Risk and prevention of transfusion-related sepsis

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Purpose of review

Transfusion-related sepsis is both the oldest recognized and most common transfusion-associated infectious risk. Despite an increased awareness and recognition of this problem, particularly with room-temperature stored platelets, strategies to prevent or reduce the occurrence of this problem have proved daunting.

Recent findings

With the recent FDA approval of culture methods for platelet bacterial testing and the promulgation of accreditation standards by the College of American Pathologists and American Association of Blood Banks to limit and detect platelet bacterial contamination, it is anticipated that the frequency of this problem will now begin to diminish.

Summary

As methods to reduce and/or inactivate pathogens emerge, it is hoped that transfusion-related sepsis will essentially disappear.

Keywords

transfusion-related sepsis, epidemiology, bacterial contamination

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Abbreviations

RBCs red blood cells

1065–6251

Introduction

Bacterial contamination of blood components is an important cause of transfusion-associated morbidity and mortality [1–8••] and represents the oldest recognized transfusion-associated infectious risk [9]. Despite remarkable advances in reducing the transmission of transfusion-associated viral infections—HIV1 and 2, hepatitis C, hepatitis B, and human T-cell lymphotrophic viruses I and II—bacterial contamination of blood products remains the greatest transfusion-associated infectious risk and is proving the most difficult to eradicate.

While all blood components are susceptible to bacterial contamination, septic reactions are most commonly associated with platelets [1,10,11]. The main reason for this is that platelet units, stored at room temperature, allow for the growth of most bacterial species; in contrast, red blood cell (RBC) units, stored at 4° C are able to support growth of only a few bacterial species, most notably, *Yersinia* spp [12,13].

Bacterial contamination of blood presents several challenges that explain, at least in part, why this problem has gone unsolved and unresolved for over 60 years (Table 1). With the recent Food and Drug Administration (FDA) approval of culture methods for platelet bacterial testing and the promulgation by the American Association of Blood Banks and College of American Pathologists of accreditation standards to limit and detect platelet bacterial contamination, it is hoped that the frequency of this problem will now begin to diminish.

Epidemiology

There are several critical parameters in understanding the magnitude of bacterial contamination of blood components. These parameters include: determination of the overall prevalence of contamination; evaluation of how often a contamination episode results in transfusion-related sepsis; and an appreciation of the case fatality rate.

From 1976 through 1985, the FDA received reports of 256 transfusion-associated fatalities with 10% resulting from bacterial contamination of blood products [14]. More recently, from 1986 to 1991, of 182 transfusion-associated fatalities reported to the FDA, 29 (16%) were caused by bacterial contamination of blood products [15]. Most recently, the BaCon study confirmed the clinical importance of bacterial contamination of blood components, identifying from 1998 through 2000, 34 symptomatic cases of transfusion-transmitted bacterial infection. Nine of these cases resulted in death. This study also showed

Table 1. Bacterial contamination of blood products: challenges

Lack of appreciation of the frequency of this problem
Unclear definition of what constitutes clinically significant contamination
Poor clinical recognition of this problem since patients receiving blood products have severe underlying disease, which may mask the clinical recognition of a septic-transfusion reaction
Presence of highly variable clinical signs and symptoms
Traditional testing with antibody and antigen methods are not suitable due to the ubiquitous nature of the bacteria implicated in contamination of blood products
Utilization of amplification methods may give false-positive results due to the detection of dead organisms and/or environmental organisms with the latter being the same organisms most frequently implicated in blood-product contamination
Presence of a wide number of bacterial species with heterogeneous growth characteristics makes a single detection strategy unlikely

that patients at the greatest risk for death received components containing Gram-negative organisms [1].

Investigators in other countries have also evaluated the occurrence of transfusion-associated bacterial contamination. In France from 1997 to 1998 of 158 suspected cases, 41 (of 4,109,077 transfusions) involved RBCs and 16 (of 473,141 transfusions) involved platelets. Gram-negative bacteria accounted for nearly half of the bacteria species involved and accounted for all six deaths [16]. A more recent report identified 185 cases of bacterial contamination and 18 fatalities in a 4-year period [17••]. In the United Kingdom from 1996 to 1998, from 366 cases of serious complications of blood transfusion reported, 12 were associated with bacterial contamination and 1 of these cases was fatal [18].

Bacterial contamination of red blood cell units

Sepsis associated with the transfusion of bacterially contaminated RBC units has been reported very infrequently. However, most reported instances are associated with a high mortality [9,19]. The FDA reported that from 1976 (when mandatory reporting of fatalities began) to 1998 there were 26 deaths related to transfusion of contaminated whole blood or red cells with an overall risk of less than 1 fatality per every 1 million units transfused [9]. The most commonly implicated organisms are *Yersinia enterocolitica*, followed by some species of *Serratia* spp. (*S. liquefaciens* or *S. marcescens*) and *Pseudomona*s spp. These organisms are cryophilic, that is, capable of growth at refrigerator temperatures and therefore can be present in large numbers, especially in units stored more than 3 weeks; however, contamination of RBC units with *Yersinia enterocolitica* has been reported in units stored for only 14 and 16 days [20,21].

Blood products become contaminated with *Yersinia* spp. as a result of occult donor bacteremia. Contamination of RBC units with *Serratia* spp. and *Pseudomonas* has been linked mainly to contamination of blood-collecting equipment and water baths rather than to donor bacteremia [22]. Contamination of RBC units with *Burkholderia cepacia* (formerly *Pseudomonas cepacia*) resulted in sepsis in three patients. The investigation identified the source of the outbreak as chlorhexidine used for donor arm cleaning [23•].

S*erratia liquefaciens*, an unusual clinical pathogen, has been an increasingly recognized cause of transfusion-related sepsis and is associated with a high mortality rate [22]. In a case report, *S. liquefaciens* was isolated from blood bottles contaminated probably during production [24]. The CDC reported five episodes of transfusion-related sepsis and endotoxic shock due to *S. liquefaciens* from July 1992 to January 1999 (four associated with RBC and one with platelet transfusions). Four of the five cases were fatal [22].

The members of the genera *Pseudomonas*, *P. fluorescens* and *P. putida*, are environmental organisms of low virulence but they can contaminate RBC units because they can colonize the skin of donors and because they can grow at 4° C [25].

In New Zealand, for reasons not clearly established, the incidence of transfusion- transmitted Yersinia infection is higher than in other countries and the fatality rate is about 80 times greater than that reported in the United States (1 in 104,000 units transfused) [26].

Contamination of autologous blood

Blood donated by patients may be more likely to be contaminated by bacteria than blood donated by healthy volunteer donors. The screening of autologous donors is generally less rigorous compared with allogeneic donors; in addition, the storage interval for autologous RBC units is typically longer than that for allogeneic units, maximizing the opportunity for bacterial proliferation [27]. Recently, a 13-year-old girl developed septic shock after receipt of an autologous RBC transfusion contaminated with *Y. enterocolitica*. A few days before the donation, she had complained of abdominal pain and was experiencing mild diarrhea [28•].

Serratia marcescens has been linked to an RBC contamination and sepsis following allogeneic as well as autologous blood transfusion [29,30]. Sepsis with a combination of *S. marcescens* and *P. aeruginosa* was observed in a patient after receiving two units of autologous blood [30].

Over a 3-year period (1998 through 2000), from suspected cases reported during the BaCon study, the rate of transfusion-transmitted bacteremia for RBC units (in events/million) was 0.21 and the rate of fatal reactions was 0.13.

Bacterial contamination of platelets

Platelet-transfusion associated sepsis is now recognized as the most frequent infectious complication of transfusion therapy—surpassing by up to two orders of magnitude the incidence (that is, 99% greater risk) of transfusion-associated viral transmission [6,7]. An estimated 1 in 1000 to 3000 platelet units (apheresis and random units) are contaminated with bacteria [5,7] and it is estimated that a severe episode of transfusion-associated bacterial sepsis occurs in connection with about one sixth of contaminated platelet units transfused [5,31]. Lack of recognition and reporting are due in large measure to the failure to associate chills, rigors, and/or fever—signs and symptoms so common in patients receiving platelet transfusion therapy—with the possibility of a bacterially contaminated platelet unit. More serious clinical events, such as shock and even death, occurring in immunocompromised platelet transfusion recipients are likewise often not linked to transfusion of a contaminated platelet unit.

Over a 3-year period (1998 through 2000), from suspected cases reported during the BaCon study, the rate of transfusion-transmitted bacteremia (in events/million) was 9.98 for single-donor platelets and 10.64 for pooled platelets. The rates of fatal reactions were 1.94 and 2.22 respectively [1]. Overall, the BaCon study estimated a fatality rate of 1 in 500,000 units for single-donor and pooled platelets.

Most commonly the organisms implicated in bacterial contamination of platelets are organisms that are part of the normal flora that gain access to the unit during the collection process. The predominant organisms of the skin flora are Staphylococci (*S. aureus*, coagulase negative staphylococci), aerobic and anaerobic diphtheroid bacilli (*Corynebacterium*, *Propionibacterium*), streptococci, and Gram-negative bacilli.

As described previously for RBC units, contamination of platelet units with Gram-negative organisms can also cause severe transfusion reactions. Sepsis and endotoxic shock due to transfusion of platelets contaminated with *Serratia liquefaciens* has been reported in two cases. These cases were identified during a look-back investigation of contaminated RBC units, as they had not been linked to the platelet transfusion. This finding demonstrates that contamination of platelet units can be overlooked as the cause of septic reactions [22].

Salmonella sepsis was observed in two patients who received a platelet transfusion from a donor with a pet snake. One of these patients died. Apparently, the donor had asymptomatic *S. enterica* bacteremia [32•].

Strategies to reduce risk or prevent contamination of blood products

Strategies to reduce the risk or prevent the transfusion of bacterially contaminated platelets have been classified as follows: bacterial contamination avoidance methods, bacterial elimination methods, bacterial growth inhibitory methods, bacterial inactivation methods, and bacterial detection methods [33]. It should be emphasized that methods in different categories are not necessarily mutually exclusive; indeed, it is possible, even likely, that the best approach to dealing with the problem of platelet bacterial contamination will be a combination of methods that act in synergy.

Bacterial contamination avoidance and elimination methods

In an attempt to prevent the entrance of bacteria into the blood collection system several measures have been recommended. Although contamination of blood products has been reported in association with donor bacteremia, more commonly, bacteria gain entry into the collection set during the phlebotomy process. Therefore, measures to avoid the entrance of bacteria into the blood collection system include exhaustive donor screening to evaluate possible causes for bacteremia, improved disinfection of the skin, and diversion or removal of the first 10 to 30 mL of blood collected [34,35••]. The diversion strategy appears particularly effective in reducing the incidence of *Staphylococcus* spp., the most common organism implicated in platelet bacterial contamination. Finally, the preferential use of single-donor apheresis platelets, in contrast to pooled random donor platelets, will reduce the risk of contamination by limiting the number of donor phlebotomies per transfusion episode [36,37].

Bacterial growth inhibitory methods

Since it is not possible to avoid the introduction of bacteria into the blood collection set during the phlebotomy process, a possible approach is to inhibit the growth of bacteria following collection. The number of bacteria entering the collection system is almost always too small to be of clinical significance. It is only during room-temperature platelet storage that the organisms grow and achieve clinical significance. Thus, if bacterial growth can be inhibited, this problem can largely be prevented. A possible strategy to accomplish this involves the cold storage of platelets. However, because transfused platelets are rapidly cleared from the circulation following cold storage, possibly due to clustering of vWF receptors [38••], the use of a cryoprotectant, such as DMSO and/or Thrombosol is needed [39,40]. Methods employing these substances, alone or in combination, are cumbersome, requiring pre- and post-processing steps, and may be toxic to the platelets and/or platelet recipients. It is anticipated that more effective cryoprotective agents will emerge in the near future [41].

Bacterial inactivation methods

As the blood supply becomes increasingly vulnerable to an ever-increasing array of infectious agents, inactivation rather than detection is becoming increasingly more attractive.

Two different inactivation systems have been evaluated for RBCs—the Inactine system (Vitex, Watertown, MA) and the Helix/Intercept system (Cerus, Concord, CA). The Inactine system uses a positively charged molecule that is chemically related to ethyleneimine, which binds to guanine in DNA or RNA of virus or bacteria. Investigators found that the Inactine process effectively prevented the outgrowth of *Y. enterocolitica*, *P fluorescens*, and *P. putida* deliberately inoculated into leukocyte-reduced RBCs [42••]. The Helix/Intercept system uses a psoralen derivative (S-303) to inactivate pathogens through intercalation and binding to the DNA, preventing replication. The inhibitory properties of this method have not yet been completely documented. There are also two inactivation systems being evaluated for platelets. The Intercept Platelet System (Cerus, Concord, CA) uses amotosalen (S-59), which when activated by light, binds to the nucleic acid of the pathogen and prevents replication. Phase 3 clinical trials using amotosalen-mediated pathogen inactivation in buffy coat and single-donor apheresis platelet units are currently in progress in Europe and in the United States [43,44]. The other system under evaluation for platelets is a photochemical decontamination process utilizing riboflavin (Navigant, Lakewood, CO). Preliminary reports are encouraging [45–47].

Although decontamination methods are fraught with numerous unanswered questions regarding platelet viability, toxicity of residual photochemical agents, and cost [48] they are potentially attractive because of their broad action against a variety of existing and emerging infectious agents [49].

Bacteria detection methods

At present, the focus for preventing bacterial contamination of blood, particularly platelets, has been on detection methods. A detection method, applied shortly after collection, must be very sensitive since the number of contaminating bacterial organisms at this time is likely to be very small. Recently, two culture methods have been approved by the FDA for detection of bacteria in leukocyte-reduced platelet units. The traditional culture approach monitors the production of CO_2 by growth of bacterial organisms in an automated system (BacT/Alert, BioMerieux Inc., Durham, NC). Evaluation studies performed in a laboratory environment have demonstrated that the BacT/Alert system was able to identify most contaminated units during the first 24 hours of incubation [50••,51••]. Additional studies have also demonstrated its efficacy in a clinical setting [52]. A novel culture approach assesses the reduction of O_2 by growth of bacterial organisms within a sample pouch (Pall-BDS, MedSep Corp., Covina, CA). Evaluation of this system showed that the BDS system was also effective in detecting most contaminated platelets units after a 24-hour period of pouch incubation [53,54]. A comparison of these two culture methods is shown in Table 2. Significantly, given the already short five-day shelf life of stored platelets, both culture methods potentially delay the use of platelets because they require a holding period prior to and after sampling to insure augmentation and detection of bacterial growth.

As platelets age during storage, however, bacteria, if present will continue to proliferate. Thus, it may be possible to employ a direct bacterial detection method for these older platelets if applied just prior to issuance for transfusion. Indeed, several such methods are currently being evaluated. These methods include: hybridization of antibody probes targeting conserved bacterial protein antigens generic to gram-positive and gram- negative organisms using bacterial class detection technology (Verax Biomedical Inc., Worcester, MA) [55]; hybridization of oligonucleotide probes specific for bacterial 16S ribosomal RNA [56]; automated fluorescence microscopy [57,58]; electrochemiluminescence [59]; a spore-based biosensor in which dormant spores respond to the presence of neighboring bacterial cells by producing light signals [60•]; and amplification methods such as real-time PCR [61]. While only the latter is likely to rival culture methods in terms of sensitivity, false-positive re-

Table 2. Comparison of culture methods

Parameter	Pall–BDS (MedSep Corp.)	BacT/Alert (BioMerieux Inc.)
Minimal holding period of the product prior to sampling	24 hrs	24 hrs
Minimal incubation of sample	24–30 hrs	Hours to five days–depends on occurrence of positive signal
Product	Leukoreduced platelets apheresis & random	Leukoreduced platelets apheresis
Sampling	Fully closed system	Partially closed system
Organisms ID	Aerobic only	Aerobic and anaerobic
Instrumentation Automation Size	Less Smaller	More Larger
End-point	Defined	Open-ended
Sensitivity	Very good	Excellent
Specificity	Excellent	Very good

sults from exogenous or dead organisms could limit its applicability.

The critical factor for the clinical use of any detection method is defining the number of bacteria (in CFU/mL) that represents clinically significant contamination. Transfusion reactions may occur with as few as 10^2 to 10^3 CFU/mL even with organisms usually regarded as non-pathogenic such as *S. epidermidis* [6,62].

Conclusion

Strategies to prevent transfusion of bacterially contaminated blood components, particularly platelets, are long overdue. Today, prevention is best achieved by a combination of methods to limit and detect bacteria. Prior to and during collection, strict screening of the donor for occult bacteremia, careful attention to the phlebotomy process, and preferential use of apheresis platelets will limit the potential for contamination. Similarly, bacterial elimination by use of phlebotomy diversion during blood collection will reduce the quantity of bacteria entering the unit. Following collection, a bacterial detection method will identify many of those contaminants that remain and grow during storage. The more sensitive the detection method, the better the assurance that most clinically significant contaminants will be interdicted prior to transfusion. It is hoped that in the near future, scientific advances that will allow for the cold storage of platelets and/or that safe pathogen reduction methods will emerge and virtually eliminate the problem of blood product-associated bacterial contamination.

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