Hemovigilance data: An effective approach for evaluating bacterial protection systems for platelet transfusions

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Abstract:

BACKGROUND AND OBJECTIVE: Septic transfusion reactions due to bacterial contamination in platelet concentrates (PCs) are continually reported to hemovigilance (HV) programs. Worldwide, blood centers use different systems to avoid transfusion-associated bacterial sepsis in PCs. Herein, national HV data were gathered to compare bacterial protection systems and to assess the risk of bacterial contamination.

MATERIALS AND METHODS: HV data with definite transfusion-associated bacterial sepsis in PCs were obtained from Australia, Canada, the United Kingdom (U. K.), and Switzerland between 2006 and 2016. These data were reviewed to evaluate bacterial protection systems including early small-volume (ESV), early large-volume (ELV), and delayed large-volume (DLV) bacterial culture screening and pathogen inactivation (PI) treatment.

RESULTS: Implementation of DLV bacterial culture screening in the U. K. and PI treatment in Switzerland resulted in significant reductions ($P < 0.05$) in transfusion-associated bacterial sepsis for the period of 2011–2016 compared to the prior 4 years (2006–2010). Approximately 1.86 million DLV bacterial culture-screened PCs and 0.21 million PI-treated PCs were issued with no reported septic fatalities nor cases of life-threatening sepsis. In Australia, two life-threatening septic transfusion reactions (1.923 per million) were reported out of almost 1.04 million ELV bacterial culture-screened PCs, and no septic fatalities were reported. Meanwhile, in Canada, four life-threatening septic transfusion reactions (3.6/million) and one fatality (0.9/million) were observed in about 1.11 million ESV bacterial culture-screened PCs.

CONCLUSION: DLV bacterial culture and PI treatment significantly reduced the incidence of septic reactions. The advantages and disadvantages of both systems merit further investigation before implementation.

Keywords:

BacT/ALERT system, bacterial screening, hemovigilance, pathogen inactivation, platelets

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Introduction

In modern transfusion medicine, bacterial contamination of blood products is implicated as the highest posttransfusion infectious risk.[1] Platelet concentrates (PCs) are the most susceptible blood component to bacterial contamination due to their storage conditions (constant agitation at 22°C ± 2°C with an additive solution containing a glucose concentration of approximately 25 g/L), which offer an ideal milieu for bacterial proliferation.[2,3] Blood centers have implemented several strategies to avoid bacterial contamination of PCs, including a donor screening questionnaire to detect potential symptoms of infection, donor skin disinfection before venipuncture, diversion of the first aliquot of donated blood, and PC

screening for bacterial contamination.[2,4] Unfortunately, even with these efforts, transfusion-associated mortality and morbidity due to contamination of PCs still occur.[5,6]

The BacT/ALERT system has been widely implemented for PC screening to detect bacterial contamination, and numerous hemovigilance (HV) programs have reported its success.[7] However, while the BacT/ALERT system has high sensitivity (1–10 colony-forming units/mL), missed detections of bacterial contamination of PCs have been reported. Such missed detections could be attributed to low initial bacterial concentrations in the PC unit, slow bacterial growth, and bacterial ability to form biofilms (cell aggregates embedded within a self-produced matrix).[7,8] Consequently, blood centers have employed several methods to prevent bacterial contamination, namely early small-volume (ESV), early large-volume (ELV), and delayed large-volume (DLV) bacterial culture screening as, respectively, practiced in Canada, Australia, and the United Kingdom (U. K.).[5-11]

Meanwhile, a new strategy known as pathogen inactivation (PI) has been implemented by some centers to prevent the transfusion of contaminated PCs. Two PI technologies, Mirasol® and Intercept™, are currently available on the market.[12] While HV data on clinical outcomes for the Mirasol PI treatment system (riboflavin/ultraviolet (UV) light; Terumo BCT, USA) are limited, the Intercept blood system (amotosalen/UV light; Cerus, USA) is approved by the US Food and Drug Administration, and clinical outcome data are available from randomized controlled trials, observational studies, and national HV programs such as in Switzerland.[12,13]

Blood centers continually strive to provide safe blood products to patients, and HV data is paramount for achieving this goal.[9-14] HV data have resulted in several changes in policy, practice, and products that have improved clinical outcomes after transfusion.[14,15] However, HV evaluation of a new strategy for preventing transfusion-associated bacterial sepsis (TABS) is difficult, as the rarity of cases and variation in its highly-imputable definition make confirmed documentation challenging. Typically, HV programs define definite TABS as cases in which the same bacteria are isolated from both the recipient's blood cultures and the residual PCs.[14,16] Under this definition, longitudinal monitoring of definite TABS is a valid method for the evaluation of new strategies.[15,16]

In this study, HV data with definite TABS in PCs were gathered from Australia, Canada, the U. K., and Switzerland between 2006 and 2016. These data were reviewed to evaluate the effectiveness of bacterial protection systems, namely ESL, ELV, and DLV bacterial culture screening and PI treatment.

Materials and Methods

This retrospective study was conducted at the College of Medicine, Imam Mohammad Ibn Saud Islamic University, Saudi Arabia, starting in November 2019 and continuing to October 2020. In this study, PCs either processed with Buffy coat method from whole blood units (pooled platelet) or apheresis platelet were gathered, with different variations each year, from Australia, Canada, the U. K., and Switzerland between 2006 and 2016. Herein, longitudinal HV data from four countries were compiled to evaluate ELV, ESV, and DLV bacterial culture screening, and PI treatment.

ELV bacterial culture screening was instituted at the Australian Red Cross Blood Service in April 2008.[17] This screening is performed for all PC products through closed sampling (via pouch or integrated sampling device) of 15 mL to 20 mL taken from each PC unit 24 h after donation, and an inoculum of 7 mL to 10 mL per bottle is incubated under both aerobic and anaerobic environments for 7 days on the BacT/ALERT system with constant monitoring. After sampling, PC units are available for issue to hospitals, with a shelf life of 5 days [Figure 1].[10,17]

ESV bacterial culture screening was implemented by the Canadian Blood Services in 2004.[2,5] All PC units are screened for bacterial contamination using an 8–10-mL aliquot of PCs (mother bag) that is inoculated 24–30 h after donation into an aerobic culture bottle and then incubated for a maximum of 6 days in a BacT/ALERT system with monitoring. PC units are available for issue to hospitals after sampling, with a shelf life of 5 days [Figure 1].[5,9]

DLV bacterial culture screening was instituted by the National Health System Blood and Transplant in the U. K. in February 2011.[14] This screening is performed for
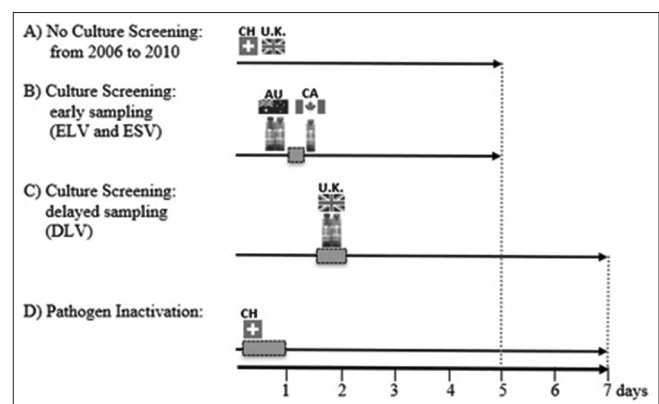
Figure 1: Bacterial protection systems of platelet transfusions. Gray box indicated the time of bacterial culture screening or pathogen inactivation treatment, and dashed lines indicated the end of shelf-life of PC units. PC = Platelet concentrate

all PCs to detect bacterial contamination using 16 mL of PCs (mother bag), which is inoculated 36–48 h after donation. An inoculum of 8 mL per bottle is incubated under both aerobic and anaerobic environments for 7 days on the BacT/ALERT system with constant monitoring. PC units are available for issue to hospitals after sampling, with a shelf life of 7 days [Figure 1].[11]

PI was introduced as a treatment for all PC products in Switzerland in 2011.[12] Briefly, exposure of PCs to UV light (320–400 nm) in combination with the photosensitizer amotosalen causes the covalent crosslinking of any nucleic acids where the amotosalen is bound, thereby preventing replication of pathogens. PC units are available for issue to hospitals after the PI treatment (a maximum of 24 h after donation) and have a shelf life of 5 days, which was extended to 7 days in 2013 [Figure 1].[12-14]

Statistical analysis
The HV reports for each country from 2006 to 2016 were compiled, and data for every 2 years were combined for analysis. Means and standard deviations (SDs) were calculated with computer software (Excel, Microsoft Corp.). Statistical analyses were performed using the two-tailed unequal variance t-test, and $P < 0.05$ was considered statistically significant.

Ethics statement
The study was approved by the Ethics Review Committee of College of Medicine, Imam Mohammad Ibn Saud Islamic University. The Ethics Committee approved the waiver of official permission to access the HV data of mentioned blood centers, with the justification that this was a retrospective and analytical study whose information was obtained from blood centers' original sites. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Results

In Australia, after the implementation of ELV bacterial culture screening from 2008 to 2016, there were 1,040,183 units of PC transfusion, with 24 instances of TABS (23.07/million), of which there were zero fatalities and two cases of life-threatening sepsis (1.923/million) that required major interventions such as vasopressors and transfer to intensive treatment units following the transfusion [Table 1].[18] However, from 2006 to 2008, there were 236,295 units of PC transfusion that were not screened for bacterial contamination, and unfortunately, no HV outcomes were stated.

In Canada, ESV bacterial culture screening was carried out from 2006 to 2016, and HV data were available from all Canadian provinces except Hema-Quebec.

Out of 1,111,285 transfused PCs, 11 TABS cases (9.9/million) were reported, including one fatality (0.9 per million) and four cases of life-threatening sepsis (3.6/million) [Table 2].[5,19,20] The fatality was attributed to contamination with *Staphylococcus epidermidis*, which transfused with 5-day-old PCs to a patient.[21]

In the U. K., the period of 2006–2010 preceded the implementation of DLV bacterial culture screening. During this time, there were 1,027,167 PCs issued, with 11 instances of TABS (10.71/million) that included two fatalities (1.95/million) and three cases of life-threatening sepsis (2.92/million).[22] The two fatality cases were due to *Klebsiella pneumoniae* contamination, which transfused with 3-day-old PCs to patients [Table 3]. From 2011 to 2016, with DLV bacterial screening, there were 1,861,687 units of PC transfusion and one case of TABS (0.54/million) reported, with no reported septic fatalities or life-threatening cases [Table 3].[22] Interestingly, after the implementation of bacterial screening, the incidence of TABS decreased significantly ($P < 0.05$) compared to the prior 4 years (2006–2010) with TABS reduction from 9.71 ± 2.12 to 0.32 ± 0.57 [Figure 2].

In Switzerland, from 2006 to 2010 and before implementation of PI treatment, there were 109,154 transfused PCs with 12 cases of TABS (109.94/million) reported, including one fatality (9.16 per million) and six life-threatening cases (54.97/million) [Table 4].[13] The one fatality was due to *K. pneumoniae* contamination, which transfused with 2-day-old PCs to a patient. From 2011 to 2016, during which PI treatment was applied to all PC products, there were 212,224 transfused PCs with no instances of TABS [Table 4].[13] The reduction in TABS with PI treatment was significant ($P < 0.05$) compared to the prior 4 years (2006–2010) from 108.59 ± 3.87 to 0 [Figure 2].

Discussion

In this study, we demonstrated that DLV bacterial culture screening and PI treatment are significantly effective
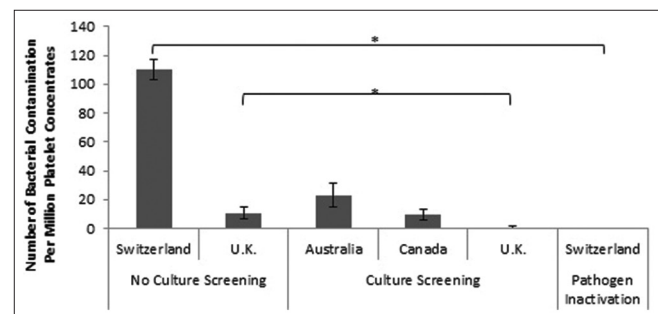
Figure 2: Rates per million of bacterial contamination of PCs identified by transfusion-associated bacterial sepsis. Results are presented as mean ± SD. *A significant difference between bacterial protection systems ($P < 0.05$), SD = Standard deviation

Table 1: Australia hemovigilance data from 2006 to 2016

Year	Number of units transfused	Transfusion-associated bacterial sepsis	Death	Life threatening*
2006-2008	236,295	NR[†]	NR	NR
2008-2010	246,743	6	0	1
2010-2012	268,853	7	0	0
2012-2014	265,174	6	0	0
2014-2016	259,413	2	0	1
Total	1,276,478	24	0	2

*Require a major intervention following the transfusion (intubation, vasopressors, and transfer to intensive treatment unit), [†]NR=Not reported

Table 2: Canada hemovigilance data from 2006 to 2016

Year	Number of units transfused	Transfusion-associated bacterial sepsis	Death	Life threatening
2006-2008	199,835	2	0	0
2008-2010	218,388	3	0	1
2010-2012	233,721	3	0	2
2012-2014	229,183	1	0	1
2014-2016	230,158	2	1*	0
Total	1,111,285	11	1	4

*Death due to *Staphylococcus epidermidis* contamination in PC unit. PC=Platelet concentrate

Table 3: United Kingdom hemovigilance data from 2006 to 2016

Year	Number of units transfused	Transfusion-associated bacterial sepsis	Death	Life threatening
2006-2008	513,893	7	2*	1
2008-2010	513,274	4	0	2
2010-2012	613,365	0	0	0
2012-2014	630,679	0	0	0
2014-2016	617,643	1	0	0
Total	2,888,854	12	2	3

*Death due to *Klebsiella pneumoniae* contamination in two PC units. PC=Platelet concentrate

Table 4: Switzerland hemovigilance data from 2006 to 2016

Year	Number of units transfused	Transfusion-associated bacterial sepsis	Death	Life threatening
2006-2008	50,500	8	0	4
2008-2010	58,654	4	1*	2
2010-2012	67,333	0	0	0
2012-2014	70,078	0	0	0
2014-2016	74,813	0	0	0
Total	321,378	12	1	6

*Death due to *Klebsiella pneumoniae* contamination in PC unit. PC=Platelet concentrate

in reducing TABS and eliminating septic fatalities. Even though other strategies for overcoming bacterial contamination in PCs are now in development or are available (e.g., frozen or cold-stored platelets and rapid bacterial testing), to confirm their clinical impact must await widespread implementation and the collection of HV data.[2,23,24] Due to successful experiences monitored by HV programs and then partly published in separate reports, the two strategies most commonly used to overcome bacterial contamination in PCs worldwide are bacterial culture screening using the BacT/ALERT system and PI treatment using amotosalen in combination with UV light.[7,12,25]

The best-in-class culture system was DLV bacterial culture screening as practiced in the U. K., due to the use of delayed testing (36–48 h postdonation), large sample volumes, and both aerobic and anaerobic cultures. The success of these features is evident in there being only one case of definite TABS (0.54 per million) from 2011 to 2016, caused by *Staphylococcus aureus*, and no septic fatalities were reported over that period.[22] Delayed testing allows more time for any bacteria present in the collected PCs to proliferate and, in combination with large sample volume, could increase the bacterial yield.[11,22] Interestingly, McDonald *et al*. demonstrated that bacteria such as *S. aureus* can escape detection even after 48 h due to their slow-growing characteristics and their ability to form biofilms, which can cause sampling error.[11] A recent screening protocol study demonstrated that using large sample volumes improved the sensitivity of bacterial culture screening, detecting bacteria that could have escaped detection when using only a single bottle of 8–10-mL volume.[8,26] Furthermore, several studies

have shown that using a large sample volume with both aerobic and anaerobic culture bottles improves the bacterial detection rate and detects a broader spectrum of bacteria, as opposed to using aerobic culture bottle (s) only.[26,27] In addition, anaerobic bacteria (e.g., *Clostridium perfringens*) have been reported to cause severe and fatal septic transfusion reactions, which indicates the necessity of anaerobic cultures.[28,29]

The two other screening methods evaluated, ELS and ESV, also demonstrated some success in reducing the incidence of TABS.[2,8,10] From 2006 to 2016, ESV bacterial screening was applied to >1.11 million delivered PCs, with 11 definite TABS cases and one report of septic fatality.[5,19-21] Interestingly, the rate of definite TABS was higher in ELV (23.07/million) compared to ESV (9.9/million); this could be due to the dissimilar donor populations and the use of whole-blood versus apheresis PCs.[18-20]

The effectiveness of PI treatment at preventing TABS is clearly reflected in the Swiss HV data. Approximately 2.1 thousand PCs have been manufactured in Switzerland without any reports of TABS or septic fatalities.[13] Moreover, a French HV program monitored approximately 3.1 thousand PI-treated PC transfusions with no reports of TABS or septic fatalities.[14] Overall, the rate of TABS with PI-treated PCs was significantly lower than in nonculture-screened PCs.[13,14] However, there are some disadvantages to PI treatment, including its limited effectiveness against bacterial spores (e.g., *Bacillus cereus*), high cost, and the lack of reliable data on the long-term safety of PCs treated with PI.[12]

It has been suggested that the rate of septic transfusion reactions attributable to bacterial contamination is underestimated, since not all reactions can be retroactively correlated to a transfusion event.[3,30] For instance, if a PC bag is not available, HV programs report the cause undetermined as a result of incomplete investigation.[3] Doctors also fail to distinguish septic reaction, and patients may not show immediate symptoms resulting from PC contamination, frequently because of the synchronized receipt of an antibiotic.[3,30] Thus, heightened vigilance for septic transfusion reactions related to PC transfusions is essential.

DLV bacterial culture screening and PI treatment have both been proven to enhance PC safety, with PI treatment in particular having a perfect record to date regarding TABS as documented by national HV programs. Unfortunately, imperfect reporting may have concealed cases that impact this record.[12-14] Bacterial spores are considered to be a high risk with PI treatment due to their resistance to inactivation.[12] In addition, Wagner *et al*. reported that PI can be overwhelmed by fast-growing

bacteria such as *K. pneumoniae*, whose replication can exceed the system's inactivation capacity.[31] The manufacturer of the PI treatment recommends early treatment to avoid complications from fast-growing bacteria.[12,13,31] On the other hand, bacterial screening is best performed as late as possible to provide the bacteria more time to multiply and increase the chance of detection.[22,32] The Canadian Blood Services uses DLV bacterial culture screening, with no reports of TABS to date since its implementation in August 2017.[9]

We have to keep in mind the comparison of HV reports from different countries suffers from limitations including dissimilar donor populations, use of different arm disinfection techniques, the use of whole-blood versus apheresis PCs, and whether the first aliquot of donated blood is diverted.[2,14] Given these limitations, internal comparisons of changes in strategy within the same country have more value than do formal comparisons of outcomes from different HV programs.

Conclusion

HV reports demonstrated that DLV bacterial culture and PI treatment significantly reduced the incidence of septic reactions. For HV programs practicing bacterial screening, it seems that DLV bacterial culture screening is easier to implement due to a lower cost than changing to PI; however, it could be debated that PI treatment would be a better option as it provides protection against most viruses and protozoa, and it can replace other costly procedures such as screening for microorganisms and gamma irradiation.[9,12,32]

Conflicts of interest
There are no conflicts of interest.

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