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Review article

Platelet transfusion in adults: An update

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ABSTRACT

Many patients worldwide receive platelet components (PCs) through the transfusion of diverse types of blood components. PC transfusions are essential for the treatment of central thrombocytopenia of diverse causes, and such treatment is beneficial in patients at risk of severe bleeding. PC transfusions account for almost 10% of all the blood components supplied by blood services, but they are associated with about 3.25 times as many severe reactions (attributable to transfusion) than red blood cell transfusions after stringent in-process leukoreduction to less than 10^6 residual cells per blood component. PCs are not homogeneous, due to the considerable differences between donors. Furthermore, the modes of PC collection and preparation, the safety precautions taken to limit either the most common (allergic-type reactions and febrile non-hemolytic reactions) or the most severe (bacterial contamination, pulmonary lesions) adverse reactions, and storage and conservation methods can all result in so-called PC "storage lesions". Some storage lesions affect PC quality, with implications for patient outcome. Good transfusion practices should result in higher levels of platelet recovery and efficacy, and lower complication rates. These practices include a matching of tissue ABH antigens whenever possible, and of platelet HLA (and, to a lesser extent, HPA) antigens in immunization situations. This review provides an overview of all the available information relating to platelet transfusion, from donor and donation to bedside transfusion, and considers the impact of the measures applied to increase transfusion efficacy while improving safety and preventing transfusion inefficacy and refractoriness. It also considers alternatives to platelet component (PC) transfusion.

Introduction: Physiology and pathophysiology

Platelets are the key cellular elements of primary hemostasis [1]. In the blood, they patrol the vasculature and microvasculature, sense attrition and make repairs, prevent vascular leakage, and heal damaged endothelium [2,3]. The daily production of platelet progenitors by bone marrow ensures that there are enough platelets to perform these functions over the 100,000 km of vasculature within the body. These processes are estimated to consume between 7×10^{10} and 10^{11} platelets daily [4], and more than double that number in case of fever or infection. The body therefore needs to produce 10^{11} platelets daily, and to clear an equivalent number. Platelets are generated by the fragmentation of megakaryocytes, which are found almost exclusively in the bone marrow. Fragmentation to generate hundreds of platelets per megakaryocyte, thus, occurs mostly in the bone marrow [5,6], although some platelets can originate from pro- and pre-platelets in the bloodstream [7], or even the lung in some mammals [8]. Thrombopoietin (TPO) is the principal stimulatory factor acting on thrombopoiesis. Aged platelets display alterations to their surface markers, which are sensed by macrophages, principally in the spleen, although reasonably large numbers of platelets can be destroyed in the lung, and some in the liver [9]. Platelets have a lifetime of about 10–12 days in the bloodstream [8]. Platelet counts in the blood vary considerably between individuals, ranging from 150 to 400x10^{11}/L in healthy individuals. There is usually no decrease in platelet levels with aging unless production slows in the bone marrow (affecting

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central production). In such cases, thrombocytopenia is associated with anemia and leukopenia, resulting in pancytopenia. Peripheral platelet counts are affected by many diseases, some of which also affect platelet function [9]. Peripheral platelet destruction may occur in several types of infection (viral, bacterial, fungal) [10,11], organ diseases [12], for mechanical reasons, due to vascular or valvular prostheses for example [13], due to treatment with unfractionated heparin [14], the presence of antibodies against platelet moieties induced by alloimmunization [15], or an autoimmune disorder involving the consumption of platelets in microangiopathies, such as thrombotic thrombocytopenic purpura [16]. Pathological conditions of the spleen can also accelerate platelet decay. Indeed, about 30 % of the total platelet mass exists as an exchangeable pool in the spleen. In hypersplenism, the platelet count is usually 50–150 $\times$ 10^{11}/L [17]. Platelets can occasionally be trapped in blood clots and atheroma plaques, although this does not generally significantly alter platelet counts in the blood. A non-negligible number of drugs can mediate allergic-type platelet destruction, which is generally profound and severe [18]. Conversely, corticosteroids, erythropoietin-stimulating agents (ESAs), and TPO analogs can stimulate central platelet production [19]. Acute and massive bleeding results in intensive platelet consumption, to repair vascular wounds and to delivery platelet factors involved in hemostasis, through the production of factor V, to initiate factor VIII activation, in particular [20].

In physiological conditions, platelets are generally restricted to the bloodstream. They may, occasionally, migrate to tissues, as cargoes of various types of leukocytes, leading to disease in the affected tissues (lung, intestine, joints, etc.) [21]. Platelets have developed molecular for sensing dangers in the vasculature. The principal danger sensed is that of vascular erosion (or attrition). Platelets can fix erosion damage thanks to the healing and trophic factors they produce [22]. Platelets also deploy a parallel strategy to inhibit infectious and non-infectious microbes, many of which can bind platelets through by-stander ligation to platelet adhesion, aggregation, and other surface receptors. This finding highlights the ambivalent role of platelets during infection: antifungal, bactericidal and virucidal on the one hand, and pro-inflammatory on the other [23–27]. Non-hemostatic roles of platelets, which may nevertheless be involved in adverse reactions to transfusion, as described below, have been covered by other recent reviews and will not be dealt with in detail here [28,29].

Particular situations may result in thrombocytopenia in patients. Platelet component (PC) transfusion is designed, primarily, to replace the missing platelets in thrombocytopenic patients, so as to reduce considerably the inherent risk of severe bleeding. Thrombocytopenia – particularly central thrombocytopenia – is, indeed, the main clinical indication for PC transfusion.

Defining thrombocytopenia

Thrombocytopenia is defined as a lower-than-normal blood platelet count. Severe thrombocytopenia is defined as fewer than $5x10^9$ platelets/L of blood. The 2020 revision of the National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) proposes the following classification: grade 1: 75 to $150x10^9$/L; grade 2: 50 to $75x10^9$/L; grade 3: 25 to $50x10^9$/L; grade 4: <$25x10^9$/L. Extremely severe situations may be encountered in which platelet count is $5x10^9$/L or less [30]. Thrombocytopenia can be central and related to platelet production, or peripheral and related to platelet destruction or consumption. Central thrombocytopenia may have multiple causes. Hypoproliferative bone marrow is one of the most common causes, but numerous metabolic etiologies, such as liver fibrosis, splenomegaly, and alcoholism, can also result in low platelet counts [31]. Sepsis is also a frequent source of thrombocytopenia, acting through various mechanisms [32,33]. Mechanical causes, such as heart valve replacement, have also been described [13], and auto- and alloimmune forms of thrombocytopenia are also not infrequent.

Thrombocytopenia commonly occurs in pregnancy, and it is important to distinguish between physiological hemodilution and pathological immune or toxic causes, such as HELPP (*Hemolysis, Elevated Liver enzymes and Low Platelet count*) syndrome [34].

Thrombocytopenia also occurs in neonates [35]. This review will not cover the causes and consequences of thrombocytopenia during pregnancy or childhood, or drug-induced or drug-associated thrombocytopenia, as transfusion is generally not an option in such cases. Indeed, drug-induced thrombocytopenia is a rare, but non-exceptional cause of thrombocytopenia, resulting from treatment with unfractionated or low-molecular weight heparin [36]. Other drugs recognized as responsible for thrombocytopenia include quinine and quinidine, fiban-dependent antibodies, such as tirofiban, monoclonal antibodies, such as abciximab, gold formulations previously used to treat arthritis, and certain antibiotics, such as trimethoprim-sulfamethoxazole, vancomycin, and haptens, like penicillin [37].

In some situations, thrombocytopenia can be treated by platelet transfusion. There is longstanding evidence that platelets, whether administered in whole blood or as separated blood components, can stop bleeding, and restore hemostasis; these historical aspects have been reviewed elsewhere [38–40]. Other than for active and massive bleeding, for which platelet transfusion is now recognized, in addition to red blood cell concentrate and fresh plasma transfusion, it is essential to determine the precise causes of thrombocytopenia, as not all patients are eligible for PC transfusion. PC transfusion is often beneficial for central thrombocytopenia, but may be contraindicated in peripheral thrombocytopenia, other than in life-threatening emergency situations with active bleeding. Furthermore, clinicians are aware that certain medical conditions and the treatment of central thrombocytopenia may complicate PC transfusion, promoting refractoriness.

Indications and contraindications

Several scientific societies, often in association with regulatory agencies, have released recommendations for platelet transfusion [41–46]. Most are based on the WHO definition of bleeding stages as modified by Slichter (Table 1) [41]. However, the use of such a scale, although essential in clinical trials, is less practical in routine clinical use. The International Society of Thrombosis and Hemostasis (ISTH) scale developed by Webert (1981) and modified in 2011 may be preferable (Table 2) [47]. Most recommendations for randomized clinical trials (RCTs) are based on GRADE scaling (*Grading of Recommendation, Assessment, Development and Evaluation*) [48]. In general, recommendations for platelet transfusion consider two separate issues: (1) therapeutic use, for patients with significant bleeding, and (2) prophylactic use, for patients exposed to a risk of bleeding. Several years ago, there was a major debate opposing the prophylaxis and no prophylaxis attitudes, with divergent studies and opinions. The two viewpoints were initially championed by Professors H Wandt (against prophylaxis) [49] and S Stanworth (for prophylaxis) [50]. These two attitudes to prophylaxis have generated innumerable viewpoints, position papers, letters to editors, and so on. However, most clinicians continue to adhere to prophylaxis, as they consider patients as individuals, rather than focusing on statistical groups, despite the weak evidence supporting this approach in meta-analyses [51]. Scientific societies still face difficulties promoting a therapeutic-use-only policy, and instead generally prefer to call for further studies [52].

Table 1
Scales for evaluating bleeding in clinical trials and routine practice (after the World Health Organization [WHO] and [41]).

Grading	Examples
Grade 1	Oropharyngeal (such as gum) bleeding or epistaxis ≤30 min in 24 hPetechia on the skin or mucosae (such as gums) Purpura: ≤2.5 cm (1 inch) in diameterSpontaneous hematoma in soft tissue (such as muscle) Positive occult blood test Microscopic hematuria or hemoglobinuria Abnormal vaginal spotting
Grade 2	Epistaxis >30 min in 24 hPurpura extending over 2.5 (1 inch) cm Joint bleeding Melena, or hematemesis, or hemoptysisGross hematuria (visible upon light examination) Abnormal vaginal bleeding exceeding the spotting Blood in body cavity fluidsUnexplained retinal bleeding (caused by ophthalmic disease) Bleeding at invasive sites
Grade 3	Bleeding requiring blood transfusion over routine needs Bleeding causing hemodynamic instability
Grade 4	Bleeding associated with severe hemodynamic instability Central nervous system bleeding on imaging study, with or without clinical dysfunction Fatal bleeding

The main indications and contraindications for PC transfusion are presented in Table 3 [52–66]. The thresholds for PC transfusion are presented and discussed below. However, it should be borne in mind that, despite the development of charts addressing the course of action in different clinical conditions, uncertainties remain on mathematical models of thresholds, as confirmed, at least for neonates, by a recent report from Curley et al [67].

Platelet components

As we can see from the last two sections, the platelets naturally present in the blood (physiological role) and transfused platelets (pathophysiological roles) may have two different functions: (1) the repair of bleeding or leaking vessels, through the formation of a clot (adhesion, aggregation, secretion) and the activation of coagulation factors; (2) circulation within the vasculature, patrolling this network to detect and fix defects, and to maintain the endothelium by detecting abnormalities and secreting mediators to correct them [68]. Therapeutic platelet transfusion to stop active bleeding is based on the first of these roles of platelets, whereas prophylactic platelet transfusion to prevent bleeding is based on the second role.

Cold-stored platelets, which have recently returned to the scene after decades of abandonment, have proved very useful for therapeutic use in in emergency protocols; they can be stored in the resuscitation room or emergency room refrigerator [69,70] and are, thus, readily available. There is no need for these platelets to circulate or recirculate. Instead, they are used as a sort of glue for injured vascular tissues, delivering onsite healing factors and coagulation initiating factors, for example. Not all blood services have qualified this type of blood component as-yet, but there is accumulating evidence from emergency situations to suggest that this option should be seriously considered [71].

Conversely, platelets for prophylactic use should be subjected to minimal levels of stress, to ensure that they are not identified as foreign by the host scavenging system and can, therefore, circulate and recirculate, thereby preventing vessel leakage and, ultimately, bleeding [72]. Cold-stored platelets are clearly not suitable for use in this situation, whereas platelets at 22 °C, with clotting prevented by gentle agitation, are ideal [73,74].

Nevertheless, blood services face a dilemma: platelets in autologous plasma (100 %) have been shown to function optimally [75,76], but their use exposes recipients to more immunological, allergic, and inflammatory risks than the use of platelet components in a reduced type of plasma [77,78], which can significantly decrease the numbers of Transfusion-Related Acute Injury (TRALI) cases [79] and bacterial contamination [80]. Over the last two decades, several types of Platelet Additive Solution (PAS) have been produced, leading to improvements in terms of both platelet functioning and clinical safety [81,82]. There is a consensus that 65 % PAS/35 % plasma provides an acceptable compromise between functionality and adverse effects [83]. Cell-washing programs based on the use of 100 % PAS have been developed for patients displaying intolerance/allergy to foreign plasma [84,85]. The use of PAS also optimizes the functioning of Pathogen Reduction/Platelet Inactivation Technologies (PR-PI-Ts), which have been shown to be safe for all patients, including those with blood cancers, without overexposure to a risk of bleeding relative to the use of untreated platelet components [86–91]; PR-PI-Ts have significantly decreased the risk of bacterial contamination, the most feared risk in the context of platelet transfusion, in blood services implementing such technologies, as demonstrated by more than 10 years of evidence [92,93]. However, complications due to bacterial residues (toxins), bacterial spores, or supply chain incidents may still be a matter of concern, despite the use of PR-PI-Ts. Furthermore, depending on the pathogen concerned, PR-PI-Ts may also decrease or completely abolish viral risks [94] and the risk of infection with parasites, such as *Trypanosoma cruzi* [95], the vector of Chagas disease, which is occasionally transmitted by platelet components [96]. Two types of PR-PI-T platforms are available, using different chemicals, wavelengths for irradiation/illumination, and durations, and with different availabilities around the world. A third approach not requiring chemicals and based exclusively on high-energy UVC, is also currently being developed. Several recent reviews have been published on this topic (e.g., [97;98]). Given the differences in the physicochemical properties of the processes used to inactivate or reduce the abundance of pathogens or cell types (infectious, or non-infectious, such as leukocytes/lymphocytes), there may be differences in the consequences for platelet pathophysiology [99].

The principal types of platelet components (PCs) that can be stored at 22 °C and distributed by blood services to hospital blood banks are listed in Table 4. The clinical equivalence of Single-Donor Apheresis Platelet components (SDA-PCs) and pooled PCs is now widely accepted, even by those who previously challenged the effi-

Table 2
A summary of the International Society of Thrombosis and Hemostasis (ISTH) bleeding scale (after [47]).[a]

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (g/dL)	>11.0	9.5 – 10.9	8.0 – 9.4	6.5 – 7.9	<6.5
Leukocytes (10^9/L)	>4	3 – 3.9	2 – 2.9	1.0 – 1.9	<1.0
Granulocytes (10^9/L)	>2	1.5 – 1.9	1.0 – 1.4	0.5 – 1.4	<0.5
Platelets (10^9/L)	>100	75–99	50–74	25–49	< 25
Hemorrhage	None	Petechiae	Mild blood loss	Gross blood loss	Debilitating blood loss

[a] This scale evaluates acute and subacute disease severity and treatment toxicity (in adults).

Table 3
Main indications and contraindications for platelet component transfusion in adults [52–66].

Indications and contraindications		Clinical situations
Main indications for platelet component transfusions	Therapeutic platelet transfusion approaches in patients with clinically significant bleeding are recommended:	1. For patients with clinically significant bleeding in whom thrombocytopenia is a major contributory factor of bleeding, even if the platelet count is above the usual target of 10^9/L (of note, the 10^9 threshold is a matter of debate for multiple myeloma patients undergoing autologous hematopoietic stem cell transplantation (HSCT) [52]; the corresponding randomized controlled study (RCT) –PATH – is still underway (https://www.clinicaltrials.gov/ct2/show/NCT02650791) 2. For patients requiring massive blood transfusion (i.e., mean >10 whole blood units, red blood cell concentrates, platelet concentrates, and fresh therapeutic plasma units) 3. For patients with congenital or acquired platelet defects and patients needing surgery, irrespective of platelet counts, as this parameter is not useful for monitoring in this case 4. For patients presenting with disseminated intravascular coagulopathy (DIC) with the aim of maintaining platelet counts above $50x10^9$/L (though this target is not itself consensual) until the coagulation factors have been replaced and the bleeding has stopped [53,54] 5. In patients suffering from immune thrombocytopenia, if, and only if the bleeding is life-threatening [55,56] 6. Under discussion: For patients on anti-platelet therapy (except aspirin alone) and needing surgery, again irrespective of platelet counts [a]
	Prophylactic platelet transfusion is recommended:	1. For patients with severe thrombocytopenia undergoing chemotherapy and HSCT when platelet count is $<10^9$/L in the absence of additional risk factors, or $<20x10^9$/L in the presence of additional risk factors, such as fever or infection 2. For patients with chronic bone marrow failure of any cause, including myelodysplastic syndromes or aplastic anemia, although monitoring in such cases is individual and values may be outside the usual $10–20x10^9$/L target range 3. For patients scheduled to undergo invasive procedures that expose them to a risk of bleeding: The consensus is generally to maintain a platelet count above $50x10^9$/L for the insertion of a central venous catheter, for endoscopy or biopsy, lumbar puncture, and laparotomy; a lower threshold is accepted for simple dental extraction, or insertion of peripheral central catheter (PICC), skin biopsy, and any case in which bleeding can be controlled by adequate surface pressure. Conversely, a higher threshold is applied for ocular and neural surgery, with a recommended platelet count >80–$100x10^9$/L (in brain trauma, a $100x10^9$/L threshold is also preferred, by consensus) 4. For patients presenting with inherited or congenital platelet defects scheduled to undergo invasive procedures before whom alternatives are not possible (to avoid overexposure to a risk of alloimmunization). However, this last indication has been challenged by recent findings [57].
Contraindications for platelet transfusions include situations such as:		1. Bleeding not related to a decrease in platelet counts or functional defects of platelets [58] 2. The cause of thrombocytopenia is heparin-induced thrombocytopenia (HIT), in which platelet transfusion can exacerbate the underlying condition, unless there is an immediate life-threatening condition (this remains consensual despite conflicting data) [59,60] 3. The cause of thrombocytopenia is thrombotic thrombocytopenic purpura (TTP), again unless there is an immediate life-threatening condition or if this is the only way to ensure the safe insertion of a central catheter for therapeutic plasma exchange (TTP) therapy (this is also true for patients with hemolytic uremic syndrome [HUS]) [61,62] 4. Patients with toxic antibodies destroying platelets and underlying autoimmune disorders, in the absence of life-threatening conditions [57]. There is no longer sufficient evidence to support routine prophylactic platelet transfusion after cardiac surgery [64].

[a] This indication has been called into question by the PATCH controlled trial [65,66].

cacy of SDA-PCs [100,101]. Pooled PCs, containing 3 to 12 units, but generally a mean of 5 or 6 units, are mostly derived from whole blood with the buffy-coat approach. SDA-PCs and pooled PCs derived from whole blood are generally preferred over platelets obtained with Platelet-Rich Plasma (PRP) technology, resulting in pools of single units, due to their higher efficacy and lower rates of adverse reactions [102,103]. For the sake of completeness, we should also mention the intermediate platelet unit (IPU) technique, used on the Reveos™ machine. This process, which resembles PRP but is fully automated, is being developed in certain European countries and the Middle East. It should be stressed that although all these components are described as "standard", blood components are not at all standardized, with many variable factors rendering each individual PC different from all others (donors, machines, filters, devices, additives, solutions, rotation, shelf-life, etc.) [104]. The physicians responsible for prescribing PC transfusion and treating patients should be aware of this when evaluating platelet recovery in patients.

PCs have a short lifetime when stored at 22 °C. Depending on the regulations in the country concerned, they are stored for between three and seven days (mean = five days). The use of PR-PI-Ts makes it possible to extend the storage period for PCs from five to seven days, because it significantly decreases the risk of bacterial contamination, the primary determinant of the "shorter the

Table 4
The main platelet component presentations in use in countries with established transfusion systems, with maintenance at room temperature or 22 ± 2 °C (excluding cold, desiccated, and cryopreserved platelet storage).

Platelet components (PCs)	Single donor or pools	Leuko-reduction	Platelet additive solutions (PAS)	Pathogen inactivation or reduction technologies (PI-PR-Ts)	Irradiation	Antigen compatibility
Whole blood	Single	N/A	N/A	Possible (under validation)	Should be applied but rarely done in countries in which whole blood (WB) is used as a surrogate for PCs	Mandatory
Single-donor apheresis platelet components (SDA-PC)	Single	In-process or after collection	Yes or No	Commonly used	Unnecessary if PI-PR-Ts applied	ABO compatibility is preferred; the reference for HLA or HPA matching
Plasma-rich PCs (PRP)	Single or pools	Leuko-reduced or non-leuko-reduced	Generally, no for single units; possible for pools	Not commonly applied to these products	Possible	ABO compatibility requested for all plasma-rich components
Whole-blood buffy coat-derived PCs (WBBC-PC)	Pools of $\leq$ 12 (5–7 on average)	Leuko-reduced	Commonly used	Commonly used	Unnecessary if PI-PR-Ts applied	ABO compatibility is preferred

better" storage strategy. We will discuss other concerns with platelet shelf-time extension below.

In physiological conditions, platelets express antigens on their surfaces. The ubiquitous A and B tissue antigens are expressed to variable degrees, depending on the genetics of the individual. Platelets express H antigens in all individuals other than those with *H* gene deficiency (mostly referred to as Bombay type, *hh*), and A and/or B antigens are expressed in all individuals with a blood group other than O. However, expression of the A and B moieties is considerably weaker on platelets than on erythrocytes (1:100 in mean), and expression varies considerably among A- and B-positive individuals [105]. This implies that natural recipient anti-A or anti-B antibodies (the levels of which also vary considerably between individuals) may target A or B antigen-expressing platelets, leading to the clearance of these platelets from the bloodstream [106]. ABH system expression on platelets was first shown to be essential in 2005 [107]. A more recent investigation in India showed significant benefits, in terms of platelet recovery, of ABO-identical PC allocation as opposed to non-ABO-identical PC allocation in patients suffering from cancer and severe infections. These findings call for sustained clinical investigation at a larger scale [108], to confirm previous French observations [109]. Platelets also express HLA class I (A,B,C) moieties, with considerable quantitative variability between individuals, at levels generally-three orders of magnitude lower than those on granulocytes [110]. HLA variants are the main source of platelet antigen immunization in individuals [111]. Another important source of immunization is the Rhesus D (RH:1) red blood cell system, which is not expressed on platelets, but is found on the residual red blood cells contaminating PCs at minimal levels. RH:1 (RhD) immunization is potentially problematic in RH:-1 (Rh-negative) recipients, given that antigens other than D (i.e., C, c, E and even e [RH:2,3,4,5]) have occasionally been reported to be immunizing in certain recipients [112,113]. Human platelet antigens (HPA) are variants of adhesion and aggregation molecules [114,115]. Most of the 35 variants described to date are expressed on the α3, or β2 chains of the GPIIBIIIa (CD61/CD41) complex, the adhesion factor for fibrinogen, von Willebrand factor, fibrin, TSP-1, fibronectin and vitronectin [116]. HPA immunization is an infrequent event in adults [117], unlike fetus-to-mother alloimmunization (not covered by this review article) [118]. The ABO, RhD, HLA and HPA antigens may be considered, in this order, when PCs are delivered to patients [115]. The replacement of two thirds of the plasma with PAS decreases the levels of natural anti-A, and anti-B antibodies, which may be of considerable interest in cases in which ABO matching is not possible [41]. Attention is increasingly being focused on ABO matching as a means of maximizing platelet recovery in patients receiving transfusions. Nevertheless, practices remain highly variable within countries and blood services [119–121].

Like other blood components, PCs are leukodepleted (leukoreduced) in most blood services, and it is recommended that there should be fewer than 10^6 residual leukocytes per final component [122]. Apheresis procedures should be implemented before storage, either during or within six hours of collection. Components derived from whole blood should undergo leukoreduction as soon as possible, preferably before storage. It has now been demonstrated that efficient leukoreduction can be performed within six hours of blood collection, decreasing both the residual number of leukocytes potentially acting as sources of HLA antigens, and the levels of products secreted by leukocytes, which are largely pro-inflammatory [123]. In some places, leukoreduction takes place at the patient's bedside; this approach is considerably less efficient for limiting the adverse effects of leukocytes and adverse reactions to these cells [124].

PR-PI-T-treated platelets do not require irradiation to prevent residual lymphocytes from mediating graft-versus-host disease (GVHD) [125], a much-feared adverse event in hematopoietic stem cell transplantation, in patients undergoing chemotherapy regimens, and in acute myeloid leukemia patients (and of course, in the rare event of family donations, such as donations from mother to neonate) [126]. In the absence of PR-PI-T treatment, platelets must be irradiated (25–45 Gy) before delivery in these specific conditions. However, it has recently been reported that PI-PR-T-treated platelets can be used safely in hematopoietic stem cell transplant (HSCT) recipients without prior leukoreduction [127].

Finally, rare-group programs have been established, as for red blood cells, for patients lacking the main HPA antigens, and inventories of cryopreserved platelets have been generated in some countries, albeit at only a few sites, given the low viable platelet recovery scores obtained after thawing [128], but improvements are being made [129]. Ground-breaking technologies have led to the development of innovative programs for platelet dehydration and for the stripping of HLA antigens from platelets, for example, and for deriving platelets from diverse progenitor sources [130–132]. However, no efficacy and safety study has yet been published to validate the routine use of such products.

There is growing interest in a new blood component — Low anti-A, anti-B Titer O group Whole Blood, or LTOWB — which is used before hospitalization, to decrease hemorrhage damage. LTOWB provides both clotting factors and cold platelets, a blood component associated with higher survival in severely injured civilians and military servants [133,134].

Precaution

Prescribing physicians should bear in mind that: (1) PC transfusion is indicated for the treatment and prevention of bleeding in patients with severe thrombocytopenia or severe platelet dysfunction; (2) each prescription of a PC transfusion should be an independent clinical decision, with consideration of the relative risks and benefits to the patient; (3) there are both indications and contraindications for PC transfusion, and the cause of the thrombocytopenia and/or bleeding must, therefore, be established; (4) specific conditions may require an adjustment of the platelet transfusion threshold according to concomitant events, such as infection and/or fever, etc.; (5) not all the transfused platelets recirculate: about one third of those transfused are immediately sequestered in the spleen, at least in healthy individuals (further studies of patient populations are required) [135]; (5) in some situations, alternative interventions may be beneficial, to improve coagulation, hemostasis, bone marrow stimulation, etc. [136]. Certain complex situations exist in which platelet transfusion may be used in conjunction with antithrombotic drugs. Practices may diverge from the major recommendations, as reported in a national survey in France, following on from similar reports in the USA and Canada [137]. Once all the items on the checklist have been checked and the PC has been ordered, the prescribing physician should also consider the characteristics of the PC product and the possibility of storage lesions occurring during the collection, processing, and storage of PCs, or after other safety procedures, such as irradiation or application of PR-PI-Ts [138].

Both SDA-PCs (from single donors) and whole-blood buffy coat-derived PC pools (pooled PCs) are generally supplied in a large volume (mean volume of 400 mL). Even if two thirds of the plasma is replaced with PAS, a residual amount of plasma remains that is far from negligible. Plasma exerts an oncotic effect on the vasculature and this effect, together with the large volume, may create a serious risk of overload, rendering precautions necessary in the most fragile patients or patients with lung injury (not uncommon in sepsis situations). The treating physician should be aware of the ABO-RH groups of both the patient receiving the transfusion and the PC in cases of RH:1/RhD mismatch. It is essential to avoid RH:1/RhD mismatch in female patients of child-bearing age and preferable to avoid such mismatches in young patients likely to undergo frequent transfusions [113]. All situations exposing patients to a pro-inflammatory situation, such as mismatched transfusion, may aggravate existing inflammatory conditions, as observed in post-hematopoietic stem cell transplantation, major surgical procedures, and trauma [139]. By contrast to red blood cell concentration transfusions, cross-matching with patient plasma is not routinely performed for PCs, other than in documented cases of a history of refractoriness to previous PC transfusions. A slow recovery of platelet counts, or increments should lead physicians to check for ABO, and possibly HLA mismatches [140]. Caution is essential in patients with demonstrated intolerance to previous transfusions, particularly PC transfusions. Clinically demonstrated or documented allergy (difficult to achieve) indicates a need for plasma reduction and washing or antibody absorption on columns. Any sign of intolerance should be considered to indicate a risk of the transmission of a bacterial infection by transfusion, even if the PCs were treated with PI-PR-technology [141]. Indeed, the bacterial load may have exceeded the reduction capacity of the technique (which also varies between the two techniques currently in use and the third, in development). There may also have been an incident in the processing chain, or toxins may have been secreted. Bacterial spores resistant to the processes used may be present; this situation is infrequent but cannot be completely ruled out [142,143]. Transfusion-transmitted bacterial infection (TTBI) should be distinguished from the mobilization of bacteria from a catheter (retrograde infections), although such mobilization has become much rarer since the introduction of treatments of implanted materials to prevent bacterial film formation [144]. However, as most of the blood products administered to cancer patients are now transfused through semi-permanent catheters, bacterial colonization and biofilm formation remain a matter of serious concern, despite the progress made [145], as shown by Ramirez-Arcos et al [146]. Importantly, many infections are known to be masked because intensive care patients frequently receive antibiotics, often in multiple-drug combinations.

The patients receiving PC transfusions are generally fragile patients who are either actively bleeding or at risk of bleeding after treatment (e.g., chemotherapy). Risks are frequently additive, and a knowledge of all the risks provides the best guarantee of patient safety. This requires prescribing physicians to have experience with blood bank issues and a knowledge of the types of blood components delivered.

Platelet dose (prophylactic platelet transfusion)

Determining the optimal dose of platelets for transfusion into a patient in need remains one of the major challenges in transfusion medicine, and this issue is of particular importance in prophylactic platelet transfusion [147]. In 1973, Roy et al demonstrated that a standard-dose platelet transfusion could safely be used instead of a higher dose of platelets, without increasing the incidence of bleeding, and many studies have since investigated the possibility of transfusing even lower doses of platelets in this context [148]. The study by Roy et al was performed in children, but the results can be extrapolated to adults, based on authors' previous works [149]. It is widely accepted that one "standard dose" is the equivalent of a single donor-PC containing a minimum of $3.0x10^{11}$ platelets or four to six whole blood-derived platelet concentrates used to make a pool. The European Directory for the Quality of Medicines and Healthcare (EDQM) Guide requires a minimum of $2x10^{11}$ platelets per pool or apheresis product, and the mean platelet content in a "standard" pool (4–5 units) is about $3.0–3.5 \times 10^{11}$. However, caution is required in interpretation of the term "standard", as PCs differ from each other for a multitude of parameters [122]. Some countries have defined the minimum content as $2.4x10^{11}$ platelets, whereas others allow so-called "jumbo" single donor-PCs ready prepared for single use or to be split in two "mini"-doses. These differences have made it difficult to interpret publications, as the standard dose in France may correspond to a "jumbo" dose in the USA, for example. The appropriate "dose" of platelets has been more carefully assessed in two randomized controlled trials. The PLADO trial was a multicenter, randomized controlled trial (RCT) enrolling 1,351 patients and comparing three different doses of platelets with a WHO grade 2 risk of bleeding [150]. The three doses were 1.1×10^{11} platelets/m^2, 2.2×10^{11} platelets/m^2, and 4.4×10^{11} platelets/m^2. Patients received platelet transfusions when their morning platelet counts were $1x10^9$/L or less. This study showed that the incidences of higher grades of bleeding and other adverse effects were similar in the three groups, but that the number of platelet transfusions administered was significantly higher in the low-dose group than in the medium-dose and high-dose groups. The PLADO study found that bleeding rates

were similar in all three arms, with bleeding occurring in ~70 % of subjects, regardless of platelet-dose strategy. The higher-dose arm not only had the longest intertransfusion interval, but also used the most platelets.

The second trial, the Strategies for Platelet Transfusion or SToP trial, another multicenter RCT, compared a "low-dose" platelet transfusion (1.5–2.9 × 10^{11} platelet product) with a "high-dose" transfusion (3.0–6.0 × 10^{11}) in patients with chemotherapy-induced thrombocytopenia [151]. Patients were transfused at a platelet count of $1x10^9$/L. This trial was specifically designed to compare platelet transfusion doses in terms of the risk of significant bleeding. The numbers of patients reaching the endpoint of WHO grade 2 (or higher) bleeding were similar in the two arms of this study, but the trial was stopped early when 5 % of the patients in the "low-dose" arm suffered grade 4 bleeding. Meta-analyses of RCTs concluded that a low-dose strategy for prophylactic platelet transfusion was not associated with a higher risk of bleeding than medium- or higher-dose strategies [152,153]. Older studies, mostly performed in Europe, showed that higher doses resulted in higher post-transfusion increases in platelet levels and longer intervals between transfusions [154]. Modeling showed that the increments and decrements observed with infused platelet doses were saw-curve shaped [155], suggesting that the medium dose was the most appropriate; the low dose was too low, and there was no additional benefit from a high dose. Bou Assi et al reviewed clinical trials of platelet doses from 1973 to 2014 and came to similar conclusions [156]. Triulzi and the AABB concluded that: "*These data support the safety of a low-dose platelet strategy for prophylactic platelet transfusion for stable adult and pediatric hematology/oncology inpatients including Hematopoietic Stem Cell Transplant (HSCT) recipients. In clinical practice, low-dose platelets are typically reserved for periods of platelet shortages. The low-dose strategy may not be appropriate for outpatients in whom a longer transfusion interval would be desirable as was seen with the higher-dose strategy in PLADO. These data derived in the prophylactic setting should not be extrapolated to patients who need platelet transfusions for active bleeding as lower-dose platelets in this setting have not been adequately studied*" [157].

The issue of dose has not been looked at again more recently, perhaps because attention has shifted to the justification of prophylaxis or non-prophylaxis approaches [158], the safety of PI-PR-Ts [91,92], ABO matching [158], and, to a lesser extent, the age of blood [159–162]. All but one of these issues (the exception being PI-PR-T) were addressed as secondary endpoints by Slichter et al in the PLADO trials, and the data obtained conflicted with those of other studies [147,163]. Economic issues also complicate the debate about the most appropriate dose because PCs are generally expensive, and this is particularly true for single donor-PCs. In their 2014 review [156], Bou Assi et al found that low platelet doses were less costly for hospitals and inpatients in situations in which they were charged by dose. However, standard, or high-dose platelet transfusion strategies are more cost-effective overall, as they decrease the numbers of transfusions and hospitalizations. It is now reasonable to conclude that there is no difference in efficacy between single-donor PCs and pooled buffy-coat PCs. A Patient Blood Management (PBM) approach might best identify optimal strategies in terms of doses and intervals, as the interval between consecutive transfusions is also an important readout of the quality and efficacy of platelet transfusion. The rationale for promoting higher doses is based largely on the aim of increasing the intervals between consecutive transfusions [164–166], thereby decreasing multiple exposures (attenuating the risks of bacterial infection and immunization, and of developing transfusion-related acute lung injury (TRALI), at a time at which such adverse reactions were relatively frequent) [167,168].

Recommendations also differ between countries. For example, in France, patients receive $5x10^{10}$ platelets per kg body weight, and the PC bag allocated is that closest to the mean content meeting the need. This dose is lower than the previous recommendation of $7x10^{10}$ platelets per kg body weight in adults [46], and the change in recommendations was probably influenced by the logistic issues faced by blood services.

Safety

One of the major risks associated with platelet transfusion is transfusion-transmitted bacterial infection (TTBI), a major concern of blood services. There is no safe level of bacteria in any blood product. Multiple precautions have progressively been established to reduce this risk, particularly at the donor and donation level, with stringent donor selection, specific skin and device disinfection, discard of the first 30–40 mL of blood from the collecting pouch (not lost, but diverted to a separate pouch for laboratory testing), filtration, rotation and inspection for dispersible clots formed in the bag (by means of the well-known "swirling test" etc.), and the assignment of lower shelf-life values to PC bags (Japan used to discard after three days in the inventory, Germany after four days, and most countries after five days) [169]. Most blood establishments worldwide used to test for bacterial contamination with one of the few systems available, none of which could guarantee sterility [170]. Depending on the study, it was estimated that bacteria were present in 1/1,000–3,000 bags, although not all these bacteria were viable, for diverse reasons (low inoculum, alteration during processing, filtration, etc.) [171,172]. Exhaustive hemovigilance is not possible because many PC recipients are on antibiotics (often administered intravenously). The switch to the use of PAS has significantly decreased bacterial contamination, and PI-PR-T has proved almost 100 % effective according to surveillance data for more than 10 years in some countries (Switzerland, some regional blood banks in Spain), five years in France, and various periods in many other countries or regions [90,92,173–175]. Several methods have emerged over the last three decades for bacterial culture and the assessment of bacterial growth (aerobic and/or anaerobic) in PCs. However, all these methods have limitations. The US FDA has issued guidance for bacterial safety [176,177], and clearance is currently waited for PI-PR-Ts, which have emerged as the safest approach.

One key concern in PC transfusion, particularly if repeat transfusions are required, is preventing refractoriness due to the immunization of recipients against elements of the HLA, or more rarely HPA systems [178,179]. Stringent leukoreduction to below 10^6 residual leukocytes/component, particularly if performed soon after blood collection, has proved effective for reducing the alloimmunization risk (indirect presentation) [180]. The use of PAS also decreases the transfer of soluble HLA antigens from donor to recipient (direct presentation) [180]. However, alloimmunization mechanisms are complex and highly dependent on the recipients' own HLA group, disease, and treatments; as a result, some cases of alloimmunization cannot be prevented [104]. The mechanisms of HLA immunization are diverse and complex and have recently been reviewed elsewhere [181,182]. Some HLA moieties can be avoided by selecting HLA-typed donors, who are invited to donate blood. This approach can prevent exposure to the HLA implicated in alloimmunization in recipients who have already produced antibodies. However, crossmatching tests are less readily available for platelets than for red blood cells. Several studies have shown that ABO pairing could limit HLA alloimmunization, providing support for the argument that ABO matching should be performed wherever possible [142,183,184].

Concern was recently expressed about the extension of shelf-life from five to seven days after PI-PR-T, and the theoretical possibility that this might favor alloimmunization [184,185]. A group in Basel, Switzerland, reviewed the available evidence and found no significant difference in alloimmunization rates between storage periods of five and seven days [186]. However, questions have been raised about the benefits of extending storage time to seven days after PI-PR-T are questioned, and arguments have been made in favor of extended hemovigilance [187,188].

The frequency of adverse reactions is higher for PC transfusion than for the transfusion of packed red blood cell concentrates, with a higher rate of inflammatory reactions, in particular [189,190]. This is understandable, as platelets are themselves pro-inflammatory cells. Indeed, the anti-inflammatory mediators of these cells, such as TGF-ß, have proved more labile than the many pro-inflammatory markers, such as TNF-α, IL-6, CD40L, IL-27, HMGB1, Ox40L, IL-13, and IL-1. Platelets that have been stressed or subjected to long periods of storage are more likely to secrete factors with particular profiles or patterns, depending on various donor and recipient parameters [191–197]. Febrile non-hemolytic transfusion reactions (FNHTRs) and allergic-type reactions (resembling allergy but with neither an identified allergen nor IgE antibody production) are the most common. The incidence of such reactions decreased considerably following the introduction of PAS-based strategies [76]. A recent retrospective survey by Mertes et al in France suggested that PI-PR-T plays a role in decreasing the frequency of adverse reactions [78]. Various hypotheses based on the "two sides of the same coin" effects of platelets in pathophysiology can be put forward. For example, it has been hypothesized that during storage, the pro-inflammatory aspects of platelets are amplified [198,199]. The IL-10 pathway may, hypothetically, be of interest for countering the inflammatory response to certain transfusions.

Finally, no consensus has been reached concerning the optimal age of platelet components at delivery, but it is possible that platelets stored for longer periods trigger stronger inflammatory reactions, implying that the use of PCs sooner after their isolation would be preferable (there seems to be a threshold at day three, as reported in large-scale studies) [165,200–202].

Technical points

When the blood bank receives a request for transfusion from the physician, the pretransfusion sample is check by the staff, and ABO and RH:1/RhD blood groups are confirmed. The PC is issued as and when required, and these details are indicated on the blood request form, which is timestamped. ABO and RH:1/RhD group-specific PC is recommended, although out-of-group PCs may be issued. When an emergency request is made for platelet transfusion, as in cases of traumatic bleeding, PCs corresponding to the patient's blood group may not be available. In such cases, "O" group platelets are given, if available, bearing in mind that even with the replacement of two thirds of the donor plasma with PAS, non-negligible amounts of natural anti-A and anti-B natural antibodies are transferred [203]. HLA- or HPA-typed PCs can be ordered if necessary due to documented refractoriness and alloantibody detection, although this requires extra time for the blood service to invite *ad hoc* donors to donate blood (single-donor PCs) [204]. Washed, reduced-plasma PCs can be made available, if necessary, in cases of documented severe allergic/anaphylactic reaction during or after previous transfusions [84]. Irradiated PCs can also be issued if required — preferably irradiated immediately before use rather than in advance [205] — but not after the implementation of PI-PR-Ts [206]. All such requests must be specified and discussed with blood bank specialists.

Informed consent must be obtained from the patient and must be traced in the patient's file before a request is sent to the blood bank. The intravenous line must be in place before the PC is issued by the blood bank. Staff at the issue counter perform final checks of various details, including patient ID, unit number, blood group, and abnormal appearance or clumps suggestive of infection in the PC bag, before issuing the unit. The hospital ward staff performs a double-check upon receipt and acknowledges the administrative, immunologic (group) and quality conformity (no non-dispersible clumps, within the expiry date, number of platelets).

The patient should be fitted with an appropriate IV cannula of from 14 G to 26 G in size (18 G to 22 G on average, in adults). The catheter may be central or peripheral. In exceptional cases in which IV access is not possible, the intraosseous route can also be used for transfusion. As for all transfusions, most regulatory authorities request that the line is dedicated to transfusion and that no other fluid is delivered via the line that could alter the transfused cells and generate neoantigens or accelerate transfused cell scavenging by the host reticuloendothelial system.

Pretransfusion medication, such as antihistamines, has been administered in certain situations, in patients with a history of allergic reaction during previous transfusions. Meperidine or corticosteroid may occasionally be prescribed in patients with a history of severe rigor during transfusion, but this approach is non-consensual [207,208]. There are no clear conclusions concerning the recommendation of IV injections of furosemide, which have been used empirically to prevent volume overload [209]. Paracetamol/acetaminophen is often used for premedication in patients receiving PC transfusions, but a randomized double-blind placebo-versus-control trial reported no decrease in inflammatory symptoms with such pretreatment [210].

The patient's pretransfusion vital signs are recorded by the transfusionist, who then aseptically pierces the PC bag to connect it to the IV line. A standard blood transfusion set, with an inline filter of 170 to 260 µm, is used. A transfusion rate of 2 to 5 mL/min is generally used, resulting in the completion of transfusion within one hour. Slower flow rates are used in patients at risk of fluid overload. The patient is closely monitored during transfusion, with a recording of vital signs every 15 minutes. If a transfusion reaction is suspected at any point, the transfusion is stopped immediately, and the appropriate management protocol is followed. The patient is then closely monitored for the next six hours. Nighttime transfusions should be avoided other than in emergency situations, so all prophylactic transfusions should take place during the daytime.

Efficacy and assessment of platelet transfusion: Factors influencing platelet transfusion efficacy

Despite the high frequency of platelet transfusion (330,000 such transfusions are performed annually in France), physicians on the wards and laboratory medicine specialists frequently have no reliable means for measuring efficacy.

In cases of active bleeding, efficacy is monitored at the patient's bedside by assessing the intensity or cessation of bleeding. It is difficult to evaluate the platelet component itself, because the patient may also be transfused with red blood cell concentrates, which have a non-negligible effect on bleeding, as red blood cell shear allows laminar flow with the adhesion of platelets to leaking or injured vessels. Hb levels below 8 g/dL amplify the risk of hemorrhage (Table 2). Plasma clotting factors (fresh therapeutic plasma, cryoprecipitate, prothrombin complex concentrates (PCCs), and, occasionally, purified, or recombinant coagulation factors, such as fibrinogen and FVIIa, may be administered in parallel. Other monitoring tools, such as global clot-forming assays, are sometimes used by intensive care specialists and anesthesiologists during sur-

gical or resuscitation procedures in which major bleeding may occur (i.e., thromboelastography (TEG) and rotational thromboelastometry (ROTEM) [211], providing algorithms to guide the choice between blood components and plasma derivatives, procoagulant drugs, and combinations). Platelet function tests, such as Verify-Now™ (platelet aggregation in whole blood) [212] and the vasodilator-stimulated phosphoprotein (VASP) assay for patients on antiplatelet drugs, have recently been introduced, but are of limited value [213].

The monitoring of prophylactic platelet transfusion is complex. It is widely accepted that both a clinical indicator, the bleeding scale score (in general, that of the WHO [Table 1] or the ISTH [Table 2]), and a laboratory indicator, the corrected count increment (CCI) should be used. Patients exposed to a risk of bleeding due to hypoproliferative thrombocytopenia, are examined at least twice daily, to check for an absence of exteriorized bleeding (epistaxis, digestive, urinary) and for micro-bleeding, focusing on the gums and retina, with constant concern about bleeding in the central nervous system.

The monitoring of platelet transfusion efficacy has limitations. One of these limitations is the non-linear effect of transfused allogeneic platelets in an individual, assessed with radiolabeled platelets in early studies, and then following transfusion in healthy individuals. Studies currently underway with biotin-labeled platelets may provide additional insight [214]. These studies have revealed considerable variation of platelet "recovery" [215,216], probably for several reasons linked to the donor, the blood service, operator processing and the recipient. Another limitation of the clinical evaluation is subjective variability between physicians. Laboratory medicine helps to provide objectivity, through determinations of actual platelet counts and count increments. An increase in platelet count is expected after PC transfusion, and the aim is to achieve an increase to a value above the critical threshold. The corrected count increment is widely used, to increase precision and to correct for the patient's body mass and the dose of platelets infused. The CCI is defined as: CCI = [(platelet count post transfusion – platelet count before transfusion)/μL × body surface area (BSA) in m^2] / number of platelets transfused × 10^{11}. A CCI value of 5500 to 7000 (or higher) is considered to constitute an adequate response, one or 24 h after transfusion. It should, however, be noted that CCI cannot predict transfusion success, but provides an indicator of any refractoriness. The recovery of platelet function is not routine. However, absolute count increment (ACI or CI) may be a better indicator, because increasing the count to a value > 10^{11} should decrease the bleeding risk, given the stronger correlation of ACI than of CCI with hemostasis [217]. CCI is a ratio taking both dose and patient body weight into account. It is not, therefore, a direct measurement of outcome. Another valuable tool for measuring transfusion efficacy is the interval between consecutive transfusions, albeit with the limitation that this interval may be influenced by the delivery of PC bags by the blood service. These intervals depend on decreases in the patient's platelet count, with a new transfusion required when the count falls below the chosen threshold or in the presence of any sign of bleeding. In situations in which blood banks can place orders with blood services round-the-clock, seven days per week, intervals of three to four days are considered to indicate a good response, and intervals of one to two days are considered to indicate a poor response [218].

In all cases, an increase of 10^4/μL at 24 h is considered a good response (the optimal response has been estimated at 15.7x10^4/μL [219]).

From bench to bedside: Is *ex vivo* platelet activation clinically relevant?

Platelets obtained from whole blood or apheresis are of equivalent quality [220,221], but other considerations, such as donor accessibility, donor comfort, ethical considerations, costs, and a desire to decrease infectious risks and the rates of other adverse reactions in recipients, may determine the platelet collection methods used within blood services.

The impact of different processes on the anti- and pro-inflammatory lesions potentially inflicted on stored platelets has received little, if any, attention. We have investigated the release of the inflammatory markers sCD40L and sCD62P by platelets during storage for single-donor PCs and pooled PCs in 9,089 samples [222]. At the end of the production stage (i.e., before storage), single-donor PCs appeared to be more activated than pooled PCs. However, the levels of pro-inflammatory soluble factors increased more in pooled PCs than in single-donor PCs during storage. The use of an alternative PAS (PAS-D) decreased sCD62P secretion but led to an increase in sCD40L secretion in SDA-PCs. The levels of activation of EA.hy926 endothelial cells exposed *in vitro* to PC supernatants were correlated with the severity of adverse reactions after PC transfusion in paired experiments [223,224].

These data highlight the importance of the PC processing and storage steps, as described above. The principal effects observed concern the non-hemostatic properties of platelets [26,28]. Clinical trials are required to determine the extent to which these secondary properties of platelets affect patient outcomes.

Adverse reactions: Common features

Platelet transfusion is largely beneficial to patients. However, this blood component is associated with more adverse reactions than red blood cell concentrates, and probably also more than with freshly frozen plasma. Hemovigilance studies have investigated adverse reactions in PC-transfused patients, who are particularly vulnerable and exposed to additional nosocomial risks [225]. However, in the meantime, we cannot rule out the possibility that some adverse reactions, particularly minor or moderate ones go unrecognized due to confounding with other adverse reactions. Table 5 shows the principal adverse reactions reported (together with their severity and attributability) after platelet transfusion in countries with reliable hemovigilance and reporting systems [226]. The reactions observed depend on the type of platelet product and the safety measures applied (refer to Table 4). They also depend on the duration of storage before delivery, and ABO compatibility. Hazards in transfusion medicine may be considered largely preventable, partly preventable, or non-preventable or essentially non-preventable (Table 6) [227–231].

As mentioned above, PCs derived from apheresis and pooled PCs derived from whole blood are of equivalent efficacy terms of efficacy [94,101,232,233], but apheresis-derived PCs are inferior to pooled PCs in terms of safety [100]. The systematic, or "universal" leukoreduction applied before storage, and the widespread use of PAS have considerably decreased the number of adverse reactions [74–77]. Bedside leukoreduction is known to be less effective than prestorage leukoreduction but can nevertheless limit adverse reactions [179,234]. The expanding use of PI-PR-Ts, which have been shown to create platelet lesions that vary according to the process selected [235,236], has been accompanied by of the almost total abolition of transfusion-transmitted viral, bacterial, and parasitic infections. However, spores are barely inactivated, and some bacteria may escape the process (the likelihood of this depends on the type of bacterium) [237,238]. Nevertheless, exhaustive hemovigilance studies have reported no increase in adverse event rates with the use of these technologies [173–175]. A few rare cases of recontamination after PI-PR-T have occurred following breaches of the integrity of platelet processing sets or storage containers, as reported by Gammon et al [239]. A large American survey reviewed over two million platelet transfusion episodes between

Table 5
Frequency of adverse and serious adverse reactions[a].

Pathological condition	All types of attributability and severity (occurrences for 100,000 blood components)	Probable and certain events and grade 3 (severe) or lethal (actual number of severe occurrences)
Allergy	119	10
Alloimmunization (isolated, including anti-RhD/RH:1)	79.7	
Febrile non-hemolytic transfusion reactions	54.3	
Immunological incompatibility	49.5	1
Inefficacy	15.7	
Unknown	6.6	
Unlisted diagnosis (other)	6.6	
Hypertensive reaction	5.1	
Hypotensive reaction	3.3	
Transfusion-associated circulatory overload (TACO)	1.8	
Transfusion-associated dyspnea (TAD; neither TACO nor TRALI)	0.8	
Transfusion-related acute lung injury (TRALI)	1.2	2[b]
Sickle cell disease hemolysis	0.4	
Viral infection[c]	0.4	

Notes: a) After platelet component transfusion, according to French hemovigilance (ANSM, report on 331,000 PC transfusion episodes in 2020 [224]). b) Meaning that TRALI presented as severe; one of the two was lethal. c) HVE infection, despite the pathogen reduction technology applied (Intercept^{TM}).

2010–2018, corresponding to one quarter of all whole blood-derived platelet transfusions and three quarters of single-donor PC transfusions. This survey reporter that single-donor PCs were associated with more frequent and serious adverse reactions than whole blood-derived platelet transfusions. Furthermore, following pathogen inactivation in single-donor PCs, reactions tended to be less severe (no transmission of infection by PR-PI-T-treated PCs) [188].

Alloimmunization and refractoriness remain important issues in the management of patients undergoing multiple transfusions [240,241]. The management of such patients requires specific organization at all levels of blood services (Blood Establishment, hospital blood bank and clinical ward) available in high-income countries [242] (but not necessarily in middle- or low-income countries).

Management of alloimmunization and platelet transfusion refractoriness

Assessments of PC transfusion efficacy are essential, and platelet transfusion refractoriness is defined as an insufficient increase in platelet count after transfusion, with two or more consecutive CCIs of < 7.5 at 1 hour or a CCI < 4.5 18–24 hours after the transfusion of less than three-day-old ABO-identical platelet concentrates [226]. Some recommendations define refractoriness as two consecutive transfusions with a CCI < 7.0. However, in routine daily practice, less than three-day-old ABO-compatible/identical platelet concentrations may not be readily available.

It is essential to distinguish between alloimmune and non-alloimmune causes of poor posttransfusion platelet recovery. It is generally agreed that a CCI < $7.5x10^9$/L or a platelet recovery rate (PRR) < 30 % one hour after transfusion is strongly suggestive of alloimmune refractoriness. A reasonable increase at one hour and falls to < $7.5x10^9$/L 24 h posttransfusion are, on the contrary, suggestive of non-immune causes. Nonimmune factors, which are thought to account for 80 % of cases [180], lead to increases in platelet consumption. Bleeding, infection/sepsis, splenomegaly, and graft-versus-host disease (GVHD) in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) are the most common nonimmune causes of refractoriness to platelet transfusions. As explained above, certain drug regimens, including antibiotics, may also cause refractoriness and should be considered in the evaluation of patients with platelet transfusion refractoriness [202,203,243].

Immune factors are responsible for platelet transfusion refractoriness in the remaining 20 % of cases. Anti-HLA antibodies are the leading factors involved, followed by anti-HPA antibodies, and combinations of the two [111]. It has been suggested that minor histocompatibility antigens, which play an important role in HSCT [244], may be involved in posttransfusion refractoriness [245], but the findings are equivocal, and these antigens are generally ignored in the clinical management of refractoriness. H-Y proteins (male versus female donors) are also thought to play no significant role in refractoriness [246].

When dealing with platelet transfusion refractoriness, the treating doctor should first consider possible nonimmune etiologies (principally inflammation and infection). If immune platelet transfusion refractoriness is suspected, tests for anti-HLA-antibodies should first be performed. If anti-HLA antibodies are detected and further platelet transfusions are required, several options are available for the selection of suitable PCs: (1) HLA-identical blood donors can be selected for single-donor PC donation; (2) HLA-compatible platelet components can be crossmatched serologically (cross-reactive groups or CREGs) or *in silico*, through computer HLA matching algorithms that identify compatibility at the epitope level, based on short sequences of polymorphic amino acids [247]; (3) HLA-permissive platelet components can be selected to avoid exposure of the recipient to antigens for which the recipient has already generated detectable antibodies, referred to as "forbidden" antigens. This last approach is particularly useful as it is the most convenient, but this convenience comes at the expense of creating additional situations in which alloimmunization may occur. Indeed, the frequency of HLA moieties is not indicative of their alloreactivity, which depends on the capacity of the recipients' antigen-presenting cells to present foreign HLA epitopes efficiently to T cells with a selected immune repertoire [109,248,249]; (4) platelet HLA antigens can be crossmatched *in vitro* with the recipient's plasma (equivalent to an indirect Coombs test). However, this test is not 100 % discriminant. Algorithms adapted to the capacities of the blood service and hospital blood bank can be used to manage such situations [249].

Alloimmunization and refractoriness remain important issues in the management of patients undergoing multiple transfusions

Table 6
Classification of adverse transfusion reactions after platelet component administration, based upon safety measures that can be implemented by the blood service, hospital blood bank or clinical ward [227–231].

Likeliness of residual risks after implementation of safety measures	Pathological condition	Sets of safety measures that can be implemented [a] [228]
Adverse reactions that are largely preventable (all situations largely dependent on donor selection, blood component production, quality systems, and good practice) [103]	Transfusion-transmitted infections (bacterial, viral, parasite)	-Blood service: Donor selection; disinfection of donor's arm and other asepsis measures; leukoreduction before storage; bacterial cultures; pathogen inactivation or reduction technologies; testing, including nucleic acid testing -Hospital blood bank: inspection at delivery and the swirling test; etc. -Clinical wards: inspection at reception; aseptic procedures to prevent retrograde contaminations
	Transfusion-associated circulatory overload (TACO)	-Clinical wards: resuscitation measures and fluid balance
	RhD/RH:1 immunization	-Hospital blood bank: selection of RhD-negative platelet components for RhD-negative recipients, whenever available
	Transfusion-associated graft-*versus*-host disease (GVHD)	-Blood services: leukoreduction before storage; PI-PR-Technology implementation -Hospital blood bank: X-ray or gamma irradiation -Clinical ward: bedside leukoreduction, if not already performed by the blood service
	Immunological incompatibility	-Blood service: possibility of mobilizing HPA-compatible SDA-PC donors, at least for fetus-to-mother HPA immunization situations and for safe transfusion in newborns -Hospital blood bank: ABO identity or compatibility whenever possible while running the PC inventory
Adverse reactions that are partly preventable (all situations in which the immunological properties of donors and recipients are matched whenever possible, and that limit occurrences of storage lesions in blood products)	Febrile non-hemolytic transfusion reactions (FNHTRs)	-Blood services: leukoreduction and PAS before storage -Hospital blood banks: delivery of platelet components that are as fresh as possible; ABO identity or compatibility between donor/product and recipient
	Transfusion-related acute lung injury (TRALI)	-Blood services: production of an inventory of products testing negative for HLA antibodies; policy of anti-HLA antibody-poor donor selection for plasma-rich components for direct therapeutic use
	Allergy	-Hospital blood bank: reduction of plasma in platelet components if the recipient has a documented allergic reaction to a prior administration of plasma-rich blood components; fresh platelet components preferable (not consensual, however)
	Inefficacy/refractoriness	-Hospital blood bank: Ability to mobilize HLA- or HPA-selected SDA-PC donors in situations in which single HLA (HPA) alloimmunization is seen; delivery of the freshest PCs possible, AB-identical/compatible PCs in refractory situations requiring further PC transfusions -Clinical wards: Application of therapeutic tools to decrease reactions (corticosteroids, rituximab, injectable immunoglobulins, plasmapheresis, etc. [229])
Adverse reactions that cannot be prevented (all situations in which causality is largely linked to recipient parameters, such as genetic particularities, existing medical conditions, or disease severity)	Transfusion-associated dyspnea (TAD) [230] Hypertensive reactions Hypotensive reactions that are not allergic manifestations [231]	

Notes: a) All measures are guaranteed by the strict application of *ad hoc* quality systems and computing systems at all steps of the procedures, and by exhaustive surveillance by hemovigilance systems that overview all steps from donors to recipients.

[250]. Specific organization is required at all levels, from the blood service to the hospital blood bank and clinical wards. An alternative — continuous platelet infusion — has been proposed for the transfusion of patients in need presenting with severe refractoriness [251,252].

Transfusion-related acute lung injury (TRALI) and the CD40/CD40-Ligand axis

Transfusion-related acute lung injury (TRALI) is a major transfusion-related complication and one of the leading causes of transfusion-related death. Nevertheless, many aspects of its immunopathogenesis, particularly in terms of recipient variables, remain unknown. Several novel hypotheses have been put forward [253] and studies are currently underway (A.P.J. Vlaar, personal communication). TRALI is an acute respiratory distress syndrome occurring within 24 hours of transfusion. It has a complex etiology involving neutrophils, platelets, and endothelial cells, together with other inflammatory cells [254–256]. Other cells, such as monocytes or pulmonary macrophages [257], may also be involved. No consensus has yet been reached concerning the cells dominating the pathophysiology of this condition (neutrophils, monocytes, pulmonary macrophages, or blood platelets), but all the candidates have a central CD40/CD40L protein complex system controlling pro-inflammatory pathways. Both CD40 and CD154 (CD40-ligand) are glycoproteins secreted by platelets and exported to their membranes and/or shed upon activation by a panoply of stimulants. This key tandem molecule plays a key role in the development of innate and adaptive immunity generally, and in inflammation, in particular [258]. It has been hypothesized that the development of TRALI could be prevented by targeting this protein complex. Mouse models of TRALI have been established, based on repeated injections of lipopolysaccharides (LPS) and anti-CMH I antibodies to generate an uncontrolled inflammatory state. One seminal finding to emerge is that the underlying mechanism prevented the migration of neutrophils and blood platelets from the vascular compartment to the alveolar region, rather than onsite cell activation, as might have been expected. Furthermore, no signs of inflammation were observed in the blood compartment after the treatment of mice with neutralizing anti-CD40L antibodies. These

antibodies limit the neutrophil and platelet activation induced by LPS and anti-MHC I antibody to some extent in the blood, and sustainably in lungs [259]. Our data suggest that a monoclonal antibody (mAb) directed against CD40L inhibits neutrophil migration, rather than activating or regulating inflammation, in mice with TRALI. In this study, inhibition of the CD40/CD40L interaction also appeared to affect monocytes, but further studies are required to investigate this aspect [259].

As a means of limiting the occurrence of TRALI, attempts were made nearly-two decades ago to target donors (especially multiparous female donors) with plasma anti-HLA antibodies. This approach has been highly successful, lower the number of TRALI cases, the residual cases being triggered by a more complex pathophysiology. Indeed, platelet components are usually rich in plasma, leading to a high risk of transferring anti-HLA antibodies to exposed recipients (predisposition identified [260]). A combination of plasma reduction and HLA antibody-reduction policies was found to significantly decrease the incidence of TRALI, as reported by most well-established hemovigilance systems [261,262]. The issue as to whether PI-PR-T treatment of PCs could reduce the risk of TRALI has been addressed by manufacturers in the past but remains unanswered in the current context of multistep policies [90]. A very recent multisite study carried out in the USA reported a global decrease in respiratory distress in patients receiving transfusions of PI-PR-treated PCs relative to those receiving conventional PCs tested for bacterial contamination and mostly gamma-irradiated [263]. This observation is consistent with a decrease in occult bacterial contamination, perhaps favoring inflammation, predominantly at pulmonary sites. Blood transfusion has been shown to be associated with a risk of thromboembolism and pulmonary embolism, predominantly in situations in which tissue factor is produced in abundance (e.g., during some surgical interventions) [264,265], but there are no specific data concerning this role of platelets in this risk. This aspect was recently discussed by Schmidt et al [266], who concluded that all situations favoring inflammation are associated with an increase in risk. Platelet microparticles are thought to bear some responsibility, again highlighting the need to limit storage lesions as an essential element of PC quality in transfusion. It has also been suggested that refrigerated PCs may favor embolism [266].

TRALI has several pathogenic features in common with other inflammatory diseases, such as pancreatitis and inflammatory bowel syndrome. A similar role for platelets was seen in experimental pancreatitis, which was orchestrated by the migration of neutrophils into the damaged tissue [267]. Indeed, deeper organs, such as the pancreas, were thought to be a secondary target during the onset of TRALI. Pancreatitis and TRALI are closely connected disorders, so the role of the CD40/CD40L protein interaction in the regulation of pancreatitis was investigated shortly after the onset of TRALI in mice. As for lung lesions, pancreatic lesions were prevented by neutralizing antibodies blocking stimulation of the CD40/CD40 axis [268].

Strategies for reducing adverse reactions to platelet component transfusions

Strategies for limiting the occurrence of adverse reactions should seek to establish ideal transfusion conditions, a personalized transfusion that is optimal for the recipient. This would require the PC to be considered in a continuum from preparation of the product to its transfusion and would also necessitate consideration of the characteristics of both the PC and the recipient.

New technical procedures for countering the inflammatory potential of PCs could be considered and assessed. For instance, washing PCs with an acid-citrate-dextrose (ACD)-supplemented buffer has been assessed and appears to maintain the *in vitro* properties of PCs during storage, while removing potentially inflammatory molecules from the plasma [269]. In addition, at least in children, the transfusion of PCs washed in ACD-supplemented in patients with cancers experiencing repeated adverse reactions upon transfusion has been demonstrated to be effective, without inducing adverse reactions, although additional clinical evaluation is required [270]. The introduction of inhibitory additives into PC preparations could extend their shelf-life. This has already been demonstrated for N-acetylcysteine, which significantly decreases the activation of platelets stored in the cold [271,272]. New antioxidant molecules, such as Caripill™, are currently being evaluated in mouse models, as a means of increasing platelet storage times [273]. The supplementation of platelet storage solution with sphingosine-1-phosphate, which enhances endothelial barrier function and downregulates ceramide-mediated deleterious effects, is also a potentially promising approach that could be explored [274].

There is also considerable interest in the elimination of citrate from PAS, as this molecule may make a significant contribution to storage lesions [275,276].

Pending the emergence and clinical evaluation of new technologies for PC preparation, it remains important to improve transfusion practices by moving towards personalized transfusion medicine. With this in mind, the first step is the characterization, as precisely as possible, of the pro/anti-inflammatory balance of PCs, by proteomics [191,192], but also by lipidomic and metabolomic techniques, and even by analysis of extracellular vesicle content [274]. In parallel, recipients should also be characterized very precisely for several parameters, including the indication for PC transfusion, geographic origin (determining antigen display), hematological and hemostatic biological features, and clinical factors, together history of the occurrence, type, and severity of previous adverse reactions (to any type of blood product), if any. Transfusion efficacy should also be noted, and all these data used in a data mining/machine-learning approach to generate an *in silico* predictive model of the occurrence of adverse reactions. This strategy could be used to guide the transfusion of PCs according to their content, ensuring that the most appropriate PCs were used for transfusion in the recipient, according to the disease treated and the risk of developing an adverse reaction [277].

Specific situations

A few specific situations must be considered. Some of these issues can be addressed by patient blood management approaches, which are generally focused on red blood cell concentrate transfusions but can, if necessary, provide guidance in situations in which there is a risk of bleeding, as is the case in Canada [278]. However, most recommendations aim to decrease wastage and to promote good practice, emphasizing the benefits of platelet transfusion and platelet recovery. Situations in which it is difficult to perform platelet transfusion (Jehovah's witnesses, some thrombopathies with antibody production and some thrombocytopenia states with auto- and/or allo-antibodies) may benefit from the use of plasma-derived medicinal products (PMDPs), prothrombotic and procoagulant drugs, hemostatic drugs, and stem-cell stimulants [136]. Recombinant thrombopoietin (TPO) has been shown to be effective in sepsis patients with thrombocytopenia [279]. Thrombopoietin analogs, such as romiplostim and eltrombopag (and others not authorized in some countries [280]), can treat cancer-associated thrombopathies, including myelodysplastic syndromes [281,282]. However, caution is required in clinical practice, and it may be necessary to limit such approaches to treating relapsing patients with selinexor [283]. Erythropoietin-stimulating agents (ESAs) may also

be useful in certain situations [284]. Provided the patient is in a fit state to withstand the treatment, some refractoriness states may be eligible for off-label IV-Ig treatment [285] and therapeutic plasma exchange, together with a corticosteroid regimen to limit the production of toxic antibodies [286–288]. The anti-CD20 monoclonal antibody rituximab has been considered in this context [289], and desensitization procedures have also been proposed, as in hemophiliacs with acquired antibodies [290].

Patients receiving palliative care may also be eligible for platelet component transfusion, in situations of major bleeding or exposure to a serious—and frightening—risk of bleeding. Such treatment is not consensual, but we believe that the use of platelet components lies within the range of compassionate care for such patients [291–294].

Patients with inherited platelet disorders, such as Glanzmann thrombasthenia, Bernard-Soulier syndrome, the *RASGRP2* mutation, and other congenital platelet defects, or acquired platelet disorders such as those observed in patients with uremia or drug-induced platelet dysfunction, are exposed to a risk of severe bleeding. In these situations, platelet transfusion is indicated only when bleeding cannot be controlled by usual means [295]. When unavoidable, use of the lowest safe level of platelets is recommended, to avoid overexposing the patient to antigens (patients with mutations receiving "normal" platelets may sense the "wild-type" moiety as foreign and are at risk of developing neutralizing antibodies, complicating the handling of future hemorrhages).

Metanalyses of RCTs, the last of which was published in 2017, have found no evidence for beneficial effects of platelet transfusion for prophylaxis before invasive procedures [295].

The situation described above applies principally to high-income countries with either centralized blood services or robust blood services run by organizations such as the Red Cross/Red Crescent, with an organized, reliable, or exhaustive hemovigilance system. These conditions do not apply in many parts of the world, in which platelet transfusion is much less well organized than the transfusion of red blood cell concentrates, as demonstrated by international surveys [296,297]; (Haddad et al, manuscript submitted for publication). In many places, PCs are delivered as plasma-rich platelet components, with little or no leukoreduction. There is room for improvement in PC accessibility for all, along the lines of the red blood cell transfusion programs proposed by WHO resolutions [298,299].

Donors, blood establishments and hospital blood bank management and ethics

Platelets have main two sources: (1) by-products of a whole-blood donation, leading to the procurement of a red blood cell component, a fresh therapeutic unit of plasma, and a dose of platelets, ready for pooling with other 5–6, ABO and RhD group-matched platelets; (2) *ad hoc*, specific, platelet donation in the form of a single-donor PC, which takes up one hour of the donor's time, plus an additional hour for administrative procedures and post-donation rest, and which requires the donor to be treated with anticoagulant, and depletes large volumes of plasma, these risks being common to extravascular circulation [300,301]. Whole-blood donations are valorized two or three times over (if the platelets can be used in a pool), but it is generally not considered unethical not to valorize platelets in the preparation of a blood component, or to waste a platelet pool if it is out of date due to excess production, to ensure patient safety. Instead, it would be considered unethical to run out of platelets when needed for a patient with bleeding (an example of "distributive justice"). It has long been considered unethical to waste any single-donor PC, for any reason (related to the blood service, hospital blood bank, clinical ward, or the views of society, which may not necessarily be the donor's views) [302,303]. It is considered good practice to train healthcare professionals in ethics (and specifically in blood transfusion ethics), so as to justify the transfusions order, without wasting components and to ensure the full and due respect of blood donors [304]. Many HSCT patient associations worldwide actively promote platelet donation and may feel frustrated by policies that do not favor single-donor PC use, for diverse reasons [305], some of which are economic.

In terms of transfusion equity, blood services do not distribute PCs equally between hospital blood banks throughout an individual country or region. As a result, some centers are more likely to handle emergency situations correctly than others [306]. However, it is very difficult to provide all hospitals with PCs while minimizing wastage and cost to the taxpayer [307]. This situation is one of many ethical dilemmas posed by transfusion, even in wealthy countries, but particularly in low- to medium-income countries.

Conclusions and perspectives

Considerable efforts have been made to improve donor selection, and product and patient safety. Considerable efforts are still being made to improve the quality and safety of PCs so as to maximize the frequency of favorable transfusion outcomes in PC recipients. Key improvements include leukoreduction shortly after collection, decreasing plasma volume by two thirds through PAS substitution, and the recent implementation of PI-PR-Ts to minimize the risk of bacterial infection from PCs stored at 22 °C, a temperature favoring bacterial growth. Doubts were cast on each of these improvements at inception, with fears of a loss of active product, and possible alterations to platelet physiology and function. Minor inconveniences were consistently counterbalanced by positive effects. The recent PR-PI-T quality trial performed in French cancer patients (EFFIPAP) provided broad evidence for the clinical non-inferiority of PCs with and without inactivation in PAS. Despite non-inferiority was not seen when PCs were in 100 % plasma, there was no excess bleeding in patients, no increase in platelet consumption (and costs), no increase in the use of additional red blood cell concentrates, and no increase in the rate of adverse reactions. Platelet recovery rates were slightly higher for untreated PCs, but efficacy was equivalent on ROTEM [86,87]. The very recent large US review on platelet transfusion-mediated adverse reactions reported that PR-PI-T-treated PCs gave rise to slightly more frequent but less severe adverse reactions than untreated PCs [189]. A Croatian study recently published in this journal pointed out that the blood service provided a relatively large university hospital with fresh (less than three days old) platelets that were potentially mostly ABO-identical or at least compatible, and RH:1/RhD-compatible too [202]. The hospital transfusion committee for hemovigilance therefore registered fewer adverse reactions than in other settings. All recent studies have confirmed the initial observation, which triggered a flurry of excitement when published, that pooled PCs cause significantly fewer adverse reactions than single-donor PCs [101].

Progress in patient blood management programs will probably further reduce the number of inappropriate transfusions and will promote alternatives. The alternatives to platelet transfusion currently available are themselves not devoid of complications (particularly human recombinant thrombopoietin hTPO). They are also expensive and not readily available everywhere, particularly in low- and middle-income countries, raising questions about distributive justice. Efforts should be made to decrease platelet transfusion refractoriness by addressing the issue of platelet alloimmunization more effectively in patients requiring repeated transfusions over a long period of time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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