Editorial Commentary

Transfusion septic reactions involving platelet concentrates contaminated with *Citrobacter koseri*

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Blood components used for transfusion therapy include platelet concentrates (PCs), red blood cell concentrates (RBCC), and cell-free plasma. Significant advances have been made to increase the safety of these blood products in recent years by reducing the occurrence of units contaminated with viruses such as HIV. However, bacterial contamination of PCs, used as a therapeutic product to treat thrombocytopenic or bleeding patients, has become the most significant post-transfusion infectious risk in developed countries (1,2). PCs are exquisitely susceptible to bacterial proliferation, in comparison to RBCC and plasma, due to their storage conditions in gas-permeable plastic containers, at temperatures of 20–24 ℃, under agitation for up to 7 days. PCs are prepared in either 100% plasma or in platelet additive solutions (PAS) containing high glucose concentration. These storage conditions are important to maintain platelet functionality; however, they also provide an ideal environment for bacterial propagation. The predominant bacteria isolated from contaminated PCs are Gram-positive organisms, which are part of the normal skin or mucosa flora of the blood donor (1,2). Less frequently, Gram-negative organisms, which may be part of transitory skin flora or originate from silent donor bacteremia, are isolated from contaminated PCs. Usually, transfusion reactions involving Gram-negative bacteria are more severe due to infused endotoxin (lipopolysaccharide of the cell wall) followed by massive cytokine release. Clinical symptoms may include fever over 38.5 ℃, hypotension, nausea, vomiting and septic shock (2).

Although bacterial contamination is usually originated from the donor, there is also a potential for PC contamination during blood collection, storage, or even retrograde contamination from the patient to the PC component (3-5). Measures implemented worldwide to mitigate the risk of transfusing bacterially-contaminated PCs include donor screening with a questionnaire, skin disinfection of the donor's venipuncture site, diverting the first aliquot (approximately 30–40 mL) of the donated blood, PC screening for the presence of bacteria with culture or rapid methods, and pathogen reduction technologies (PRT) (1,2).

In the February 2020 issue of *Transfusion* (6), Emery *et al.* reported a genotypic study of five *Citrobacter koseri* strains isolated from contaminated PCs in France from 2012 to 2017. The Gram-negative bacillus *C. koseri* is part of the normal flora of human and animal digestive systems. Two of the isolates were traced back to the donors. Strain PAR was isolated from the donor's nose and strain NAN was retrieved from the donor's armpit. It is therefore likely that *C. koseri* can transiently colonize human skin and mucosa. Three of the five *C. koseri* strains described in this study were implicated in septic transfusion events with two resulting in fatalities (7,8). The other two strains were isolated from contaminated PCs that were discarded prior to transfusion into patients. The authors conducted comprehensive phylogenetic analyses of the five PC *C. koseri* isolates in comparison to five *C. koseri* strains recovered from human samples but unrelated to transfusion

Table 1 Summary of definite and probable transfusion-transmitted *C. koseri* cases

Year of transfusion event	Origin	Blood component	Clinical outcome	Reference
2008	Brazil	RBCC	Severe septic reaction	(10)
2012	France	Apheresis PCs	Septic reaction	(6)
2015	France	Apheresis PCs	Fatality	(6,7)
Unknown	France	PCs	Septic shock	(11)
2017	France	Whole-blood-derived PCs	Fatality	(6,8)
2016	Japan	Apheresis PCs	Severe septic reaction. Patient recovered with sequelae	(12)

RBCC, red blood cell concentrates; PCs, platelet concentrates.

events. The genomes of the strains were sequenced and assembled along fifteen *C. koseri* genomes available in NCBI databases. A genome multilocus sequence typing (cgMLST) scheme was constructed. The genomic comparison identified 4,950 genes shared by ≥96% of the selected genomes. This approach was used to visualize evolutionary relationships within the *C. koseri* isolates. Results of the genomic study showed that the PC isolates were nonclonal and did not share specific genes. However, one cluster of 11 strains, including three of the five PC isolates (BES, PAR and NAN), was identified. The origin of the 11 strains is distributed worldwide and therefore a potential common origin is unlikely. The authors also tested the growth characteristics of the PC isolates in PCs prepared in plasma or PAS and found no differences in growth characteristics.

Clusters of transfusion-associated septic reactions involving bacterially-contaminated PCs have been reported in the past. In 1991, six patients in Denmark and Sweden developed septicemia with *Serratia marcescens* after PC transfusion (3). The source of contamination was found on the exterior of blood bags produced in Belgium. In 2017, two separate clusters of fatal septic transfusion reactions involving PCs contaminated with *Clostridium perfringens* and *Klebsiella pneumoniae* were documented in the US, in Utah and California, respectively (9). More recently, multiple septic reactions with a potential common source were reported in three US states involving PCs contaminated with *Acinetobacter calcoaceticus-baumannii* and *Staphylococcus saprophyticus* (4). Investigation of these cluster cases with molecular testing of isolates from the donors, PC bags and platelet incubators concluded that a potential common source of contamination was likely responsible for the multiple septic transfusion cases. Unfortunately, in the *C. koseri* outbreak case discussed herein, there was not microbiological investigation of the PAS used for PC manufacturing, or the equipment and materials used during PC collection, production, or storage. Such investigation would have been especially relevant to further study the relationship of *C. koseri* strains BES and NAN, which were both isolated in 2017 from whole-blood derived PCs. These two strains belong to the cluster identified during cgMLST. Although they were isolated in different French cities, the possibility of a common source of contamination covering different geographic locations exists as demonstrated in the *Acinetobacter calcoaceticus-baumannii* and *Staphylococcus saprophyticus* case mentioned above (4).

Definite and probable published transfusion septic cases of PCs contaminated with *C. koseri* are summarized in *Table 1*. In addition to the three PC contamination cases reported by Emery *et al.* (6), there was another report of a septic transfusion case involving PCs contaminated with *C. koseri*, also in France, in 2015 (11). It is interesting that these reports are concentrated in France during the period of 2012 to 2017. *C. koseri* was first described to be involved in a septic transfusion event implicating contaminated RBCC in Brazil, in 2012 (10). The Japanese Red Cross also documented a severe septic transfusion case with PCs contaminated with *C. koseri* in 2016 (12). The Japanese report emphasized the importance of visual inspection prior to transfusion of PCs. *C. koseri* induces platelet clump formation when grown in PCs as shown in bulletins of the Japanese Red Cross and the Australian Red Cross Blood Service (12,13). Platelet aggregation in contaminated PCs is a common feature triggered by other species including *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Enterobacter aerogenes* (12,14-16).

As stated by the authors, in France, blood products suspected of being contaminated with bacteria are quarantined and discarded, and definite or probable transfusion-transmitted cases are reported to the French

hemovigilance organization. Several mitigation strategies to prevent transfusion of contaminated PC units have been implemented in France although PC screening is not one of them. Automated culture systems are effective in capturing contaminated PCs with Gram-negative bacteria which in general proliferate fast in this blood component (17,18). As shown in the supplemental material, of the Emery *et al.* publication (6), *C. koseri* reaches concentrations >10^3 colony forming units (CFU)/mL after 24 hours of PC storage. These results indicate that *C. koseri* grows fast in PCs and could be captured by automated culture systems preventing transfusion of contaminated PCs with this bacterium as reported by Canadian Blood Services (17). Although there are no published reports of inactivation of *C. koseri* with PRT, it is important to note that the PRT Intercept™ (CERUS Corp.) was implemented in France in 2017. Since then, there have not been reports of septic transfusion reactions involving PCs contaminated with *C. koseri*. It is however imperative to consider the potential of bacterial contamination post-PR treatment during PC storage or transportation as discussed by Jones *et al.* (4).

Overall, bacterial contamination of PCs poses the most prevalent transfusion-transmitted infectious risk due to their storage conditions. Several interventions have decreased but not eliminated the occurrence of transfusion-associated septic events involving contaminated PCs. Although Gram-positive skin/mucosa flora are the predominant PC contaminants, Gram-negative bacteria, such as *C. koseri*, can contaminate PCs posing a major infectious risk due to endotoxin release, resulting in septic shock in transfusion patients. A cluster of five PCs contaminated with *C. koseri* documented in France from 2012 to 2017 has been discussed herein. Importantly, no more septic cases involving PCs contaminated with this organism have been reported since the implementation of PRT in France in 2017. Outbreaks of transfusion septic events require through investigations of the PC donor, PC recipient, and equipment involved during blood collection, and PC production and storage. Recognizing, investigating, and reporting septic transfusion reactions to hemovigilance systems is highly recommended to interdict the transfusion of contaminated PC units.

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References

1. Levy JH, Neal MD, Herman JH. Bacterial contamination of platelets for transfusion: strategies for prevention. Crit Care 2018;22:271-9.
2. Ramirez-Arcos S, Goldman M. Bacterial Contamination in "Practical Transfusion Medicine". 5th edition. 2017: 177-84.
3. Högman CF, Fritz H, Sandberg L. Posttransfusion Serratia marcescens septicemia. Transfusion 1993;33:189-91.
4. Jones SA, Jones JM, Leung V, et al. Sepsis Attributed to Bacterial Contamination of Platelets Associated with a Potential Common Source - Multiple States, 2018. MMWR Morb Mortal Wkly Rep 2019;68:519-23.
5. Drews SJ, Lesly P, Detsky M, et al. A suspected septic transfusion reaction associated with possible bedside environmental/reverse contamination of a platelet pool by Vancomycin-resistant Enterococcus faecium. Transfusion 2020;60:430-35.

6. Emery A, Marpaux N, Naegelen C, et al. Genotypic study of Citrobacter koseri, an emergent platelet contaminant since 2012 in France. Transfusion 2020;60:245-9.
7. Hauser L, Menasie S, Bonacorsi S, et al. Fatal transmission-transmitted infection due to Citrobacter koseri. Transfusion 2016;56:1311-3.
8. Marcandetti M, Hocquet D, Bourcier V, et al. Citrobacter koseri transmise par transfusion plaquettaire. Transfus Clin Biol 2017;24:360-1.
9. Horth RZ, Jones JM, Kim JJ, et al. Fatal Sepsis Associated with Bacterial Contamination of Platelets - Utah and California, August 2017. MMWR Morb Mortal Wkly Rep 2018;67:718-22.
10. Fernandes C, Oliveira MC, Jorge MT. A case report of Citrobacter koseri bacteremia after transfusion of contaminates red cells. Transfus Med 2012;22:450-1.
11. Tichit R, Saumet L, Marchandin H, et al. Septic shock following platelet transfusion contaminated with Citrobacter koseri in a child with postchemotherapy febrile neutropenia. Arch Pediatr 2016;23:86-9.
12. Transfusion Transmitted Bacterial Infection through Platelet Components. Transfusion Bulletin from the Japanese Red Cross Society. Available online: http://www.jrc.or.jp/mr/english/pdf/yuketsu%20johou_1712_156.pdf. Accessed on May 29, 2020.
13. I need to know about bacteria in blood. Bulletin from the Australian Red Cross Blood Service. Available online: https://mytransfusion.com.au/sites/default/files/I_need_to_know_about_bacteria_in_blood.pdf. Accessed on May 29, 2020.
14. Loza-Correa M, Kou Y, Taha M, et al. Septic Transfusion Case Caused by a Platelet Pool With Visible Clotting Due to Contamination With Staphylococcus aureus. Transfusion 2017;57:1299-303.
15. Wendel S, Morato LE, Fontão-Wendel R, et al. Double, double, toil and trouble. Transfusion 2005;45:1241.
16. Thakral B, Dhawan HK, Das A, et al. Bacterial contamination of platelets: abnormal appearance. Transfusion 2007;47:1961-2.
17. Ramirez-Arcos S, DiFranco C, McIntyre T, et al. Residual risk of bacterial Contamination of platelets: six years of experience with sterility testing. Transfusion 2017;57:2174-81.
18. McDonald C, Allen J, Brailsford S, et al. Bacterial screening of platelet components by national health service blood and transplant, an effective risk reduction measure. Transfusion 2017;57:1122-31.

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