

Microbiological Screening of Platelet Concentrates in Europe

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Keywords

Bacterial contamination · Blood safety · Infection · Sepsis · Platelet concentrates · Pathogen inactivation · Transfusion-associated infections

Abstract

The risk of transfusion-associated sepsis due to transmission of bacteria is a persistent problem in the transfusion field. Despite numerous interventions to reduce the risk, cases of bacterial sepsis following transfusion are repeatedly being reported. Especially platelet concentrates are highly susceptible to bacterial contaminations due to the growth-promoting storage conditions. In Europe, blood establishments and national authorities have implemented individual precaution measures to mitigate the risk of bacterial transmission. To obtain an overview of the different approaches, we compiled information from national authorities, blood establishments, and the current literature. Several aspects such as the shelf life of platelets, time of sampling and the applied control measures are compared between the member states. The analysis of the data revealed a broad heterogeneity of procedures on a national level ranging from platelet release without any safety testing up to mandatory screening of all platelet concentrates prior to transfusion. Despite the substantial progress made in recent years, several bacterial reports on transfusion-associated sepsis indicate that further efforts are needed to increase the safety of blood transfusions in the long term.

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Introduction

Since the first successful administration of platelets to treat hemorrhagic disorders in 1910, platelet concentrates (PC) have become one of the most effective and indispensable medicinal products [1]. This is corroborated by their listing in the World Health Organization (WHO) “List of Essential Medicines” [2]. Platelet transfusion is generally applied in cases of thrombocytopenia with platelet counts less than 10×10^9 counts/L caused either by severe hemorrhage, stem cell therapy, or malignancies [3]. In 2015, more than 2.8 million PC were produced by blood establishments (BE) in Europe, of which 2.2 million were actually transfused to patients [4].

Blood products are subject to regulation with the objective of quality and safety assurance for both donor and recipient. In Europe, the European Parliament and the Council adopted general guidelines for the quality and safety of blood and blood components in the directives 2002/98/EC and 2004/33/EC [5, 6]. These directives provide quality standards for the collection, testing, processing, storage, and distribution of human blood and blood components. In addition, a description of some practical principles for BE is provided in the regularly updated “Guide to the Preparation, Use and Quality Assurance of Blood Components” issued by the European Directorate for the Quality of Medicines & HealthCare (EDQM) [7]. Regarding the microbial quality control of blood components, specific requirements have to be fulfilled by BE. These recommendations ensure

a concept to minimize the risk of microbial contamination in all blood products, and, therefore, the wording in the guidance documents is general in nature. According to these guidelines, national authorities are responsible to adopt these specifications on a national level. Moreover, individual measures that exceed the current requirements can be approved. As a result, different strategies and methodologies can be found among European countries, each having both advantages and disadvantages.

This article provides an overview of the different approaches in bacterial safety control of PC in Europe with a special emphasis on safety screening of PC. Furthermore, individual aspects affecting bacterial detection are discussed and compared between different member states (MS). A survey of European BE as well as information obtained from national authorities served as primary source for this review and was complemented by data published in the current literature.

It should, however, be noted that the information provided in this review does not cover all strategies applied in Europe in detail because individual BE in the respective MS might follow other nationally justified guidelines. However, some general variations will be highlighted and discussed in regard to their efficiency. Nevertheless, the authors emphasize that the analysis disregards other aspects such as platelet quality, logistic problems in implementing certain test methods, or cost factors.

Susceptibility of PC to Microbial Contaminations

Compared to other blood components, PC are highly susceptible to bacterial contamination. This is mainly attributed to the general PC storage conditions, which facilitate the proliferation of bacterial contaminants. The recommended storage temperature of 20–24 °C permits growth of many bacterial species originating from both the human microflora and environmental sources. Moreover, bacterial growth is promoted by the comparably high oxygen supply supported by continuous mixing of the gas-permeable PC bags. Frequently employed additives in the storage solution might serve as an additional energy source for some microorganisms resulting in a growth advantage [8]. The clinical relevance of bacterial PC contamination is confirmed by hemovigilance reports of transfusion incidents [9]. According to current knowledge, clinical complications caused by bacterial transmission range from mild septic reactions accompanied by fever up to severe septic shock and death of the recipients [10–12]. Moreover, delayed effects of transfusion-related bacteremia and subsequent infections cannot be entirely ruled out. Therefore, PC require adequate quality control measures to minimize the risk of bacterial transfusion-transmitted infectious diseases (TTID).

Preventative measures to decrease the risk of bacterial TTID have been implemented in the past by defining donor deferral criteria of at-risk patients, effective skin disinfection procedures, aseptic blood collection and processing by utilization of sterile equipment, predonation sampling, and leukocyte depletion. Especially the implementation of predonation sampling revealed a high potential of a simple but efficient preventive procedure. In 2 studies, diversion of the first milliliters of blood donation reduced the contamination rate from 0.35 to 0.21% for whole blood and from 0.17 to 0.05% for PC [13, 14]. A separation of the initial 20 ml of blood in combination with an improved skin disinfection using a two-step procedure resulted in a 77% decrease of contaminated platelets [15]. These interventions have significantly reduced the number of patients with bacterial sepsis following transfusion in the last decade. However, a low PC percentage still displays bacterial contaminations when appropriate quality control measures are performed [16–18].

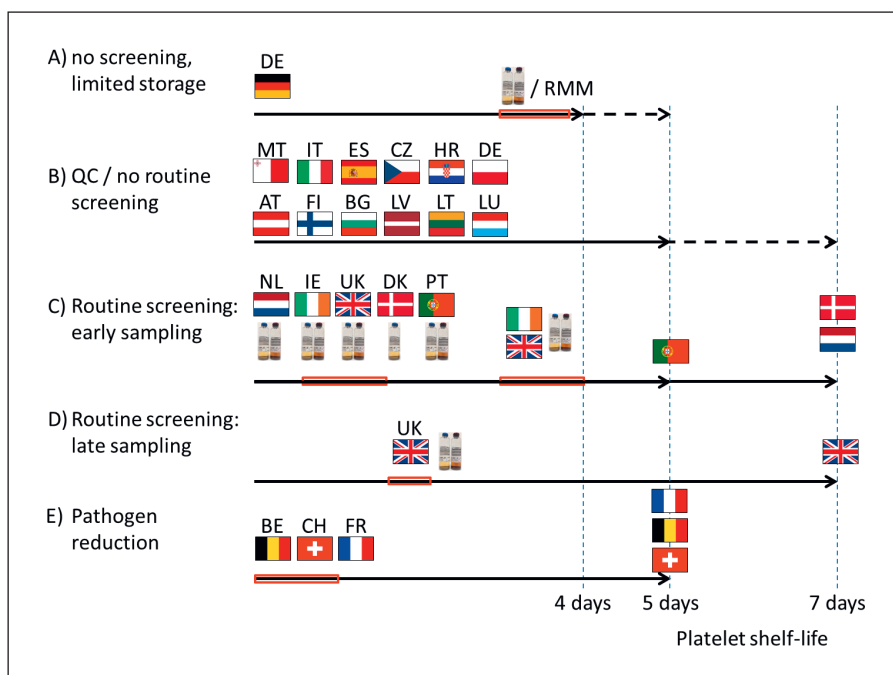
Asymptomatically infected donors or an inadequate disinfection of the venipuncture site are persistent sources of contamination. Referring to various publications, the rate of confirmed contaminated platelets is in the range of approximately 100–2,000 per million PC [16, 18–20]. These contaminated PC are transfused if no further safety measures are in place. To ensure high safety standards for patients, different strategies can be pursued in order to prevent bacterial transmission via contaminated PC. However, the success rate for bacterial detection is strictly dependent on the parameters of the respective methodology.

Data that have been collected during the analysis revealed a remarkable northwest-southeast divide in Europe with respect to bacterial safety measures (Fig. 1). A rather rudimentary strategy is followed in southeastern European countries where testing is performed either only as quality control or not at all. In contrast, the majority of MS in the northwest part of Europe have implemented different safety control strategies to mitigate the risk of transfusion-associated bacterial sepsis. These individual approaches will be described and discussed in the following sections.

Risk Mitigation through Platelet Storage Limitation

The duration of storage is one of the most critical factors which has a decisive impact on the severity of bacterial contaminations in PC. In contrast to viral contaminations, bacteria have the ability to proliferate. Thus, the initial bacterial counts can increase tremendously over time. This is exemplified by the platelet transfusion-relevant bacterial strain panel that was established by the

Fig. 2. Detailed strategies of individual member states (MS) to prevent contaminated platelet concentrate (PC) transfusion. A) Shelf life reduction to 4 days with an extension to 5 days by additional testing with culture-based or rapid microbiological methods (dashed line). B) Implementation of a random quality control (QC) testing; release of platelets up to day 7 is possible in individual MS dependent on additional measures to detect bacteria (dashed lines). C) Routine culture-based screening with early sampling. A 2-bottle strategy (aerobic and anaerobic) is followed except for Denmark, where an aerobic culture bottle is used. Shelf life varies between 5 and 7 days among the respective MS. Ireland and UK allow additional testing on day 4 for shelf life extension to day 7. D) Routine culture-based screening with late sampling and a corresponding shelf life of 7 days. E) Implementation of pathogen reduction; red boxes indicate the sampling period.



BacTec (Becton Dickinson). Both technologies analyze cell growth via the detection of CO₂ as a by-product of the metabolism of bacteria in the medium. The release of CO₂ leads to a colorimetric (BacT/Alert) or fluorescent (BacTec) signal, which is continuously monitored. The exact specification of the sampling and incubation procedures differs according to national guidelines and varies among the different countries.

For stratification and analysis, here, we distinguish 2 major approaches based on the sampling time, e.g., “early sampling” defined as sampling within 36 h after blood donation and “late sampling,” when cultivation is initiated later than 36 h. Notably, most countries with mandatory PC screening have implemented early sampling (Table 1). For instance, the time of sampling in the Netherlands is designated within a range of 18–26 h for pooled platelet preparations. Apheresis platelets are tested within 12 h after collection. In Ireland, apheresis platelets are sampled 1 day after donation (12–24 h) whereas pooled platelets are tested following the “late sampling” strategy, 1 day after pooling, which corresponds to day 2 after collection (36–48 h). In the UK, BE can choose from 2 different sampling schedules. Samples can either be taken 18 h after collection limiting storage duration to 5 days, or sampling can be performed at ≥36 h allowing a shelf life of 7 days. In Portugal, testing is performed 24 h after collection with restriction of storage time to 5 days. In Denmark, samples are taken 1 day after donation for apheresis platelets and 1 day after donation of whole blood on the day of pooling with storage duration lasting 7 days. The rationale behind this early sampling is to ob-

tain microbiological results as early as possible. However, due to the low initial concentration of microbial contaminants, the detection of pathogens within the first 24 h bears the risk of sampling errors and false-negative results [29].

So far, the initial bacterial load of a natural contamination has not been clearly enumerated. Based on bacterial screening data, a bacterial count <60 CFU/bag is predicted to be present in a naturally contaminated PC [30, 31]. This extremely low concentration is prone to sampling errors, especially when samples are collected shortly after donation when the bacterial load is far below 1 CFU/mL and knowing that bacteria tend to grow in aggregates and are not evenly distributed in solutions. Therefore, the estimated frequency of false-negative results associated with the “early sampling” strategy is alarming: only 10–50% of the contaminated blood cultures are detected as positive [18, 29].

With this reasoning, “late sampling” for bacterial detection was introduced to allow microbial contaminants to replicate and to reach concentrations above the detection limit. Furthermore, late sampling strategies allow the discrimination of replicating bacteria from residual bacteria killed by PC components, in particular complement. Currently, late sampling is implemented as a stand-alone screening procedure and criterion for PC release in the UK only. More frequently “late sampling” – often performed on day 4 or 5 of storage – serves as an additional safety measure that allows extension of the PC shelf life by BE, as is the case in Germany, Ireland, Finland, Latvia, Lithuania, Portugal, and Poland.

Table 1. Summary of safety test strategies for platelet concentrates (PC) applied in Europe

	No routine testing	Shelf life reduction	Early sampling (<36 h) culture based	Late sampling (>36 h) culture based	Pathogen reduction
Pro	Cheap No logistical efforts Highest availability of PC	Cheap Prevention of transfusion of highly contaminated PC	Detection of some contaminated PC Increased safety for patient	Detection of contaminated PC Increased safety for patient Possibility of an extended shelf life	Elimination of pathogens High level of microbiological safety
Contra	High risk for transfusion-associated sepsis	Residual risk of bacterial transmission Supply shortage	High sampling error due to low inoculum or bacteria Limited shelf life Disposal of PC due to false-positive test results Additional costs	Logistically complex Disposal of PC due to false-positive results Additional costs	Insufficient killing of spores and/or biofilm-producing bacteria Possible risk of pyrogenic reaction due to bacterial components Time critical Logistically complex Additional costs
Strategy used in	Poland, Italy, Malta, Bulgaria, Czech Republic	Germany	Denmark, Portugal, Netherlands, Ireland, UK	UK	Belgium, Switzerland, France

Quarantine of PC during Screening

Even for highly contaminated platelet samples, it takes several hours to yield a positive result in a culture-based screening process. For example, culture bottles inoculated with PC samples with a bacterial load of $>10^8$ CFU/mL of *K. pneumoniae* or *Escherichia coli* still require a minimum of 4 h to generate a positive alarm signal in aerobic and anaerobic culture bottles [32]. Similar results were obtained with gram-positive bacteria, e.g., *Staphylococcus aureus* or *Bacillus* spp., with concentrations $>10^6$ CFU/mL resulting in a positive signal at a minimum incubation time of 4 h. The time between the inoculation step and the test result might, however, be critical if platelets are released with a negative-to-date result. In order to prevent the transfusion of bacterially contaminated platelet units, PC could be quarantined for a predefined period. Such an approach is pursued in the UK, where a hold time for PC is authorized in combination with a culture-based screening approach. Using either a single or 2-test strategy, PC are put on hold for 6 or 24 h, respectively, after the inoculation of the culture until they are released on a negative-to-date result. The implementation of such quarantine time slots allows the detection of potential contaminants without the risk of PC release on the basis of false-negative results. In the context of the “late sampling” approach, the use of the quarantine principle as an additional safety measure should be considered. As “late sampling” is often performed after several days of storage, potential contaminants can have multiplied to significant and life-threatening levels [22, 33]. Recently published data justify an appropriate and efficient hold period for

the prevention of TTID. An extensive study was performed by Vollmer et al. [32] for the implementation of a culture-based method for shelf life extension of PC from day 4 to day 5. PC were spiked with few CFU of various bacterial isolates comprising species with both low and high pathogenicity. Within the first 24 h of incubation, a positive signal was obtained in all samples. The reduction in the testing period down to less than 12 h resulted in the detection of only 59% of bacteria from the low-pathogenicity group, whereas 100% detection of high-pathogenicity isolates was achieved. The detection rate was significantly improved to more than 97% if the detection time was increased to 18 h. Similar results were also observed in an early sampling setting (24 h after blood donation) utilizing a 2-bottle approach and a volume of 7–10 mL [16]. These examples demonstrate that product release directly after sampling might lead to severe transfusion reactions due to highly contaminated platelet units, which can be prevented by the introduction of a hold time by a risk-based approach. However, the short quarantine only confers prevention of severe transfusion-associated sepsis. A longer hold time is necessary to ensure the identification of slow-growing bacteria and samples with a low starting inoculum as a prerequisite for the efficient prevention of clinical septic reactions.

Improved Safety through Increased Sample Volume

A low bacterial concentration, particularly shortly after blood donation, is one of the major challenges for bacterial screening methods. Parameters that can be altered to

increase sensitivity, e.g., the minimum detection rate of contaminants, are currently limited. The sample volume is one factor that has a significant influence on the detection rate. The maximum sample volume for both semi-automated culture detection methods (BacTec and BacT/Alert) is 10 mL per culture bottle according to the manufacturer's specifications. Based on this volume, the theoretical detection limit of these systems would be 0.1 CFU/mL. However, analysis revealed a lower sensitivity of the systems when applied as routine control systems [34]. BE that have implemented culture-based screening of PC inoculate different volumes per bottle. For example, a maximum volume of 10 mL is used in Portugal and Denmark. Smaller volumes are inoculated in Ireland and the UK (8 mL/bottle) as well as in the Netherlands (7.5 mL/bottle). Although the general effect of the sample volume on the detection rate is limited, an extensive data analysis revealed a significant increase of 57% for true-positive results using 8 versus 4 mL of sample volume [35]. An alternative to the inoculation of a fixed volume is depicted by a so-called proportional sample volume approach [36]. Based on a Poisson model, inoculation of 3.8% of the total platelet product volume might lead to an improved detection rate compared to a fixed volume of 8–10 mL [37]. The verification of the hypothesis revealed a 2-fold increase in true-positive rates using the proportional sample volume strategy. It should, thus, be noted that a sample volume of 10 mL is sufficient for the 200- to 250-mL PC unit. The maximum sample volume of 10 mL per bottle can be expanded using a second culture bottle, which can additionally be used to implement both aerobic and anaerobic culture conditions. Although larger sample volumes used for bacterial screening improve the detection rate, other specifications of platelet components such as minimum platelet count per unit should be considered.

Anaerobic Screening – Is it Worth the Effort?

Potential contaminants of PC comprise a broad spectrum of species that require specific growth conditions. A ranking of transfusion-transmitted bacteria considering several risk factors showed that all relevant pathogens except for *Clostridium* spp. can be cultivated under aerobic culture conditions [38]. In Europe, the screening of PC using a single aerobic bottle is implemented in Denmark (Fig. 2). Finnish BE perform random testing of PC with 1 aerobic bottle as a quality control. In contrast, BE from Ireland, Portugal, the Netherlands, and the UK use a 2-bottle strategy comprising both aerobic and anaerobic bottles. It is conceivable that strict anaerobic isolates such as *Clostridium perfringens* or *Cutibacterium acnes* (formerly *Propionibacterium*) will not grow under aerobic conditions. Therefore, a strategy utilizing both bottles

types offers several advantages. Firstly, the use of an anaerobic culture bottle extends the bacterial spectrum that can be identified as a contamination. This benefit has been confirmed by several reports [11, 18, 39, 40]. For instance, a study from NHS Blood and Transplant showed that 66% of all confirmed positive results were only detected in anaerobic culture bottles, whereas 8% were positive in an aerobic and 26% in both bottle types [17]. It should, however, be noted that if both bottles are removed as soon as one of both is flagged as positive, it is unknown whether the second bottle would have led to a positive signal afterwards. Data from Australia confirmed an increase in safety with the 2-bottle strategy as several bacterial contaminants were only detected in anaerobic culture bottles [16]. Secondly, inoculation of 2 culture bottles increases the sample volume and thereby decreases the sampling error particularly when early sampling is performed. Notably, many bacterial pathogens are facultative anaerobes and grow under aerobic and anaerobic conditions, among them *S. aureus*, *E. coli*, and *Candida albicans*. Moreover, some bacteria particularly from the enteric flora show even a faster detection time in anaerobic bottles compared to aerobic conditions [16]. A negative aspect connected to the anaerobic culture is the relatively high rate of false-positive alarms leading to a withdrawal of non-contaminated PC [17]. Furthermore, the clinical relevance of anaerobic pathogens as contaminants in platelets is still under debate. For instance, 35–81.8% of confirmed positive results in anaerobic bottles are caused by *C. acnes* isolates [16]. But, to our knowledge, there are only rare reports on infections caused by *C. acnes*, which mainly focus on biofilms on iatrogenic implants [41]. Moreover, growth studies of 10 *C. acnes* PC isolates in platelets showed lack of proliferation, which indicates either persistence or death within 10 days of incubation [42]. Nevertheless, sporadic cases of transfusion incidents involving anaerobic bacteria have been reported. In 2017, two fatalities caused by the same *C. perfringens* isolate were documented by the Centers for Disease Control [10]. The routine safety test of these 2 PC units by aerobic culture was negative during the whole incubation period. Although it is not clear whether an anaerobic culture would have prevented the administration of these PC, the reports of transfusion-associated fatalities involving *C. perfringens* highlight the necessity of a 2-bottle strategy [43], especially because no donor-related risk factors have been identified that would assist in identifying donors with anaerobic bacteremia.

Role of Direct Methods as Safety Measures

In addition to these conventional systems, rapid microbiological methods (RMM) represent a promising alternative for BE to minimize the risk of TTID. Examples

of RMM comprise direct methods such as flow cytometry, amplification of nucleic acids, or detection of bacterial compounds, e.g., lipopolysaccharides or peptidoglycans. Particularly when applied shortly before administration, RMM might identify contaminated PC that were approved during the initial sampling procedure. Several systems are available on the market with different analytical sensitivities dependent on the detection principle. An overview of available methods and their test principles is provided by Störmer and Vollmer [44]. With regard to the time-to-result parameter, RMM are superior in comparison to culture-based methods. Depending on the method, results are obtained within a few minutes to hours, which allows for a fast release decision. However, in practice, RMM are only rarely used by BE or clinicians as final release tests. This might be due to several drawbacks of these systems such as low sensitivity, high costs, and increased hands-on time leading to logistic challenges.

In Europe, routine application of RMM as safety measures was so far only performed in Germany, where it is implemented by BE to extend the shelf life of platelets from 4 to 5 days [45]. The flow cytometry-based BactiFlow (Biomerieux) system is most frequently used by German BE, although technology based on nucleic acid amplification is approved for single BE, too. Due to a relatively short time-to-result window, platelets tested by this approach can be administered without putting them on hold. However, the implementation of RMM will not result in a complete elimination of transfusion-associated bacterial transmissions due to the relatively low sensitivity of these methods [46]. Samples with low bacterial counts will not be detected. Yet, when applied directly prior to transfusion, fatal incidents caused by highly contaminated platelet units can be prevented. Considering potential replication of PC pathogens, RMM results are usually valid for no more than 24 h. Afterwards, the number of contaminating microorganisms may increase dramatically devaluating previous results for fast-growing bacteria.

Septic Reactions due to False-Negative Results

Screening of platelets using semiautomated culture systems is a valuable tool to increase patient safety, which is emphasized by several studies on method efficacy. However, positive outcomes are repeatedly overshadowed by reported transfusion-related fatalities and transfusion incidents with false-negative PC. This indicates the existence of a safety gap despite the aforementioned measures being implemented. Bacterial transmission of *S. aureus* was recently reported by the Northern Ireland Blood Transfusion Service in spite of the use of a semiautomat-

ed culture system [47]. Further analyses suggested that biofilm formation might have been responsible for the false-negative result in the respective culture bottles. Due to adhesion of bacterial cells to the inner surface of the platelet bags, a sampling error is very likely [48]. Similar findings are reported for *S. aureus* isolates, which escaped from the screening process despite late sampling [17]. To this end, *S. aureus* can form aggregates by direct interaction with platelets [49]. This aggregation might increase the sampling error due to an uneven distribution of bacterial cells in the platelet bag.

Even though semiautomated bacterial detection systems provide a benefit in regard to safety, it should be stressed that a classical visual PC inspection should still be part of the routine quality control at all stages of the delivery chain. In many cases, transfusion of microbially contaminated PC was prevented due to visual anomalies, e.g., clot formation, lack of swirling, or color change [47, 50].

Elimination of Bacterial Contaminations Using Pathogen Reduction Techniques

Bacterial screening of PC using automated culture systems as any screening method is limited by sensitivity and specificity, i.e., by false-negative or false-positive results [16], leading to transfusion of contaminated or discarding of microbiologically safe PC, respectively [18]. Pathogen reduction (PR) technologies as a tool to prevent transfusion-related septic infections are, therefore, worthwhile mentioning. Here, the main advantage is the simultaneous depletion of potential pathogens including bacteria, many viruses, and parasites. Two systems, the Intercept Blood System (Cerus Corp., Concord, CA, USA) and Mirasol (Terumo BCT Inc., Lakewood, CO, USA) are currently on the market, and the Theraflex system (MacoPharma, Mouvoux, France) will be submitted for market authorization presumably in 2019. All 3 systems received the CE mark approval for treatment of platelets. The general mechanism of all 3 systems is based on an irreversible damage to the bacterial DNA preventing nucleic acid replication. The mechanisms of the PR system are out of scope of the current review and described elsewhere [51, 52].

Several countries implemented PR treatment for PC. In Belgium, PR is performed for all platelet units and is obligatory since the royal decree of June 28, 2009. Along with PR implementation, the shelf life of platelets was reduced from 7 to 5 days due to concerns on platelet efficacy. A similar situation is found in Switzerland, where the Intercept system was generally introduced in 2011. Recently, Jutzi et al. [28] assessed the implementation of PR by comparing the number of reported adverse reac-

tions related to both traditional and PR-treated PC. Before PR implementation, 2–4 septic reactions per year or 125 adverse reactions per million platelets units were reported. This number decreased to 0 directly after PR introduction, indicating the absence of transfusion-transmitted bacterial infection since then. After a 5-year regional test phase in France, nationwide PR implementation started in 2017 [53]. Future analysis of PR efficiency in PC in France will provide further evidence on the success of this strategy.

Similar to growth-based methods, time is a critical parameter for the successful implementation of PR. Fast-growing bacteria can reach a high bacterial load within a short time, thereby exceeding the reduction capacity of the PR systems. In the worst case, a single bacterial cell that survived the treatment might be the cause of a lethal PC transfusion. Even if a successful elimination of all bacteria was achieved, remaining pyrogenic cell wall components from gram-negative bacteria or exotoxins may constitute a threat for recipients. For instance, PR of 15 PC 30 h after low-CFU inoculation revealed 1 positive PC on day 5, whereas an earlier treatment 24 h after inoculation resulted in 100% culture-negative PC [54]. Similar results were obtained when blood components were inoculated with higher concentrations (100–1,000 CFU/bag) of transfusion-relevant reference strains. Here, occasional contaminations following a reduction procedure due to bacterial loads $>10^6$ CFU/ml are reported [55]. Another challenge is presented by biofilm-positive isolates or spores, which show increased resistance towards PR treatment [56, 57]. In contrast to the preferred late bacterial culture, it is, therefore, important to treat PC with PR as early as possible to avoid high bacterial loads. BE producing PR-treated platelets are required to follow the specifications and instructions given by the respective manufacturers to guarantee efficacy and safety. Taken together, use of PR methods requires establishment of a comprehensive quality assurance procedure including proficiency testing.

Concluding Remarks

Despite the implementation of numerous interventions, the risk of transfusion-associated bacterial sepsis still remains. In the European MS, different strategies – from routine screening of PC to release in the absence of adequate safety measures – are applied. The latter is certainly the most controversial approach due to the implicit acceptance of an increased risk of transfusion-associated morbidity and mortality. The decrease in the number of platelet transfusion-transmitted infections, particularly in the last 2 decades, should not divert from the fact that a substantial risk for patients still exists [10, 50].

For instance, it is clear that the significance of the data is strictly dependent on the identification of septic transfusion reactions and their subsequent reporting. However, it is assumed that the incidence of transfusion-associated sepsis is underestimated, thereby not reflecting the real risk. Based on data from Hong et al. [58], a high proportion of transfusion-associated bacterial infections are not recognized. Active surveillance by platelet sample analysis at the time of release revealed a 10–40 times higher risk for platelet-associated bacterial transmission compared to passive surveillance. The major reason for this underreporting is that the administration of a bacterially contaminated PC does not necessarily lead to overt clinical symptoms in the recipient [47]. The outcome is influenced by several factors, e.g., pathogenicity of the strain and the bacterial count at the time of administration. Moreover, both the clinical status and the ongoing therapy of the patient, including administration of antibiotics, might affect the manifestation and severity of the reaction. Delayed infections upon transfusion of a bacterially contaminated PC cannot be excluded. To date, there is no documented evidence for such a scenario although delayed infections caused by nonsterile pharmaceuticals are known [59]. Therefore, the relatively low number of transfusion-associated sepsis cases should not provide a justification for the implementation of a “no-testing” strategy. However, several European MS enforce routine testing of PC (Fig. 1).

The efficacy of the different measures on the frequency of septic reactions described has recently been reported [59]. For instance, culture-based screening reduced the number of contaminated PC to 5.4 per million compared to 16.3 before routine screening was introduced in the UK. Focusing on adverse transfusion reactions, the number even decreased by 90% [17]. Moreover, no fatalities were reported since the implementation of culture-based screening. In Belgium, France, and Switzerland, where PR treatment for PC was introduced in recent years, no septic reactions were reported since its implementation. Compared to historical data, the rates of microbiologically contaminated PC decreased significantly from 19, 82.9, and 35.6 per million cases to zero cases in France, Switzerland, and Belgium, respectively [9].

Several safety measures are conceivable, which vary in their costs and effort. On the basis of the current knowledge, PC might be released without any additional testing only up to 12 h after platelet production. The release of platelets without further microbiological control after this time should not be regarded as state of the art and might be driven by economic arguments. In this case, PC should be subjected to quarantine for at least 18–20 h. In addition, at least 10 mL of sample per 250 mL PC should be inoculated in both aerobic and anaerobic culture bottles. If the culture remains negative after 18 h, PC can

be released on the negative-to-date principle with a shelf life up to 7 days.

An even higher safety level with respect to transfusion-associated bacterial transmission is provided by the implementation of PR systems. Data from pathogen-inactivated platelets have so far shown promising results on the reduction of PC transfusion-associated sepsis. Prior to the marketing authorization, numerous studies on the performance of these systems were conducted. Focusing on the efficacy of PR, all 3 systems demonstrated significant log reduction of bacteria in platelets [60, 61].

The Good Practice Guidelines of the EDQM stated that "(...) blood and blood components are not released for distribution, until their quality has been judged to be satisfactory and that the necessary and relevant tests have been carried out." As a consequence of the nonbinding nature of this guidance, a clear lack of harmonization of safety measures across Europe with respect to the microbiological safety of PC becomes apparent (Fig. 1). However, it is clear that the implementation of additional safety measures is associated with higher expenses, which may represent an obstacle for both MS with limited financial resources and smaller BE. Taken together, on the basis of our current knowledge, it is, however, not appropriate to omit safety measures for mitigation of microbiological quality control of blood components.

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M.P. and O.K. wrote the manuscript, and I.B.-D. contributed to the final manuscript.

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