Improving platelet transfusion safety: biomedical and technical considerations

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Abstract

Platelet concentrates account for near 10% of all labile blood components but are responsible for more than 25% of the reported adverse events. Besides factors related to patients themselves, who may be particularly at risk of side effects because of their underlying illness, there are aspects of platelet collection and storage that predispose to adverse events. Platelets for transfusion are strongly activated by collection through disposal equipment, which can stress the cells, and by preservation at 22 °C with rotation or rocking, which likewise leads to platelet activation, perhaps more so than storage at 4 °C. Lastly, platelets constitutively possess a very large number of bioactive components that may elicit pro-inflammatory reactions when infused into a patient. This review aims to describe approaches that may be crucial to minimising side effects while optimising safety and quality. We suggest that platelet transfusion is complex, in part because of the complexity of the "material" itself: platelets are highly versatile cells and the transfusion process adds a myriad of variables that present many challenges for preserving basal platelet function and preventing dysfunctional activation of the platelets. The review also presents information showing - after years of exhaustive haemovigilance - that whole blood buffy coat pooled platelet components are extremely safe compared to the gold standard (i.e. apheresis platelet components), both in terms of acquired infections and of immunological/inflammatory hazards.

Keywords: transfusion, platelet components, apheresis platelet components, whole blood platelet components.

Introduction

Transfusion safety has increased tremendously over recent decades. The risk of transfusion-related infections is lower than ever[1], and every possible effort has been undertaken to minimise immunological hazards[2]. New strategies have been introduced such as traceability, haemovigilance and surveillance, and most blood establishments have introduced quality assurance in a context of continuous quality and safety improvement, under the supervision of certifying and accrediting authorities[3]. Despite these strategies, new infectious threats continue to appear as a result of globalisation and the constant emergence of new pathogens[4]; furthermore, as transfusion recipients are now principally onco-hematology patients whereas there were formerly patients in trauma wards[5], recipients tend to be transfused more than once and often many times, which exposes them to cumulative risks[6].

In platelet transfusion, safety includes maintenance of an adequate platelet concentrate (PC) inventory, allowing timely delivery of appropriate products to all patients in need, control of transfusion transmissible infection risks, containment of immunological hazards and the achievement of transfusion targets[7]. Finally, safety also includes the avoidance of unnecessary blood transfusions and the detection of adverse events through an effective monitoring system[8]. As will be detailed, there are basically two ways to produce a PC: (i) a single donor apheresis collection, often referred to as the gold-standard and the principal for PC used in, for example, the USA, Canada, and the UK, and (ii) whole blood (WB)-derived PC. The latter type can be platelet-rich plasma (9% in the USA, for example) or pools of buffy-coat extracted PC, preferred in Europe where they can account for 80% of PC (the Netherlands). In France, nearly 55% of PC now issued are WB buffy-coat pooled PC[9]. Mathematics would predict more hazards (infectious and perhaps immunological) in patients receiving pools prepared from an average of five or six donations than in patients receiving single donor components. However, a 15-year, active haemovigilance survey carried out in Europe in general and in France in particular did not confirm the mathematics, actually showing the opposite[10,11]. This review also presents these data, which are still considered controversial.

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Thus, the main purposes of this review are to address safety issues of platelet transfusion therapy linked with the donor/donation process and the intrinsic properties of the blood components (BC), and to consider the prospective of platelet transfusions in the light of the major expert recommendations. The review also aims to provide an update for clinicians who may be confused by novelties in the PC manufacturing process and safety procedures, who want to understand the risks better (so that they can present them as accurately as possible to patients) and want to know how to limit the hazards.

Platelet concentrate production and inventory

The production of PC involves various steps, as follows.

Recruitment and selection of blood donors

PC can basically be obtained through two production processes:

- Separation and pooling of platelets from WB, either through the manufacture of platelet-rich plasma (PRP) or platelet-containing buffy coats; WB-derived PC prepared from buffy coats commonly come from "pools" of four to six or more donations, either prepared manually or with semi-automated systems[12].
- Production of single donor PC through apheresis (SDA-PC) on a variety of instruments.

Selection criteria for WB and apheresis donors are very similar; apheresis donation does, however, require a suitable donor platelet count and robust venous access. Donors are expected to be voluntary and non-remunerated according to the charter on ethics of the International Society of Blood Transfusion (ISBT) and World Health Organization (WHO) statements. Although both types of donation are open to the same donor public, practical constraints make some differences.

WB-derived PC generally have lower production costs than SDA-PC and are associated, theoretically, with a higher risk of infection with undetected pathogens, because they are derived from a mean of five different donors. On the other hand, it is possible that low level bacterial contamination may be neutralised through phagocytosis by coexisting leucocytes, as leukocytes are removed after a minimum of 6 h (on average) of contact (maximum time is either 18 or 24 h, depending on the regulations of each country); plasma antibodies and complement fractions are meant to facilitate bacterial lysis if needed[13,14]. Furthermore, the dose of bacteria from a single donor may be higher, because of the greater volume of PRP collected, than that from one donor in a larger pool of multiple donors.

Apheresis donations take significantly longer to collect than other types of donation. Not typically made in mobile collection drives and permitted less frequently than donations of WB, they often lead to dedicated, smaller donor groups. Apheresis provides a flexible response to rapidly fluctuating clinical needs and allows the collection of specific products (human leucocyte antigen [HLA] - or human platelet antigen [HPA]-compatible; possibly cytomegalovirus-negative) for patients with particular needs. The method of collecting platelets by apheresis requires very thorough skin disinfection because of a potentially higher risk of bacterial contamination[15]. Apheresis involves the exposure of donors to extracorporeal circulation, which constitutes an additional risk of citrate intoxication and to bone demineralisation, especially if the safety of the collection process is not optimised[16,17]. Plasticisers present in the apheresis disposables may become a safety issue in the near future as well.

Production of platelet concentrates: advantages and disadvantages with specific relevance to safety

The quality and safety of PC, be they WB-derived PC or SDA-PC, may be influenced by a number of variables (type of automated instruments [for SDA-PC], method of platelet separation from WB, use and type of filter, use and type of additive solution [platelet additive solutions, PAS], type of container [devices, disposables and plastics], use and type of pathogen reduction technology [PRT], use of X-ray or gamma irradiation, and shelf life of the platelet product), leading to an impressive list of combinations (Figure 1). Comparisons should take into account all these variables that can potentially affect product quality, and not merely compare pooled *vs* SDA-PC. Lastly, SDA exposes donors to specific risks at the time of donation or after it; these need to be considered in a process that is summarised by the term "donor haemovigilance"[18].

Platelet stock management and creation of a platelet concentrate inventory

PC stock management is hampered by the short shelf-life of PC, which varies between 3 and 7 days (mean, 5 days) in different countries, as defined by regulatory authorities[19]. Epidemics or outbreaks of infections may, therefore, threaten adequate blood supply. Any delay caused by testing or need for quarantine (such as when bacteria are detected, or when the risk of an acute viral infection requires post-donation information) may dramatically affect PC availability, as was observed during the Chikungunya outbreak in La Réunion, or during dengue epidemics in various locations[20-24].

PC outdating is a serious economic problem for some Blood Establishments, while excessive limitation of PC production may expose patients to PC shortages; both situations raise serious ethical concerns. The outdating

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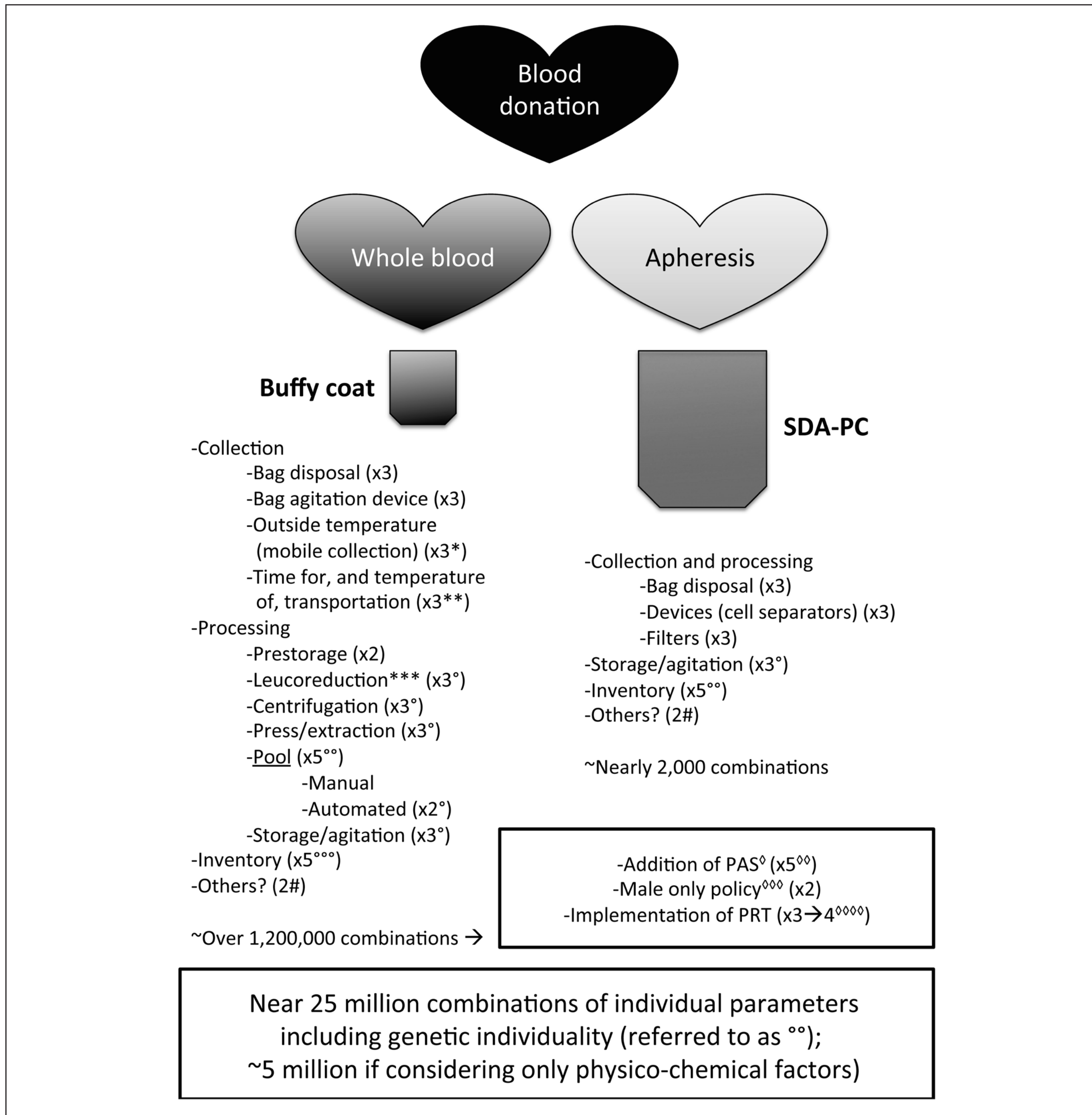

Figure 1 - Platelet components are far from being standardised, manufactured medicines[117], as there are several million distinct products throughout the world.

Shown in cartoon form here are some of the major possibilities for obtaining PC by two major processes: WB-derived-PC and SDA-PC (platelet-rich plasma is not featured here). Numbers in parentheses indicate the major choices: for example, we considered here that, with regards to WB-derived-PC (buffy-coat pools), there are three main brands of bags, three main brands of agitation devices for whole blood collection, etc. (these are probably largely underestimated but deduced from the French market). Here some more details.

* It is considered that there are three external temperatures that may influence the quality of blood: extreme heat, extreme cold, and standard medium. ** Time for transportation from the collection site to the processing site has been limited to three scenarios: short distance, medium distance and long distance. *** Leucoreduction has been considered to require any of three major commercially available kits (° same for centrifugation with 3 main centrifuge types, and extraction with 3 main extraction machines, while there are basically 2 systems for pooling buffy-coats automatically). °°° Regarding inventory, we estimated that each day from 1 to 5 (thus excluding day 0) represents a factor of variability of the final PC). # Not precisely defined factors, probably related to the Blood Establishment, which may, at some point, affect the quality and characteristics of the final component (this multiplication by a factor of 2 is largely speculative, but likely). ◊ Estimated number of commercially available PAS. ◊◊ As the male policy only (or female testing for anti-HLA antibodies of significant titres and clinical relevance) is applied or not, this has been attributed 2 (Yes or No). ◊◊◊ The numbers for PRT are as follows: 1) no PRT; 2) amotosalen-treatment; 3) riboflavin-treatment; 4) future or possible UVC-treatment. Of note, the steps applying to both WB-derived PC and SDA-PC are shown within the box.

PC: platelet concentrate; WB: whole blood; SDA-PC: single donor apheresis PC; PRT: pathogen reduction technology.

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and wastage of PC is barely acceptable in most blood services as donors - usually voluntary and unpaid - have given this BC purposefully, attribute it a high value[25] and have been exposed to certain risks to give it[18,26].

Platelet inventories should also take into account the biological specificities of every product, such as ABO group, Rh-K phenotype, HLA and/or HPA phenotype and cytomegalovirus-negative status (although this last characteristic is no longer critical after the widespread implementation of stringent leucoreduction, and even less with the introduction of PRT systems). Highly specific needs can be met either through the maintenance of a fully typed donor registry, or storage based on deep freezing, lyophilisation, or even dehydration[27,28].

Platelet concentrate safety: main targets

From a technical point of view, after having made sure that an adequate inventory is available, PC safety is based on targeting two main issues: the now minimal risk of transmitting common blood-borne microbial pathogens, and the reduction or the minimisation of immunological risks. One crucial process that links the afore-mentioned two issues is leucodepletion/ leucoreduction.

Leucodepletion/leucoreduction

About 15-20 years ago, leucodepletion of all types of BC, or more precisely leucoreduction because leucocyte content is only reduced by 2-3 $\log_{10}$, was implemented by most Blood Establishments worldwide; its implementation was accelerated in particular to maximise the theoretical benefit of prion risk reduction. Leucodepletion can be achieved directly through collection with modern apheresis instruments under optimal conditions, obtaining PC with leucocyte contents below (sometimes greatly) 1×10^6 cells/BC. In other cases, leucodepletion can be performed by filtration, either prestorage - early after blood collection (generally within 18-24 hours), or at the bedside at the time of transfusion. The introduction of universal leucodepletion has made possible a drastic reduction in the transmission of intracellular viruses, such as cytomegalovirus, human T-cell lymphotropic virus and Epstein-Barr virus. Despite some individual claims, it is clear that leucodepletion is no longer a matter of controversy to most specialists in transfusion medicine[29].

Immunomodulation and immunological hazards

As the majority of immunomodulatory effects of transfusion are linked to the presence of leucocytes in blood components, leucodepletion is associated with reduced transfusion-related immunomodulation (TRIM), whose effects are principally deleterious, because they can also affect inflammation[30]; for completeness, transfusion-related immunomodulation does mediate some beneficial effects, as reported in a couple of well-documented reviews on this topic[31,32].

Leucodepletion is thus commonly acknowledged to reduce leucocyte-linked inflammatory mechanisms, such as release of inducible nitric oxide synthetase, cytokines and chemokines, chiefly responsible for the chills, fever and rigors causing febrile non-haemolytic transfusion reactions (FNHTR). The anti-inflammatory effects of early leucodepletion are considered superior to the effects of bedside leucodepletion, because leucocytes start to degrade and to release pro-inflammatory factors in the BC within 24 hours after collection[33,34]. For the same reason early leucodepletion reduces alloimmunisation, because it prevents the transfusion of donor soluble leucocyte antigens and the antigen-presenting capacity of professional cells (referred to as antigen-presenting cells)[35]. Leucodepletion of PC is particularly relevant in two domains: reducing NHFTR and limiting alloimmunisation.

PC cause nearly half of all reported NHFTR although they account for only 10% of delivered BC[6]. It is estimated that platelets themselves are the source of the majority of inflammatory factors; however, it cannot be excluded that pro-inflammatory factors released by leucocytes potentiate platelet activation and release of platelet inflammatory factors[36].

The mechanisms of alloimmunisation in transfusion are not yet fully understood and are probably multifactorial; however, some progress has been achieved in the field of PC transfusion with good evidence that residual B-lymphocytes are crucial actors among professional antigen-presenting cells[35].

Platelet concentrate safety with respect to infectious risks

Common safety measures apply to all blood components, including platelet concentrates

Donor selection is one of the cornerstones of transfusion safety. Figure 2 displays the successive steps and outlines those of particular relevance for infectious safety. Of note, in the recent past, medical selection has been based on an increasing number of restrictive criteria. Although aimed at improving recipients' safety, the rationale for some of these criteria is neither obvious nor evidence-based, and an excessive number of questions can compromise the reliability of answers given to more relevant ones.

The specific case of bacterial contamination: is detection valuable?

Because the storage temperature of PC (22±2 °C) allows the growth of almost all bacterial species, these BC are at increased risk of bacterial contamination[37,38]. According to the 2013 French haemovigilance report[6],

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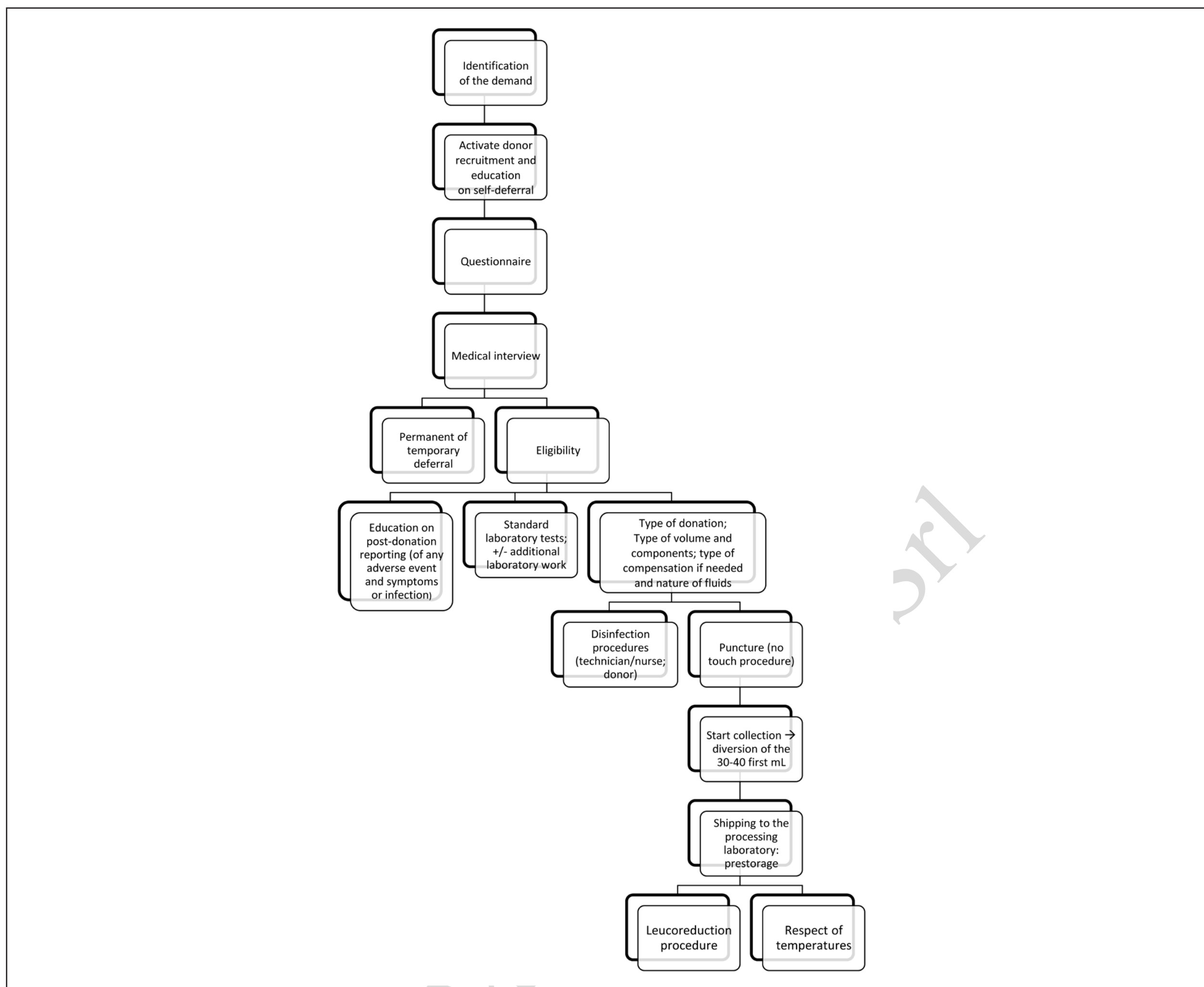

Figure 2 - The various steps that contribute to the containment and/or the reduction of infectious risk associated with blood donation to make a safe platelet concentrate.

The process begins with donor recruitment and education to self-deferral. It continues with the compilation of a donor questionnaire, which is reviewed by a medical health worker (a physician in several countries) and completed by a medical interview, in which the donor should be able to ask all relevant questions and receive adequate explanations on the reason for his/her eventual deferral. Importantly, this step can be used to sensitise candidate donors to report post-donation hazardous events, allowing blood/blood components to be discarded or quarantined if necessary. The establishment of a computer-assisted, extensive post-donation information system strengthens global donor and recipient safety in transfusion medicine.

At the end of this interview, the health worker makes a decision on:
1) Eligibility, temporary or permanent deferral;
2) Type of donation (WB or apheresis), type and volume of components to be collected;
3) Eventual volume of compensation fluids;
4) Need for additional tests [for both immunological [immunisation to blood cell Ags] and infectious risks].

In this sequence, steps 1) and 4) are particularly relevant to prevent transmission of any infectious pathogens from donor to recipient. Avoidance of blood component-related infection continues with the strict application of procedures during the collection process: hand-washing, skin disinfection, no-touch procedure for the puncture, protection of the needle, etc. The use of a satellite pouch, allowing the diversion of the first 30-40 mL of blood in a side bag used for testing purposes, washes out donor skin bacteria that have escaped disinfection. The efficacy of this measure in terms of bacterial contamination has been proven[118]; as the bacterial risk is greater in PC transfusion, this step appears crucial for SDA-PC in particular, but is also valuable for WB donations from which platelets are separated to make pools, though some phagocytosis can occur before the leucocytes that eliminate bacteria are removed[10,11]. Finally, platelet donations undergo biological testing according to the rules applied to all other blood components. Tests performed on donors have been standardised among countries, and global polices have been proposed, for example by the Council of Europe[42]. Most tests are standard and universally applied; some remain optional, such as nucleic acid testing for conventional or emerging viruses, or are linked to potential donor exposure, such as testing for transfusion-transmissible protozoa (*Plasmodium* spp., *Babesia* spp., *Trypanosoma cruzi*[119-121]). Interestingly, although the former two protozoa are barely considered issues in PC transfusion, *Trypanosoma* transmission has rarely if ever been associated with RBC transfusions, but has been well-documented in the case of PC transfusion[122]. In countries in which no effective PRT is applied to PC, a policy to detect *Trypanosoma* infection in exposed donors should be considered. Given that quarantine is not feasible for PC, in the case of virus outbreak and epidemics, Blood Establishments in affected regions may be forced to set up additional testing, usually based on nucleic acid amplification testing, to detect carriers (for example, dengue virus, West Nile virus or Chikungunya virus), if no effective PRT has been introduced[123].

WB: whole blood; Ags: antigens; PC: platelet concentrate; SDA-PC: single donor apheresis PC; RBC: red blood cell; PRT: pathogen reduction technology

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3.4 and 0.87 (mean, approximately 2.2-2.3) of every 100,000 SDA-PC and WB-derived PC transfusion, respectively, led to clinical bacterial infections (2.3 in all in 2012, and 2.3 in all in 2013, demonstrating stability despite efforts to eradicate such events through various methods[39]). It is noteworthy that there is consistent evidence from France in the past 5 years that SDA-PC lead to bacterial infections almost five time more frequently than do WB-derived PC[41]. There is a recent indication that PRP-PC are also less frequently incriminated in bacterial contamination than SDA-PC in the USA (as reported by Dr M Yazer at the BEST meeting in Lille; 9th of April, 2015).

Several methods are available for detecting bacteria in PC. Most of them are culture-based, with the most representative techniques being BactAlert™ (BioMérieux, Craponne, France) and BacTec™[40,41] (Becton-Dickinson, Franklin Lakes, NJ, USA). Although widely used in Blood Establishments, the status of these methods remains variable: bacterial detection can be part of the production process, a mandatory step for product release, or merely a quality control parameter. Blood culture-based systems require a lapse of time in order to detect growth. Blood Establishments do, therefore, have to make difficult decisions. They may consider that a PC is free of bacterial contamination if the test is still negative 24 or 48 hours after inoculation; this policy is associated with a reduced availability of components (at least for 24 hours) that already have a limited shelf-life; it also implicitly forsakes optimal sensitivity, as in a minority of cases, bacterial growth is only evident after several days.

Another policy consists in qualifying PC under a conditional release, i.e. PC can be transfused as long as no bacterial growth is detected in the culture bottle, which is kept in culture during the entire shelf-life of the component. This policy is quite different from the ordinary testing process, in which initial test results are deemed to be definitive. It requires the capability to recall a BC on a 24-hour basis, which may be problematic in the case of decentralised PC inventories. Moreover, Blood Establishments using this policy have noted an impressive rate of false positives; in more than half of the cases, the positive test result only becomes positive when the PC has already been transfused, leading to rather difficult and awkward interpretation and communication issues.

A European Directive from 2005[42] allows the shelf-life of platelets to be extended from 5 to 7 days when either bacterial detection or PRT is applied. In order to minimise time loss and organisational problems, a certain number of new tests have been developed, some of which can even be done at the bedside. Their performance is often inferior to the results of BactAlert™ and BacTec™, considered as gold standards. In several studies these methods yielded positive tests in one-third of the samples after inoculation on day 1 as opposed to positive results after inoculation on day 7.

Besides the canonical BactAlert™ test, novel tests have been developed which are "release-tests". BacTx™ (Immunetics, Boston, MA, USA), based on protein affinity to peptidogycans, has proven reliable but requires some expertise and time for its processing. Another test, a cocktail of polyclonal antibodies (PGD-Test™, Verax Biomed, Marlborough, MA, USA), has proven extremely convenient but needs improvement to detect Gram-negative bacteria. Other tests are being developed which are based on different types of ligands to capture bacterial moieties[43].

The main challenge of all these methods remains the implementation of PRT, which has led to active debate in some countries[44-46].

The issue of viruses transmissible by platelet concentrates

In theory, PC are not different from packed red blood cell (RBC) concentrates with regards to harbouring viruses, except, as will be described, PC can undergo PRT active against most DNA- and RNA-based infectious agents, including those which are not tested for specifically, because they are uncommon or emergent. In theory as well, exposing a recipient - often immunosuppressed - to multiple donors (WB-PC) when exposure to a single donor would be (SDA-PC) would multiply the residual infectious risk. In a country such as France, which issues as many WB-PC as SDA-PC, active surveillance would be expected to be informative on this residual risk. Actually, viral infection by blood is so rare (especially if one considers that PC account for "only" 10% of BC), being in the range of 10^{-6} or less, that conventional statistics do not appear suitable for analysing this risk. What haemovigilance can determine is that there is no apparent inferiority of WB-PC compared to SDA-PC regarding any testable viral risk[6]. The residual risk of non-testable viral infections should be higher, but this is not confirmed by post-transfusion surveillance (for example, in patients having undergone stem cell transplantation, who are particularly prone to developing viral infections, including non-conventional ones)[6]. This issue is now under consideration, also investigating liberally transfused patients (all blood components) *vs* patients transfused with restrictions.

The issue of pathogen reduction technologies applied to platelet concentrates

PRT - also often called pathogen inactivation or pathogen reduction - has long been used for plasma and

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plasma derivatives, with very few failures (none so far with pooled plasma-derived components, and very few with single donor plasma for direct therapeutic use). More recently, PRT has also been introduced for PC. Two methods are currently commercially available. One of these is the nucleic acid intercalating agent amotosalen-HCl and UV-A irradiation (INTERCEPT™ Blood System [Cerus Inc., Concord, CA, USA]), the other is sensitisation with riboflavin and UV-broad spectrum irradiation (Mirasol™; TerumoBCT, Lakewood, CO, USA]). An additional method is under development and involves high energy UV-C and wave agitation (THERAFLEX™; MacoPharma, Mouveaux, France). The former two methods are in use in several countries, and the INTERCEPT™ Blood System method has undergone large, independent safety trials. In some countries and regions (Belgium, the Alsace region and Overseas departments in France) there is about a decade of practical experience with INTERCEPT™[46].

The use of PRT is supported by three major claims. It is claimed that these methods inhibit bacterial multiplication almost totally, making them highly competitive in comparison to bacterial detection, which is often unable to detect low-level contamination, such as may occasionally occur in asymptomatic donors with low-level bacteraemia. No breakthrough bacterial infections have been reported in large series of INTERCEPT™-treated PC transfusions[6,46]. While currently available PRT techniques fail to inactivate spores, they are active against parasites and fungi, making them particularly useful for the inactivation of protozoa predominantly associated with PC transfusions or for parasites that may be present in the plasma supernatant of PC (*Plasmodium* sporozoites, *Toxoplasma gondii*, *Leishmania* spp., etc.)[47]. As the various PRT are based on different physicochemical principles, the spectrum and the extent of their antimicrobial activity may differ, and results obtained with one technique cannot simply be generalised to another. Extensive review papers comparing the documented efficacy of different PRT have been published recently[48,49].

Existing PRT also reduce the level of infectivity of transfusion-transmissible viruses. Once again, proven efficacy and log-reduction may vary between different methods. Contrary to what is seen in the case of bacterial contamination, in which high levels of bacteria are only seen in patients with severe sepsis, very high levels of viraemia may occasionally be found in asymptomatic donors, who are totally unaware of being virus carriers. The INTERCEPT™ method has proven to be implementable within 10 days in a setting of a virus outbreak (e.g. Chikungunya at La Réunion [2005] and dengue in the French Caribbean [2006][24]). However, it has been reported to lack total efficacy for some non-enveloped viruses, such as hepatitis A virus and hepatitis E virus[50].

Although implementation of PRT is still debated at national levels in Europe and North America, several consensus conferences have come out in favour of its introduction[44,45]. An approach to evaluate PRT efficacy was outlined in a recent meta-analysis[51].

In vitro experiments show that all available PRT methods cause an additional degree of platelet activation[52,53]. However, apart from one study with disparate results, but with debatable methodology[54-56], most haemovigilance studies corroborated the findings of previous phase III trials that showed no increase in platelet transfusion needs or bleeding in recipients of INTERCEPT™-treated PC.

Novel trials have been set up in different countries to validate these findings. It is suspected that the introduction of PRT is more often delayed for economic reasons than for medical ones. Oddly, the decision-making process may sometimes be accelerated by unfortunate events such as a fatal bacterial transfusion-transmitted infection in a child that led medical authorities in Switzerland to require countrywide PRT implementation within 2 years.

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Still unmet safety concerns in transfusion: the prion

Although the agent of variant Creutzfeld-Jakob disease (vCJD) is transmissible by labile BC (and possibly also by plasma-derived drugs), the actual number of cases transmitted by the causative prion has been maintained very low in the United Kingdom, and no case has ever been reported elsewhere despite exhaustive haemovigilance programmes[57]. The prion risk is, therefore, minimal to date, but it is theoretically a concern for all types of BC, as it is carried by residual leucocytes and plasma. Even when PAS are used, the amount of residual plasma in PC is far from negligible and may reach the equivalent of one fresh-frozen bag of plasma in "jumbo" PC. Although leucodepletion was initially targeted at the prevention of prion-transmission almost 20 years ago and has proven very valuable in many other instances, it has been rather disappointing at the prevention of prion transmission, as half of the transmissible prion load in plasma is in a soluble form. Furthermore, traditional safety steps (donor selection, product testing, post-collection treatment) have hitherto been ineffective in the prevention of prion transfusion-transmitted infections, although the number of cases of clinical infection reported can be counted on the fingers of one hand.

Detection methods with increased sensitivity and specificity are under development[58-60], but raise serious ethical concerns about informing donors of positive test results regarding a chronic, fatal disease for which there is currently no treatment or cure available. Progress is

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being made with capture methods to eliminate prions through adherence filters[61].

However, transmission of prions by transfusion has been reported only in the UK and in an extremely low number of cases: this prevents any valid statistical analysis or even extrapolation of findings indicating a superiority of SDA-PC over WB-PC in non-UK countries considered "at (potential) risk", such as France. Nevertheless, it is worth noting that the development of SDA collection in France at the beginning of the new millennium was based on this argument.

Platelet transfusion safety and focus on factors that compromise efficacy and lead to undesired/ hazardous events

Patients who receive PC transfusion are in general fragile (besides being often immunosuppressed) and frequently have severe co-morbidities; they are also obviously prone to bleeding. It is of the utmost importance that the transfused PC is fully effective (in increasing the number and often the haemostatic quality of circulating platelets). In other words, the selected PC must be haemostatic and must not lead to refractoriness (avoiding antigens - on donors' platelets - and antibodies in recipients' plasma which may lead to impaired efficacy). Furthermore the transfused PC must not be accompanied by adverse events, which are generally mediated by either antibodies (present in the PC - meaning also in the donor) or biological response modifiers (BRM) (generally with inflammatory consequences).

Undesired constituents remaining in platelet concentrates: strategies for avoidance, dilution or depletion

Greater safety presupposes insight into platelet transfusion pathophysiology. Transfusion of PC is known to cause FNHTR more frequently than other BC, and to provoke a substantial number of cases of transfusion-related acute lung injury (TRALI), allergic reactions, and bacterial TTI, which are - at least in part - preventable by specific approaches[62]. Undesired and possibly noxious PC constituents can basically be divided in two categories: antibodies, mostly anti-HLA, resulting from donors' allo- or iso-immunisation, and BRM, generally with a pro-inflammatory effect. Anti-HLA antibodies in donors' blood may result from previous transfusions (although increasingly Blood Establishments tend to exclude donors with a history of transfusions); however, the most common cause of humoral alloimmunisation to blood cell antigens such as HLA is a previous pregnancy. The frequency and the titre of these antibodies increase with the number of pregnancies. A small percentage of males and nulliparous women may have low titre, weak affinity anti-HLA antibodies, generally IgM type, of little clinical relevance[63]. To overcome the risk of TRALI due to HLA antibodies, a large number of Blood Establishments follow a "male-donor only policy" for therapeutic plasma or SDA-PC[64-66]; it is expected that platelet pools would also benefit from the limitation of female donors.

The use of PAS has been recommended over the last decade, and enables the plasma content to be reduced by two-thirds. Almost all modern apheresis devices allow direct re-suspension in PAS, manually or automated for WB-PC pools. Nevertheless, some experts consider that platelets function better in 100% plasma, because the platelets need functional support proteins. However, PC with 100% plasma provoke an increased number of adverse effects or serious adverse effects; the number of these events were reduced after the introduction of PAS[67]. Although PAS may affect platelet function *in vitro* slightly, no significant effects in terms of transfusion efficacy have been reported to date. The composition of the various PAS differs and is evolving, which may explain the differences in platelet activation and inflammatory markers induced by these solutions[68-70].

The relationship between the age of a PC and its clinical efficacy and propensity to cause inflammation is an important matter of debate[71,72]. Release of pro-inflammatory cytokines and other BRM has been shown to increase with time after 3 days of storage[73,74]. We (and others) have also demonstrated that BRM are likely causally responsible for certain adverse events and serious adverse events[75-79]. Although not scientifically proven, inflammation could possibly be limited by not using PC older than 3 days. An alternative to PAS is the selective removal of BRM from PC[80,81]. Although still speculative and technically challenging, this approach could be of benefit particularly to patients at risk of hyper-inflammation. The presently available PAS dilute plasma by two-thirds, which reduces the incidence of FNHTR but does not abolish such reactions, demonstrating that some recipients may be highly susceptible, or that in some PC the BRMs load is exceptionally high. Every manipulation of platelets may theoretically lead to the activation or apoptosis of the cells[82,83]. Platelet exposure to plastics, centrifugation, filters, gases, solutions and temperature changes may create a stress, leading to alterations (Figure 1). Furthermore, recent research has shown that, surprisingly for non-nucleated cells, platelets may respond differently to distinct danger signals[84,85]. Overall, some PC seem to present a particular risk for certain recipients. A possible explanation could be that some donors are particularly high producers of BRM, or some recipients are particularly prone to develop inflammatory symptoms, or both[86,87]. Although still

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speculative, interruption of this vicious cycle might be benefit for these patients.

Practically speaking, the immunological and inflammatory hazards that remain in patients after safety measures have been implemented are, according to the French surveillance and regulatory body ANSM, allergic reactions, FNHTR, and transfusion-transmitted bacterial infections[6,88-91].

Avoidance of transfusion-associated Graft-versus-Host disease

Certain conditions in patients require that irradiation is used to prevent transfusion-associated Graft-versus-Host disease (TA-GvHD). The main technique for inactivating residual leucocytes - in particular, lymphocytes - for GvHD prophylaxis is traditionally based on irradiation by either X- or gamma-rays. Although the energy applied is not sufficient to inactivate infectious pathogens, it provokes an alteration of platelet (and RBC) membranes, and can increase activation and apoptosis[92]. This loss of quality is poorly addressed in the literature, and changing techniques require new evaluations. Indications for irradiation should, however, also be reviewed in the light of increasingly efficient leucodepletion techniques, leading to residual leucocyte contents that are frequently in the order of 10^5. The substantial experience of emerging countries, in which prophylactic irradiation cannot be performed even for transfusions in fludarabine-treated patients and yet no serious side effects occur, raises the question of whether irradiation is truly needed, and whether abolishing the policy of irradiation, in order to minimise platelet damage, might be worthwhile. Interestingly, there are claims by the major industrial companies promoting PRT that intercalating drugs are highly efficient at preventing TA-GvHD. Validated PRT techniques do not alter the overall quality of platelets[93,94]. Results obtained through both limiting-dilution analysis and cytokine secretion with, for example, INTERCEPT™, have shown that the safety margin for TA-GvHD obtained with this method is superior to prophylaxis based on gamma-irradiation or X-rays[95].

Avoidance of alloimmunisation

As patients receiving PC transfusions often do so within the context of repeated transfusions, much care must be given to preventing the development of allo-antibodies, which would compromise the efficacy of future PC transfusions. Cross-matching PC with recipients' plasma is not currently common practice. There are no reliable means to prevent alloimmunisation to platelet-specific antigens; active programmes based on individual selection of HPA- or HLA-matched PC would compromise a viable inventory or increase wastage, with unaffordable economic and ethical consequences. Leucoreduction dramatically mitigates formation of anti-HLA antibodies in patients receiving myeloablative chemotherapy, but few data are available for non-immunosuppressed patients. It has been reported that both INTERCEPT™ and MIRASOL™ reduce the rate of alloimmunisation against HLA and possibly HPA[94,95]. The mechanism of this effect is still under investigation. If confirmed, it would add significant value to PRT.

Of note, PC do contain a few RBC: it is possible that RH:1 (and also other RBC antigens) harboured by these RBC could immunise for example RH:-1 patients, unless specific prevention by anti-D immunoglobulins is proposed when available. Indeed, according to our unpublished and as-yet unconsolidated data, there should be three times more anti-RBC antigen alloimmunisation with WB-PC than with SDA-PC (0.1% *vs* 0.03%, respectively); this does not seem to occur in the USA with platelet-rich plasma, as reported by colleagues (*personal communication*), although this is not consolidated information either.

Best platelet concentrate selection and handling for patients' safety

Other safety issues involve PC storage and distribution. PC are normally stored at 22±2 °C, under gentle agitation in a clean environment. Although these conditions are generally met, it may be wise to check platelet viability through a simple swirling test before issuing the component.

In our opinion, Blood Establishments can improve PC transfusion practice by providing help in answering two questions: what is the best PC for an individual patient?[96-98] And, how can it be guaranteed that a selected PC is handled appropriately?

Unlike RBC transfusions, PC transfusion is not restricted by absolute immunological barriers, and, apart from particular situations linked to known alloimmunisation, no cross-match is routinely performed. PC transfusion generally occurs on a first first-in/first-out out basis, with or without (depending on local policies) ABO preferential matching (at the cellular level first and then, at the serological level). Additional steps for the prevention of TRALI, such as employing fresher PC containing fewer cytokines and oxygenated lipids, are rarely recommended[99-101]. In exceptional cases, consideration should be given to the avoidance of dramatic inflammatory responses by targeting either donor or patient parameters. Secondary, PC sub-processing in order to address specific needs (foetuses, neonates, documented allergies, certain transfusion or transplantation programmes) is seldom performed, especially in small Blood Establishments. However, routine measures have been proposed to increase safety and PC transfusion efficacy:

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- during the selection process, use of ABO identical platelets will improve platelet recovery and recirculation[102,103]. Avoidance of RH:1 incompatibility will avoid alloimmunisation, which can be caused by even low level RBC contamination, unless anti-RhD prophylaxis is available.
- PC should be visually inspected to ascertain bag integrity and the presence of swirling. If bacteria are detected, bags with positive growth should automatically be removed from the system. Shipping conditions of the PC to the site of transfusion should be tightly controlled.
- Safety should be promoted by robust information based on better integration of patients' characteristics and features of the PC. Risks to safety are best minimised through continuous education and strengthened quality programmes. Issuing fresh PC may benefit particular patients by reducing the amount of pro-inflammatory markers transfused, although only indirect evidence is available to support this practice. In the case of alloimmunisation leading to platelet transfusion refractoriness or neonatal alloimmune thrombocytopenia, the delivery of HLA- or HPA-compatible PC is very valuable for some patients[104]. Major Blood Establishments should, therefore, keep an inventory of selected components, or at least have a registry of fully phenotyped platelet donors committed to donate whenever needed. Optimal management of platelet transfusion refractoriness also involves information exchange and collaboration between Blood Establishments. The logistics of Blood Establishments should allow rapid responses to urgent needs, which presupposes the possibility of issuing products in the case of necessity on a daily basis, even during weekends. Practices vary considerably worldwide regarding the offer of SDA-PC *vs* pooled PC. As there is no formal advantage or disadvantage for a patient from receiving one or the other type of PC, the concern about maintaining an adequate supply is to maintain the clinician's freedom of choice. A similar precedent exists for the introduction of additional safety measures, such as PRT. It is vital that clinicians always receive adequate information and their involvement in transfusion safety is essential. Patients' safety is closely linked to the full deployment of Good Practices, including the prescription of components to patients with special requirements. Constant communication between blood bankers and clinicians is essential in order to maintain a quantitatively and qualitatively adequate inventory. The collaboration of both sides is also crucial to minimise the delay between reception of a PC in the hospital and the transfusion itself. Clinicians should keep Blood Establishments informed of their future needs, such as the choice between prophylactic *vs* therapeutic only platelet transfusion. Although prophylactic transfusion is routine practice in most countries, this practice is motivated by limited clinical evidence, and further investigations are required in order to make definite recommendations[105-109].

Similar observations can be made about the optimal platelet dose. Optimal collaboration between Blood Establishments and clinicians requires ongoing definition of patients' needs. Finally awareness-raising in the clinical ward regarding notions such as traceability and incident-reporting are of the utmost importance to make the entire transfusion process safe. All relevant information should be carefully collected and feedback reporting systems should be organised at hospital, Blood Establishment and national (regulatory) levels.

What can be proposed/recommended?

Considering the evidence presented here and personal experience, we propose our preferences whenever this is possible:

1) As there is no evidence-based superiority of SDA-PCs over pooled, random WB-derived PC, we recommend the use of WB-PC, restricting SDA-PC to certain alloimmune indications (HPA-, HLA-matched; rare groups; etc.).
2) Although platelet function is better with full plasma, no inferiority of PAS has been recorded with respect to full haemostasis, so PAS should be preferred whenever possible; other safety measure that have proven highly efficient are anti-HLA detection and an antibody avoidance policy.
3) After 10 years of observation, there has been no clear indication that PRT are deleterious for full haemostasis (only one study so far has cast serious doubts[110]). It seems that most experts prefer PRT over bacterial detection.
4) ABO compatibility seems to increase the efficacy of PC transfusions, leading to better patients' outcomes and cost reduction, because fewer transfusions are needed overall: thus, ABO compatibility should be strongly encouraged at each reasonable and possible occasion.
5) There is increasing evidence that adverse events are more frequent when PC are 3 or more days old, because of the large secretion of platelet BRM after this time. Transfusion of 3-day old PC has also proven to be less efficient (leading to increased morbidity and - by extension - total costs). It is recommended that greater attention is paid to this issue and that the appropriate changes are made to the inventory.
6) Although much has been learnt from past trials, there is still a lot to be done: trials must be performed to address in particular the question of PRT and to

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enable more robust and universal recommendations on the prophylactic *vs* liberal policy[110].

7) Lastly, although the corrected count increment is currently considered the gold standard for monitoring the efficacy of PC, there is increasing evidence that bleeding is the actual end-point to follow up[111-115].

Concluding remarks

There has been remarkable progress in safety of transfusions, especially PC transfusions, over the past decades, thanks to measures that targeted infectious and immunological risks. Although rare, nearly 25-30% of adverse events recorded in exhaustive haemovigilance systems are related to PC[6], so there is still room for improvement.

As has been discussed already, practices are not completely harmonised among Blood Establishments. Conferences will assist in reaching a consensus on the best protocols for patients; however, transfusion is generally regarded as expensive in health care systems and much attention is now being paid to reducing all possible costs, while maintaining the safety of patients - especially regarding the risk of bleeding. Policies cannot always be compared between countries: for example, what is considered a "jumbo" dose in country or setting "A" may well be a normal dose in country or setting "B" (this holds true for both donation and transfusion). Evaluating transfusion protocols must be regarded also within the full range of what is comparable. Given the increasing disparity between established practices and novel proposals - based on medical, economic, quality and possibly other reasons (the other reasons are largely outlined in Patient Blood Management studies) - there is much need for further clinical trials, focusing on similarities and differences (platelet collection, processing, storage, distribution, including studies on plastic composition, filtration for leucodepletion, addition of PAS, implementation of PRT, etc.); re-evaluation of clinical end-points (bleeding: which scale for measurement?) would also be valuable to allow the best possible comparisons between protocols, with or without PRT implementation[116]. Finally there is still place to discuss both transfusion thresholds and targets, and the parameters to be chosen for the assessment of transfusion efficacy, and quality assessment.

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