

Hazards of Transfusion : An Institutional Study

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Abstract

Background: Platelet contamination with bacteria is a significant global public health concern. Contamination can occur through external routes during collection and processing or through endogenous (donor) sources. This study aimed to determine the extent of bacterial contamination in platelets and assess the antimicrobial susceptibility patterns of the identified bacteria. **Methods:** A cross-sectional study was conducted from January to September 2022, involving a total of 772 platelet concentrates. Aerobic and anaerobic blood culture vials were inoculated and incubated until positive results were obtained. If no positive results were obtained within 48 hours, incubation and inoculation were extended for one week at a temperature of 35°C using BD BACTEC™ FX40. Positive culture vials were then sub-cultured on solid media for microbial isolation and identification. The platelet components showing positive culture results were subsequently tested. **Results:** Bacterial contamination was observed in 25 out of 772 platelet concentrate units (3.23%). The most commonly isolated gram-positive bacillus was Coagulase-negative Staphylococcus, found in 8 units, followed by Staphylococcus aureus in 4 units. Enterococcus was detected in 2 units, while Streptococcus contaminated 3 units. Among gram-negative bacilli, Klebsiella was isolated in 2 units, Pseudomonas in 2 units, Acinetobacter in 1 unit, and Proteus in 3 units. **Conclusion:** This study emphasizes the need for universally applicable measures to detect, manage, and reduce transfusion-transmitted bacterial infections (TTBI) in platelet concentrates. These measures include implementing effective phlebotomy techniques, routine use of diversion pouches, and automated bacterial detection systems. While these measures can reduce the risk of TTBI, complete elimination is challenging. The findings of this study will raise awareness among stakeholders and contribute to enhancing the safety of blood transfusion services.

Key words: Anti-microbial susceptibility, Platelets, Bacterial culture, Hemovigilance.

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Introduction

Blood safety encompasses more than just the absence of transfusion-transmitted infections (TTI). It relies on various factors such as the prevalence of infections among eligible donors, strict adherence to donor deferral criteria, and the use of advanced blood screening techniques like nucleic acid testing. Implementing haemovigilance protocols during blood bank procedures helps minimize transfusion-related risks and prioritize donor safety. Human platelets, stored at room temperature, pose a higher risk of contamination and sepsis compared to other blood components. Contamination can occur due to asymptomatic bacteremia in donors, inadequate disinfection at the phlebotomy site, and contamination during collection and separation processes [1]. Surveillance data shows that platelets stored for up to five days have a high incidence of septic reactions, with fatal reactions predominantly occurring on the fourth and fifth day [2,3]. Understanding the factors contributing to blood product contamination during collection, processing, and storage is crucial for implementing preventive measures and ensuring universal blood safety for both donors and recipients.

Objectives

Objectives of this study are as follows:

- Determine the occurrence of bacterial contamination in human platelets stored at room temperature.
- Identify the specific bacterial pathogens present and determine their susceptibility to antimicrobial treatments.
- Evaluate the usefulness of pH and swirling as indicators for detecting bacterial contamination in the platelets.
- Provide recommendations for preventive measures to reduce or eliminate bacterial contamination in stored platelets.

Methodology

A cross-sectional study was conducted at RLJH Blood Bank in Kolar, Karnataka, over a period of nine months, from January 2022 to September 2022. Prior to blood donation, donors underwent pre-donation counseling and physical examination, adhering to the institution's donor deferral criteria protocol. The inclusion criteria for donors were as follows: age between 18-60 years, hemoglobin level greater than 12.5 g/dl, weight between 60-65 kg, and a platelet

count greater than 1.5×10^9 cu/mm³ as per Drugs and Cosmetics Act, 1945, by the Ministry of Health, Government of India. Written informed consent was obtained from all eligible donors.

Several exclusion criteria were applied, including the following: donors who had taken analgesics on or before the day of donation, and donors who had taken antibiotics 7-10 days prior to the donation. The sample size for the study was determined using the WHO and Raosaft sample size calculator, considering a 5% probability of platelet component contamination and a confidence level of 95%.

$$n = \frac{Z_{1-\alpha}^2(p)(q)}{d^2}$$

n= Sample size
 $Z_{1-\alpha/2}$ at 95% 1.96 (power)
 n=772

Before blood collection, the venipuncture site was cleaned by swabbing with povidone-iodine (7% w/v) for 30 seconds, followed by swabbing with isopropyl alcohol for another 30 seconds, moving from the inward direction to the outward direction. Phlebotomy was then performed, and an initial aliquot of 20 mL of whole blood was collected in a triple bag with diversion pouches. Platelet-rich plasma (PRP) was obtained by centrifuging the collected blood, first with a light spin at $2,000 \times g$ for three minutes, followed by a heavy spin at $5,000 \times g$ for five minutes at a temperature of 20-22°C. This process yielded platelet concentrates (PCs) which were stored at 20-22°C under continuous agitation using a platelet agitator at 70 cycles per minute. All the prepared PCs underwent serological testing to ensure they were free from transfusion-transmitted infections (TTIs) such as HIV, HBV, and HCV. Only seronegative units were included in the study. The pH of the PCs and their swirling characteristics were used as surrogate markers to evaluate bacterial contamination. The pH estimation was performed using a digital pH meter, while the swirling test involved visual inspection and scoring based on the presence and clarity of swirling in different parts of the bag (scores ranging from 0 to 3). The BacT/ALERT3D system, an FDA-approved automated colorimetric blood culture diagnostic tool, was used for bacterial detection. One blood culture bottle was aseptically inoculated with 3 mL of PC under a laminar airflow hood, and the bottle tops were cleaned with alcohol. The bottles were then incubated in the BacT/ALERT3D system for 96 hours, with regular monitoring of signals. Additionally, 10 mL of the sample was inoculated into both aerobic and anaerobic culture vials and incubated in the BD BACTECTM FX40 system at 35°C. Positive culture vials were subcultured on various agar media for identification of the causative microorganisms. Repeat isolation of the same organism on subsequent sampling days confirmed a positive result. When a positive signal was detected, appropriate actions were taken, such as blocking the concerned PC units from being issued, recalling already transfused units, or immediately informing the clinician if the unit had already been transfused. All relevant data were recorded in Microsoft Excel and analyzed using SPSS statistical software (Version 21.0, United States of America).

Results

The results of the study included various quality characteristics of the RDP (Random Donor Platelets). The parameters are discussed as follows:

Volume: Out of the 617 units analyzed, 80% of cases (495 units) showed an appropriate volume ranging from 10-70 ml (Table 1).

Swirling: The majority of units in the current research (425 units)

exhibited satisfactory swirling (Table 1). The utilization of second-generation bags in this study allowed for free gas exchange and met the storage standards set by the Directorate General of Health Services (DGHS) (Table 1).

pH: In the present research, 83% of the units (633 units) showed a pH value greater than 6.4, indicating that most of the units had an appropriate pH level. All the RDP units in the current research had a pH greater than six, meeting the requirements set by DGHS (Table 1).

There was a significant statistical difference observed in the mean pH of RDP units between swirling Grade 2 and Grade 3 (Table 2). Additionally, a substantial statistical difference was noted in the platelet counts of RDP units with swirling Grade 1 and Grade 2 (Table 2). In summary, the study findings indicated that the majority of RDP units had appropriate volume, satisfactory swirling, and pH levels in accordance with DGHS requirements. The analysis also revealed significant statistical differences in pH and platelet counts based on swirling grades.

In the current study, out of 772 PCs (Platelet Concentrates) analyzed, 96.76% (747 units) showed no growth of bacteria, indicating a low rate of contamination during the storage period. However, 3.23% (25 units) of PCs demonstrated bacterial growth (Table 3). Among the isolated bacteria, Coagulase-negative Staphylococcus was the most common gram-positive bacillus found in 8 units, followed by Staphylococcus aureus in 4 units. Enterococcus was found in 2 units, and Streptococcus was found in 3 units. Among the gram-negative bacilli, Klebsiella was observed in 2 units, Pseudomonas in 2 units, Acinetobacter in 1 unit, and Proteus in 3 units (Table 3). Antibiotic susceptibility testing was performed using the Kirby-Bauer procedure on Mueller-Hinton agar. After overnight incubation at 37°C, the zone of inhibition surrounding the antibiotic discs was measured, and the results were recorded (Table 4 and 5). In summary, the study showed a low rate of bacterial contamination in the stored PCs, with the majority of units demonstrating no growth. The isolated bacteria included both gram-positive and gram-negative bacilli, with Coagulase-negative Staphylococcus being the most common. Antibiotic susceptibility testing provided information on the susceptibility patterns of the isolated microbes.

Among the Gram-positive (GP) bacilli CONS and staphylococcus aureus were 100% sensitive to vancomycin, amikacin, Linezolid [Table 4]

Most of the antibiotics tested demonstrated favourable susceptibility against various bacterial species. However, variations in susceptibility were observed among the different antibiotics and bacterial species as indicated in Table 5. This antibiogram provides valuable insights for clinicians regarding the susceptibility of microorganisms associated with transfusion-transmitted bacterial infections (TTBIs) in blood products. By utilizing this information, healthcare providers can make informed decisions about antibiotic usage, thereby reducing the inappropriate use of antibiotics and minimizing the emergence of multidrug-resistant organisms [5].

Table 6 displays the varying distribution of transfusion-transmitted bacterial infections (TTBIs) in blood products among developed countries like the USA and Canada, as well as other countries. Norway, in particular, exhibited a lower occurrence of contaminated blood products, indicating the implementation of effective and safe blood transfusion service (BTS) practices in the country. On the other hand, developing countries, including our center, demonstrated a relatively higher frequency of contaminated blood products due to suboptimal blood transfusion services.

Table 1: Quality characteristics of the random-donor platelets units studied (n=772)

	Number of units (%)
The volume of PCs (ml)	116 (15)
<40	617 (80)
10-70	39 (5)
>70	
Swirling grade of PCs	
Grade 1	77 (10)
Grade 2	270 (35)
Grade 3	425 (55)
pH	
>6.4	633 (82)
6.2-6.4	139 (18)

Table 2: Post hoc analysis between swirling and other variables (multiple comparisons)

Grades of swirling	Mean pH	Mean platelet count (x 10 ¹⁰)	Volume (ml)	Statistical Significance
1 (n= 137)	6.82 (6.417-0.07)	6.98 (5.65-8.87)	5.75 (38.92-68.58)	P=0.037 (Between swirling Grade 1 & 2) for platelet count
2 (n= 210)	6.87 (6.58-7.28)	6.75 (5.58-7.95)	52.45 (39.82-62.47)	
3 (n= 425)	6.89 (6.48-7.12)	6.82 (5.66-7.98)	53.15 (42.66-62.97)	P=0.001 (Between swirling Grade 2 & 3) for pH
	6.88 (6.48-7.18)	6.79 (5.8-7.99)	51.85 (40.66-62.78)	
Total (n=772)				

Table 3: Shows the frequency of PC units showing bacterial growth during the storage period.

Storage time (days)	Isolated Bacteria	Number of units depicting growth N (%)
5	Coagulase negative Staphylococcus aureus	2(0.25)
2	Coagulase negative Staphylococcus aureus	3(0.38)
1	Coagulase negative Staphylococcus aureus	3(0.38)
3	Streptococcus	3(0.38)
3	Staphylococcus aureus	4(0.51)
3	Enterococcus	2(0.25)
3	Pseudomonas aeruginosa	2(0.25)
4	Acinetobacter species	1(0.12)
4	Klebsiella	2(0.25)
4	Proteus	3(0.38)
	No growth	747(96.76)
	Total number of bacterial contaminated PCs	25 (3.23)
	Total number of PCs collected	772

**Table 4: Antibiotic sensitivity pattern
[Staphylococcus]**

Antibiotic	Staphylococcus (%)	CONS (%)	Enterococcus (%)	Streptococcus pneumoniae (%)
Vancomycin	100%	100%	80	80
Amikacin	100%	100%	0	0
Linezolid	100	100	70	70
Chloramphenicol	97.83	98.1	0	90
Gentamicin	93.5	96.5	60	0
Doxycycline	97.83	95.80	90	80
Cefoxitin	60.87	63.8		40
Clindamycin	54.35	69.89	0	47.5

Table 5: Antibiotic sensitivity pattern for Gram-negative bacilli

Antibiotic	Pseudomonas Species (%)	Proteus Species	Klebsiella Species	Acinetobacter Species
Piperracillin - tazobactam	91.43	100%	100%	100%
Amikacin	91.75	93.75	100%	100%
Gentamicin	92.58	93.75	100%	100%
Levofloxacin	80.96	81.25	80	100%
Imipenem	96.25	100%	100%	100%
Ciprofloxacin	81.46	81.25	60	80
Meropenem	94.83	100%	100%	100%
Doripenem	97.27	100	100%	100
Amoxiclav	0	85.5	85	75
Cefoperazone - sulbactam	92.48	100%	100%	100%

**Table 6: Percentage of platelets contamination
[Global distribution]**

Name of country	Percentage of Contaminated Platelets
Ethiopia ⁶	12.5%
Ghana ⁷	9.0%
Nigeria ⁸	8.8%
Zimbabwe ⁹	3.1%
Norway ¹⁰	0.03%
USA ¹¹	0.02%
Canada ¹²	0.01%
Our study	2.59%

Discussion

Transfusion-transmitted bacterial infection (TTBI) in platelet concentrates (PCs) is a significant public health concern, with a higher risk of sepsis compared to other blood products [13]. The reported frequency of TTBI in PCs ranges from 1:1000 to 1:2500 [14]. However, the exact incidence of TTBI, as well as the associated morbidity and mortality, remains unknown. Bacterial contamination in PCs occurs at a rate of approximately 1 in 1000 to 3000. Although fatal sepsis is not directly linked to transfusion of contaminated PCs, the estimated mortality due to TTBI in PCs is 1 in 500,000 [4]. However, there is a lack of published scientific literature, particularly in rural and resource-constrained settings like yours, regarding the exact data on TTBI in PCs. Currently, there are no uniform policies mandating the testing of PCs to rule out bacterial contamination. The AABB criteria for diagnosing TTBI [15] include: a) no other plausible causes of infection, b) onset of infection

within 1 day of transfusion, and c) consistent positive culture results in both the patient and the transfusion sample. However, the criteria have limitations in terms of diagnostic significance. Transfusion bags are typically discarded after use and are not available for microbiological investigations. Additionally, patients are often started on antibiotic therapy, which can result in negative blood cultures, further limiting the diagnostic utility of the criteria. This study was conducted to determine the precise incidence of TTBIs in PCs within our region. The objective was to raise awareness about the various risks associated with TTBI and develop appropriate prevention strategies. The variability in reported TTBI cases among PCs can be attributed to several factors, including: a) differences in phlebotomy techniques, b) variations in surveillance systems utilized, and c) clinical similarities between TTBIs and febrile non-hemolytic transfusion reactions (FNHTR), as well as the frequent administration of pre-medications such as antipyretics and analgesics to recipients, which can mask the clinical features of

septic transfusion reactions (STR) and lead to underreporting of adverse effects related to TTBI in routine clinical practice [16]. In the current study, all 25 PC units that tested positive for bacterial contamination remained in the blood bank stock, thereby preventing any STRs from occurring in the recipients. Post-donation counseling was provided to all 25 donors who tested positive, and they were referred for further treatment and follow-up.

Therefore, it is crucial to educate transfusion physicians about the key aspects of a hemovigilance system [17]. In recent years, several recommendations have been put forth to mitigate the risks associated with TTBI in PCs. These include:

- a) Thorough pre-donation counseling to ensure donor suitability;
- b) Adherence to strict phlebotomy techniques and proper skin disinfection prior to venipuncture;
- c) The routine use of blood bags equipped with aliquot diversion pouches;
- d) Strict implementation of standard operating procedures (SOPs) pertaining to PC preparation, storage, and testing, and;
- e) The routine use of FDA-approved automated bacterial culture systems [18].

TTBI among PCs is a real issue that often goes underdiagnosed and underreported for various reasons [19], despite the implementation of certain measures such as the regular use of diversion pouches, as demonstrated in the present study. Diversion pouches redirect the initial flow of blood from the donor, preventing bacterial entry into blood components [20].

A study conducted by Rathore et al. yielded similar results to the present research, emphasizing that despite best efforts, the process of skin disinfection can only significantly reduce, but not completely eliminate, bacterial contamination. It was found that skin fragments containing live microbes may still be dislodged into diversion pouches during phlebotomy, leading to TTBI [22]. Additionally, both studies identified gram-positive cocci, such as coagulase-negative staphylococci (CoNS), which are normal skin commensals primarily found in donor arms. This suggests that external sources, mainly inadequate skin disinfection, contribute to contamination. These findings underscore the importance of proper and adequate phlebotomy techniques to decrease the prevalence of TTBI in PCs [23]. Simple measures like pH estimation and the swirling test can be routinely employed in various blood centers, especially those in rural and resource-constrained settings, these tests are subjective and require further standardization [24]. Additionally, blood centers should explore the feasibility of using blood bags with diversion pouches as a routine practice. However, the higher cost of such bags often prevents their widespread adoption, particularly in rural blood centers [25]. Therefore, efforts should be made to develop cost-effective alternatives and promote the universal usage of blood bags with diversion pouches, particularly in rural settings. Although FDA-approved automated culture systems are increasingly available, their extensive implementation in rural blood centers faces challenges such as high capital investment, the need for highly skilled technical staff, and complex procedural issues [26]. Therefore, it is important to develop cost-effective and innovative solutions to overcome these barriers and ensure proper training for technical staff working in various blood centers [27].

Currently, clear guidelines for the management of TTBI are lacking. However, the FDA has recently issued a guidance titled “Bacterial Risk Control Strategies for Blood Collection and Transfusion

Services and Available Platelets for Transfusion.” Some key points from the FDA guidance include: a) Primary culture should be taken after 24 hours of collection, followed by a rapid test within one day of transfusion. b) Secondary culture should not be performed before the third day. c) Large volume delayed sampling (LVDS) should not be done before 36 hours after collection [28].

Bacterial growth rates in platelets cannot be predicted and can vary from unit to unit based on starting inoculum levels and nutritional factors. Late-growing bacteria may not be detected by culture methods during the early storage period. To overcome this, LVDS is proposed to be used on a larger scale. LVDS involves collecting a 16ml sample of platelet concentrate, which is then equally divided into aerobic and anaerobic culture media and incubated for a minimum of 12 hours [29].

Furthermore, the utility of rapid tests for evaluating TTBI in platelet concentrates can be explored. The Verax Pan Genera Detection (PGD) rapid detection technology has been used for transfusion safety procedures for 16 years. This technology utilizes a solitary-usage lateral flow immunoassay to detect Gram-positive and Gram-negative bacteria, requiring only 200µL of sample. It can detect bacterial growth even during the log phase. Efforts should be made to obtain necessary legal approvals to ensure its regular use, particularly in rural setups [30].

In consideration of the needs of developing countries with suboptimal quality standards in their blood centers, AABB has issued guidance with the following key features [15]:

- a) Improving donor screening and phlebotomy procedures.
- b) Minimizing the storage time of platelets.
- c) Ordering platelet concentrates for transfusion only when the patient is ready to receive them.
- d) Utilizing pooled platelets within 4 hours.
- e) Restricting instances where platelet pools are subjected to manipulation (e.g., reduction of plasma volume or saline re-suspension) as these manipulations increase the risk of bacterial contamination.

Conclusion

While control measures such as implementing effective phlebotomy techniques, routine usage of diversion pouches, and employing automated bacterial detection systems can significantly reduce the risk of TTBI in PCs, they cannot completely eliminate it. Therefore, it is crucial to expedite the process of obtaining necessary regulatory approvals for the utilization of point-of-care testing (POCT) methods such as rapid card tests and pathogen reduction technologies (PRT). These advancements will help address the challenges associated with TTBI more effectively.

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