Editorial

Bacterial contamination of platelet components

Sandra Ramirez-Arcos[1,2], Carl McDonald[3]; ISBT Transfusion Transmitted Infectious Diseases Working Party Bacteria Subgroup

[1]Medical Affairs and Innovation, Canadian Blood Services, Ottawa, Ontario, Canada; [2]Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Ontario, Canada; [3]NHS Blood and Transplant, London, UK

Correspondence to: Sandra Ramirez-Arcos, PhD. Senior Scientist, Medical Affairs and Innovation, Canadian Blood Services, Ottawa, Ontario, Canada; Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Ontario, Canada. Email: Sandra.ramirez@blood.ca.

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The Bacteria Subgroup of the ISBT Transfusion Transmitted Infectious Diseases Working Party (TTID-WP) undertakes activities focused on the enhancement of blood safety and dissemination of knowledge. This special series comprises eight papers including original and review articles, written by experts in the field, that discuss the latest developments aimed at enhancing the safety of platelet component (PC) transfusion.

Strategies implemented worldwide to mitigate the risk of transfusing contaminated PC include the implementation of optimal donor screening and skin disinfection methods, diversion of the first 30–40 mL of collected blood, bacteria screening methods and treatment with pathogen reduction (PR) technologies (1). These strategies have decreased the incidence of transfusion-associated septic events. However, this safety risk has not been eliminated as is illustrated in the article by Freudenburg-de Graaf *et al.* (2). The authors report a retrospective analysis of transfusion-transmitted bacterial infectious (TTBI) reported to the Transfusion and Transplantation Reactions in Patients (TRIP) in the Netherlands from 2008 to 2019. Sixteen cases were reported including eight possible cases, six probable cases and two definite cases, one of them was a fatality involving *Staphylococcus aureus* as the contaminant organism. Except for three Gram-negative isolates, all other organisms were Gram-positive, mostly staphylococci and streptococci. Importantly, the authors also provided additional information on cases in which positive results of PC screening for bacterial contamination were obtained after the units have been transfused during 2013–2019. This novel approach is valuable to address unrecognized and unreported TTBI cases. There were 20 transfusion reactions reported in this period, but only five of them were possibly contaminated with bacteria. In 4 of the 5 cases the skin flora anaerobe aerotolerant bacterium *Cutibacterium acnes* (*C. acnes*) was isolated. Although *C. acnes* cannot proliferate in the aerobic PC storage environment (3), and therefore does not reach clinically significant levels in PC to cause acute transfusion reactions, *C. acnes* is an organism of clinical relevance in hospital settings often involved in infectious endocarditis and prosthetic infections (4,5). Careful consideration should be given to this bacterium as a cause of unrecognized chronic transfusion infections.

As one of the important mitigation strategies to decrease the incidence of TTBI, PC screening for bacterial contamination was implemented in the 1990s in Europe and later in the early 2000s in North America. The review article by Jacobs (6) describes the guidance on bacterial contamination risk control strategies issued by the Food and Drug Administration (FDA) with recommended implementation in US centers by October 2021 (7). The guidance includes single-step strategies for apheresis and whole-blood-derived PC units that can be stored for up to 5 days. It also comprises several two-steps schemes that allows PC storage for up to 7 days. The complex combination of multiple scenarios of the FDA guidance is based on three different strategies already in use by blood collection centers worldwide: PC screening with automated culture methods, PC testing with rapid methods, and treatment of PC with PR technologies. As discussed by Jacobs, all strategies proposed in the FDA guidance have advantages and limitations for an effective operational implementation.

Centers which have implemented PC screening with

automated culture methods often use the BACT/ALERT 3D System (bioMérieux, Marcy l'Etoile, France). The evolution of the BACT/ALERT 3D System into the new generation BACT/ALERT VIRTUO Microbial Detection System was reviewed by Daane *et al.* (8). The authors presented data showing higher efficiency of the BACT/ALERT VIRTUO System due to improved architecture that allows for better temperature stability and workflow resulting in enhanced detection (i.e., shorter time to detection) of positive cultures. Performance studies showed that the VIRTUO system detected bacteria between 2.1 and 2.8 hours faster than the 3D system (8). As the VIRTUO system has not been broadly implemented yet, it is difficult to assess the impact of this small improvement in time to detection on prevention of transfusion of contaminated PC. It is expected that the incidence of false positive results is lower with the VIRTUO System when compared to the 3D system due to a reduction of temperature fluctuation since culture bottle loading and unloading is done automatically in the VIRTUO System. However, more data are needed to support this prediction as the performance studies conducted by the company did not show differences in false positive rates between the 3D and VIRTUO Systems (8).

PC screening protocols with automated culture have evolved from inoculation of 4 mL of PC into an aerobic culture bottle to an enhanced testing approach using a large volume delayed sampling (LVDS) algorithm. LVDS was first implemented by the NHS Blood and Transplant (NHSBT) (9), and then by the two Canadian blood operators, Héma-Québec (10) and Canadian Blood Services (11). It is also one of the recommended bacterial contamination risk control strategies by the FDA (7). The LVDS algorithm, which is described by Delage and Bernier in their review article (12), aims at increasing detection of contaminant bacteria by inoculating two or more culture bottles with 8–10 mL of PC and sampling the component at least 36 hours post-blood collection to allow proliferation of slow growing organisms and enhance microbial capture in the test sample. As stated by Delage and Bernier (12), implementation of LVDS for PC stored for up to 7 days has resulted in enhanced component safety, which is evidenced by a three-fold decrease in the incidence of septic transfusion reactions. However, this screening method has some disadvantages that need careful consideration. The first one is the increase in false positive results due to the inclusion of anaerobic cultures, which can be ameliorated with approaches to reduce temperature fluctuation in the culture incubators. Importantly, a LVDS approach implies transfusion of older PC with concerns about increased use of components or poorer clinical outcomes. However, data from the NHSBT and Héma-Québec indicate that transfusing older PC is not inferior to the transfusion of younger PC regarding corrected counts increments, bleeding, and intervals between PC transfusions (12). Although using more culture bottles results in an increased operational cost, both Héma-Québec and Canadian Blood Services have shown that the increased cost was offset by reduction in PC outdates (10,11).

Screening early in the PC shelf-life has resulted in reduction of septic transfusion events; however, this safety risk has not been eliminated. As outlined in the FDA guidance on bacterial contamination risk control strategies (7), primary testing with automated culture methods can be complemented with either secondary cultures or with PC testing with rapid methods later in the PC shelf-life. The PGD*prime* qualitative immunoassay is one of the rapid methods used for bacterial detection in contaminated PC; its sensitivity and specificity was discussed by Mintz and Vallejo in their review article (13). The PGD*prime* test has been approved by the FDA as a safety measure to extend the shelf-life of apheresis PC prepared in plasma from 5 to 7 days in the US (14). In the review by Mintz and Vallejo, the sensitivity of the PGD*prime* test was reported to be equal or better than that of the original Platelet Pan Genera Detection (PGD) Test when tested with apheresis PC prepared in plasma (13). Similarly, high specificity was reported after evaluation of the PGD*prime* test in different types of PC and in multiple sites. Two septic transfusion events with PC contaminated with *Acinetobacter calcoaceticus-baumannii* and *Staphylococcus saprophyiticus*, which yielded non-reactive results with the PGD test have been documented (15). The PGD*prime* test has since then improved its design for an efficient detection of *Acinetobacter* spp. (16). The applicability of PGD testing is supported by clinical studies showing interdiction of contaminated PC that yielded negative primary culture results but had reactive PGD testing results (17).

Alternative to PC screening, is the proactive approach of treating PC with PR Technologies. Schulze and colleagues reviewed the advantages and limitations of the THERAFLEX ultraviolet C (UVC)-based PR technology for bacterial inactivation in PC (18). This technology uses UVC (254 nm), without a photosensitizing agent, to disrupt nucleic acids of infectious agents that can contaminate PC including bacteria, viruses, and parasites. PC prepared in platelet additive solution (30–40% plasma)

are irradiated in large bags that are vigorously mixed allowing optimal exposure to UVC in less than 1 min (18). Spiking experiments have shown inactivation of ≥3 logs of several Gram-positive and Gram-negative bacteria that are part of the WHO bacterial repository strains (19) in PC with a volume of 325–375 mL treated with a UVC dose of 0.2 J/cm^2. Importantly, Schulze *et al.* emphasize the importance of time to PR treatment considering that bacteria have different growth rates. In their time-to-treatment experiments, the authors concluded that THRAFLEX treatment should be performed within 6 hours post-bacteria spiking, especially to target fast-growing organisms, to reach PC sterility after 7 days of storage (18). It is acknowledged that THERAFLEX has limited efficacy to inactivate bacterial spores as well as high bacterial concentrations and therefore timely PR treatment post-PC treatment is essential.

Both PC screening with a LVDS approach and PR treatment can affect PC productivity. Garcia and Razatos used an algorithm-based model derived from the Trima Accel Automated Blood Collection System software version 7 to predict apheresis PC productivity and availability in centers that have implemented PR technologies or screening using a LVDS method (20). The authors used a donor database of 10,000 PC donations and the model was run for transfusion doses of 2.0×10^{11}, 2.5×10^{11} and 3.0×10^{11} platelets per unit. The authors concluded that the upgraded software supports implementation of either PR or LVDS maintaining PC availability.

Although great progress has been made to improve the safety of PC in developed countries with the implementation of screening strategies or PR technologies, low-income-countries are unfortunately behind in the adoption of these approaches. The review article by García-Otálora *et al.* provides a great overview of the status of TTBI in Latin America (21). The authors presented a comprehensive summary of information collected by 18 Latin American countries. None of the surveyed countries has implemented 100% routine screening and only a few private blood banks have adopted PR treatment of PC. Regulations in different countries vary and microbiological testing of PC for quality control fluctuate between 1% and 5% of the collected components. Similarly, only five of the 18 countries have haemovigilance programs and only 2 out of the 5 have unified case definitions at the national level for reporting of TTBI. It is therefore difficult to get accurate information about the incidence of septic transfusion reactions. A total of 296 TTBI cases were reported in Latin America between 2006 and 2020 and Garcia *et al.* discuss that these numbers are between 20–24-fold lower than expected and therefore there is chronic underreporting of TTBI due to lack of recognition and standard definitions (20). This situation is not unique to Latin America and creates a unique opportunity for the ISBT TTID-WP Bacteria Subgroup to survey other world regions about their practices to improve the safety of blood components and disseminate knowledge.

This special series provides an excellent update on the interventions available and those in development to the transfusion community to increase the safety of the blood supply. It also highlights that further work is necessary to reduce the risk of transmission of bacteria by PC transfusion.

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