Evolution of surveillance methods for detection of bacterial contamination of platelets in a university hospital, 1991 through 2004

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BACKGROUND: Platelet (PLT) bacterial contamination (PBC) is the most common transfusion-associated infection. It is important to understand the impact of interventions addressing this problem.

STUDY DESIGN AND METHODS: PBC was studied by prospective (active) and transfusion-reaction triggered (passive) surveillance from July 1991 to December 2004. Active surveillance, utilized for 10 years, included bacterial culture of all or 4- and 5-day-old PLTs at issue and intermittent use of Gram stain, pH measurements, and early (24-hr) culture of single-donor plateletpheresis (SDP) units.

RESULTS: Active surveillance detected 38 instances of PBC, 7 in SDP units (1:2213) and 31 in random-donor PLT units (1:2090 units, $p = 0.89$; or 1:418 pools of 5 units, $p < 0.001$). Contaminants were coagulase-negative staphylococci (CONS; n = 27), *Staphylococcus aureus* (4), *Bacillus cereus* (1), *Serratia marcescens* (2), streptococci (2 *S. bovis*, 1 *S. uberis*), and CONS with viridans group streptococcus (1). Only one instance of contamination, caused by *Pseudomonas aeruginosa*, was detected by passive surveillance, with fatal outcome. Colony counts of contaminants ranged from 0.5×10^2 to 4×10^{11} colony-forming units per mL at time of issue. PBC was interdicted before transfusion in 6 cases through Gram stain screening. Transfusion reactions occurred in 13 of 32 recipients (41%), with 9 severe reactions (28%) and 3 deaths (9%). pH testing failed to detect 5 contaminated units and resulted in discard of nearly 2 percent of units, whereas culture of SDP units at 24 hours failed to identify a contaminated unit.

CONCLUSION: Improved active surveillance methods for detecting PBC are needed to improve the safety of PLT transfusions.

Although considerable progress has been made detecting viral agents in blood products, bacterial contamination, primarily of platelets (PLTs), is an ongoing problem associated with significant transfusion-associated morbidity and mortality.[1-10] PLT transfusion–associated sepsis is now recognized as the most frequent infectious complication of transfusion therapy, surpassing by up to 2 orders of magnitude the incidence of transfusion-associated viral transmission.[1,11,12] PLT bacterial contamination (PBC) is a major problem because of the current requirement to store PLTs at room temperature to preserve PLT function.[13] At 22 to 24°C, bacteria grow more easily than under refrigeration, so that small bacterial inocula can grow into very high numbers within a short time period. Consequently, older units are most likely to have high bacterial inocula and therefore are more likely to result in sepsis in recipients.[14,15] When the allowable storage period of PLTs was extended from 5 to 7 days in 1984, there were an increased number of clinically evident PLT transfusion–associated

ABBREVIATIONS: CONS = coagulase-negative staphylococci; PBC = platelet bacterial contamination; RDP = random-donor platelet (units); SBA = sheep blood agar; SDP = single-donor plateletpheresis.

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septic events reported, with a predilection for the oldest transfused units. In 1986, following a discussion by the FDA Blood Products Advisory Committee, the storage time of PLTs was rolled back to 5 days.[10,16] In 2005, the FDA sanctioned use of leukoreduced apheresis PLTs stored for 7 days in an approved storage container provided that aerobic and anaerobic "release" cultures are procured from all units 24 to 36 hours after collection with an additional set of "study" cultures procured from all outdated units after 7 days of storage.[17,18]

Despite increasing attention, the reported prevalence of PBC is highly variable and has been difficult to generalize owing to the differing methods of bacterial detection used in studies as well as differences in case definitions. Most reports estimate that as many as 1 in 2000 to 3000 PLT units, both single-donor plateletpheresis (SDP) and random-donor PLT (RDP) units, are contaminated with bacteria.[1,5,6] Transfusion of a contaminated PLT unit is often not recognized or directly associated with subsequent sepsis. Based on the reported prevalence of transfusion reactions and the detection rate of contaminated PLT units, however, it is estimated that a severe episode of transfusion-associated bacterial sepsis occurs in connection with approximately 17 percent of contaminated units transfused.[1,5,6]

A major problem in determining the magnitude of the problem of PBC is the lack of recognition and reporting of cases, due in large measure to the failure to associate chills, rigors, and fever—signs and symptoms common in patients receiving PLT transfusion therapy—with the possibility of transfusion of a bacterially contaminated PLT unit.[19] More serious clinical events, such as shock and death occurring in immunocompromised PLT transfusion recipients, are likewise often not linked to transfusion of a bacterially contaminated PLT unit.

A patient death in our facility in December 1989, linked to contamination of an RDP pool with *Enterobacter aerogenes,* heightened our facility's awareness of the problem of PBC. This resulted in increasing numbers of transfusion reactions being reported in our institution and led to the detection of two index cases of PBC, one with *Pseudomonas aeruginosa* and the other with *Bacillus cereus* on June 27 and July 20, 1991.[20] This was followed by the introduction of an active surveillance program to determine the magnitude of the problem.[20] The goal of this surveillance program was to determine the incidence of bacterial contamination in PLT units used in our institution and to develop a useful PLT unit screening protocol to limit and eventually prevent transfusion of bacterially contaminated units. The surveillance methodology used evolved over a 14-year period, and is the most comprehensive study of this problem to date. This report summarizes these findings and describes the effectiveness of various surveillance and detection methods in identifying and preventing transfusion of bacterially contaminated PLT units.

MATERIALS AND METHODS

Patient population

The patients reported herein were treated between July 1991 and December 2004 at the University Hospitals of Cleveland (UHC), a 900-bed academic tertiary-care center. Patients underwent transfusion during the 14-year period of study with individual, whole blood–derived, RDP units, usually in pools of 5 units, and single-donor derived apheresis PLT (SDP) units. Most PLTs, as reported by other similar tertiary-care facilities,[21] were given to adult hematology-oncology patients, especially those undergoing allogeneic or autologous marrow transplantation, or to acute leukemia patients undergoing induction, reinduction, or consolidation chemotherapy.

PLT sources and preparation

During the study period, RDP and SDP units were procured from three outside blood collection facilities, with the majority of units obtained from two of these facilities. In addition, some SDP units were collected in the UHC Donor Apheresis Center. PLTs were generally supplied on a standing order basis with the oldest units issued first. Outdate time was 5 days for all PLT units.

Pooled RDP units were prepared for transfusion to adults by combining 5 individual units, with aseptic technique, into a single transfer pack (pool bag), with contents transfused within 4 hours. The nearly empty source PLT bags used in each pool were stored under refrigeration at 4°C within a plastic overwrap for future testing, if needed. SDP units were issued for transfusion without any further processing if supplied in one bag. If supplied as two conjoined bags, the contents of one was transferred into the other before transfusion. Dosing of PLT transfusions in children was based on body weight.

Surveillance methods

Passive surveillance (transfusion reaction–triggered). Transfusion reactions reported to the transfusion service were investigated by reviewing patient findings recorded in the medical and transfusion records, by direct patient interview and examination when indicated, and by culturing samples of remaining portions of transfusion components (see culture methods below). While passive surveillance was performed for the entire study period, it was the only surveillance method performed from March 2000 through February 2004 (Fig. 1).

Active surveillance (prospective methods)—I. July 1991 to February 2000. Active PLT unit surveillance began in July 1991 with a sample for culture being procured on all transfused PLTs at issue and, from August 1991, with Gram-stain of the aliquot being negative before the units were released for transfusion. Results of the cultures were

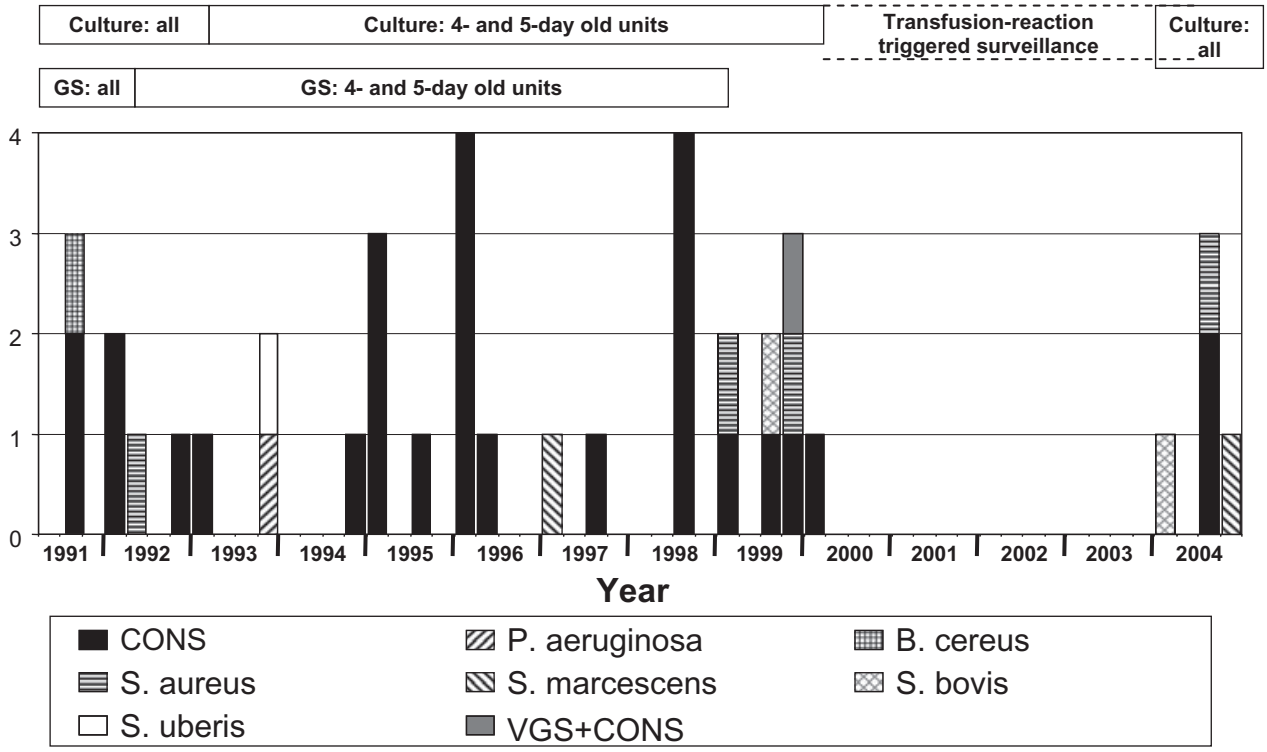

Fig. 1. Histogram of bacterial contaminants isolated during study period with surveillance procedures in use. Data are shown by quarter in each year. GS = Gram stain; CONS = coagulase-negative staphylococcus; VGS = viridans group streptococcus.

available only following transfusion. From June 1992 to February 1993, only high-risk pools—those with 4- or 5-day-old RDP units underwent Gram stain at issue, while all PLT pools had a culture performed. Starting in March 1993, only pools with 4- and 5-day-old units had both Gram stain and culture performed; this practice continued until January 1999, at which time at-issue Gram stain was discontinued (see Discussion). No active surveillance was performed during the period February 2000 through February 2004.

II. March 2004 to December 2004. Beginning in March 2004, to comply with new CAP and AABB requirements for a quality control (QC) program for testing of PLT units for bacterial contamination,[22-24] all transfused PLT products underwent a prospective surveillance procedure as follows:

1. *RDP units.* Beginning March 1, 2004, all RDP units underwent pH testing just before pooling, and samples of all RDP pools were procured for culture at time of issue.
2. *SDP units drawn in our facility.* From March 1, 2004, to July 31, 2004, all these units underwent pH testing at time of issue, with samples procured for culture at this time. The pH testing of SDPs procured in our facility was terminated on July 31, 2004, after a false-negative pH test result,[25] and replaced, beginning August 1, 2004, with a prospective culture method (see below), and samples from all these SDP units were cultured at time of issue.
3. *SDP units procured from outside vendors.* Beginning March 1, 2004, these units were tested by a culture method, either BDS/eBDS (Pall Corporation, Covina, CA) or BacT/ALERT (bioMérieux, Durham, NC), at the blood center before shipment to our facility. Samples from all these SDP units were cultured at time of issue.

Microbiologic procedures

Samples (1-2 mL) were removed from the PLT bags or pools at issue, with aseptic techniques, by blood bank personnel, and Gram stain and culture were performed by microbiology laboratory personnel as described below, with the remainder of each specimen stored at 4°C for further testing if required.

Gram stain. During periods of active surveillance requiring Gram stain before issue, dried smears of PLT specimens were prepared from 10 to 15 µL of specimen spread over an area of about 5 cm^2 on a glass microscope slide. These smears were stained according to standard methods, examined microscopically for 3 to 5 minutes at 1000× magnification under oil and interpreted as follows:

negative, <1 organism per 20 fields; 1+, 1 organism per 10 to 20 fields; 2+, 1 organism per field; 3+, 2 to 10 organisms per field; and 4+, >10 organisms per field. In instances where cultures were positive and Gram stains were negative, the entire area of the Gram stains was reviewed. During periods of passive surveillance Gram stains were only performed in instances where cultures were positive on the aliquot stored at 4°C. An interpretation of "rare bacteria seen" was used if rare bacteria morphologically consistent with culture findings were detected on Gram stains performed retrospectively or reviewed retrospectively.

Culture. For active surveillance, aliquots from PLT units were cultured by inoculating a 5 percent sheep blood agar (SBA) plate (trypticase soy base) with 0.1 mL of the aliquot with a calibrated pipette and incubating for up to 48 hours in 5 percent CO_2 at 35°C. For passive surveillance, transfusion reactions were investigated by inoculating the following media with 0.1 mL aliquots from saved PLT units with a calibrated pipette: a SBA and a chocolate agar plate, incubated in 5 percent CO_2 at 35°C; a second SBA plate, incubated aerobically at room temperature; and a thioglycolate broth incubated at 35°C. All positive cultures were verified by isolation of the same organism on repeat culture from the same source. If bacteria were detected on the Gram stain or culture, a quantitative culture was prepared from the aliquot and the remnants of the contents of source PLT bags using multiple serial 1-in-10 dilutions, with inocluation of plates with 0.1 mL volumes. The detection limit of plate cultures was 10 colony-forming units (CFUs) per mL, and quantitative endpoints were determined from dilutions yielding 30 to 300 colonies. Isolates were identified to the species level and antibiotic susceptibilities determined with standard methods.

pH testing. pH testing was performed on all PLT units with a pH meter (IQ120 miniLab pH meter, Scientific Instruments, San Diego, CA) just before pooling RDPs or just after combining SDP portions from an aliquot obtained from a segment of thrice stripped tubing sealed with a heat sealer and separated from the unit with scissors and placed in a test tube. A drop was then placed onto the probe of the pH meter, covering both the reference junction and the pH sensor. Units with pH values of 6.6 or higher were interpreted as acceptable for use, whereas those with pH values of less than 6.6 were interpreted as unacceptable and were discarded.[25,26]

Statistical analysis

Differences in prevalence were tested by the Fisher exact method, and differences in bacterial counts were compared by the t test. p Values of less than 0.05 were regarded as significant. Sensitivity and specificity analyses of test effectiveness were determined by the predictive value model.[26,27]

RESULTS

Index cases of PBC, June to July 1991

Heightened awareness of bacterial contamination of PLTs in response to a patient death in December 1989 resulted in the subsequent detection of two additional cases of contamination—referred to as index cases—in patients with transfusion reactions.[20] The first contaminant was *P. aeruginosa* and the second *B. cereus*, and these were detected in products transfused on June 27 and July 20, 1991, respectively. An active surveillance program was then initiated by culturing all PLT products at issue. Two additional instances of contamination, one with *Staphylococcus epidermidis* and the other with *B. cereus*, were detected 9 days later. These four cases were investigated by the CDC and FDA, and no deficiencies in procedures or common sources could be identified.[20,28] It was concluded that this cluster was most likely associated with heightened awareness and initiation of culturing of all PLT products at issue. Continued culture surveillance of PLT units was recommended by the CDC to identify the magnitude of the problem, to treat affected patients appropriately, and to identify risk factors.

PLT utilization

During the entire surveillance period, 216,283 PLT units were utilized, of which 48,067 were SDP units and 168,216 were RDPs issued in approximately 33,637 pools. Distribution of SDP and RDP transfusions by year is shown in Table 1. The proportion of transfusions with SDP units compared to RDP pools increased from 33 to 46 percent during 1991 to 1993 to 60 to 72 percent during 2000 to 2004. The evolution of surveillance methods used and instances of bacterial contamination detected are shown in Table 2 and Fig. 1.

Bacterial contamination detected by active surveillance

A total of 57,040 PLT units or pools (32,199 SDP and 124,180 RDPs in 24,836 pools) were issued for transfusion during the 10-year period where active surveillance was performed. Aliquots from 28,454 SDP units or RDP pools (49.9%; 15,493 SDP and 12,961 RDP pools) were obtained for culture (Table 3). Thirty-eight instances of bacterial contamination, confirmed by repeat isolation (see Materials and methods), were detected, 7 in SDP and 31 in RDP units (Tables 2 and 3). Details of the bacterial species and inocula found at time of issue in the contaminated units are shown in Table 2, and the distribution of contaminants over time is shown in Fig. 1. In all instances of contamination of RDP pools, contamination was traced to only a single unit in the pool. In an additional five instances cultures were initially positive with scant growth, but were

TABLE 1. Number of units transfused and number bacterially contaminated, by year and unit type, June 1991 to December 2004*

	Number of units transfused				Number bacterially contaminated	
Year	SDP units	RDP units	RDP pools†	Percent SDP‡	SDP	RDP
1991§	1,238	7,241	1,448	46.1	0	3
1992	2,414	16,480	3,296	42.2	0	4
1993	2,214	22,188	4,437	33.3	1	2‖
1994	3,775	14,635	2,927	56.3	0	1
1995	3,478	9,211	1,842	65.4	2	2
1996	3,478	7,678	1,535	69.4	0	5
1997	3,541	6,351	1,270	73.6	0	2
1998	3,638	13,804	2,760	56.9	0	4
1999	3,745	17,823	3,564	51.2	2	5
2000	4,239	14,037	2,807	60.2	0	1
2001	4,039	8,922	1,784	69.4	0	0
2002	4,116	10,408	2,081	66.4	0	0
2003	3,474	10,649	2,129	62.0	0	0
2004	4,678	8,789	1,757	72.7	2	3
Total	48,067	168,216	33,637	58.8	7	32

* Samples were obtained for culture at time of issue on all units and pools for 2 years 6 months (July 1991-February 1993) and on 4- to 5-day-old units and pools for 6 years 11 months (March 1993-January 1999 and March 2004-December 2004). No active microbiologic surveillance was performed during the period March 2000-February 2004.
† Based on 5 RDP units per pool.
‡ SDP transfusions as percentage of SDP units and RDP pools transfused.
§ 1991 surveillance began in July, and numbers of units transfused are from July to December for that year.
‖ One detected by passive surveillance.

negative upon repeat investigation and deemed to be false-positive. The contamination rate for RDP products based on number of transfusions (1:418) was significantly higher than that for SDP units ($p < 0.001$; Table 3). Contamination rates, however, based on numbers of SDP units cultured and numbers of RDP units used in pools, were 1:2213 SDP units (0.045%) and 1:2090 RDP units (0.048%); these rates were not significantly different ($p = 0.89$).

Bacterial contamination detected by passive surveillance

Of the 48,067 SDP units and 168,216 RDP units issued in 33,637 pools during the entire 14-year study period, only one instance of bacterial contamination was detected by passive surveillance, caused by *P. aeruginosa* contaminating a 3-day-old RDP unit used to make up a pool (Table 2; the index cases referred to in the introduction are not included in this analysis as they preceded initiation of surveillance). The contaminated unit did not meet the age-based prospective screening criteria in use at the time, but was detected upon investigation of the PLT bags after a transfusion reaction was reported.

During the 4 years, from March 2000 to February 2003, during which investigation was limited to clinically apparent transfusion reactions reported to the blood bank, no bacterially contaminated PLT units were detected, despite investigation of 237 PLT transfusion reactions during this period and 800 over the entire study period. The most common reaction noted was the combination of chills and rigors, but hypotension, fever, back pain, and respiratory distress were also reported. Culture of the returned PLT unit bags showed bacterial growth in only the one instance described above.

Gram stain results. Bacteria were detected by Gram stain of PLT aliquots obtained at time of issue, performed prospectively as well as retrospectively, in 20 of the 39 bacterially contaminated products (Table 2). During periods of active surveillance where Gram stains were performed prospectively at time of product issue, during which 24 of these products were found to be bacterially contaminated by culture, 16,477 Gram stains were performed, with 6 true-positive (Table 2), 16 false-negative, and 3 false-positive results (Table 4). PLT transfusion was interdicted before issue in the 9 instances where Gram stains were positive (i.e., the 6 true-positive and the 3 false-positive instances). Retrospective review of the 16 false-negative cases confirmed 14 as negative, detected rare organisms in 1 case, and showed 4+ bacteria in the last case, which was traced to inadequate mixing of a pool of 5 RDP units before obtaining an aliquot for Gram stain and culture. Correlation between Gram stain results and quantitative bacterial counts showed that Gram stain was positive in 19 of the 21 instances (90%) where bacterial counts were greater than 10^5 CFUs per mL and negative in 17 of the 18 (94%) instances where bacterial counts were less than 10^5 CFUs per mL (Fig. 2).

Gram stains of aliquots from the 14 additional culture-positive cases detected by active surveillance during periods where Gram stains were not required before issue

TABLE 2. Surveillance methods used and details of the 39 confirmed instances of bacterially contaminated units identified during the study period 1991 through 2004*

Surveillance method (at issue unless noted)	Date	Unit type	Contaminated unit age (days)	Organism	Gram stain	Organism quantitation (CFUs/mL)†	Unit transfused	Transfusion reaction
Jul 1991 (1 month)	Jul 1991	Pool	5	*B. cereus*	4+	2.0×10^6	Yes	Yes
Culture all	Jul 1991	Pool	5	CONS	4+	2.5×10^8	Yes	No
Aug 1991-May 1992 (10 months)	Sep 1991	Pool	5	CONS	4+	4.0×10^{11}	No‡	
Gram stain all	Jan 1992	Pool	5	CONS	4+	8.0×10^6	No‡	
Culture all	Mar 1992	Pool	2	CONS	Negative	5.0×10^1	Yes	No
Jun 1992-Feb 1993 (10 months)	Jun 1992	Pool	3	*S. aureus*	Negative	1.0×10^3	Yes	No
Gram stain if day 4 or 5	Nov 1992	Pool	3	CONS	Negative	1.0×10^4	Yes	Yes
Culture all	Jan 1993	Pool	5	CONS	4+§	2.4×10^{11}	Yes	Yes
Mar 1993-Jan 1999 (5 years 10 months)	Oct 1993	Pool	3‖	*P. aeruginosa*	2+	1.1×10^6	Yes	Yes
Gram stain if day 4 or 5	Oct 1993	SDP	4	*S. uberis*	Negative	5.6×10^6	Yes	No
Culture if day 4 or 5	Dec 1994	Pool	4	CONS	2+	9.0×10^7	No†	
	Jan 1995	Pool	5	CONS	2+	1.6×10^7	No†	
	Feb 1995	SDP	4	CONS	Negative	2.0×10^3	No¶	
	Mar 1995	SDP	4	CONS	Negative	1.0×10^4	Yes	No
	Jul 1995	Pool	4	CONS	2+	1.1×10^9	No‡	
	Feb 1996	Pool	4	CONS	Negative	1.0×10^2	Yes	Yes
	Mar 1996	Pool	2**	CONS	Negative	1.6×10^3	Yes	No
	Mar 1996	Pool	5	CONS	4+	5.0×10^7	No‡	
	Mar 1996	Pool	4	CONS	Negative	6.0×10^2	Yes	No
	Apr 1996	Pool	4	CONS	Negative	3.0×10^3	Yes	No
	Feb 1997	Single RDP	4	*S. marcescens*	Rare	5.0×10^8	Yes	No
	Jul 1997	Pool	4	CONS	Negative	2.4×10^4	Yes	No
	Jul 1998	Pool	4	CONS	Negative	9.5×10^2	Yes	No
	Jul 1998	Pool	5	CONS	Negative	2.5×10^2	Yes	No
	Jul 1998	Pool	5	CONS	Negative	8.0×10^1	Yes	No
	Jul 1998	Pool	4	CONS	Negative	1.4×10^3	Yes	No
	Jan 1999	Pool	5	CONS	Negative	1.6×10^4	Yes	No
Feb 1999-Feb 2000 (1 year, 1 month)	Feb 1999	Pool	4	*S. aureus*	Negative	5.6×10^3	Yes	Yes
No Gram stain	Jul 1999	SDP	5	*S. bovis*	2+	9.0×10^6	Yes	Yes
Culture if day 4 or 5	Sep 1999	SDP	5	CONS	1+	2.0×10^4	Yes	No
	Oct 1999	Pool	5	CONS	4+	1.0×10^8	Yes	Yes
	Nov 1999	Pool	4	*S. aureus* (MRSA)	4+	1.6×10^8	Yes	Yes
	Dec 1999	Pool	4	VGS + CONS	Negative	VGS, 1.1×10^3 CONS, 4.0×10^2	Yes	No
	Feb 2000	Pool	5	CONS	4+	4.8×10^9	Yes	No
Mar 2004-Jul 2004	Mar 2004	Pool	5	*S. bovis*	2+	1.2×10^6	Yes	Yes
pH at issue, RDP and SDP (5 months)	Jul 2004	SDP	5	*S. aureus*	Rare	1.3×10^6	Yes	Yes
Culture all	Jul 2004	Pool	5	CONS	Rare	4.6×10^5	Yes	Yes
Aug 2004-Dec 2004 (5 months), culture SDP at 24 hr	Sep 2004	Pool	3	CONS	Negative	3.0×10^2	Yes	No
pH at issue RDP, culture all	Dec 2004	SDP	4††	*S. marcescens*	2+	8.50×10^7	Yes	Yes

* Thirty-eight instances were detected by active surveillance and one by passive surveillance. VGS = viridans group streptococcus.
† In contaminated unit or pool.
‡ Not transfused due to positive Gram stain.
§ Gram stain originally negative due to technical error.
‖ Found by passive surveillance; unit was less than 4 days old.
¶ Not transfused for unrelated reasons.
** Other units in pools were 4 days old.
†† Culture performed when unit was 24 hours old was negative.

TABLE 3. Number of instances and rates of bacterial contamination detected by active surveillance, and number of cases and rates of transfusion reactions and bacteremia for PLT transfusions by transfusion episode and by PLT unit for all PLT transfusions*

		RDP units				
Variable	SDP units	Per unit	p Value†	Per pool	p Value‡	All transfusions§
Bacterial contamination‖	7/15,493 (1:2,213)	31/64,805 (1:2,090)	0.89	31/12,961 (1:418)	<0.001	38/28,454 (1:749)
Contaminated units transfused¶	6/48,067 (1:8,011)	26/168,216 (1:6,470)	0.68	26/33,637 (1:1,294)	<0.001	32/81,704 (1:2,556)
Transfusion reaction¶	3/48,067 (1:16,022)	10/168,216 (1:16,822)	0.75	10/33,637 (1:3,364)	0.01	13/81,704 (1:6,285)
Bacteremia¶	1/48,067 (1:48,067)	6/168,216 (1:28,036)	0.66	6/33,637 (1:5,606)	0.02	7/81,704 (1:11,672)

* Data are reported as number of cases (rate).
† p Value by Fisher exact method for RDP units compared to SDP units.
‡ p Value by Fisher exact method for RDP pools compared to SDP units.
§ Based on total of SDP unit and RDP pool transfusions.
‖ Numerators used for these calculations are the number of cases detected by active surveillance, while denominators are the numbers of PLT units and/or pools cultured during active surveillance.
¶ Numerators used for these calculations are the number of cases detected by active and passive surveillance, while denominators are the number of PLT units and/or pools transfused. Note that 7 of the 38 contaminated units identified by active surveillance were not transfused, while the contaminated unit detected by passive surveillance is included in these calculations, resulting in transfusion of 32 contaminated units.

TABLE 4. Details of findings in patients with transfusion reactions (n = 13) or asymptomatic with positive blood cultures (n = 2) or leukocytosis (n = 1) after transfusion of bacterially contaminated PLTs

Date	Unit type	Contaminated unit age (days)	Organism	Gram stain	Organism quantitation (CFU/mL)	Transfusion reaction	Transfusion reaction features
Jul 1991	Pool	5	*B. cereus*	4+	2.0×10^6	Yes	Transfusion stopped due to rigors and fever
Jul 1991	Pool	5	CONS	4+	2.5×10^8	No	Asymptomatic, but positive blood culture
Nov 1992	Pool	3	CONS	Negative	1.0×10^4	Yes	Fever, hypotension several hours after transfusion
Jan 1993	Pool	5	CONS	4+†	2.4×10^{11}	Yes	Fever, hypotension during transfusion, positive blood culture
Oct 1993	Pool	3‡	*P. aeruginosa*	2+	1.1×10^6	Yes	Hypotension, multiorgan failure; died 5 days later
Feb 1996	Pool	4	CONS	Negative	1.0×10^2	Yes	Delayed fever (5 hr)
Feb 1997	Single RDP	4	*S. marcescens*	Rare	5.0×10^8	No	Asymptomatic leukocytosis in 10-day-old 800-g premature infant with multiple medical problems, on gentamicin at time of transfusion
Jul 1998	Pool	4	CONS	Negative	1.4×10^3	No	Asymptomatic, but positive blood culture
Feb 1999	Pool	4	*S. aureus*	Negative	5.6×10^3	Yes	Delayed fever, positive blood culture
Jul 1999	SDP	5	*S. bovis*	2+	9.0×10^6	Yes	Fever, hypotension
Oct 1999	Pool	5	CONS	4+	1.0×10^8	Yes	Rigors, positive blood culture
Nov 1999	Pool	4	*S. aureus* (MRSA)	4+	1.6×10^8	Yes	Fever, hypotension during transfusion, but patient was hypotensive and unstable before transfusion was started and died later that day
Mar 2004	Pool	5	*S. bovis*	Positive	1.2×10^6	Yes	Delayed chills, rigors, and fever
Jul 2004	SDP	5	*S. aureus*	Rare	1.3×10^6	Yes	Delayed fever, hypotension, positive blood culture
Jul 2004	Pool	5	CONS	Rare	4.6×10^5	Yes	Fever, hypertension, positive blood culture
Dec 2004	SDP	4	*S. marcescens*	2+	8.5×10^7	Yes	Fever, hypotension, multiorgan failure in 700-g premature infant; death after 3 days

* Fifteen cases were detected by active surveillance and 1 by passive surveillance. VGS = viridans group streptococcus.
† Initially negative due to technical error.
‡ Detected by passive surveillance.

were positive in 9 instances, with only rare organisms being detected in 2 cases (Table 2). Gram stain of the 1 case detected by passive surveillance was positive.

Bacterial species isolated. Coagulase-negative staphylococci (CONS) was the most frequently isolated bacterial species (n = 27), followed by *Staphylococcus aureus* (4), *B. cereus* (1), *P. aeruginosa* (1), *Streptococcus bovis* (2), *Serratia marcescens* (2), and *Streptococcus uberis* (1) and 1 case of viridans group streptococci with CONS. Table 2 and Fig. 1 show details of each case of bacterial contamination of PLT units, including type and age of unit, bacterial counts, Gram stain result, and whether there was a

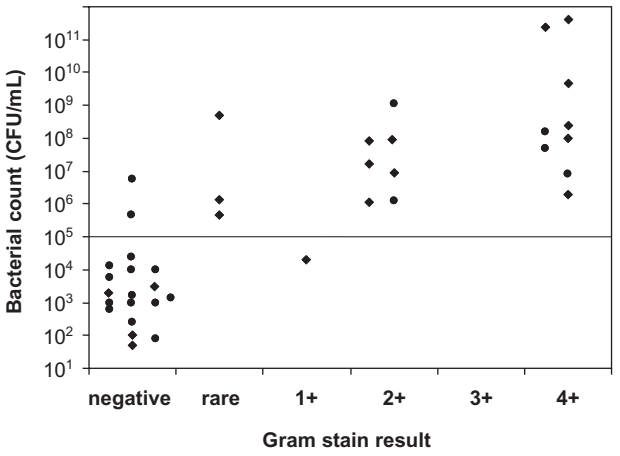

Fig. 2. Correlation of bacterial counts in PLT units with Gram stain findings.

transfusion reaction in the recipient. Donors were contacted and advised to obtain medical consultation when *S. bovis* and methicillin-resistant *S. aureus* were isolated.

Bacterial counts. The counts ranged from 0.5×10^2 to 4×10^{11} CFUs per mL. The 13 transfused units associated with transfusion reactions had mean counts of 2.2×10^6 CFUs per mL compared to 1.6×10^4 CFUs per mL for the 19 transfused units not associated with a transfusion reaction ($p = 0.0185$, by t test).

Correlation between receipt of bacterially contaminated units with transfusion reactions and bacteremia: Of the 38 contaminated units or pools detected by active surveillance in this study, 6, as noted above, were not transfused because of a positive Gram stain result before issuing the units and 1 additional contaminated unit was not used for other reasons. Thirty-one contaminated units detected by active surveillance and 1 additional unit detected by passive surveillance were transfused (Table 2). Based on all transfusions, 1:2533 transfusions was contaminated with bacteria, with RDP pool transfusions more likely to be contaminated than SDP unit transfusions (1:1294 vs. 1:8011; $p < 0.001$). In all but the case identified by passive surveillance and 2 of the cases identified by active surveillance, signs and symptoms attributable to a transfusion reaction were associated with the transfusion only following knowledge that the PLT product was culture-positive. Knowledge that the PLT products were culture positive and/or signs and symptoms of sepsis not initially attributed to transfusion of a bacterially contaminated PLT product triggered the procurement of blood cultures in all cases. The same isolate contaminating the PLT unit was isolated from blood cultures in 7 instances. Many patients, however, were receiving antimicrobials during and following PLT transfusions, resulting in negative blood cultures despite severe reactions in some cases. Thirteen of the patients who received these 32 contaminated units (41%) developed transfusion reactions, including 5 cases that had posttransfusion positive blood cultures with the same isolates found in the contaminated units (*S. aureus* in two cases and CONS in 3 cases). Two asymptomatic patients had positive blood cultures, both with CONS, and 1 asymptomatic patient developed leukocytosis after transfusion of a unit contaminated with *S. marcescens*. Severe transfusion reactions, based on transfusion being stopped due to a reaction or development of hypotension, occurred in 9 cases (28.1%). Transfusion reaction rate, based on all transfusions, was significantly higher in patients receiving RDP pools than in patients receiving SPD units (1:3364 vs. 1:16,022; $p = 0.01$; Table 3). The bacteremia rate was also significantly higher in RPD pool transfusions than in SDP transfusions (1:5606 vs. 1:48,067; $p = 0.02$). The higher rates in RDP pool transfusions were attributable to use of pools of 5 RDP units because rates were not significantly different based on individual PLT units (Table 3). Three patients died of complications likely to be associated with the transfusion of contaminated PLTs. In these cases, the PLT units were contaminated with *P. aeruginosa*, *S. aureus,* and *S. marcescens*. The first death occurred in October 1993 in a 39-year-old male with multiple myeloma who received a PLT transfusion contaminated with *P. aeruginosa* and developed septic shock and multiple organ failure. The second death occurred in November 1999 in a 54-year-old man with terminal refractory lymphoma who received a unit contaminated with methicillin-resistant *S. aureus*.[29] The third death was in a 700-g premature infant who received two aliquots on subsequent days of a SDP unit in December 2004 contaminated with *S. marcescens* and developed septic shock.[25,30] The signs and symptoms of transfusion reactions, and the associated organisms, observed among the other 10 patients were fever (5 cases, with delayed onset of fever in 3 cases, *B. cereus* [1], *S. bovis* [2], CONS [2]); delayed fever and bacteremia (2 cases), both *S. aureus*; rigors and posttransfusion bacteremia (1 case), CONS; hypotension and bacteremia (1 case), CONS; and hypertension and bacteremia (1 case), CONS. Nineteen patients (59%) who received bacterially contaminated PLTs (15 CONS; 1 each *S. aureus*, *S. uberis*, and *S. marcescens;* and 1 combined viridans group streptococci and CONS) did not present with any transfusion reaction and continued to be asymptomatic for at least 7 days.

Association of Gram stain results, bacterial species, and bacterial inocula with transfusion reactions

Thirty-two of the 39 contaminated units were transfused, and 13 (41%) of the recipients presented with a transfusion reaction or complication related to the transfusion of contaminated PLTs. In 10 (77%) of the 13 patients who had transfusion reactions, the Gram stain was positive for the PLT unit transfused, whereas 4 of the 19 patients who had

no transfusion reactions (21%) received PLT units with a positive Gram stain ($p < 0.005$, by Fisher's exact test). Nine of the 13 (69%) transfusion reactions were associated with bacterial counts of greater than 10^6 CFUs per mL, compared to only 4 of 19 (21%) not associated with transfusion reactions ($p < 0.01$, by Fisher's exact test). The virulence of the contaminant appeared to be more important than bacterial load, however, with transfusion reactions occurring in 8 of 10 instances involving highly virulent contaminants (*P. aeruginosa*, *S. marcescens*, *S. aureus*, *S. bovis,* and *B. cereus*) compared with 5 of 22 instances involving contaminants of low virulence (CONS and viridans group streptococci; $p < 0.005$, by Fisher's exact test). Transfusion of units contaminated with CONS, however, were associated with transfusion reactions, including fever, rigors, and hypotension, with reactions occurring with organism loads of as low as 10^2 CFUs per mL (Table 3).

pH determination. pH was determined on 6590 RDP units just before pooling from March 1, 2004, to December 31, 2004, and from 671 SDP units, collected by our donor center, at issue from March 1, 2004, to July 31, 2004. Cultures were positive on 3 RDP and 1 SDP units, while pH was within the acceptable range in these cases (Table 4). pH values, however, were below the acceptable range for 143 units (1.97%), which were discarded; none of these units was found to be contaminated on culture.

Early culture of SDP units. From August 1 through December 31, 2004, a total of 596 SDP units collected on site were cultured by the same method used at issue when units were 24 hours old. None of these early cultures were positive, while culture at time of issue was positive in one instance, with *S. marcescens* isolated when the unit was issued on Day 4 (Table 2).

Sensitivity and specificity of detection methods used

While specificity and negative predictive value of all methods used were high, sensitivity and positive predictive value varied considerably (Table 5). Passive surveillance detected only 1 of 32 transfused contaminated units (sensitivity, 0.031), whereas no instances of contamination were found in 799 patients with reported transfusion reactions (positive predictive value, 0.001). Active surveillance by culture at time of issue detected 38 of 39 contaminated units (sensitivity, 0.974; positive predictive value, 0.826). Gram stain performed prospectively had low sensitivity (0.27) but reasonably high positive predictive value (0.667). The sensitivity and positive predictive value of pH determination was 0. Gram stain and pH determination, the only methods used that provided results shortly before units were transfused, both have low sensitivity. Prospective plate cultures on SDP units at 24 hours after collection showed sensitivity of 0 and specificity of 1. Because only 596 SDP units were tested by plate culture with no true positive samples, however, the reliability of the sensitivity and specificity values obtained for this method are limited, and positive predictive value could not be calculated because no true-positive samples were found.

TABLE 5. Sensitivity and specificity of various methods for detection of bacterially contaminated PLTs

Variable	Gram stain*	pH†	Active surveillance by at-issue culture‡	Passive surveillance§	SDP culture at 24 hr
Number tested	16,477	7,261	28,454	81,704	596
SDP	8,761	671	15,493	48,067	596
RDP	7,716‖	6,590¶	12,961‖	33,637‖	0
True-positive	6	0	38	1	0
True-negative	16,452	7,113	28,407	80,873	595
False-positive	3	143	8	799	0
False-negative	16	5	1	31	1
Sensitivity	0.27	0	0.974	0.031	0
Specificity	>0.999	0.98	>0.999	0.99	1
PPV	0.667	0	0.826	0.001	**
NPV	0.999	0.999	>0.999	>0.999	0.998

* Data shown for results of Gram stains performed prospectively on aliquots from SDP units and PLT pools before release of PLT products.
† Data shown for results of pH testing performed prospectively on aliquots from SDP units and individual RDP units before release of PLT products.
‡ Data shown for results of bacterial culture performed prospectively on aliquots from SDP units and RDP pools at time of issue of PLT products. True-positive samples were those confirmed by repeat culture of the original product, whereas false-positive samples were those not confirmed by repeat culture of the original product.
§ Data shown for results of passive surveillance, with total number of SDP units and RDP pools issued during the entire study period as the basis for these calculations.
‖ Number of RDP pools
¶ Number of RDP units.
** Undefined because there were no true-positive results.

DISCUSSION

No currently available screening technology is perfectly sensitive and adequately rapid for determining the bacterial contamination status of PLTs at the time of transfusion. Detection of PBC by culture at time of use is the most sensitive method and provides the gold standard against which all other tests are measured.[9,19] Nonetheless, with a 24- to 48-hour incubation period, it is mostly useful as a retrospective test. Screening methods for bacterial detection with culture methods, with samples from PLT units procured early in the storage period, typically 24 hours after donation and then held for an additional 24 hours, are presently available. Two commercial culture methods applicable for PBC screening are currently FDA cleared for QC testing in the United States, BacT/ALERT and Pall BDS and eBDS.[31-33] These systems, however, have not detected all contaminated units in clinical use.[33,34] Gram stain at issue is a rapid test, but requires a minimum of 10^5 to 10^6 organisms per mL to be positive, as well as considerable expertise and time to perform accurately.[19] A method for direct detection of bacteria labeled with a fluorescent dye and scanned with a laser-based, solid-phase scanning cytometry method, the Scansystem (Hemosystem, Marseille, France), applied to leukoreduced PLT aliquots, has recently been licensed in the United States and is suitable for use at time of issue.[35] This method has been shown to reliably detect PBC at inocula of 2.05×10^1 to 1.05×10^8 CFUs per mL with comparable sensitivity to a commercially available early culture method.[36] Testing for pH and/or glucose content at issue are methods that are theoretically promising,[26] but have proved, especially with pH testing, in the clinical setting, to be unable to detect several contaminated units while leading to unnecessary discarding of uncontaminated units[25] as we also demonstrated. Several methods for at-issue detection of PBC are being developed based on detection of common bacterial antigens or gene products.[37,38]

The study described here is unique as it is the first long-term prospective surveillance study of bacterial contamination of PLTs reported in the literature. This surveillance program lasted for 14 years and, for more than half of the study period, Gram stain results were available before PLTs units were issued for transfusion. During the entire surveillance period documented in this study, 39 bacterially contaminated PLT units were detected, 38 by active surveillance and 1 by passive surveillance. In 7 of these cases, units were not transfused, 6 due to positive Gram stain results and 1 for other reasons. In 32 cases, the contaminated units were transfused; transfusion reactions occurred in 13 (41%) patients with fatal outcomes in 3 (9%). Our data provide, for the first time, the correlation between receipt of bacterially contaminated units, transfusion reactions, and positive blood cultures. We noted, however, that bacteremia did not correlate with transfusion reactions, with two bacteremic patients showing no other features of a transfusion reaction, and bacteremia was not documented in the three patients with fatal outcomes. The absence of bacteremia was likely related to patients receiving antimicrobial agents and delays in obtaining blood cultures after transfusion. Additionally, we show that bacterial contamination, transfusion of contaminated units, transfusion reactions, and bacteremia rates for RDP pool transfusions were significantly higher than those for SDP unit transfusions. We also documented that these differences are associated with the use of pools of 5 RDP units per transfusion because these rates were not different based on number of individual PLT units transfused. Our study also demonstrates the superiority of active surveillance over passive surveillance in detecting PBC, with 38 of the 39 instances of PBC being detected only by active surveillance. Although we used a relatively insensitive culture method (plate culture with a detection limit of 10 CFUs/mL, rather than broth culture, which can detect lower levels of contamination) at time of issue and did not include culture under anaerobic conditions, our incidence of contamination was similar to that reported in the literature.[19] Although our experience also highlights the finding that the vast majority of transfusion reactions with signs and symptoms consistent with sepsis are not due to PBC, paradoxically it demonstrates that the majority of patients who received bacterially contaminated PLT units and developed signs and symptoms of sepsis were not recognized or reported to the blood bank or transfusion service for further evaluation.

Our study reveals limited success in prevention of PBC by performing a Gram stain at the time of issue, which was predominantly performed on "high-risk" 4- and 5-day-old products. Nonetheless, six RDP pools with positive Gram stain findings were detected and interdicted before transfusion during the 7.5 years that this method was in use. Despite its partial success, use of Gram staining was terminated after much consideration in 1999 based on its labor-intensive nature, logistic issues of relocation of the blood bank away from the microbiology laboratory, and failure of this method to detect Gram negative contaminants.

Our experience with pH determination confirmed its lack of analytical sensitivity,[19] with 5 instances of PBC not being detected by this method, whereas almost 2 percent of products without PBC had abnormal pH values and were discarded. Indeed, as recently reported, the inability of the pH method to identify a SDP unit containing 1.3×10^6 CFUs per mL *S. aureus* at time of issue, leading to significant clinical morbidity, was the impetus to rescind pH testing for PBC testing on single-donor apheresis units, which was replaced by early plate culture.[25] We continue to use pH testing for our RDP units to detect PBC in the absence of more sensitive methods, such as culturing prepooled RDP units, because this has not been approved

by the FDA.[39] Our experience with culture of 596 SDP products drawn at our center with sample procurement after a 24-hour hold showed no positive samples, but failed to detect an SDP contaminated with *S. marcescens* when issued on Storage Day 3. Other examples of failure to detect PBC with early culture with commercial methods have recently been reported.[33,34]

Although our efforts have concentrated on detecting PBC, considerable emphasis has been placed on preventing or at least reducing the incidence of PBC by donor screening and skin disinfection.[19] In addition, diversion of the first 10 to 30 mL of blood during collection has been shown to significantly reduce contamination, most notably with CONS.[40] Other approaches to this problem include photochemical inactivation of bacteria,[41,42] addition of antibiotics to products,[23] and most recently, refrigerated storage of PLTs by addition of UDP-galactose solution to cap aggregated GP1bα receptors, which protects PLTs from removal by the reticuloendothelial system while maintaining PLT function.[43]

In conclusion, our study has documented the continuing problem of bacterial contamination of PLT products, underestimation of the magnitude of the problem by a posttransfusion reaction–triggered surveillance method, the clinical significance of transfusion of these contaminated products, the partial success of performing Gram stain at time of issue in preventing transfusion of contaminated PLT products, and failure of pH testing to do so. Our study has also shown the limitations of early culture-based detection systems and highlighted the need for a sensitive and specific method to detect bacterial contamination at time of issue. Our data and those of others supports use of SDP units rather than RDP pools as a means of reducing the number of donor exposures and therefore reduce the risk of a bacterially contaminated transfusion.[12,20,44] This safety gap is further augmented by testing of SDPs for bacterial contamination by culture with a sensitive culture method, whereas few RDP units currently undergo culture. The ideal single detection method is yet to be identified, but it is hoped that such a method would offer definitive at-issue screening. In the interim, the best solution appears to be the combination of a culture method early in the storage period able to identify a small inoculum of bacteria, combined with a rapid, at-issue assay able to identify a larger inoculum of bacteria. With a "belt-and-suspenders" type approach, it is likely that most clinically significant organisms missed by the culture method will be identified by the at-issue assay.

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