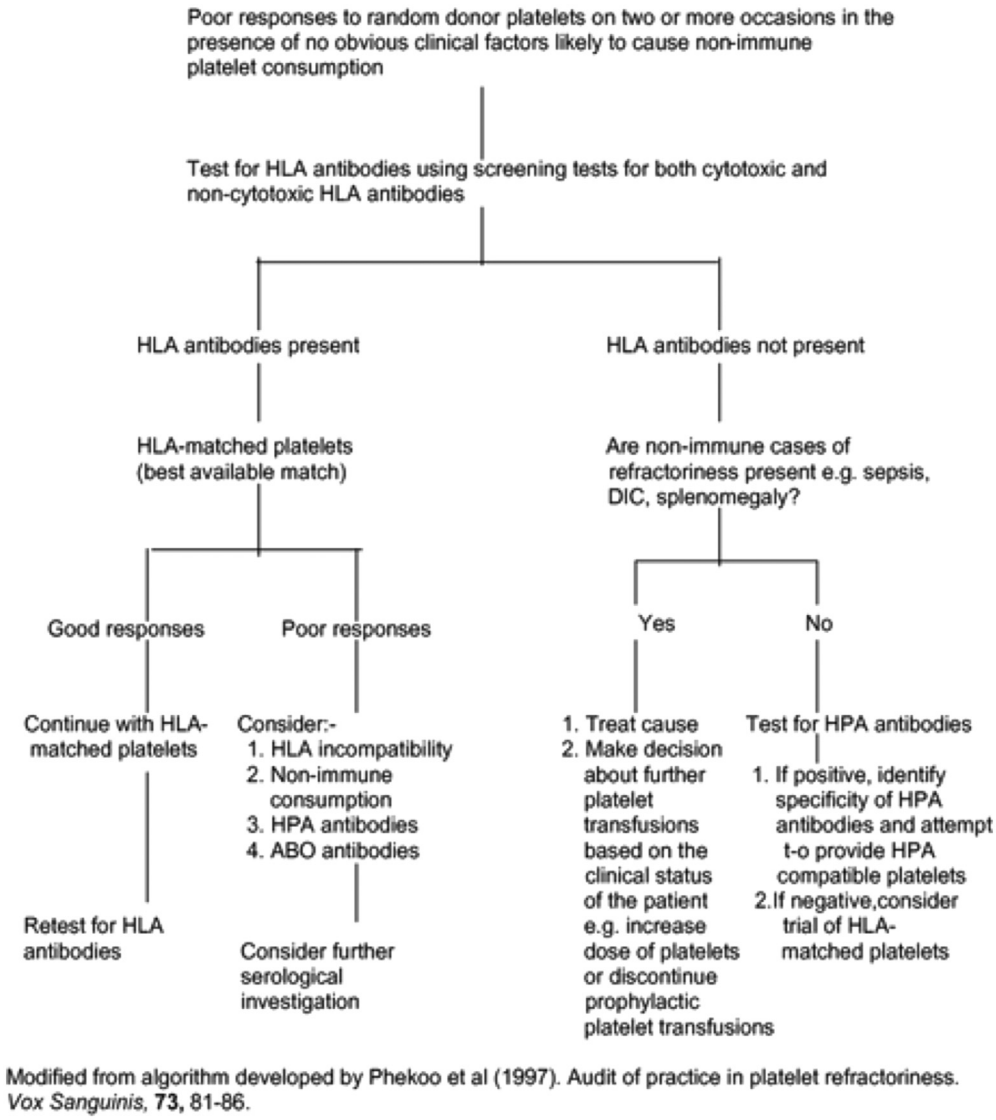

Fig. 1. Algorithm indicating how to manage platelet refractoriness [64].

A systemic review of 23 articles assessing the effect of decision support systems found cost savings in all 7 of the studies that reported financial outcomes along with good evidence of improved transfusion practice [80].

Summary and areas for future research

Platelet transfusion practice has come a long way since it was first demonstrated to be of benefit in 1910. Increasingly the focus has expanded from simply the most efficient ways to stop and prevent hemorrhage to recognition of the potential of platelet transfusions. There is a general trend towards recommending less platelet use, for example prophylactically before bone marrow biopsy and in critical care patients.

The population of patients receiving platelets is diverse and their differing needs are starting to be addressed. Trauma patients in remote military zones who have a normal functioning bone marrow require a fast-acting product that can be easily stored and transported. For these patients cryopreserved platelets and lyophilized platelets may offer an acceptable balance between logistical and functional concerns. Chronically thrombocytopenic patients on the other hand, are likely to require many more platelet transfusions over their lifetimes, and so for them strategies to reduce the incidence of alloimmunization, allergic reactions and transfusion-transmitted infections are of greater priority.

One of the greatest developments in recent years has been the establishment of national audit programs and national and international initiatives specifically to monitor and educate clinicians about good platelet transfusion practice. One of the key messages that these initiatives promote is involving patients in transfusion decisions. This is very appropriate and reflects broader changes in how medicine is delivered. As well as creating a population of well-informed patients, technology has huge potential to influence transfusion practice in a positive way. Some initial steps in this direction have been taken, in the form of clinical decision support systems, and no doubt this will be an area of great growth in the future.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest or competing financial or personal relationships that could inappropriately influence the content of this article.

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