# Transfusion-transmitted bacterial infection in the United States, 1998 through 2000

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**BACKGROUND:** Bacterial contamination of blood components can result in transfusion-transmitted infection, but the risk is not established.

**STUDY DESIGN AND METHODS:** Suspected cases of transfusion-transmitted bacteremia were reported to the CDC by participating blood collection facilities and transfusion services affiliated with the American Red Cross, AABB, or Department of Defense blood programs from 1998 through 2000. A case was defined as any transfusion reaction meeting clinical criteria in which the same organism species was cultured from a blood component and from recipient blood, with the organism pair confirmed as identical by molecular typing.

**RESULTS:** There were 34 cases and 9 deaths. The rate of transfusion-transmitted bacteremia (in events/million units) was 9.98 for single-donor platelets, 10.64 for pooled platelets, and 0.21 for RBC units; for fatal reactions, the rates were 1.94, 2.22, and 0.13, respectively. Patients at greatest risk for death received components containing gram-negative organisms (OR, 7.5; 95% CI, 1.3-64.2; p = 0.009).

**CONCLUSION:** Bacterial contamination of blood is an important cause of transfusion-transmitted infection; infection risk from platelet transfusion is higher compared with that from RBCs, and, overall, the risk of infection from bacterial contamination now may exceed that from viral agents. Recipients of components containing gram-negative organisms are at highest risk for transfusion-related death. The results of this study may help direct efforts to improve transfusion-related patient safety.

Bacterial infections transmitted by blood transfusion are associated with the rapid onset of sepsis and high mortality, and they remain an underrecognized, underreported, serious patient safety issue.[1-3] However, recent attention has been focused primarily on the prevention of transmission of HIV, HBV, HCV, and other blood-borne viruses through blood transfusion. With the advent of highly sensitive and specific screening methods, the transmission of viral agents has been reduced, but the risk of transfusion transmission of bacterial infection has remained.[4-7] Bacterial contamination of blood components is the most frequently reported cause of transfusion-related fatalities reported to the FDA after hemolytic reactions, accounting for >10 percent (77/694) of transfusion-associated fatalities from 1985 to 1999.[8]

**ABBREVIATIONS:** ARC = American Red Cross; BaCon = Assessment of the Frequency of Blood Component Bacterial Contamination Associated with Transfusion Reaction; DoD = Department of Defense; IDR = incidence density ratio; PFGE = pulsed-field gel electrophoresis; SDP(s) = single-donor platelet(s).

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The prevalence of bacterial contamination of whole blood at collection has recently been estimated to be 0.2 percent.[9] The prevalence of blood component contamination is higher for platelets than for RBCs, but estimates are highly variable and depend on methods of culture, processing, or storage; estimates range between 0.002 and 1.0 percent for RBCs and 0.04 and 10 percent for platelets.[3,10-14] The frequency of bacterial contamination of blood components resulting in transfusion-transmitted infection has not been well quantified. National estimates for deaths, largely based on FDA reporting, range from 1 in 6 million to 1 in 9 million blood components transfused overall and 1 in 1 million platelet transfusions.[3,15-17]

Nonfatal transfusion reactions resulting from bacterial contamination of blood components, particularly platelets, are underrecognized, for several reasons. First, many febrile episodes are misdiagnosed as nonhemolytic reactions triggered by transfused RBCs or are thought to be due to the recipient's underlying illness, and they are not fully investigated to rule out bacterial contamination.[2,3,18] Second, the FDA requires (CFR 21 606.170 [b]) that only fatal complications of blood collection or transfusion be reported; reporting of nonfatal transfusion reaction due to bacterial contamination is voluntary. Finally, the use of antimicrobials and anti-inflammatory agents in frequently transfused populations may account for the partial masking of symptoms normally associated with sepsis.

From 1987 to 1999, the CDC received increasing reports of sepsis and death due to bacterial contamination of blood components.[19-23] However, the data reported often were insufficient to allow the determination of a definite association between component contamination and transfusion reaction. Hence, a standard approach was needed to further describe these events and better assess recipient risk.

A prospective reporting system was created by the AABB, American Red Cross (ARC), CDC, and Department of Defense (DoD) blood programs. The Assessment of the Frequency of Blood Component Bacterial Contamination Associated with Transfusion Reaction Study (BaCon ) was initiated to achieve the following objectives: 1) to determine national rates of transfusion-transmitted bacteremia, 2) to identify pathogens and associated risk factors, and 3) to identify predictive factors for recipient mortality.

## MATERIALS AND METHODS

### Study design

In August 1997, personnel from AABB, ARC, DoD, and CDC developed case criteria, definitions, and standardized report forms for reporting of suspected transfusion-transmitted bacterial infections (Fig. 1). Methods were developed by consensus based on previous case reports from these organizations.[21,22] Educational materials for blood bank and clinical personnel, including didactic presentation materials and transfusion reaction work-up cards describing steps to evaluate, respond to, and report suspected cases, were sent to all AABB-, ARC-, and DoD-affiliated blood collection facilities. Materials also were made available on the Internet (http://www.cdc.gov/ncidod/hip/bacon). The study was conducted from January 1, 1998, through December 31, 2000.

**Fig. 1. BaCon Study Case Reporting outline.**

Characteristics of transfusion recipients and implicated components were collected through paper report forms. Participation of collection facilities was determined through mail-in survey at initiation of the study. Respondents were included as participants. Net distribution—that is, the number of units distributed subtracted from the number returned—was used to estimate the number of units transfused. Distribution data were collected from ARC monthly and from DoD quarterly. AABB distribution data were collected semi-annually through mail-in survey in 1998; National Blood Data Resource Center data were used to estimate changes in AABB component distribution in 1999 and 2000.[24] Pooled platelets were defined as composed of an average of 6-unit concentrates, which was estimated as the national average.[24]

Clinical criteria for further evaluation of potential cases of transfusion-transmitted bacteremia were the presence of any of the following signs or symptoms within 4 hours of transfusion: fever $\geq$39°C or a change of $\geq$2°from pretransfusion value, rigors, tachycardia $\geq$120 beats per minute or a change of $\geq$40 beats per minute from pretransfusion value, or a rise or drop of $\geq$30 mm Hg in systolic blood pressure. If an event met case criteria, personnel would record the pertinent transfusion reaction and recipient information, save the implicated blood component, and draw recipient blood for cultures. If cultures of the blood bag contents and the recipient's blood grew the same organism, isolates and implicated blood bags were transported to the CDC. If organisms from both the blood bag and recipient were identical by pulsed-field gel electrophoresis (PFGE), the event was included as a confirmed case. This study was approved by the institutional review board of the CDC.

### Statistical analysis

Data were collected on standardized forms, entered, and analyzed using software (EpiInfo 6.04, available from the CDC; SAS, SAS Institute, Cary, NC), [25] Fatal and nonfatal events

**TABLE 1. Number of units distributed, number of cases, number of fatalities, and estimated rate of transfusion-transmitted bacteremia by type of blood component, BaCon Study, January 1998-December 2000**

| | | Platelets | |
|---|---|---|---|
| | RBCs | Single-donor | Pooled |
| Units distributed | 23,711,169 | 1,804,725 | 1,033,671* |
| Cases (deaths) | 5 (3) | 18 (4) | 11 (2) |
| Cases per million units distributed (95% CI | 0.21 (0.03-0.40) | 9.98 (5.4-14.9) | 10.64 (4.4-16.9) |
| Fatalities per million units distributed (CI | 0.13 (0-0.27) | 2.22 (0.04-4.4) | 1.94 (0-4.62) |

* Average pool = 6 random-donor platelet concentrates.

were compared by using the likelihood ratio test or Fisher's exact test as appropriate for categorical variables and Wilcoxon's rank-sum test or the *t* test for continuous variables. OR, relative risk, and 95% CIs were calculated. Logistic regression was used to evaluate the independent effects of risk factors. The incidence density ratio (IDR) was used to calculate rates; IDR was defined as the number of cases divided by the number of blood component units distributed.

### Laboratory methods

Identification of organisms received on slanted media were confirmed by standard methods. Blood component bags sent to the CDC for culture were sampled by using a coupler placed in an outlet port; each sample was inoculated onto media or into broth by standard methods. When there was insufficient product for culture, the empty unit was cultured with 20 mL of 0.9-percent sodium chloride (USP grade; nonbacteriostatic) injected into the unit through the sampling-site coupler, and then the solution was inoculated directly into blood culture bottles. Endotoxin levels were determined by using the limulus amebocyte lysate test (Associates of Cape Cod, Falmouth, MA). PFGE was performed and interpreted using previously described methods.[26,27]

## RESULTS

During the study period, 35 AABB-, 36 ARC-, and 23 DoD-affiliated blood collection facilities participated. Collectively, these facilities made net distributions of 23,711,169 RBCs, 1,804,725 single-donor platelets (SDPs), and 1,033,671 pooled platelets from participating AABB, ARC, and DoD collection facilities over the study period, or approximately 60 to 70 percent of all blood components distributed nationally during the study period (Table 1).[24] These distributions resulted in 56 reports that met one or more clinical criteria for possible inclusion; 34 represented confirmed events.

Characteristics of cases are listed in Table 2. Patient signs and symptoms varied, but rigors, fever, and tachycardia were the most common (Table 3). Either fever or rigors were documented in 33 (97%) of 34 cases. The 34 implicated blood components associated with these reactions included SDPs (N = 18), pooled platelets (N = 11), and RBC components (N = 5). Platelets were associated with a significantly greater risk for transfusion-transmitted bacteremia (IDR, 49; CI, 28-83; p<0.0001) and death (IDR, 16; CI, 6-44; p = 0.0001) than were RBCs. Differences between event and death rates for SDPs and for pooled platelets were not significant. Of the 34 pathogens, 20 (59%) were gram-positive and 14 (41%) were gram-negative bacteria (Table 4). A Gram's stain of the implicated component was done in 28 cases; bacteria were visible by Gram's stain in 26 (93%). Implicated units were stored for a median of 4 days (range, 2-5) for platelets and a median of 22 days (range, 9-35) for RBCs. The difference in storage times for platelet units contaminated with gram-negative and

**TABLE 2. Characteristics of recipients and implicated components associated with transfusion-transmitted bacteremia, BaCon Study, January 1998-December 2000**

| Characteristics | Number (%) | Median (range) |
|---|---|---|
| Categorical | | |
| Sex (males) | 17 (50) | |
| Underlying illness | | |
| Leukemia | 11 (32) | |
| Other hematologic disorder | 10 (29) | |
| Solid tumor | 5 (15) | |
| Acute bleed | 5 (15) | |
| Other | 3 (9) | |
| Neutropenia | 8 (24) | |
| Location at transfusion | | |
| Inpatient ward | 13 (38) | |
| Outpatient | 13 (38) | |
| Intensive care unit | 7 (21) | |
| Operating room | 1 (3) | |
| Continuous | | |
| Recipient age (years) | | 48 (3-90) |
| Time from transfusion start to reaction (min) | | 45 (5-230) |
| Volume of implicated component transfused (cc) | | 150 (10-550) |

**TABLE 3. Signs and symptoms of 34 cases of transfusion-transmitted bacteremia, BaCon Study, January 1998-December 2000**

| Sign or symptom | Number (%) |
|---|---|
| Rigors | 30 (88) |
| Fever | 27 (79) |
| Tachycardia | 24 (75) |
| Nausea or vomiting | 14 (44) |
| Shortness of breath | 12 (35) |
| Decreased blood pressure | 15 (47) |
| Lumbar (low back) pain | 9 (26) |
| Increased blood pressure | 8 (24) |

**TABLE 4. Pathogens associated with confirmed transfusion-transmitted bacteremia, BaCon Study, January 1998-December 2000**

| Organisms | Number |
|---|---|
| Gram-positive (n = 20) | |
| *Staphylococcus epidermidis** | 8 |
| *Staphylococcus aureus* | 4 |
| *Streptococcus agalactiae* | 2 |
| Group G Streptococcus | 1 |
| *Staphylococcus lugdenensis* | 1 |
| *Staphylococcus saprophyticus* | 1 |
| *B. cereus* | 1 |
| *E. faecalis* | 1 |
| *Streptococcus pneumoniae* | 1 |
| Gram-negative (n = 14) | |
| *E. coli* | 5 |
| *Serratia marcescens** | 3 |
| *Serratia liquefaciens** | 2 |
| *Enterobacter aerogenes* | 1 |
| *Enterobacter cloacae* | 1 |
| *P. rettgeri* | 1 |
| *Y. enterocolitica* | 1 |

* Associated with RBC transfusions.

gram-positive organisms was significant (median storage time, 2.5 vs. 5 days; p<0.0001).

Upon posttransfusion inspection, 8 (24%) residual blood components were reported to be hazy or discolored. The implicated blood component was modified in 25 episodes (74%); of these components, 25 (74%) were WBC reduced and 13 (28%) were irradiated. None were washed, deglycerolyzed, or warmed. In 14 events (41%), the transfusion was not interrupted in response to the transfusion reaction. Ten patients (29%) were receiving antimicrobials at the time of transfusion, and all 34 patients received antimicrobials after the septic reaction to transfusion. Median time from reaction to receipt of antimicrobials was 120 minutes (range, 0-390). Neither receipt of antimicrobials before transfusion nor time to antimicrobial receipt after transfusion reaction was associated with survival.

Nine (27%) of the 34 reactions resulted in death; 3 involved RBCs, 4 SDPs, and 2 pooled platelet units. Death was associated with gram-negative organisms, older recipient, smaller volume transfused, shorter time from start of transfusion to reaction, and, for platelet transfusion, shorter storage time (2.5 vs. 5 days, p = 0.009) when each variable was analyzed separately (Table 5). On logistic regression, only gram-negative organisms were independently associated with death (OR, 7.5; CI, 1.3-64.2; p = 0.009); recipient age had some effect but was not significant (OR, 5.0; CI, 0.9-35.9; p = 0.07). Because storage time was closely correlated with the presence of gram-negative organisms, this variable was excluded from the final model. Endotoxin was present in the implicated component in all fatal cases caused by gram-negative organisms in which the component was available for testing (Table 6). Endotoxin levels in fatal and nonfatal cases were not significantly different.

## DISCUSSION

The BaCon Study is the largest prospective study to examine the frequency of and risk factors for transfusion-transmitted bacterial infection in the United States. Previously, estimates of the frequency of these infections have been largely based on summary case reports and anecdotal reports to the FDA. Moreover, detailed data concerning the epidemiology of transfusion-transmitted bacterial infection have previously not been systematically collected in a multicenter study in the United States.

Compared with viral agents, bacteria may be a more frequent cause of transfusion-transmitted infection, particularly in platelets. We estimate rates of transfusion-transmitted bacteremia of 1 in 100,000 units for SDPs and pooled platelets and of 1 in 5 million units for RBCs; we also estimate fatality rates of 1 in 500,000 units for SDPs and pooled platelets and of 1 in 8 million units for RBCs. In comparison, estimates calculated after implementation of pooled NAT in 2000 found the risk of transfusion-transmitted viral disease in the United States per units transfused to be less than 1 in

**TABLE 5. Risk factors for fatal transfusion-transmitted bacteremia, BaCon Study, January 1998-December 2000**

| | Fatal (N = 9) | | Nonfatal (N = 25) | | |
|---|---|---|---|---|---|
| | Number (%) | Median (range) | Number (%) | Median (range) | p values |
| Categorical factor | | | | | |
| Gram-negative organism | 7 (78) | | 7 (28) | | 0.009 |
| Continuous factors | | | | | |
| Platelet storage (days) | | 2.5 (2-4) | | 5 (2-5) | 0.009 |
| Time from start of transfusion to reaction (min) | | 23 (5-60) | | 60 (5-230) | 0.05 |
| Recipient age (years) | | 74 (17-90) | | 20 (3-84) | 0.05 |
| Volume (mL) | | 86 (20-215) | | 228 (10-550) | 0.02 |

**TABLE 6. Characteristics of components associated with fatal transfusion-transmitted bacteremia, BaCon Study, January 1998-December 2000**

| Implicated component | Organism | Storage days | Endotoxin level (eu*/mL) |
|---|---|---|---|
| SDP | Group B Streptococcus | 4 | NA† |
| SDP | *E. coli* | 2 | Unknown |
| SDP | *P. rettgeri* | 3 | 9,090 |
| SDP | *E. cloacae* | 3 | 408,000 |
| Pooled platelet | *S. marcescens* | 2 | Unknown |
| Pooled platelet | *S. marcescens* | 2 | 28,600 |
| RBC | *S. epidermidis* | 22 | NA* |
| RBC | *S. liquefaciens* | 35 | 13,000 |
| RBC | *S. liquefaciens* | 16 | 273,500 |

* Endotoxin-forming units.
† Endotoxin is produced only by gram-negative organisms.

100,000 for HBV, 1 in 500,000 for HCV, and 1 in 2 million for HIV, which suggests progressive risk reduction when compared with previous estimates.[5,28]

Efforts to determine the incidence of serious transfusion reaction due to bacterial contamination have been limited by either concerns over generalizability or a lack of standardized definitions for confirmation.[11] In the United Kingdom, the Serious Hazards of Transfusion (SHOT) initiative, a passive surveillance system, has reported four bacterial infections and one death over 2 years.[29] The French hemovigilance system, which requires reporting by law, has reported 16 deaths suspected to be due to transfusion-associated bacterial infection in a 2-year period.[30] Single-center studies have reported platelet transfusion reaction rates of 0.02 to 0.28 percent, with rates of <0.01 percent for RBCs.[31-33] In these single-center studies and national reporting systems, reactions were not required to be confirmed by matching component and recipient cultures, and molecular typing to ascertain relatedness was not done. As a result, transfusion-transmitted bacteremia could not be confirmed.

A lower incidence of transfusion reaction after the transfusion of SDPs than after that of pooled platelets has been suggested, but most studies have lacked sufficient power to demonstrate a difference.[31] BaCon Study results showed no significant difference between the rates of transfusion-transmitted bacterial infection associated with SDPs and that associated with pooled platelets. A much lower rate of SDP-associated septic transfusion reactions was shown in a recent study (SDP, 0.007% vs. pooled platelets, 0.04%; $p<0.0001$); however, because comparisons were made with historical data during a period in which the institution shifted to the almost exclusive transfusion of SDPs, it is possible that other factors may have contributed to this observation.[34]

The spectrum of agents reported as contaminating blood and blood components has been broad; greatest attention has been given to those associated with sepsis and death, including *Yersinia* and *Pseudomonas* species in RBCs and *Staphylococcus*, *Serratia*, and *Salmonella* species in platelet transfusions.[2,3,8] Etiologic agents in the BaCon Study were both gram-positive and gram-negative organisms, including *Staphylococcus* and *Streptococcus* species and members of the *Enterobacteriaceae*. Gram-negative organisms, particularly *Yersinia enterocolitica*, have been the cause of a high proportion of infections involving bacterially contaminated RBCs described in case reports. The risk of contamination by and proliferation of cryophilic gram-negative organisms in RBCs may be due to collection and storage conditions that increase endotoxin production and the risk of fulminant sepsis. Gram-negative organisms also were predominant in RBCs in the BaCon Study; however, *Serratia* species accounted for the majority of cases, and there was only one episode of contamination by *Y. enterocolitica*. *Staphylococcus* species were the most common organisms isolated in platelet units, followed by *Streptococcus* species; gram-negative organisms implicated included *Escherichia coli, Serratia* and *Enterobacter* species, and *Providencia rettgeri*. Most deaths associated with RBC or platelet transfusions were caused by gram-negative organisms.

As expected, overall, reactions from contaminated units of RBCs and platelets were significantly associated with prolonged storage time.[32] However, for platelet transfusion, deaths were more likely to be associated with components transfused earlier in storage than were nonfatal reactions. Most platelets associated with fatality were associated with gram-negative organisms and were transfused within 3 days of storage; in contrast, most platelets associated with nonfatal events were associated with gram-positive organisms and were transfused after 5 days of storage. The presence of endotoxin, which may arise rapidly in significant amounts within hours to a day after collection of a platelet unit contaminated with a gram-negative organism, most likely explains the association among gram-negative organisms, short storage time, and death.[35]

Blood component units inoculated with $10^1$ to $10^3$ bacteria can generate $>10^8$ organisms per cc during the time and under the conditions of current platelet storage.[36] The extension of allowable platelet storage time from 3 to 5 days in 1982, and to 7 days in 1983, improved the availability of platelets but was associated with an increased risk of transfusion reaction from bacterial contamination, which resulted in shortening of the allowable storage time to 5 days in 1986.[32] From our data, further shortening of storage time would not have a significant impact on deaths due to contaminated platelets, as only one death in our study would have been prevented if a 3-day storage time limit was used.

The BaCon Study has at least three primary limitations. First, cases of transfusion-transmitted bacteremia were defined to maximize positive predictive value. Reports in which recipient or blood component cultures either were not done or were negative, even if the patient was receiving antimicrobials at the time of blood cultures, were excluded. Second, not all United States blood collection facilities and transfusion services participated in the study. Although adjustment of the denominator for participation was designed to minimize the impact of missed reports on the estimation of incidence rates, nonuniform participation may have led to selection bias. Finally, despite efforts to improve the awareness of clinical personnel, events likely went undetected in participating centers because of a lack of recognition. Thus, our results may be substantial underestimates of the problem, particularly when compared with hospital-based, more intensive surveillance methods.

These data, if published estimates of the prevalence of component contamination are accurate, suggest that only a small percentage of contaminated units result in clinically diagnosed transfusion-transmitted bacteremia. Increased health care worker awareness about bacterial contamination as a potential cause of transfusion reactions can raise

the detection rate more than 20-fold.[18] Because signs and symptoms (including fever, rigors, and change in blood pressure) described in recipients of contaminated blood are similar to those expected from sepsis due to any cause, many clinicians may not consider bacterial contamination of the blood component in the differential diagnosis of transfusion reaction. Prompt recognition is critical, as diagnosis leads to the identification and recall of co-components that also may be contaminated. The clinical outcome of transfusion-associated sepsis may depend on a number of factors, including the type of organism, the immunocompetency of the recipient, and the promptness of antimicrobial therapy.[14,15] The lack of prompt antimicrobial therapy in these confirmed reports underscores the lack of understanding by clinical personnel of the underlying cause of these events; in more than half of these events, antimicrobial therapy was delayed for >2 hours after reaction onset. Study results did not show a correlation between the timing of antimicrobial therapy and survival; this may reflect the large proportion of fatal cases associated with measurable endotoxin. As alternative therapies for sepsis become available, promptness of treatment may be associated with improved outcome.[37]

Blood components can be contaminated by donor bacteremia, at collection through introduction of skin flora, or during processing.[16] Suggested approaches for reducing the incidence of transfusion-transmitted bacterial infection have included expansion of donor screening, improved donor skin antisepsis, discarding an initial aliquot of donated blood to reduce skin contaminants, limitation of component storage time or lowering storage temperature, diagnostic screening of components, and photochemical decontamination.[15,16,38-41] Although reducing skin contamination may reduce transfusion-transmitted infection by gram-positive organisms, BaCon Study results suggest that such measures are unlikely to prevent the majority of deaths, which are more likely associated with gram-negative organisms.

Future efforts will be directed toward continuing to improve clinical detection and reporting. In addition to the FDA requirement that fatal complications of blood collection or transfusion be reported, a separate regulation (21 CFR 600.14) now requires all blood collection facilities or transfusion services to report blood components contaminated with bacteria.[42] As new processing, detection, and reporting methods are implemented, it will be important to evaluate whether such changes improve the safety of the nation's blood supply.

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