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Platelet transfusion: basic aspects

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Summary

Platelet transfusions have been shown to prevent major haemorrhage and improve survival in thrombocytopenic patients. Since then, advances in the preparation of platelet components, including the introduction of pathogen reduction techniques, have been achieved. The number of transfused platelet components is still growing owing to the increasing number of patients treated for haemato-oncological diseases. Additionally, indications have been extended, for example to patients with drug-induced platelet dysfunction. This review focuses on current platelet component production and storage techniques, including pathogen reduction, indications for platelet transfusion and safety issues including alloimmunisation and management of platelet refractoriness.

Key words: *platelets; transfusion; refractoriness, safety*

Introduction

Platelet (PLT) transfusions were shown to reduce mortality from haemorrhage in patients with leukaemia in the 1950s [1]. Since then, although their use has grown and continues to grow [2, 3], a number of questions related to optimal preparation and storage of PLT components, and the indications, safety and efficacy of PLT transfusion have arisen. Nowadays PLT transfusions are an essential part of the supportive care of thrombocytopenic patients, such as those with haematological diseases. Additionally, inborn and acquired – mainly drug-induced – platelet dysfunctions can be overcome through transfusion of PLT components.

In this review we provide an overview of the basic aspects of PLT transfusions and indicate the still open questions related to this practice.

History

The discovery of blood circulation by William Harvey in 1628 was the premise for transfusion medicine [4]. Afterwards, the first animal-to-animal transfusions were performed, soon leading to early experiments with animal-to-men transfusions in the mid of the 17th century. The first men-to-men transfusions were performed in 1818 [5]. In 1900, the discovery of the ABO blood group by Landsteiner was the cornerstone for further improvements in transfusion medicine [6].

As major and fatal haemorrhage due to thrombocytopenia was a leading cause of death in children with acute lymphoblastic leukaemia, major efforts were undertaken to improve the supportive care of thrombocytopenic patients [7]. The first studies of PLT transfusions showed not only feasibility but also efficacy in preventing major haemorrhage in thrombocytopenic patients, thus improving overall survival [1, 8]. PLT component production and clinical use were further improved by technical developments, improvements in apheresis techniques, development of PLT additive solutions and studies on storage conditions [9–12].

In the last few years, pathogen reduction techniques have been successfully implemented for PLT components and have reduced, in particular, the risks of morbidity and mortality due to bacterial contamination, one of the most feared consequences for the transfusion recipient [13, 14].

Nowadays, more than 4 million PLT components are transfused worldwide each year [2, 15].

Platelet components: manufacturing, storage and pathogen reduction

Manufacturing of platelet components

PLT components can be obtained either from whole blood donations or by single-donor apheresis. Both techniques have advantages and disadvantages (table 1) [16, 17].

PLT components derived from whole blood donations are produced by pooling either platelet rich plasma or buffy coats from multiple donors, using different sequential centrifugation steps [18]. The buffy coat pooling technique is the one most widely used in Europe. Whole blood donations are selected and centrifuged (hard spin) to separate plasma and red blood cells from the buffy coat layer containing leucocytes and PLTs. Four to six buffy coats of the same ABO blood group are pooled and a second centrifugation is performed (soft spin) to separate leucocytes and residual red blood cells from the PLTs. The remaining PLTs are resuspended in plasma or in a mixture of additive solution and plasma (about 2:1).

For the production of single-donor apheresis PLT concentrates, various blood-separating devices are in use and licensed. Donor availability is a major limitation of this pro-

cess. Although specific adverse effects of PLT apheresis are well described [19, 20], PLT apheresis is considered safe and can be safely performed even in donors with mild anaemia and low iron stores [21].

In Europe, virtually all PLT components are leucocyte-depleted in order to reduce side effects [22].

Overall, the properties and efficacy of the above-described PLT preparations are similar [23–27], although some centres still prefer single donor apheresis components for patients with haematological diseases in order to reduce donor exposure.

Specifications of the final PLT product are stipulated by various regulations (Standards for Blood Banks and Transfusion Services, 26th edition. Bethesda, Maryland, AABB, 2009 and Guide to the Preparation, Use and Quality Assurance of Blood Components, 16th edition, Strasbourg, Council of Europe Publishing, 2010). In Switzerland the minimal PLT content has to be >2.4 x 10^{11}/unit, and the number of residual leucocytes and red blood cells has to be <1 x 10^{6}/unit and <5 x 10^{9}/unit, respectively.

Platelet storage

In contrast to red blood cell concentrates, PLT components are stored at 22±2 °C under gentle agitation. Studies have shown a better transfusion response if they are stored at room temperature [10]. Because possibly contaminating bacteria can grow well under these conditions, duration of storage is limited to 4–7 days, depending on whether bacterial detection methods or pathogen reduction are used. The introduction of pathogen reduction techniques might solve this problem, but possibly at the price of a slight impairment of PLT function. After the introduction of universal pathogen reduction in Switzerland, PLT storage is now limited to a maximum of 7 days. PLT concentrates have to be agitated during storage in order to assure optimal oxygen and carbon dioxide exchange through the storage bag and to avoid a fall of pH, which would compromise PLT recovery and survival after transfusion [28]. Once delivered by the blood bank, PLT components can be kept safely at room temperature and removed from the rotator for at least 6 hours [29].

The short storage period of PLT components requires optimal inventory management by blood banks, best achieved through a close cooperation with the clinicians.

Pathogen reduction

Various pathogen reduction techniques have been developed in recent years [13]. In Switzerland, the amotosalen/UVA based INTERCEPT® (Intercept Blood System, Cerus Corporation, Concord, CA, USA) has been introduced nationwide and deemed mandatory in 2011. Amotosalen, a psoralen derivative, is added to PLT concentrates, binds to deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and – upon activation by ultraviolet-A (UVA) irradiation – crosslinks DNA and RNA. An absorbing device then removes residual amotosalen. With this technique, replication of viruses, bacteria, protozoa and residual leucocytes is reduced (fig. 1). To date, amotosalen, at the concentrations used, is reported to be nontoxic and nonmutagenic [30–33]. Concerns regarding the efficacy of pathogen-reduced PLT components in preventing bleeding have arisen. Studies showed discrepancies in PLT recovery, measured as the platelet corrected count increment (CCI; see below): some studies showed lower CCI of pathogen-reduced PLT compared with standard PLT components [34–36]. Other trials could not detect any significant difference [32, 37].

However, in all these studies the standard PLT components used for comparison were prepared in different additive solutions or in plasma, and were partly gamma irradiated, raising concerns about the influence of product factors on CCI. Our own study comparing single-donor apheresis PLTs treated with amotosalen/UVA versus gamma-irradiated PLTs, both resuspended in the same additive solution (PAS III), showed no significant differences in CCI [38]. Clinical endpoints, measured as incidence and severity of World Health Organisation (WHO) grade 2 bleeding complications, were shown to occur slightly more frequently in patients supported with pathogen-reduced PLT [36]. However, there was no significant difference in severe bleeding complications, thus arguing in favour of pathogen-reduced PLT components, which are associated with improved safety concerning microbial contamination [39]. Two different meta-analyses [40, 41] reached conclusions different from the available studies as to the risk of WHO grade 2 bleeding. However, WHO grade 2 bleeding might not be the right surrogate outcome in PLT transfusions studies [42]. Since the nationwide introduction of pathogen reduction of PLT components in Switzerland in 2011, no transfusion-transmitted infection related to bacterial contamination has been reported to the national haemovigilance office, whereas the incidence of mortality due to bacterially contaminated PLT transfusions was estimated to be 1.5 cases/year before implementation of this method [3]. Two other methods are also on the way; however they are not yet licensed for use in Switzerland. Mirasol® (Terumo BCT, Tokyo, Japan) uses riboflavin, which associates with DNA/RNA and mediates an oxygen-independent electron transfer upon UV exposure causing irreversible damage to nucleic acids [43, 44]. Theraflex® (Macopharma, Tourcoing, France) uses UVC without any additional photochemically active compound [45]. The clinical experience with PLT components treated with these methods is still limited.

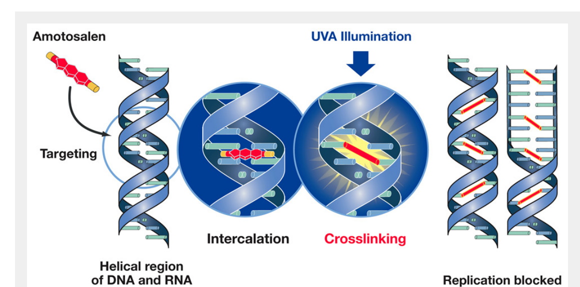

Figure 1

Pathogen reduction with the INTERCEPT® method.
Schematic representation of the mode of action of INTERCEPT®. Amotosalen intercalates within DNA/RNA. DNA/RNA crosslinks upon UVA irradiation. This blocks reproduction of pathogens and leucocytes.
Courtesy of Cerus Corporation, Concord, CA, USA.

Indications for platelet transfusions

PLTs can be transfused in order to prevent bleeding (prophylactic indication) or to stop bleeding (therapeutic indication) both in thrombocytopenic and in patients with normal PLT counts.

The vast majority of PLT transfusions are performed in thrombocytopenic haemato-oncological patients. Drug-induced PLT dysfunctions, such as in patients undergoing major cardiovascular surgery or, less frequently, due to inborn defects, are further indications for PLT transfusions. In patients with thrombotic thrombocytopenic purpura (TTP) and heparin-induced thrombocytopenia (HIT), PLT transfusions are in general indicated only in the case of severe bleeding.

For prophylactic PLT transfusions, many studies have shown that in patients with chronic stable thrombocytopenia a lower threshold of 5–10 x 10^9/l is safe [46, 47]. Today this threshold is widely accepted by clinicians and is generally indicated as standard in the various published guidelines for PLT transfusion [48, 49]. Based on the available studies and guidelines, every institution should establish its own transfusion triggers in collaboration with the blood bank and transfusion specialists.

The efficacy of prophylactic PLT transfusions in thrombocytopenic patients has been evaluated in studies comparing prophylactic and therapeutic PLT transfusions regimens in haemato-oncological patients. A recent trial showed an increase in severe and fatal haemorrhage in patients with acute leukaemia who received therapeutic rather than prophylactic transfusions [50]. This finding was confirmed by another recent noninferiority study in haematological patients, who did not receive prophylactic PLT transfusions when morning PLT counts were less than 10 x 10^9/l, but only in the case of bleeding [51].

Factors affecting efficacy of platelet transfusions

Assessment of PLT transfusion efficacy is a major challenge. Several criteria have been developed and evaluated, most of them including the post-transfusion PLT count (fig. 2).

Clinical endpoints (i.e. bleeding) are the most important method for evaluating effectiveness of PLT transfusions. Different scores have been developed with the goal of objectively assessing bleeding, but lack of standardisation of these methods is still a major problem [52, 53].

It has to be emphasised that CCI, the most widely used marker for measuring efficacy of PLT transfusions, does not necessarily correlate with clinical bleeding (see below, "platelet transfusion refractoriness").

Various factors have a direct or indirect influence on the efficacy of PLT transfusions:

Product factors

Platelet dose

In Switzerland the standard therapeutic adult dose is more than 2.4 x 10^{11} PLTs per unit. This varies according to different guidelines and national transfusion policies. However, PLT dose per unit has no effect on the incidence of bleeding in patients undergoing haematopoietic stem-cell transplantation or chemotherapy for haematological cancers or solid tumours [54].

ABO compatibility

ABO mismatched transfusions have a lower PLT recovery than ABO-compatible PLT transfusions [55]. Guidelines recommend that, whenever possible, PLT units issued for transfusion should be of the same ABO blood group as the patient's.

Other

Other product factors include storage time, resuspension of PLT in additive solutions vs plasma, PLT irradiation and pathogen reduction.

Interestingly, ABO blood group, PLT storage time and PLT source, which all have a moderate impact on CCI, had no impact on clinical bleeding [39].

Patient factors

Patient's gender, height and weight, several clinical conditions (listed in table 2), and drugs all have an impact on transfusion efficacy (see below, "platelet transfusion refractoriness"). On the basis of standard CCI or percent PLT recovery calculations, male patients showed inferior recovery rates, irrespective of donor sex. However, using an adjusted percent of platelet recovery, which takes into account differences in blood volume between males and fe-

Method		Adequate response	
Absolute platelet increment (API):	PLT_{post} (x 10^9/l) – PLT_{pre} (x 10^9/l)		
Platelet recovery (PR; %):	$\frac{\text{API x blood volume (l)}}{\text{PLT dose}}$	10-60 min. > 20%	18-24 h > 10%
Corrected count increment (CCI):	$\frac{\text{API x body surface (m2)}}{\text{PLT dose}}$	10-60 min. > 7.5	18-24 h > 4.5

PLT = platelet; PLT_{post} = post-transfusion platelet count; PLT_{pre} = pretransfusion platelet count.
PLT dose in 10^{11}/l.

Figure 2

Methods for assessment of platelet transfusion efficacy.

Table 1: Comparison of platelet components produced from whole blood donations or by apheresis.		
	Advantages	**Disadvantages**
Whole-blood derived PLTs	Availability PLT dose modification Avoids product waste No additional donor risk	Multiple donor exposure Difficult HLA/HPA matching
Apheresis PLTs	Less donor exposure Automation and standardisation HLA/HPA matching	Donor availability Higher production costs Limited PLT dose Donor risk from apheresis procedure
HLA = human leucocyte antigen; HPA = human platelet antigen; PLT = platelet		

males (according to Nadler's formula), neither donor nor recipient sex played any role in PLT recovery after transfusion in non-HLA-immunised patients [56].

Platelet transfusion refractoriness

As described above, assessment of PLT transfusion efficacy is very important. Fig. 2 shows different criteria for evaluating PLT transfusion efficacy.

Platelet transfusion refractoriness is defined as an insufficient post-transfusion PLT count increment. Usually it is defined as two or more consecutive CCIs of <7.5 at 1 hour or a CCI <4.5 18–24 hours after transfusion of ABO-identical PLT concentrates less than 3 days old (fig. 2) [57]. However, in daily routine practice the provision of these products (ABO-compatible and younger than 3 days) may be difficult and they are not always readily available. Nonimmune and immune factors are associated with PLT transfusion refractoriness (table 2) [58, 59].

Nonimmune factors lead to increased PLT consumption. Bleeding, infection/sepsis, splenomegaly and graft-versus-host disease (GVHD) in patients receiving allogeneic haematopoietic stem-cell transplantation are the most common nonimmune causes for refractoriness to PLT transfusions. Drugs are also an important cause and should be considered in the evaluation of patients with PLT transfusion refractoriness.

Immune factors are responsible for PLT transfusion refractoriness in approximately 20% of cases, with HLA antibodies being most commonly involved [58].

Less frequently, human platelet antigen (HPA) antibodies – or a combination of HLA and HPA antibodies – cause transfusion refractoriness. Minor histocompatibility antigens play an important role in haematopoietic stem-cell transplantation [60]. H-Y proteins are ubiquitously expressed Y chromosome-encoded minor histocompatibility antigens. These antigens however have no influence on the outcome of PLT transfusions [56].

In refractory patients, nonimmune aetiologies have first to be excluded (table 2 and fig. 3). If immune PLT transfusion refractoriness is suspected, a search for HLA-antibodies should be initially performed. If HLA antibodies are detected, various options for the selection of suitable PLT units are available. All of them require HLA class I typing of PLT donors:

(A) Selection of HLA-identical PLT components from HLA-matched apheresis donors

(B) Selection of HLA-compatible PLT products according to cross-reactive groups (CREGs) or in silico matching (HLA matchmaker). HLA matchmaker is a computer algorithm that identifies compatibility at the epitope level, which is determined by short sequences of polymorphic amino acids [61, 62].

(C) Selection of HLA-permissive PLT products, avoiding the recipient HLA antibody specificities by selection of donors lacking the corresponding antigens. Provision of HLA permissive PLT products is especially useful if HLA typing of the recipient is not available.

It is important to note that the presence of HLA-antibodies is – on the other hand - not always associated with PLT transfusion refractoriness. An *in-vitro* method to test compatibility is a PLT crossmatch, i.e., testing the patient`s serum against donor PLTs.

Fig. 3 shows a proposed algorithm, which may help in the case of PLT transfusion refractoriness [63].

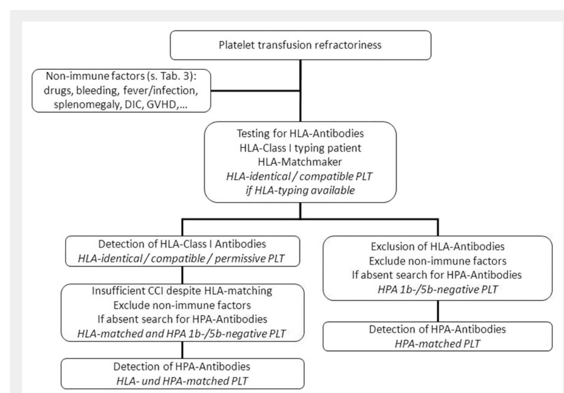

Figure 3

Proposed algorithm for the management of patients with platelet transfusion refractoriness.

DIC = disseminated intravascular coagulation; GVHD = graft-versus-host disease; HLA = human leucocyte antigen; HPA = human platelet antigen; PLT = platelet components

Definitions:

– HLA-identical: same class I HLA antigens (HLA-A and HLA-B) patient and donor

– HLA-compatible: according to HLA matchmaker (see text)

– HLA-permissive: recipient has no HLA antibodies against donor HLA antigens

Safety of platelet transfusions

PLT transfusions can be associated with various transfusion reactions (see table 3) [64].

Table 2: Factors associated with platelet transfusion refractoriness.
A. Nonimmune factors:
– Clinical factors: fever, infection/sepsis, splenomegaly, DIC, GVHD, bleeding
– Drugs*: vancomycin, heparin, GPIIb/IIIa antagonists, ...
– Product factors: storage duration, platelet dose, ABO compatibility, use of additive solution, irradiation, pathogen reduction
– Patient factors: sex, weight/height, history of pregnancy and transfusions
B. Immune factors:
– ABO incompatibility
– HLA-antibodies
– HPA antibodies
DIC = disseminated intravascular coagulation; GVHD = graft-versus-host disease; HLA = human leucocyte antigen; HPA = human platelet antigen * See also reference [58].

Febrile transfusion reactions are the most frequently observed side effects after PLT transfusions [3, 65]. Immune-haemolytic complications and microbial contamination of PLT components have to be excluded. Cytokines in PLT concentrates and anti-HLA antibodies of the recipient are the main causes for febrile transfusion reactions [66].

Allergic reactions are generally mild. Foreign donor plasma antigens are responsible for these. Patients with IgA deficiency and anti-IgA antibodies are at particular risk for severe anaphylactic transfusion reactions [67, 68]. In patients with IgA deficiency, these can range from urticarial to severe anaphylactic reactions including hypotension, dyspnoea and shock [69].

Haemolysis due to donor isohaemagglutinins (anti-A and anti-B) can occur after PLT transfusions [70, 71].

As already mentioned above, the risk of *microbial contamination* of PLT components can be reduced by pathogen reduction techniques [13]. Before the introduction of universal pathogen reduction in Switzerland, bacterial contamination occurred with an incidence of 1:3,000–1:10,000 [14]. Sepsis due to bacterial contamination is one of the most feared transfusion reactions as it can be fatal.

Transfusion related lung injury (TRALI) is a severe pulmonary transfusion complication, caused by HLA and human neutrophil antibodies against recipient antigens [72]. Storage of PLT in PAS has shown to reduce the incidence of TRALI [73, 86].

Transfusion associated circulatory overload (TACO) is seldom associated with isolated PLT transfusions. It occurs after rapid transfusion of large volumes of blood, as in cases of massive transfusion. Older patients and patients with cardiovascular diseases and renal failure are at increased risk of TACO [74].

Transfusion associated graft-versus-host disease (taGVHD) occurs in severely immunosuppressed patients after engraftment of donor lymphocytes and is often fatal. It can be prevented by gamma irradiation of PLT concentrates (25–30 Gy). Pathogen reduction techniques are equivalent to gamma irradiation in this respect [75].

Alloimmunisation can be a problem in patients receiving multiple transfusions. It is related to residual red blood cells and leucocytes in the PLT components, as well as PLT antigens. PLTs express carbohydrate blood groups like ABO, P, I and Lewis antigens [76]. Additionally HLA class I molecules are expressed, as PLT contain messenger RNA for the synthesis of these molecules [77]. PLT-specific antigens (HPAs) are glycoproteins involved in haemostasis [78]. Both HLA and HPA can stimulate the production of alloantibodies and thus cause PLT transfusion refractoriness. Additionally, HPA can cause neonatal alloimmune thrombocytopenia (NAIT), caused by maternal alloantibodies against paternally inherited HPA of the foetus. These HPA alloantibodies pass the placenta and are responsible for severe thrombocytopenia in the foetus and the newborn [79].

Although PLT express HLA class I antigens, the main cause for the development of HLA antibodies in chronically transfused patients are leucocytes contaminating PLT products. Universal leucoreduction is thus an efficient measure for the prevention of HLA immunisation [80–82]. Additionally, a careful evaluation of transfusion indications in order to avoid unnecessary exposure to antigens is of primary importance. Besides transfusions, HLA and HPA antibodies can develop during pregnancy, which is the most important cause of alloimmunisation [83].

Alloimmunisation against rhesus (Rh) D antigen can also occur following PLT transfusions, although PLTs do not express Rh antigens. Alloimmunisation against red blood cell antigens due to PLT transfusions are related to residual red blood cells in PLT products. Transfusion of Rh D negative PLT components is therefore especially important in Rh D negative female recipients of childbearing age [84]. In the case of transfusion of Rh D positive PLT concentrates to a Rh D negative recipient, which is sometimes unavoidable because of inventory shortages, administration of Rh immunglobulin has to be considered (120–300 µg IV).

Future directions

As demand for PLT transfusions will continue to increase, donor availability poses a major challenge for blood banks. For optimal management of PLT supply, a close collaboration between clinicians, blood banks and transfusion specialists is mandatory.

Alternative pathogen reduction techniques are under development and may contribute substantially to safer PLT transfusions.

Table 3: Transfusion reactions after platelet transfusion.

	Cause	Prevention
Febrile transfusion reaction	Cytokines; recipient HLA antibodies	Leucocyte reduction
Allergy/anaphylaxis	Anti-IgA antibodies in patients, donor plasma antigens	Antihistamines, steroids, washed PLT products
Haemolysis	Donor isohaemagglutinins	ABO identical transfusion, washed PLT products, use of PAS
Microbial contamination	Viruses, bacteria, parasites, fungi	Donor selection and testing, pathogen reduction, leucocyte reduction (CMV), limitation of storage duration
Transfusion associated lung injury (TRALI)	Donor HLA and HNA antibodies	Male donors, exclusion of donors with HLA and/or HNA antibodies
Transfusion associated circulatory overload (TACO)	Volume overload	Identify patients at risk (neonates, old patients, patients with cardiac and renal diseases), diuretics
Transfusion associated GVHD	Donor lymphocytes in immunosuppressed patients	Gamma irradiation (25–30 Gy), pathogen reduction
Alloimmunisation	HLA antigens on residual leucocytes HPA antigens on PLT Residual RBC in PLT component	Leucocyte reduction, donor selection, Anti-D prophylaxis

CMV = cytomegalovirus; GVHD = graft-versus-host disease; Gy = Gray (J/kg); HLA = human leucocyte antigen; HNA = human neutrophil antigen; PAS = platelet additive solutions; PLT = platelets; RBC = red blood cell

Additionally, studies on alternatives to PLT transfusions and other methods to improve haemostasis in bleeding patients are under investigation. Until then, a personalised and individualised patient transfusion management is the safest and most efficient approach to patients requiring PLT support.

Development of PLTs from haematopoietic stem cells, human embryonic stem cells and human induced pluripotent stem cells and expansion of *ex-vivo* generated PLT are further exciting fields of research [85].

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Figures (large format)

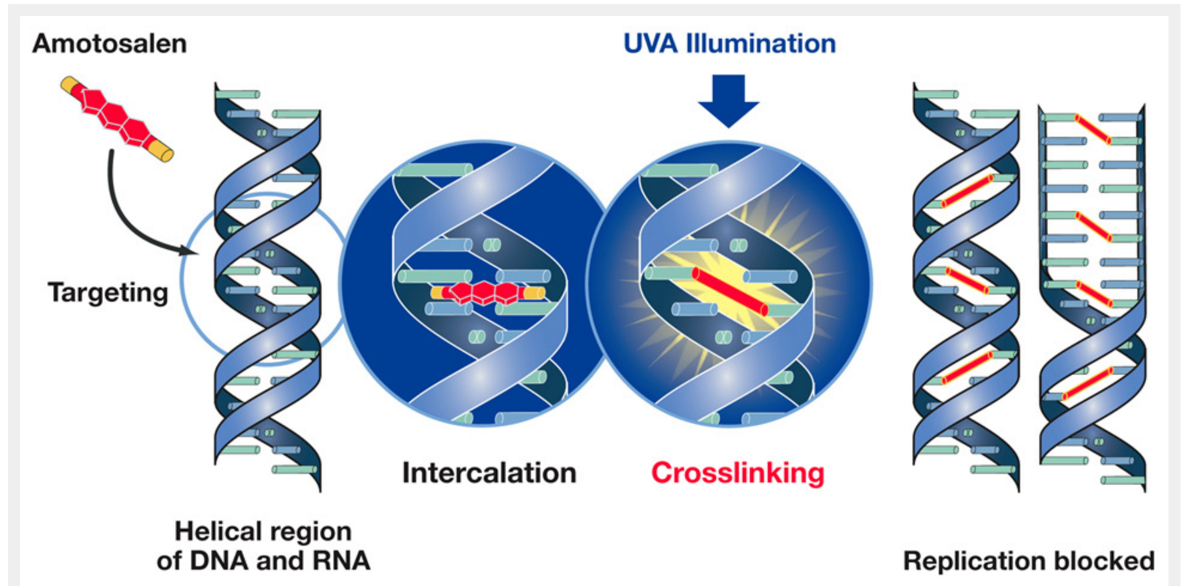

Figure 1

Pathogen reduction with the INTERCEPT® method.
Schematic representation of the mode of action of INTERCEPT®. Amotosalen intercalates within DNA/RNA. DNA/RNA crosslinks upon UVA irradiation. This blocks reproduction of pathogens and leucocytes.
Courtesy of Cerus Corporation, Concord, CA, USA.

Method		Adequate response	
Absolute platelet increment (API):	PLT_{post} (x 10^9/l) – PLT_{pre} (x 10^9/l)		
Platelet recovery (PR; %):	$\frac{\text{API x blood volume (l)}}{\text{PLT dose}}$	10-60 min. > 20%	18-24 h > 10%
Corrected count increment (CCI):	$\frac{\text{API x body surface (m2)}}{\text{PLT dose}}$	10-60 min. > 7.5	18-24 h > 4.5

PLT = platelet; PLT_{post} = post-transfusion platelet count; PLT_{pre} = pretransfusion platelet count.
PLT dose in 10^{11}/l.

Figure 2

Methods for assessment of platelet transfusion efficacy.

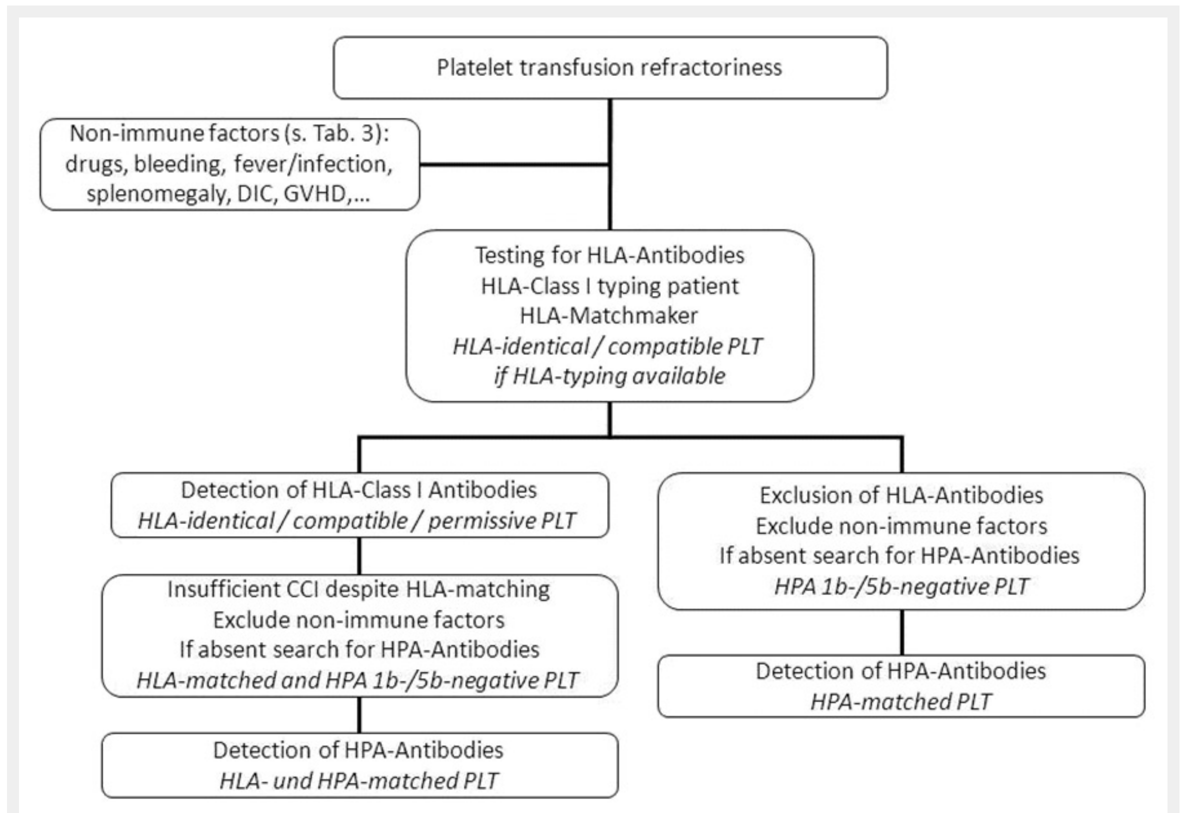

Figure 3

Proposed algorithm for the management of patients with platelet transfusion refractoriness.
DIC = disseminated intravascular coagulation; GVHD = graft-versus-host disease; HLA = human leucocyte antigen; HPA = human platelet antigen; PLT = platelet components
Definitions:
– HLA-identical: same class I HLA antigens (HLA-A and HLA-B) patient and donor
– HLA-compatible: according to HLA matchmaker (see text)
– HLA-permissive: recipient has no HLA antibodies against donor HLA antigens