Original Article

Transfusion transmitted bacterial infections (TTBI) involving contaminated platelet concentrates: residual risk despite intervention strategies

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Background: Transfusion transmitted bacterial infection (TTBI) due to contamination of platelets is an important risk of blood transfusion. Our strategies to decrease bacterial contamination include skin disinfection, diversion of the first blood flow, and bacterial screening. Despite these intervention strategies, a residual risk remains.

Methods: To assess this remaining risk, we retrospectively examined TTBI cases registered in the national notification database Transfusion and Transplantation Reactions in Patients (TRIP) during 2008–2019. In addition, we retrospectively examined all cases in which platelets that tested positive in the bacterial screening had already been transfused from 2013 to 2019. The bacterial screening was performed by sampling platelet concentrates 17–25 hours after blood collection, followed by a 7-day incubation of aerobic and anaerobic blood culture bottles in the BacT/ALERT® system. The distribution of bacterial species in the bacterial screening of platelets was also characterized.

Results: We found 16 cases of possible/probable/certain TTBI associated with platelet transfusion in 2008–2019, including two certain TTBI (with one fatal case); in all of these cases, bacterial screening was negative. From 2013 to 2019, 1,382 out of 432,305 distributed platelets were positive (0.32%) in the bacterial screening, and 469 had already been transfused. In 20 of these 469 cases, a transfusion reaction was reported, 5 potentially related to contaminated buffy coat-derived platelets. Bacterial screening showed mostly skin bacteria, including Cutibacterium spp. and coagulase-negative staphylococci. Most virulent bacteria were detected within 48 hours.

Conclusions: In summary, our two approaches demonstrate a small residual risk of TTBI due to platelet contamination, with two certain TTBIs, including one fatal case, per 668,896 distributed platelets during 12 years.

Keywords: Transfusion transmitted bacterial infection (TTBI); contaminated platelets; BacT/ALERT®

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Introduction

Transfusion transmitted bacterial infection (TTBI) due to contamination of platelets is a major risk of blood transfusion (1,2). Measures to decrease the degree of platelet contamination include skin disinfection, diversion of the first blood flow after skin puncture, bacterial screening of blood products and application of pathogen reduction technology. Diversion of the first flow, in combination with an optimized disinfection method, has been shown to reduce initially positive cultures of pooled platelet concentrates (PC) from 0.95% to 0.37% (3). This finding led to the introduction of the diversion pouch in the Netherlands in 2004 and is currently common practice in blood banks across the world (3-5). To detect remaining bacterial contamination, various bacterial testing approaches are used, including culture-based or rapid detection tests. In many countries, including the Netherlands, pooled PC and apheresis platelets are tested for bacterial contamination by culturing a sample in the BacT/ALERT® system (6). The effectiveness of this approach is dependent on multiple parameters, including number and type of bottles, sampling volume and timing of sampling (7). Recommended strategies by the Food and Drug Administration (FDA) guideline on the safety of platelets include large volume delayed sampling, for example, applied in the United Kingdom (8,9).

Whereas these intervention strategies have significantly decreased septic transfusion reactions from bacterial contamination, a residual risk remains. In the European Union, all serious transfusion reactions possibly related to the quality and safety of blood products are notifiable and reported annually to the European Commission. In our country, Transfusion and Transplantation Reactions in Patients (TRIP) registers reports of transfusion reactions of all severity levels (passive surveillance). The TRIP database provides the opportunity to analyse reported cases of post-transfusion bacteremia/sepsis that were judged to be TTBI. In this study, we examined all cases of TTBI associated with platelet transfusions in 2008–2019 and reviewed the corresponding bacterial screening results of the platelet products.

In addition, we used a second approach to detect the remaining risk of TTBI due to contaminated platelets. PC are released as "negative-to-date" during BacT/ALERT® incubation. Whereas growth of bacteria is usually detectable during the time period between sampling and transfusion, transfusion does occur of platelets which subsequently have a positive result during the 7-day BacT/ALERT® incubation. In this study, we retrospectively examined transfusion reactions in cases in which platelets had been transfused and subsequently tested positive in the bacterial screening, during 2013–2019. Additionally, we characterized the bacterial species found in our bacterial screening.

Methods

Data on reported transfusion reactions

In the Netherlands, transfusion reactions, including those which may be related to the quality and/or safety of blood products are registered by TRIP, the national hemo- and biovigilance office (https://www.tripnet.nl/en/). TRIP defines post-transfusion bacteremia/sepsis as follows: clinical symptoms of bacteremia/sepsis arising during, directly after or some time subsequent to a blood transfusion, with a relevant positive patient blood culture result; a causal link to a transfused blood component may or may not be confirmed, through a finding of the same bacterial species in the component or material from the donor (10). TTBI is defined as a case of post-transfusion bacteremia/sepsis in which blood cultures of the recipient are positive with the same bacterial species as the culture from the transfused component; all information supplied by the hospital including resistance spectrum and occasionally genotyping is included. A team of experts within TRIP evaluates all TTBI cases and since 2011 has formally adjudicated the TTBI imputability, or likelihood that the reported septic reaction was caused by transmission of bacteria in the blood component (10). For this study, data on all TTBIs in 2008–2019 were provided by TRIP (11).

In addition, we reviewed transfusion reactions reported to TRIP in 2008–2019, other than TTBI, where bacteria were cultured from the remnant of the transfused platelet concentrate by the hospital while bacterial screening by the blood establishment remained negative.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The IRB ethical approval and individual informed consent are waived due to the retrospective nature of the study.

Bacterial screening with BacT/ALERT®

Buffy coats (BC) are produced from overnight hold whole blood (14–20 hours at room temperature) and pooled from 5 whole blood donations to produce a pooled BC-

derived, leukocyte-depleted PC. Platelets are currently stored in platelet additive solution, but during 2013–2019 platelets were in plasma, platelet additive solution/plasma or platelet additive solution only, changing over the years. Products are sampled within 2 hours after production (i.e., 17–25 hours after donation) and anaerobic and aerobic blood culture bottles are inoculated (7.5 mL each) in a laminar flow cabinet. The bottles are incubated in the BacT/ALERT® (BioMerieux) system for a maximum of 7 days. Gram staining and culture are performed on bottles with a positive BacT/ALERT® signal. Confirmed positive results are defined as a positive BacT/ALERT® signal confirmed by a positive culture from the BacT/ALERT® bottle (majority of cases), or a positive Gram staining but a negative culture. Apheresis PC, which account for only about 7% of transfused PC in the Netherlands, are sampled within 12 hours after collection and are cultured according to the same procedure.

All platelet products are released to hospitals on a "negative-to-date" basis, i.e., the culture bottles are negative for bacterial growth at the moment of distributing the product. If the product becomes positive after release, the product is recalled and destroyed. However, the product may have been transfused already.

Positive bacterial screening after transfusion and description of cases

All results of our BacT/ALERT® screening, including both pooled BC derived PC as well as apheresis PC, are maintained in a database for quality control including trend analysis. In case of a positive BacT/ALERT® result of an already distributed product, hospitals are always informed and the product is recalled. If the PC has already been transfused, hospitals are asked whether any transfusion reaction occurred and whether blood cultures have been performed. These data are registered in our database using TrackWise Enterprise Quality Management Software (EQMS). The blood establishment assesses whether each transfusion reaction was possibly related to a contaminated PC.

For this study, BacT/ALERT® data, including number of confirmed positive results and number of transfused products, were obtained from our database for a 7-year period [2013–2019]. In addition, clinical data were obtained from TrackWise EQMS, including the assessment whether the transfusion reactions were potentially related to contaminated PC.

Characterisation of bacterial species found in the bacterial screening

We used our database of the BacT/ALERT® screening to characterise the distribution of bacterial species for all confirmed positives identified in the BacT/ALERT® during 2013–2019. The database includes information on time to positivity of the blood culture bottles. We analysed the contribution of bacterial species that were isolated within 48 hours or after 48 hours incubation. Analysis was restricted to pooled BC-derived platelets as the main platelet product.

Statistical analysis

No statistical analyses were performed.

Results

Post-transfusion bacteremia/sepsis and TTBI

In 2008–2019, 633 cases of post-transfusion bacteremia/sepsis were reported in the Netherlands, corresponding to an average of approximately 50 reactions per year. Of the 633 post-transfusion bacteremia/sepsis cases, only 23 cases met criteria for TTBI. Sixteen/23 TTBI cases involved PC. Seven/twenty-three cases occurred with red blood cell transfusion and were not included in this study. The total number of distributed PC during this time period was 668,896. Thus, TTBI occurred in 16 cases out of 668,896 distributed PC, corresponding to 1 in every 42,000 PCs (or 24 per 1,000,000 or 0.002%).

Characterisation of TTBI cases

The 16 TTBI cases associated with platelets were characterised (*Table 1*). A severity score was assigned to all TTBI cases, based on the International Haemovigilance Network/International Society for Blood Transfusion grading system. The severity grade was 1 (non-severe) in two cases, grade 2 (severe) in 11 cases, grade 3 (life-threatening) in two cases and grade 4 (death) in one case. The cultured bacterial species in the TTBI cases were the following: coagulase-negative staphylococci (7 cases), beta-hemolytic streptococci (3 cases), *S. aureus* (2 cases), *E. faecalis*, *E. coli*, *Salmonella* group B and *Acinetobacter ursingii*. TTBI imputability was assigned by TRIP experts based on clinical and microbiological information. There were two definite TTBI cases, six probable cases and eight possible cases (12).

Table 1 TTBI cases in platelet products reported to TRIP in 2008–2019 [source: Transfusion and Transplantation Reactions in Patients (TRIP) Foundation. Trip Reports Hemovigilance Extended version, 2008–2019]

Case number	Year	Severity grade	TTBI imputability	Symptoms	Patient blood culture results	Culture result from remnant of transfused blood component identical to patient blood culture[†]
1	2008	2	Possible	Fever, rigors and vomiting	Coagulase negative staphylococci	Yes
2	2009	2	Probable	Fever and rigors	*Staphylococcus epidermidis*	Yes
3	2010	2	Certain	Fever, rigors, hypotension and swollen face	*Streptococcus dysgalactiae*	Yes
4	2010	1	Possible	Fever and dyspnoea	*Staphylococcus warneri*	Yes
5	2010	1	Probable	Fever, rigors and tachycardia	*Acinetobacter ursingii*	Yes
6	2011	2	Probable	Fever, rigors, hypertension, tachycardia, dyspnoea and vomiting	*Salmonella* group B	Yes
7	2012	2	Probable	Fever, rigors, tachycardia, dyspnoea, cyanosis and vomiting	*Hemolytic streptococcus* group C	Yes
8	2013	2	Possible	Fever, dyspnoea, vomiting and collapse	*Staphylococcus hominis*	Yes
9	2014	4	Certain[‡]	Fever, rigors and chest pain	*Staphylococcus aureus*	Yes
10	2014	2	Possible	Rigors	*Staphylococcus epidermidis*	Yes
11	2015	3	Possible	Fever and vomiting	*Enterococcus faecalis*	Yes
12	2016	3	Possible	Fever, rigors, dyspnoea and chest pain	*Staphylococcus epidermidis*	Yes
13	2016	2	Probable	Fever, rigors, dyspnoea, hypertension, tachycardia and chest pain	*Streptococcus dysgalactiae*	Yes
14	2016	2	Possible	Fever, rigors, hypotension, tachycardia and decreased O_2 saturation	*Staphylococcus epidermidis*	Yes
15	2017	2	Possible	Fever, rigors, hypertension and tachycardia	*Escherichia coli*	Yes
16	2019	2	Probable	Fever, rigors, dyspnoea, hypertension and tachycardia	*Staphylococcus aureus*	Yes

[†], a sample was taken after transfusion from the platelet bag and was cultured. The culture result was compared with the patient blood culture result. [‡], case described in 2014 hemovigilance report as 'probable to certain' transmission, based on genotyping. Identical species were found in patient blood culture, culture from remnant of transfused component and nasal swab from 1 of the 5 donors, but not in the associated red blood cell concentrate. TTBI, transfusion transmitted bacterial infections.

Importantly, we examined if the bacterial screening with BacT/ALERT® had become positive after release of the TTBI-associated blood products, since our blood products are released as negative-to-date. In all 16 TTBI cases, the BacT/ALERT® remained negative during the 7-day incubation period.

Positive bacterial screening with BacT/ALERT®

In 2013–2019, all pooled BC-derived PC (n=400,433) and

Table 2 Confirmed positive BacT/ALERT® bacterial screening, number of transfused products and numbers of transfusion reactions, 2013–2019 (source: Data from Sanquin Blood Supply Foundation)

Blood product	Total products cultured	Confirmed positive bacterial screen					Positive units that had been transfused	Transfusion reactions in recipients of positive units
		Total positive (% of products cultured)	Aerobic and anaerobic bottle	Aerobic bottle only	Anaerobic bottle only	Data about type of bottle missing		
BC derived PC	400,433	1,300 (0.32%)	88	177	995	40	439	20
Apheresis platelets	31,872	82 (0.26%)	6	15	61	0	30	0

BC, buffy coat; PC, platelet concentrate.

apheresis PC (n=31,872) were cultured using the BacT/ALERT® culturing system (*Table 2*). A total of 1,300 pooled BC-derived PC (0.32%) and 82 apheresis PC (0.26%) were confirmed positive in the bacterial screening. For BC derived PC, both aerobic and anaerobic bottles were positive in only 7% of all positive screens, only the anaerobic was positive in 77% and only the aerobic bottle was positive in 14%. The findings were similar for apheresis platelets: in 7% of cases both bottles were positive, in 74% of cases only the anaerobic bottle and in 18% only the aerobic bottle.

Since products are released on a "negative-to-date" basis, a portion of products that were positive had already been distributed and transfused to a patient: 439/1,300 BC derived PC and 30 units/82 apheresis platelets. For the BC derived PC, a transfusion reaction was reported to Sanquin Blood Bank in only 20/439 cases. For the apheresis platelets, no transfusion reactions were reported in these cases.

Cases with positive bacterial screening after transfusion and a transfusion reaction

To examine the significance of the positive bacterial screening results in cases with transfusion reactions, we obtained clinical and microbiological data from TrackWise EQMS for the 20 cases with a positive bacterial screening after transfusion and a transfusion reaction (*Table 3*). Importantly, in none of these cases the same bacterial species was isolated from the blood of the patient and from the BC derived PC. Thus, none of these cases meet the criteria for TTBI. Furthermore, in none of the cases samples were taken from the PC bag after transfusion, suggesting that there was no clinical suspicion of TTBI directly after transfusion, when the unit might have been sampled for culture. At the time of recall sampling was not possible anymore.

In 5 out of 20 cases with a positive bacterial screen and a transfusion reaction, the transfusion reaction was potentially related to a contaminated BC-derived PC. In one case, the bacterial screening was positive with hemolytic streptococci group G. This patient was transfused with red blood cells, platelets and plasma because of bleeding during vascular surgery, and shock was reported. The bacterial screening became positive after only 0.5 days. The patient's blood cultures remained negative. The patient did not recover and died a few weeks after the transfusion. The transfusion reaction was classified by the blood establishment as possibly related to contaminated platelets with hemolytic streptococci group G. This transfusion reaction was reported to TRIP as bacterial contamination of blood component. Following review by the Expert Committee an additional category of other reaction was recorded: subgroup of nonconfirmed sepsis, severity grade 4, imputability probable (12). In 4 cases, bacterial screening was positive with *Cutibacterium* spp., no positive blood cultures of the patients were reported by the hospitals, and the imputability was classified as possible, based on clinical information, even though TTBI caused by *Cutibacterium* spp. have only sporadically been reported (13).

In 15 out of 20 cases, imputability was unlikely. In 5 of these cases, highly virulent pathogens were cultured from the blood of the patients (*Pseudomonas aeruginosa*, *Morganella* spp., *S. aureus*, Enterobacterales, *Candida* spp.), which likely were the causative agents of the clinical presentation and the bacteria with relatively low pathogenicity in the bacterial screening seemed unrelated to the transfusion reaction. In two cases, the bacterial screening showed

Table 3 Transfusion reactions reported in patients who received a subsequently confirmed positive PC in 2013–2019 (source: Data from Sanquin Blood Supply Foundation)

Case number	Year	Severity grade	Imputability	Symptoms/diagnosis	Culture in PC sample	Patient blood culture
1	2013	4	Unlikely	Fever in patient with perforated diverticulitis and multi-organ failure	*Cutibacterium* spp.	Unknown
2	2013	1	Unlikely	Fever in patient with pneumonia after stem cell transplantation	*Cutibacterium* spp.	Negative
3	2013	4	Unlikely	Sepsis in patient with complicated abdominal surgery and peritonitis	*Cutibacterium* spp.	Unknown
4	2014	4	Unlikely	Clinical decline in patient with complicated cardiac surgery and multi-organ failure	*Staphylococcus epidermidis*	*Pseudomonas* spp.
5	2014	4	Unlikely	Clinical decline in patient with complicated pancreatitis and multi-organ failure	*Cutibacterium* spp.	*Morganella* spp.
6	2015	1	Unlikely	Fever (present before transfusion) without other symptoms	*Cutibacterium* spp.	Unknown
7	2015	1	Possible	Fever without other symptoms	*Cutibacterium* spp.	Unknown
8	2015	1	Unlikely	Fever (present before transfusion) without other symptoms	*Cutibacterium* spp.	Unknown
9	2016	1	Unlikely	Fever in AML patient treated with antibiotics before transfusion because of *E. Coli* infection	*Staphylococcus saccharolyticus*	*Candida* spp.
10	2016	1	Unlikely	Fever (present before transfusion) without other symptoms	*Cutibacterium* spp.	*Grampositive cocci*
11	2016	1	Unlikely	Fever without other symptoms	*Cutibacterium* spp.	*Staphylococcus aureus*
12	2016	4	Possible	Shock after vascular surgery	*Hemolytic streptococcus group G*	Negative
13	2016	1	Unlikely	Fever without other symptoms	*Cutibacterium* spp.	*Staphylococcus epidermidis & Staphylococcus haemolyticus*
14	2017	1	Unlikely	Fever (present before transfusion) without other symptoms	*Staphylococcus saccharolyticus*	Unknown
15	2017	1	Possible	Fever without other symptoms	*Cutibacterium* spp.	Unknown
16	2018	1	Possible	Fever and CRP raise in patient after vascular surgery	*Cutibacterium* spp.	Unknown
17	2019	1	Unlikely	Urticaria without fever	*Cutibacterium granulosum*	Unknown
18	2019	1	Possible	Fever without other symptoms	*Cutibacterium* spp.	Unknown
19	2019	1	Unlikely	Fever and rigors, as seen after previous transfusions	*Grampositive rods*	Unknown
20	2019	1	Unlikely	Fever without other symptoms	*Cutibacterium* spp.	Enterobacterales

PC, platelet concentrate; AML, acute myeloid leukaemia; CRP, C-reactive protein.

Table 4 Number of reactions reported to TRIP with a positive culture of the platelet unit in the hospital [source: Transfusion and Transplantation Reactions in Patients (TRIP) Foundation. Trip Reports Hemovigilance Extended version, 2008–2019]

Reaction	Total number of reports	Reports of grade 2 or higher[†]
Anaphylactic transfusion reaction	3	2
Other allergic reaction	6	
Mild (nonhemolytic) febrile reaction	2	
Nonhemolytic transfusion reaction (NHTR)	13	
Other transfusion reaction	19	3
Post-transfusion bacteremia/sepsis	5	
Total	48	5

[†], imputability certain, probable or possible.

Cutibacterium spp. and the blood culture became positive with Gram positive cocci (no further identification possible) and coagulase negative staphylococci, respectively. In 8 cases, bacterial screening showed bacteria with limited pathogenicity (mostly *Cutibacterium* spp.), no positive blood cultures of the patients were reported by the hospitals and imputability of the transfusion reaction to the contaminated PC was unlikely, based on clinical information.

Reactions reported to TRIP with a positive culture of the platelet unit in the hospital

Table 4 summarizes 48 reports to TRIP in 2008–2019, other than TTBI cases, where a bacterial species was cultured in the remnant of the transfused platelet concentrate by the hospital. For all cases bacterial screening remained negative. In the absence of a positive patient blood culture assessment of potential TTBI is not applicable. All five serious reactions (severity grade ≥2 and imputability certain, probable or possible) were reviewed at case level. One case (reported as "other reaction") was reported with clinical features suggestive of bacteremia/sepsis (fever, rigors, dyspnoea, desaturation, tachypnoea, hypotension, flank pain, nausea, diarrhoea). The culture (in the hospital) of the remnant of the blood component was positive for *Escherichia coli*. Blood cultures taken from the patient at the time of the reaction were negative. Therefore, this case is considered as a potential septic reaction with false negative bacterial screening and false negative patient blood culture. The symptoms of the two severe anaphylactic reactions were clinically regarded as consistent with an allergic mechanism. The other two severe cases classified as other reactions were associated with arrhythmia and hypotension in a normothermic patient and dyspnoea in a patient with bilateral pneumonia receiving treatment with antibiotics. Thus, only one additional case of potential septic transfusion reaction was identified by the review of reported cases with a positive culture of the platelet unit in the hospital.

Characterisation of bacterial species found in bacterial screening

We examined the distribution of bacterial species found in our screening of pooled BC derived platelets from 2013 to 2019. As shown in *Figure 1*, more than half of cases of positive bacterial screening are caused by *Cutibacterium* spp., cultured from anaerobic bottles. Over a quarter of cases are caused by coagulase-negative staphylococci, including the anaerobic coagulase negative staphylococcus *S. saccharolyticus*. *Figure 1* also shows the varieties of bacteria that are found occasionally.

Platelets are released as negative-to-date, but are mostly administered >48 hours after production and inoculation. Therefore, we compared the bacterial species that were found in cultures turning positive within 48 hours and after 48 hours. As shown in *Figure 2*, the commensal and relatively slow-growing skin bacteria *Cutibacterium* spp. are by far the most commonly cultured bacteria after 48 hours, accounting for 78% of cases. *S. saccharolyticus*, an anaerobic coagulase-negative staphylococcus, accounts for 12% of cases. Before 48 hours, coagulase-negative staphylococci, also part of the commensal skin flora, are found most frequently, in 74% of cases. More virulent bacteria, including beta-hemolytic streptococci and *Viridans streptococci*, are usually positive in the bacterial screening

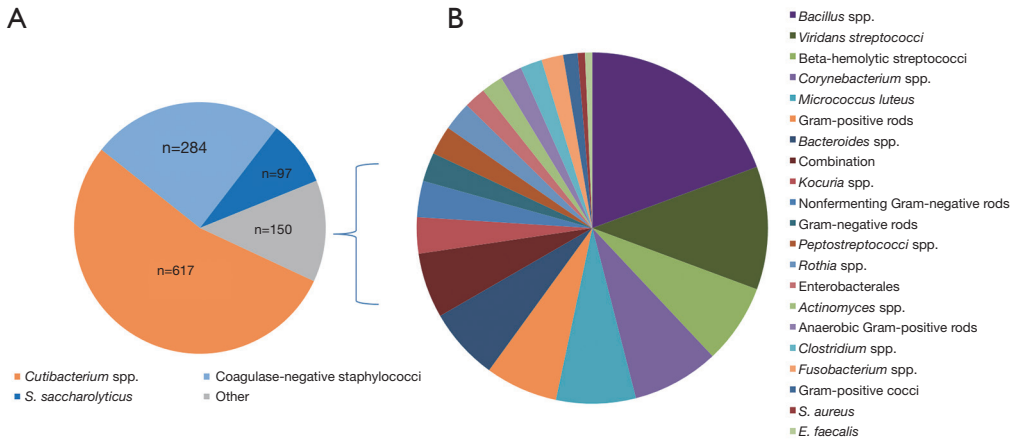

Figure 1 Distribution of bacterial species in confirmed positive BacT/ALERT® screening of pooled BC derived platelets [2013–2019]. The proportions and absolute numbers of bacterial species are shown in (A), and the composition of species in the group "Other" (n=150) is shown in (B). BC, Buffy coats.

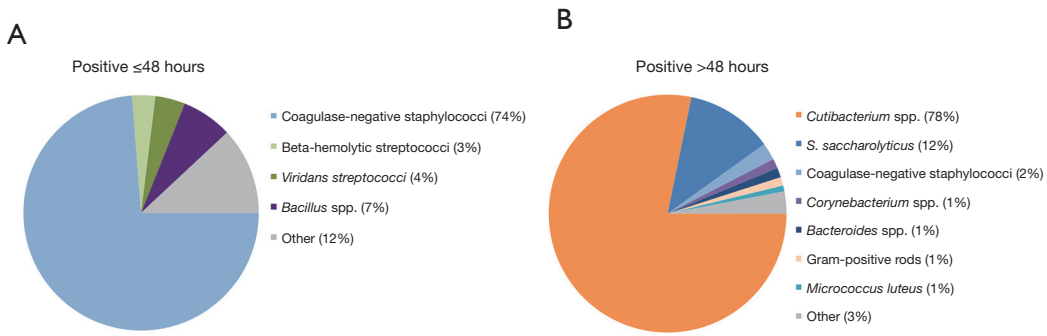

Figure 2 Bacterial species in BacT/ALERT® screening of pooled BC derived platelets positive before (A) and after (B) 48 hours [2013–2019]. BC, Buffy coats.

within 48 hours (*Figure 2*). Other pathogenic bacteria, including Enterobacterales and *S. aureus* were seen only sporadically. We found *S. aureus* once, *Klebsiella oxytoca* once, *Citrobacter freundii* once, all detected before 48 hours, and *Campylobacter fetus* once, detected just after 48 hours (data not shown). None of these 4 PC had been administered to a patient. Together, these results show that virulent bacteria are detected only occasionally and usually within 48 hours, and thus mostly before administration.

Discussion

In this study, we examined the residual risk of septic transfusion reactions due to bacterial contamination of platelets. Based on hemovigilance data from TRIP, we identified 16 potential TTBIs [2008–2019]. Based on positive BacT/ALERT® screening data, we identified 5 cases in which contaminated platelets had possibly resulted in a transfusion reaction [2013–2019]. Including findings from both approaches, only two cases were definite TTBI, with one fatal case.

In the first approach, analysing cases of TTBI reported to the TRIP database, we found two definite TTBI cases, 6 probable cases and 8 possible cases. The definite TTBI cases involved a *Streptococcus dysgalactiae* and *S. aureus* (fatal). All these cases had a negative BacT/ALERT® screening of platelets, and thus demonstrate a small residual risk (16 cases per 668,896 distributed platelets) despite bacterial screening. Since the BacT/ALERT® remained negative during the 7-day incubation, a longer hold (later release) of platelets would not have prevented these 16 TTBI cases. However, a longer delay of sampling for culture may have prevented some cases.

After reviewing all TRIP reports, other than TTBI,

where a bacterial species was cultured in the remnant of the transfused platelet concentrate by the hospital, we found one additional case that is considered a possible septic transfusion reaction with false negative patient blood culture.

In our second approach, examining all cases with positive bacterial screening of transfused platelets, we identified 5 cases in which a transfusion reaction was possibly resulting from a contaminated platelet product. The bacterial screening of the platelets showed hemolytic streptococci in 1 case and *Cutibacterium* spp. in the other 4 cases. There was no overlap in cases found using these two approaches.

Previously, transfusion reactions in cases with transfused, and subsequently positively screened, platelets were examined during a 2-year period [2006–2007] (14). A transfusion reaction occurred in two of 158 platelet transfusions that later became positive in the bacterial screening, but imputability of both cases was classified as unlikely. Our data from 2013 to 2019 confirms these earlier findings.

Since we found no TTBI cases resulting from transfused platelets that subsequently became positive in the bacterial screening, the value of continued incubation in the BacT/ALERT® after distribution could be questioned. Importantly, positively screened platelets that have been distributed, but have not yet been transfused, are recalled, preventing potential TTBI. Therefore, continued incubation after distribution of platelets contributes to minimizing the risk of TTBI.

In our study, we provided a detailed characterization of bacterial species found in our BacT/ALERT® screening. As in previous studies, skin bacteria, including *Cutibacterium* spp. and coagulase-negative staphylococci, accounted for the majority of cases (3,9). This distribution of bacterial species in the bacterial screening is highly similar to the distribution of bacterial species on the forearm and antecubital fossa (15), consistent with the skin of the donor as the main origin of bacterial contamination of PC (16). Whereas *Cutibacterium* spp. are mostly considered low pathogenic bacteria, they have emerged as pathogens of healthcare-associated infection, mostly in association with foreign devices, including prosthetic valve endocarditis, cardiac implantable electronic device infections and prosthetic joint infections (17). However, in the context of transfusion, the pathogenic role of these bacteria still appears low. In contrast to the frequent finding of *Cutibacterium* spp. in bacterial screening, only a few cases of transfusion-related sepsis due to *Cutibacterium* spp. have been reported (13). This may be due to low pathogenicity in combination with low bacterial load. *Cutibacterium* spp. do not proliferate under platelet storage condition and thus do not reach clinically significant bacterial loads (18). Virulent bacteria and high bacterial loads are associated with more-severe transfusion reactions (19).

In addition to the overall distribution of bacterial species in the screening, we also compared the distribution of species that became positive in the BacT/ALERT® before and after 48 hours. Platelets are only sporadically transfused within 48 hours from production, but release of platelets as negative-to-date poses a potential risk. As expected, but reassuring, the majority of positive screening results after 48 hours showed *Cutibacterium* spp. Virulent bacteria, including hemolytic streptococci, were mostly cultured before 48 hours. Interestingly, hemolytic streptococci were responsible for one certain TTBI case, for one probable TTBI case, as well for one case with a transfusion reaction possibly associated with the subsequently positive screen. These cases emphasize the important finding that these species were mostly detected within 48 hours (*Figure 2*).

S. aureus was detected in our bacterial screening in 1 case in 2013–2019, within 48 hours, and the product had not been transfused. In 2008–2012, *S. aureus* was detected in the bacterial screening in 6 cases, and in all cases the bacterial screening also became positive within 48 hours and blood products had not been transfused (*unpublished data*). *S. aureus* was responsible for one probable and one definite, fatal, TTBI during 2008–2019. The BacT/ALERT® remained negative in these cases. In the United Kingdom, *S. aureus* failed to be detected by the BacT/ALERT® in 4 cases during screening of 1,239,029 platelets [2011–2015], of which 3 were not transfused due to visual detection of clumps in the platelet bag (9). These findings emphasize the importance of visual inspection before transfusion as a final strategy to decrease the risk of TTBI.

The BacT/ALERT® remained negative in all TTBI cases. The number of false negatives may be reduced by later sampling of the product, first allowing proliferation of bacteria to a level above the limit of detection. Such late sampling is recommended by the FDA guideline and nowadays common practice in the United Kingdom (8,9). We have not postponed the time of sampling because this is difficult to introduce due to logistic challenges, and because our current numbers of TTBI are low. Later sampling may result in release of older products, with potentially lower quality (20), as well as more outdating. The other parameters recommended by the FDA guideline, including large volume sampling in two bottles, have been standard

practice in the Netherlands since the introduction of bacterial screening in 2001 (6).

The 48 cases where hospital culture of the remnant of the PC yielded a bacterial species should theoretically also be considered as false negative BacT/ALERT® screening results. However, the majority of the transfusion reactions which led to culturing of the bag were not clinically diagnosed as cases of sepsis caused by the cultured bacteria and in no case a patient culture was positive for the same species. Obtaining samples from the remnant of the PC for culture is not standardised in most hospitals and is likely to be prone to contamination (21).

As an alternative approach to reduce occurrence of TTBI, various pathogen reduction technologies for platelets have been studies (22-24). These techniques use ultraviolet light to target nucleic acids without destroying platelet membranes, thereby preventing proliferation of bacteria. Limitations of this strategy include breakthrough of fast-growing and spore-forming bacteria and potential decrease in the quality of platelets (25-27).

To conclude, recognizing post-transfusion sepsis by clinicians, obtaining blood cultures from the patient as well as cultures of the PC are required to identify a TTBI. Therefore, adequate follow-up in case of suspicion of post-transfusion sepsis and reporting reactions to the platelet supplier and hemovigilance office are crucial. Combining information from these sources, we identified a small remaining risk of TTBI due to platelets contamination despite intervention strategies.

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