Original article

Comparison of bacterial culture and pathogen inactivation to reduce transfusion-transmitted bacteria in platelet transfusion

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Abstract:

Introduction: *Transfusion-transmitted bacterial infection (TTBI) is a severe transfusion reaction commonly found in platelet transfusion. Currently used preventive methods are automated bacterial culture detection (ABCD) and pathogen inactivation (PI).* ***Objective:*** *The objective of this study is to compare the prevalence of TTBI in patients who received non-ABCD screened platelets with ABCD screened and PI platelets.* ***Materials and Methods:*** *The data of the patients who received non-ABCD screened, ABCD screened and PI platelets were analyzed for evidence of TTBI from August 2018 to April 2021. ABCD screened platelet units were from the National Blood Centre, Thai Red Cross Society (NBC, TRCS) and PI platelet units in platelet additive solution (PAS) were produced in Ramathibodi Hospital.* ***Results:*** *Seven thousand one hundred and seven non-screened ABCD, 11,494 screened ABCD and 1,430 PI platelet units were transfused to patients in Ramathibodi Hospital. The prevalence of TTBI was 1 in 7,107 for non-screened ABCD platelet units (14.07:100,000 transfused platelets). The causative organism was Staphylococcus epidermidis. No TTBI was observed in ABCD screened and PI platelet transfusion. Nineteen in eleven thousand four hundred and ninety-seven (0.17%) platelet samples from ABCD screened platelet units had positive culture results. Sixteen platelet units were already transfused, 2 units were recalled and sent back to the NBC, TRCS and 1 unit was expired. Cutibacterium acnes, Cellulosimicrobium cellulans and Cutibacterium granulosum were identified by subculture in 16, 2 and 1 platelet samples, respectively.* ***Conclusion:*** *Both ABCD and PI can reduce the risk of TTBI from platelet transfusion. The most commonly found organism in platelet samples by ABCD was Cutibacterium acnes. The decision to choose which preventive method provides more management effective depends on the resources and workflow of each blood production center.*

Keywords : ● *Transfusion-transmitted bacterial infection* ● *Platelet transfusion* ● *Automated bacterial culture detection* ● *Pathogen inactivation*

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นิพนธ์ต้นฉบับ

การเปรียบเทียบการป้องกันการติดเชื้อแบคทีเรียจากการให้เกล็ดเลือดโดยวิธี bacterial culture และ pathogen inactivation

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บทคัดย่อ

บทนำ *Transfusion-transmitted bacterial infection (TTBI) เป็นปฏิกิริยาไม่พึงประสงค์จากการให้เกล็ดเลือดที่พบได้บ่อยและอาการรุนแรง ปัจจุบันมีวิธีการป้องกันได้แก่การตรวจ automated bacterial culture detection (ABCD) หรือใช้ pathogen inactivation (PI) ก่อนให้เกล็ดเลือดแก่ผู้ป่วย* ***วัตถุประสงค์*** *การศึกษานี้ต้องการการเปรียบเทียบความชุกของการเกิด TTBI ในผู้ป่วยที่ได้รับเกล็ดเลือดที่ไม่ได้ผ่านการตรวจ ABCD กับผู้ป่วยที่ได้รับเกล็ดเลือดที่ผ่านการตรวจ ABCD หรือได้รับ PI platelets* ***วัสดุและวิธีการ*** *เก็บและวิเคราะห์ข้อมูลผู้ป่วยที่ได้รับเกล็ดเลือดซึ่งผ่านและไม่ได้ผ่านการตรวจ ABCD จากศูนย์บริการโลหิตแห่งชาติ สภากาชาดไทย และเกล็ดเลือดที่ผ่านการทำ PI ซึ่งผลิตโดยคลังเลือด โรงพยาบาลรามาธิบดี ตั้งแต่เดือนสิงหาคม พ.ศ. 2561 ถึงเดือนเมษายน พ.ศ. 2564* ***ผลการศึกษา*** *มีการให้เกล็ดเลือดที่ไม่ได้ผ่านการตรวจ ABCD ในโรงพยาบาลรามาธิบดีจำนวน 7,107 ยูนิต พบความชุกของ TTBI เป็น 1/7,107 (14.07:100,000 transfused platelets) เชื้อที่ก่อให้เกิด TTBI คือ Staphylococcus epidermidis มีการให้เกล็ดเลือดที่ผ่านการตรวจ ABCD 11,494 units และผ่านการทำ PI 1,430 units ไม่พบว่ามีผู้ป่วยเกิดอาการของ TTBI มีตัวอย่างเกล็ดเลือดทั้งหมด 19/11,497 ตัวอย่าง (0.17%) ที่มีผลตรวจ ABCD เป็นบวก ได้ให้ผู้ป่วยไปแล้วทั้งหมด 16 ยูนิต ส่งคืนศูนย์บริการโลหิตแห่งชาติ 2 ยูนิต และอีก 1 ยูนิต หมดอายุ ผล subculture จำนวน 16 ตัวอย่างจาก 19 ตัวอย่าง พบเชื้อ Cutibacterium acnes อีก 2 ตัวอย่างพบเชื้อ Cellulosimicrobium cellulans และอีก 1 ตัวอย่างพบเชื้อ เป็น Cutibacterium granulosum* ***สรุป*** *ทั้ง ABCD และ PI สามารถลดความเสี่ยงการเกิด TTBI จากการให้เกล็ดเลือด เชื้อที่พบมากที่สุดในตัวอย่างเกล็ดเลือดจากการตรวจ ABCD คือ Cutibacterium acnes การพิจารณาเลือกว่าจะใช้วิธีใดในการป้องกันการเกิด TTBI ขึ้นอยู่กับทรัพยากรและขั้นตอนการปฏิบัติงานของคลังเลือดแต่ละแห่ง*

คำสำคัญ : ● *การติดเชื้อแบคทีเรีย* ● *การให้เกล็ดเลือด* ● *การเพาะเชื้อแบคทีเรียในเกล็ดเลือด* ● *การยับยั้งเชื้อ*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2565;32:9-17.

Introduction

Transfusion-transmitted bacterial infection (TTBI) is a transfusion reaction that causes severe, life-threatening or fatal outcomes in 70% of the cases[1]. The incidence of TTBI is more common in platelet transfusion (1.95 per 100,000 transfused platelet units), compared to red blood cell (0.53 per 100,000 transfused RBC units)[1]. Platelet is the blood product with the highest risk of TTBI because the bacterial overgrowth can happen at the storage temperature of 22±2˚C. The platelet contamination rates during collection, process and storage were around 1:1,000-1:3,000 platelet units depending on the effectiveness of the hemovigilance system[2,3]. The sources of contaminating bacteria mostly came from donor skin during phlebotomy and asymptomatic bacteremia donors. The common organisms found from skin contamination are gram-positive bacteria such as *Staphylococcus epididermidis, Coagulase-negative Staphylococcus, Streptococcus spp*. and *Cutibacterium acnes*[4]. For red cell products, the organism that can cause TTBI must be able to tolerate the storage temperature of 4˚C such as *Yersinia enterocolitica* which are found in asymptomatic bacteremia donors[5].

The universal precaution to reduce the risk of bacterial contamination during blood collection are effective skin disinfectants which are povidone-iodine or 2% chlorhexidine in 70% alcohol and diversion of the first 30 mL of blood into the diversion pouch. Both methods can decrease the bacterial contamination rate by 77%[6]. The other risk factor of TTBI in platelet is the storage time of platelet[7]. It was found that platelet aged 6-7 days have a higher amount of bacteria[8]. The United States (US) Food and Drug Administration (FDA) recommended screening tests for TTBI such as an automated bacterial culture detection (ABCD), a rapid bacterial test (RBT) and using a pathogen inactivation (PI) technology[9]. The commercial ABCD systems which have been approved by US-FDA include BacT/ALERT (bioMe´rieux, Durham, N.C., USA) and BACTEC (BD Microbiology, Cockeysville, MD, USA)[10]. For PI technologies, Intercept (Cerus Corporation, Concord, CA, USA) and Mirasol (CaridianBCT, Lakewood, CO, USA) have been approved by US-FDA.

The National Blood Centre, Thai Red Cross Society (NBC, TRCS) has implemented ABCD for all platelet units since 14 August 2019. The blood bank, Faculty of Medicine Ramathibodi Hospital has implemented PI in apheresis platelet with platelet additive solution (PAS) since 2015 and finally in all platelet units. This study is a descriptive study collecting and analyzing the data of patients receiving platelet transfusion in Ramathibodi Hospital. The objectives of this study are to compare the prevalence of TTBI in patients receiving platelet transfusion before implementing ABCD with patients receiving ABCD screened platelets and PI platelets.

Materials and Methods

Study Population

The data of the patients in Ramathibodi Hospital who received platelet transfusion before and after ABCD screening and PI were analyzed for bacterial sepsis from 14 August 2018 to 7 April 2021. The patients were divided into two groups: Group 1 consisted of patients who received platelet units from NBC, TRCS and was further divided into before and after ABCD was implemented (Figure 1). Group 2 consisted of patients who received PI platelet in PAS produced by Ramathibodi Hospital blood bank (Figure 2). The recalled platelet units from the NBC, TRCS due to initially positive results of ABCD and expired platelet units weren't included in the study population.

Bacterial Culture Method

The ABCD system performed at NBC, TRCS used BD BACTEC aerobic/F and anaerobic/F culture vials (BACTEC FX, BD Microbiology, Cockeysville, MD, USA) which are Soybean-Casein digest broth.

The platelet sample was collected from a satellite bag that was attached to a platelet unit. Then after 18 hours of collection, the sample was inoculated in each aerobic and anaerobic culture vials which were incubated for 6 hours. If the culture result was initially

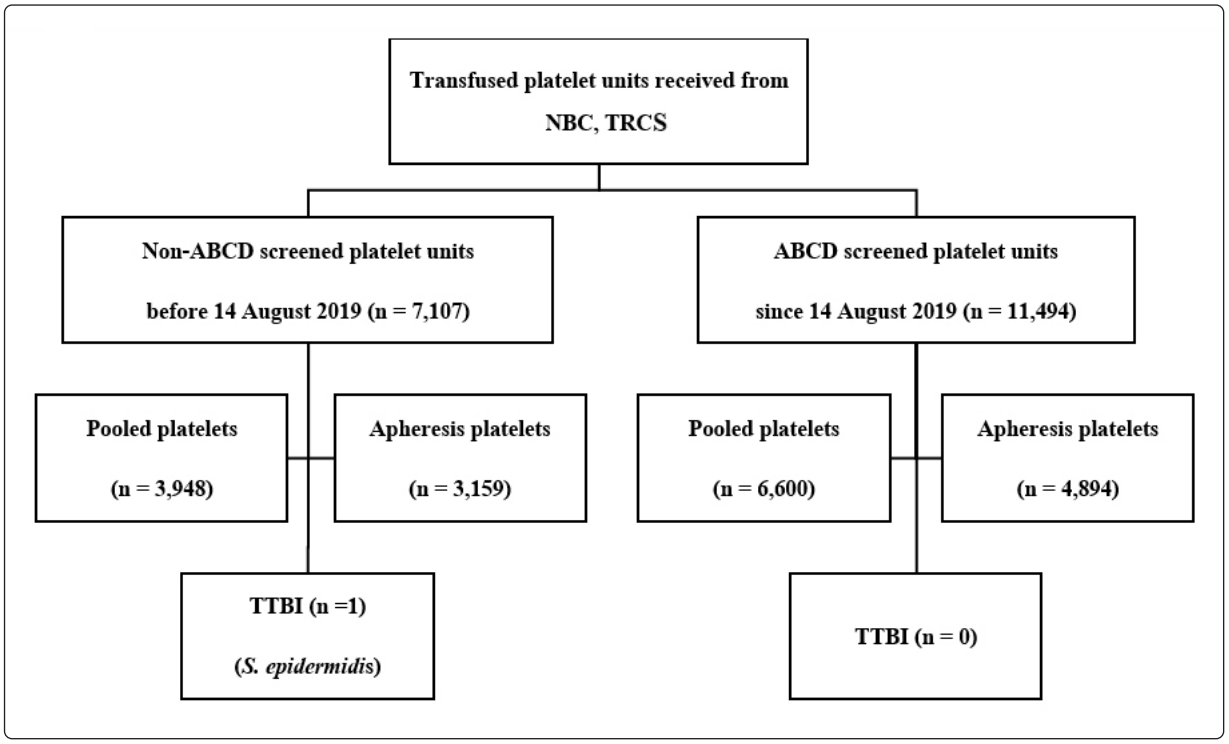

Figure 1 Study population of NBC, TRCS platelet transfused in Ramathibodi Hospital

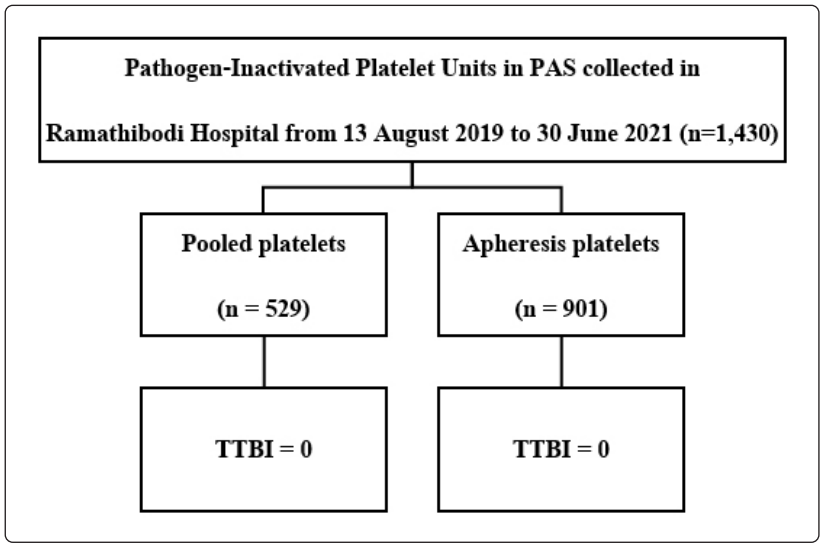

Figure 2 Study population of pathogen-inactivated platelets collected and transfused in Ramathibodi Hospital

positive, the subculture of the broth would be done to identify the organism and that platelet unit would be quarantined. If the culture result was negative, the platelet unit would be released to a hospital, but the vials would be monitored until the 7-day storage of the platelet (Figure 3). However the NBC, TRCS would notify and recall platelets from the hospital if the culture results became positive after platelet distribution to hospitals. The sample from the recalled platelet unit was cultured and compared with the subculture result of the platelet sample of that unit to confirm if the platelet sample culture results were true or false positive. If the platelet was already transfused, the clinician would be notified to observe the recipient sign of TTBI for 72 hours.

Pathogen inactivation method

Platelet units in PAS produced by the blood bank, Faculty of Medicine Ramathibodi Hospital were pathogen-inactivated by the Intercept system (Cerus Corporation,

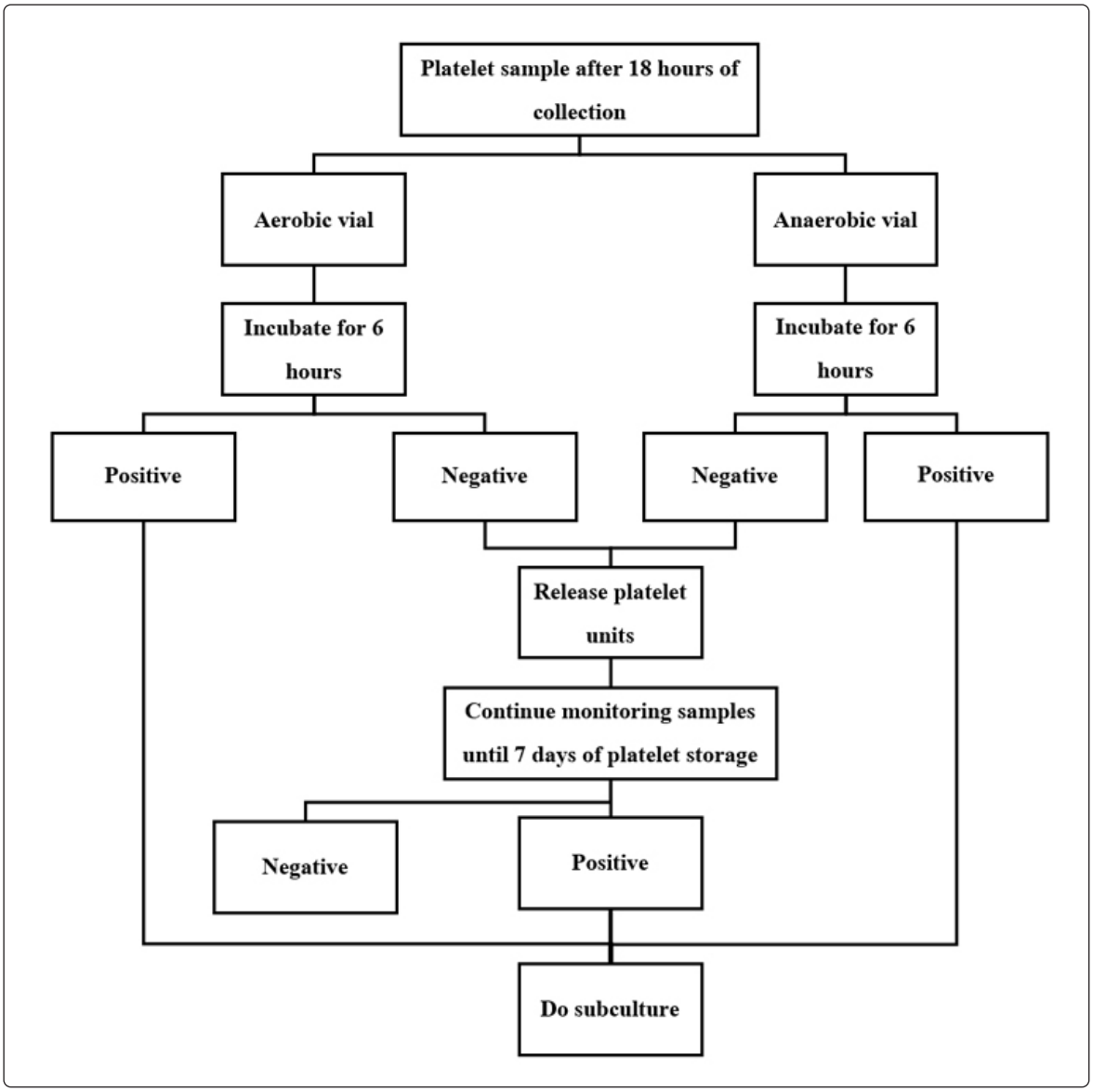

Figure 3 NBC, TRCS' confirmatory protocol for positive culture

Concord, CA, USA). Amotosalen was added into platelet units within 24 hours after collection. Platelets then were irradiated with ultraviolet A (UVA) for 8 minutes. Amotosalen was removed by a component absorber device (CAD) for 6 hours in a platelet incubator.

Data analysis

Patient transfusion reaction records were collected and analyzed. The recipient's signs and symptoms and transfusion reaction workup records were analyzed and discussed with the attending physicians. ABO grouping, crossmatching, direct agglutination test and bacterial culture from platelet units were performed to determine whether the recipient had TTBI or other transfusion reactions. The diagnostic criteria of TTBI[11] are; Body temperature of more than 39° Celsius or change after transfusion for more than 2° Celsius, chill, heart rate more than 120 beats per minute or change more than 40 beats per minute and, systolic blood pressure change more than 30 mmHg after transfusion. All the changes above happened within 4 hours after starting transfusion.

The prevalence of TTBI was reported per 100,000 transfused platelet units. In case the platelet was already transfused when the NBC, TRCS notified the blood bank, the bacterial culture results from the NBC, TRCS and the recipient hemoculture after transfusion were compared. At present, the NBC, TRCS has changed the protocol to perform ABCD screening after 36 hours of collection to extend platelet shelf-life from 5 to 7 days. All the

Table 1 Bacterial species identified in the initially positive cultured samples of transfused platelet

Bacterial species	Number of platelet samples in vials	Percent
Cutibacterium acnes	13	81.25
Cellulosimicrobium cellulans	2	12.5
Cutibacterium granulosum	1	6.25
Total	**16**	**100**

data collected in this study finished before the new protocol is implemented, therefore the study population included in this study did not include platelet units from the current protocol.

Results

Regarding this retrospective study, one septic transfusion reaction occurred from a total of 7,107 platelet units from the NBC, TRCS before the ABCD implementation. The recipient received post-storage filtered pooled leukocyte-poor platelet concentrate (LPPC) in PAS. She then developed fever with a body temperature of 38.1˚C and urticarial rash 70 minutes after transfusion. The platelet bag was sent from the blood bank for culture in the microbiology laboratory and the result was positive for *Staphylococcus epidermidis*. The patient's hemoculture was not done so the imputability of the transfusion reaction was graded as probable TTBI[12]. The recipient's symptoms improved after intravenous antibiotics. The prevalence of TTBI before implementation of ABCD and PI was 14.07 per 100,000 platelet units.

After ABCD implementation, 11,494 platelet units from the NBC, TRCS were transfused to patients at Ramathibodi Hospital. For platelet with PAS units that had been collected and processed in Ramathibodi Hospital, there were a total of 1,430 pathogen-inactivated platelet transfusions. After ABCD screening and PI, no evidence of TTBI was observed.

Regarding this study, 19 in 11,494 platelet samples in the ABCD screening vials were positive. Of these 19 positive samples, 16 platelet units were already transfused to the patients. Three from nineteen units were not transfused with their subculture results from platelet sample were all positive for *Cutibacterium acnes*. One unit out of three was already expired and discarded while the other two units were returned to the NBC, TRCS for culture. For the culture results of those 2 recalled platelet units, only one was positive for *Cutibacterium acnes*, while the other was found to have no growth, therefore the ABCD result from the platelet sample of the latter platelet unit was a false positive.

Concerning 16 transfused platelet units, 13 platelet samples were positive for *Cutibacterium acnes*, 2 platelet samples were positive for *Cellulosimicrobium cellulans* and 1 platelet sample was positive for *Cutibacterium granulosum* (Table 1). The patients who received those 16/19 ABCD screened platelet units showed no signs or symptoms of TTBI and the result of the patient's hemoculture taken from 12 out of 16 recipients showed no growth. For the other 4 recipients, the hemoculture wasn't taken due to them already being discharged from the hospital before the platelet sample result was notified. None of the patients who received 1,430 PI platelets showed signs and symptoms of TTBI.

Discussion

ABCD is an automated culture system for the detection of bacterial contamination by measuring carbon dioxide released from growing bacteria. It has been used in the United Kingdom (UK) and the US. From European and Australian hemovigilance, ABCD can reduce the risk ratio of TTBI by 3.0 and 4.2, respectively[13,14]. From the US study, ABCD can also decrease TTBI incidence and fatalities by two-fold[15]. The main advantages of ABCD are its low cost and non-invasive method. Its disadvantage is the loss of 8-10 mL of platelet volume

per vial for aerobic and anaerobic cultures. There is also a concern about false-negative results due to the low amount of bacteria in the platelet that cannot be detected at the beginning of storage. During storage, bacteria can overgrow to a clinically significant level. A delayed sampling of more than 36 hours of collection or two-step sampling can be used to detect increased contaminated bacteria at the detectable level when cultured[9]. Seven cases of septic transfusion reactions from 489,847 transfused platelet units were reported from the study of Canadian National Blood Center despite the result of their ABCD being negative[16]. Another disadvantage of ABCD is a false positive result due to instrumental error and within-lab contamination, resulting in unnecessary wastage of platelet units[17,18]. However, it could be the cause of bacterial sepsis in implant-associated infection of orthopedic patient[19]. The explanation was that *C. acnes* could proliferate better in anaerobic vials but could not proliferate to the amount that could cause clinically significant infection (10^5 CFU/mL) in platelet units stored in the aerobic environment[18] which could cause one false positive case in recalled platelet unit culture in this study. Moreover, all 13 patients who received platelet units notified later as positive ABCD for *C. acnes* showed no clinical signs and symptoms of TTBI, possibly due to the inability of *C. acnes* to cause clinically-significant TTBI.

There was a proposition to remove anaerobic vial culture from ABCD to decrease the positive result and wastage of platelet due to *C. acnes*[6] and would also remove the need for 10 mL of platelet sample for an anaerobic vial. The downside of this proposal is the inability to detect clinically significant anaerobe such as *Clostridium perfringens* which was reported to cause fatal septicemia[20,21]. Using both aerobic and anaerobic vials also improves the detection of facultative anaerobic such as *S. aureus* and *E. coli*. It was found in one study that skin cleansing via chlorhexidine digluconate needs higher concentration and exposure time to remove *C. acnes*, compared with the other cleansing agent such as povidone iodide[22]. The other study reported that *C. acnes* detection rate was 12% after applying 2% chlorhexidine digluconate in 70% isopropyl alcohol[23]. This was due to the inability of alcoholic chlorhexidine to reach the sebaceous gland, which was the normal habitat of *C. acnes*.

The other two organisms identified in platelet sample vials in this study were *Cellulosimicrobium cellulans* (originally known as *Oerskovia*) and *Cutibacterium granulosum*. *C. cellulans* was aerobic or facultative anaerobic Nocardia-like bacilli found in dirt and it did not cause disease in normal humans but can cause disease in the immunocompromised patient such as hematopoietic stem cell transplant patients. It can cause infection via foreign body such as central line catheter, heart valve or prosthetic joint resulting in bacteremia, endocarditis, peritonitis, cellulitis, keratitis, pyelonephritis and ventriculitis. There was no report of *Cellulosimicrobium*-associated TTBI[24–27]. Two patients who received platelet units that their samples in vial contained *C. cellulans* also show no signs and symptoms of TTBI in this study. However, due to the immunocompromised nature of most platelet-transfused patients, recipients of *Cellulosimicrobium*-contaminated platelets should be monitored carefully.

There were no TTBI observed in patients receiving PI platelet unit in Ramathibodi Hospital, implying that PI can reduce the risk of TTBI from platelet transfusion. PI is a TTBI-reducing method used in Europe and the US[13]. PI interferes with pathogen genetic material and stops its propagation. The advantage of using the PI system is that it can also inactivate viruses and parasites, especially emerging pathogens that cannot be detected by current immunological or molecular screening assays. Another advantage of PI is that it can inactivate viable lymphocytes and prevent transfusion-associated graft-versus-host diseases (TA-GVHD) so it can substitute blood irradiation. Although PI is more expensive than ABCD[28], it has improved blood management effectiveness. Platelet can be issued for transfusion earlier and there

is no platelet loss for testing and also no cost of blood irradiation[29]. The disadvantage of PI is its inability to inactivate spore-forming bacteria such as *B. cereus* or a certain strain of fast-growing *K. pneumoniae*[30]. There were also reports of decreased corrected increment count (CCI) from PI platelet transfusion, thus increasing the frequency of platelet transfusion[31,32]. However, it was observed that PI platelet was not associated with increased clinical bleeding[31,33,34].

In a comparison of the preventive method for TTBI, there was no evidence of TTBI in patients who received ABCD screened platelet and PI platelet. Even though ABCD is a cheaper method, it is labour-intensive and there is a loss of platelet volume for sampling. Moreover, the platelet cannot be issued early for platelet transfusion because the platelet samples are needed to be taken at least 18-36 hours after collection. In case the ABCD results of the platelet samples are positive, the attending physicians need to be notified and monitor the patients even though TTBI did not happen at the time of transfusion. It was also observed in the previous studies that ABCD caused false-positive and false-negative results. The current practice of ABCD included delayed sampling after 36 hours of collection or two-step sampling to prevent false-negative results that can cause TTBI in the patients. PI has the advantages of a simpler workflow and can replace blood irradiation. It can also inactivate non-bacterial organisms especially emerging pathogens and provide safer blood products. The disadvantage of PI is the higher cost, but it may be better management-effective due to earlier platelet release and no volume loss for sampling.

Conclusion

Regarding our study, both ABCD and PI could effectively prevent TTBI. The decision to choose which preventive method is more management-effective depends on the resources and workflow of each blood production center.

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