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ORIGINAL ARTICLE

Risk Factors for Nosocomial Primary Bloodstream Infection in Pediatric Intensive Care Unit Patients: A 2-Year Prospective Cohort Study

Alexis M. Elward, MD; Victoria J. Fraser, MD

OBJECTIVE.   The primary objective was to determine the rate of and risk factors for nosocomial primary bloodstream infection (BSI) in pediatric intensive care unit (PICU) patients in order to determine the validity of our previously published findings. The secondary objective was to analyze whether risk factors for primary BSI differed by organism type, particularly whether device use was more strongly associated with BSI due to gram-positive organisms.

DESIGN.   Prospective cohort study.

SETTINGS.   St. Louis Children's Hospital, a 235-bed academic tertiary care center with a 28-bed combined medical and surgical PICU.

PATIENTS.   PICU patients admitted between September 1, 1999, and September 1, 2001.

OUTCOME MEASURES.   Nosocomial primary BSIs.

RESULTS.   Of 2,310 patients, 55% were male, and 73% were white. There were 124 episodes of primary BSI in 87 patients (3.8%). Coagulase-negative *Staphylococcus* organisms were the leading cause of BSI (42 of 124 episodes). The rate of BSI was 9 BSIs/1,000 central venous catheter–days. Multiple logistic regression analysis showed that independent predictors of nosocomial primary BSI included higher number of arterial catheter–days (adjusted odds ratio [aOR], 5.7 per day of arterial catheterization; 95% confidence interval [CI], 3.4-9.8), higher number of packed red blood cell transfusions (aOR, 1.2; 95% CI, 1.1-1.4), and genetic syndrome (aOR, 4.7; 95% CI, 1.8-12). Severity of illness, underlying illnesses, and medications were not independently associated with increased risk of nosocomial BSI.

CONCLUSION.   Arterial catheter use and packed red blood cell transfusion are potentially modifiable risk factors for nosocomial primary BSI in PICU patients. Genetic syndromes may be markers for unrecognized immune defects that impair host defense against microorganisms.

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Bloodstream infection (BSI) is the most frequent nosocomial infection reported in pediatric intensive care unit (PICU) patients.[1-4] Central venous catheter (CVC)–associated BSI rates in PICUs range from 7.7 to 46.9 infections per 1,000 CVC-days.[4-9] These rates are comparable to BSI rates found in burn units and neonatal intensive care units.[6] Coagulase-negative staphylococci are the most common pathogens identified among patients with catheter-related BSI (38% of episodes), although gram-negative rods are isolated in 25% of PICU bacteremia cases.[2] Several studies have shown an association between BSI and mortality in PICU patients in univariate analysis.[3,4,10] The mean attributable cost of BSI in the PICU ranges from $39,000 to $50,000 per patient.[11-13]

Several studies involving PICU patients have sought to determine risk factors for nosocomial primary BSI.[1,3,4,14,15] Longer duration of CVC use,[3,14] increased number of CVCs used,[14] arterial catheter use,[1,3] and receipt of extracorporeal membrane oxygenation,[14] dialysis,[14] total parenteral nutrition,[3] and mechanical ventilation[1,3] are each associated with primary BSI. Some studies have been limited because of a short duration of arterial catheterization among participants and small sample size.

We performed a 2-year prospective cohort study to determine the rate of and risk factors for nosocomial BSI in PICU patients in order to enlarge our study population and validate the previously published analysis of data from the first 9 months of the study.[4] In addition, we analyzed whether risk factors for BSI due to gram-negative pathogens differed from risk factors for BSI caused by coagulase-negative staphylococci, with the specific goal of determining whether device use was more strongly associated with BSI due to gram-positive organisms.

METHODS

Setting

This study was performed at St. Louis Children's Hospital, a 235-bed teaching hospital affiliated with Washington Uni-

versity School of Medicine (St. Louis). St. Louis Children's Hospital is located in the St. Louis metropolitan area and has a referral base in southeastern Missouri and southwestern Illinois with a 483-km (300-mile) radius. St. Louis Children's Hospital has a combined medical and surgical PICU with 22 beds. Six beds were added after construction of a new facility in 2000. There are approximately 1,400 admissions to the PICU per year. In the new facility, patient rooms are separated by walls rather than curtains, and each room has a sliding glass door and a sink placed next to the door. There were 12 sinks and 22 beds in the old facility.

Patients

Subjects for this study were patients admitted to the PICU between September 1, 1999, and September 1, 2001. We excluded patients who were older than 18 years of age, who died within 24 hours after admission, or who were from the neonatal intensive care unit and receiving extra corporeal membrane oxygenation in the PICU. Approval for this study was obtained from the Washington University School of Medicine institutional review board. A waiver of written informed consent was granted because of the observational nature of this study.

Data Collection

All eligible study patients were monitored for the development of nosocomial infection from the day of PICU admission until 48 hours after PICU discharge. Data on demographic characteristics; underlying medical conditions; surgeries and procedures performed; antibiotics, steroids, stomach acid suppressants, and immunosuppressants received; duration of hospital and PICU stays; PICU discharge disposition; and durations of CVC, arterial catheter, and ventilator use were collected from the medical records and daily flow sheets. Severity of illness at PICU admission was calculated using the Pediatric Risk of Mortality III (PRISM) index. The PRISM score is weighted and was estimated on the basis data on 17 physiological characteristics recorded during the first 24 hours after PICU admission.[16] Research assistants were trained by the principal investigator (A.M.E.) by means of written guidelines. Interrater reliability with a κ score of 0.7 or greater was required before independent data collection occurred. PRISM scores for time points more than 24 hours after admission were obtained retrospectively by review of patient flow sheets and laboratory results, using the same written guidelines. Information on potential risk factors was collected on all PICU patients during the study period. There were no clusters of infection or outbreaks of infection or colonization during the study period.

Definitions

Patients with more than 1 CVC placed simultaneously were defined as having multiple CVCs. Transfusion data (ie, type of blood product, date of administration, and amount re-

ceived) were obtained from the blood bank and from individual medical records. Lung disease was defined as a history of restrictive or obstructive pulmonary disease (including asthma, bronchopulmonary dysplasia, and cystic fibrosis) or chronic hypoxemia or hypercapnia requiring administration of oxygen or mechanical ventilation at home, as documented in the admission history and during physical examination. Congenital heart disease was defined as abnormal cardiac anatomy at birth, including an abnormal number of chambers, an intracardiac shunt, or abnormally structured circulation, valves, or coronary arteries. Developmental delay was defined as a significant lag in development or an inability to attain normal developmental milestones, and genetic syndrome was defined as a chromosomal abnormality or cluster of physical findings consistent with a recognized genetic syndrome, as documented in the medical record. Transfusion was defined as receipt of packed red blood cells, platelets, fresh frozen plasma, or cryoprecipitate at any time during the PICU stay. Transport out of the PICU was defined as physical movement of the patient from the PICU to another location, such as the operating room or radiology unit.

Only events that occurred before the development of nosocomial BSI (ie, use of an arterial catheter and/or a CVC, receipt of medication and/or total parenteral nutrition, transport out of the PICU, and receipt of a transfusion) were entered into the multiple logistic regression model as potential risk factors for nosocomial primary BSI. The period of risk was considered to be the duration of stay in the PICU.

Centers for Disease Control and Prevention definitions were used to diagnose nosocomial primary BSIs.[17] Primary BSI was defined as infection that began 48 hours or more after PICU admission and was due to bacteria or fungi in the blood that were not present or incubating before hospital admission. Patients without CVCs were eligible to receive a diagnosis of primary BSI. All cases of BSI were incident cases. Microorganisms causing BSIs were isolated by means of routine blood cultures, and their antibiotic susceptibility profiles were obtained from microbiology laboratory reports. Coagulase-negative *Staphylococcus* species were reported as a cause of BSI only if 2 or more cultures of blood drawn on different occasions yielded coagulase-negative *Staphylococcus* species. Staphylococcal strains were not speciated. These criteria are not definitive but were used in the attempt to distinguish true infection from contamination. Only the first episode of BSI was analyzed for children with more than 1 episode of nosocomial BSI.

Data Analysis

SPSS, version 10 (SPSS), was used in statistical analyses. The mean rate of nosocomial primary BSI was calculated as the number of episodes of primary BSI divided by the number of CVC-days × 1,000. Differences between mean values of nonnormally distributed variables were analyzed by means of the Mann-Whitney U test, and differences in the distribution

of categorical variables were analyzed with the χ^2 test. All statistical tests were 2-tailed. Because of the number of variables examined for an association with nosocomial primary BSI, a Bonferroni adjustment for multiple comparisons was made to avoid spurious associations, and a *P* value of less than .001 was considered to be statistically significant in univariate analysis. Clinically relevant variables from univariate analysis were used to create a logistic regression model to assess the differences between patients with and patients without BSI, with a *P* value of less than .1 as an entry criterion. A forward stepwise model was used. Variables affecting less than 10% of patients were not considered for entry into the logistic regression model. Interaction effects between variables that were statistically significant in multivariate analysis were tested, and no significant interaction effects were found. The fit of the model was evaluated using the Hosmer-Lemeshow goodness-of-fit test. The multivariate analysis was performed using the same methods involved in our previous analysis of the first 9 months of data for this cohort.[4]

RESULTS

A total of 2,310 patients were enrolled in the study from September 1999 through August 2001. Data on demographic characteristics, underlying diseases, procedures, and medications are summarized in Table 1. There was a slight predominance of male patients and a marked predominance of white patients. The mean age was 5.76 years (median age, 3.26 years). The mean PRISM score ($\pm$SD) was 5.67 $\pm$ 6.27 (median PRISM score, 4.00). The most common underlying diseases were congenital heart disease (in 29% of patients) and lung disease (in 22% of patients), whereas burns and congenital immunodeficiency were uncommon. A total of 65% of patients were intubated. Thirty-four percent of patients had a history of blood transfusion, 23% were treated with steroids, and 29% received histamine type 2–receptor blockers. Of the 795 patients who received a blood transfusion, 38% received packed red blood cells, and 37% received platelets; less commonly transfused were cryoprecipitate (in 19% of patients) and fresh frozen plasma (in 35% of patients).

There were 124 episodes of primary nosocomial BSI in 87 patients. The mean rate of primary BSI was 9 episodes/1,000 CVC-days. Patients with primary BSI had been in the PICU for a mean duration ($\pm$SD) of 13.4 $\pm$ 11.51 days (median duration, 10 days) before the development of primary BSI. The microbiological characteristics of primary BSI for patients in the PICU are summarized in Table 2.

Results of univariate analysis comparing patients with and patients without primary BSI are summarized in Table 1. This comparison demonstrated an association between primary BSI and each of the following underlying illnesses or conditions: congenital heart disease, developmental delay, failure to thrive, and genetic syndrome. Primary BSI was associated with receipt of transfusion, transport out of the PICU, use of a central line, use of multiple CVCs, use of an arterial catheter, receipt of steroid therapy, and receipt of total parenteral nutrition. A total of 98% of arterial catheters were placed peripherally in the radial artery.

To determine the association between organism type and each potential risk factor, crude odds ratios (ORs) were calculated, using uninfected patients as the comparison group. In univariate analysis, patients with primary BSI due to gram-negative organisms were associated with transfer from another facility, congenital heart disease, failure to thrive, genetic syndrome, age of 30 days or less, receipt of total parenteral nutrition, receipt of prednisone, and receipt of any transfusion (Table 3). Primary BSIs caused by coagulase-negative staphylococcal species were also associated with each of these factors; in addition, burns were associated with an increased risk of BSI due to coagulase-negative *Staphylococcus* species (Table 3). For gram-positive organisms other than coagulase-negative *Staphylococcus* species (ie, for *Staphylococcus aureus* and *Enterococcus* species), male sex and transplantation were associated with primary BSI. A comparison between patients with BSI due to coagulase-negative *Staphylococcus* species and all other patients with BSI revealed that only transfusion of packed red blood cells was associated with an increased risk of BSI due to coagulase-negative *Staphylococcus* species (crude OR, 3.37; 95% CI, 1.31-8.63; *P* = .018).

Multivariate analysis revealed that higher number of arterial catheter–days, higher number of packed red blood cell transfusions, and the presence of a genetic syndrome were independent predictors of nosocomial primary BSI (Table 4). Age and severity of illness at PICU admission did not independently predict nosocomial primary BSI.

Seven of the 26 patients with primary BSI and genetic syndrome had DiGeorge syndrome, 6 had Down syndrome, 4 had defined chromosomal abnormalities (1 had associated congenital neutropenia, 1 had hypogammaglobulinemia, and the other 2 had no recognized immunodeficiency), 1 had Turner syndrome, 1 had Noonan syndrome, 5 had multiple congenital anomalies with dysmorphic features (1 had polysplenia, and 1 had hypogammaglobulinemia), 1 had medium-chain fatty acid deficiency, 1 had severe combined immunodeficiency, and 1 had Beckwith-Weidemann syndrome. Thus, only 13 of these patients (50%) had recognized associated immunodeficiencies that are possible risk factors for BSI.

DISCUSSION

We performed a 2-year prospective cohort study to determine the rate of and independent risk factors for nosocomial BSI in PICU patients in order to enlarge our study population and validate our previously published analysis of the first 9 months of data.[4] In addition, we analyzed whether risk factors for BSI due to gram-negative pathogens differed from risk factors for BSI caused by coagulase-negative staphylococci, with the specific goal of determining whether use of an invasive device was more strongly associated with BSI due to gram-positive organisms. Multivariate analysis revealed that

TABLE 1. Univariate Analysis of Factors Associated With Nosocomial Primary Bloodstream Infection (BSI) in a Pediatric Intensive Care Unit (PICU)

Characteristic	All patients (n = 2,310)	Patients with BSI (n = 87)	Patients without BSI (n = 2,223)	P
Age				
Median y	3.3	0.6	3.45	<.001
Mean y ± SD	5.8 ± 6.0	…	…	
≤30 d (neonate)	216 (9)	17 (20)	199 (9)	.002
>30 d but <1 y (infant)	549 (24)	36 (41)	513 (23)	<.001
≥1 y but <12 y (child)	1,062 (46)	25 (29)	1,037 (47)	<.001[a]
≥12 y (adolescent)	483 (21)	9 (10)	474 (21)	<.001[a]
PRISM score				
Median	4	…	…	.011
Mean ± SD	5.67 ± 6.27	…	…	
Race or ethnicity				
White	1,696 (73)	68 (78)	1,628 (73)	
African American	519 (22)	12 (14)	507 (23)	.386
Other	95 (4)	7 (8)	88 (4)	
Male sex	1,279 (55)	47 (52)	1,232 (56)	
Underlying illness or condition				.826
Failure to thrive	128 (6)	11 (13)	117 (5)	
Lung disease	505 (22)	21 (24)	484 (22)	.007
Genetic syndrome	387 (17)	26 (30)	361 (16)	.598
Congenital heart disease	673 (29)	41 (47)	632 (28)	<.001[a]
Invasive device use				<.001[a]
Multiple central catheters	291 (13)	59 (68)	232 (10)	
Central venous catheter	699 (30)	34 (39)	665 (30)	<.001[a]
Arterial catheter	1,101 (48)	53 (61)	1,048 (47)	.074
Mechanical ventilation	1,509 (65)	74 (85)	1,435 (65)	.022
Surgery or procedure				
Dialysis	55 (2)	13 (15)	42 (2)	<.001[a]
Transplantation	143 (6)	13 (15)	130 (6)	.001[a]
Cardiovascular surgery	460 (20)	26 (30)	434 (20)	.002
Transfusion				
History of transfusion	795 (34)	72 (83)	723 (33)	.027
Packed RBCs transfused, U				
Median	0	3	0	
Mean ± SD	0.7 ± 3.6	7.4 ± 13.1	0.4 ± 2.2	<.001[a]
Location where procedures were performed				
Outside of the hospital	137 (6)	6 (7)	131 (6)	.642
Cardiac catheterization laboratory	82 (4)	11 (13)	71 (3)	.007
Operating room	1,446 (63)	62 (71)	1,384 (62)	.091
PICU	546 (24)	65 (75)	481 (22)	.001[a]
Medication				
Immunosuppressive agents[b]	127 (5)	14 (16)	113 (5)	<.001[a]
Histamine-2–receptor blockers	681 (29)	47 (54)	634 (29)	<.001[a]
Steroids	546 (24)	34 (39)	512 (23)	.003
Inotropes	588 (25)	47 (54)	541 (24)	<.001[a]
Total parenteral nutrition	333 (14)	60 (69)	273 (12)	<.001[a]
Other				
Transferred from another facility	439 (19)	36 (41)	403 (18)	<.001[a]
Transport out of the PICU	398 (17)	50 (57)	348 (16)	<.001[a]

NOTE. Data are no. (%) of patients, unless otherwise indicated. PRISM, Pediatric Risk of Mortality III.
[a] After the Bonferroni adjustment.
[b] For transplant recipients.

TABLE 2.   Pathogens Causing Nosocomial Primary Bloodstream Infection in a Pediatric Intensive Care Unit

Organism	No. (%) of patients with BSI ($n = 124$)
CoNS	42 (34)
Enterococcus species	18 (14.5)
Candida species	17 (14)
Staphylococcus aureus	9 (7.3)
Pseudomonas aeruginosa	9 (7.3)
Serratia marcescens	10 (8)
Klebsiella pneumoniae	6 (4.8)
Enterobacter species	8 (6.5)
Escherichia coli	3 (2.4)
Acinetobacter lwoffii	1
Micrococcus species	1
Bacillus species	1

NOTE.   CoNS, coagulase-negative *Staphylococcus* species.

increased number of arterial catheter-days, increased number of packed red blood cell transfusions, and the presence of a genetic syndrome were each independently associated with an increased risk of nosocomial primary BSI in PICU patients.

In our previous analysis of the first 9 months of data from this cohort, multivariate analysis revealed that use of multiple CVCs, use of arterial catheters, invasive procedures performed in the PICU, and transport out of the PICU were independent predictors of nosocomial primary BSI.[4] Methods of data collection and statistical analysis did not change in the interval between the 2 analyses. The previously published interim analysis was reported to PICU nurses and physicians as well as the hospital's infection control and quality improvement departments, and a number of changes in policies and procedures subsequently occurred, including creation of an educational self-study module for nurses and physicians that described the process of CVC care and placement of physical barriers (ie, yellow tape and screens) around the bedside of PICU patients receiving surgery at the bedside in order to prevent unnecessary traffic through the area. In the multivariate model, we examined the influence of a time variable before and after reporting, as well as possible differences between the first 9 months of the study (from September 1999 through May 2000) and the second part of the study period (from June 2000 through September 2001) with respect to the number of CVC-days, the number of arterial catheter–days, transport out of the PICU, and the number of invasive procedures performed in the PICU. We found no significant differences between these 2 periods in the percentage of patients who underwent an invasive procedure in the PICU, were transported out of the PICU, or had a genetic syndrome. Arterial catheters were used by a slightly greater percentage of patients during the second study period than during the first period (49% vs 45%; $P = .056$). There were no significant differences in the percentage of patients with

CVCs between the 2 periods. However, mean duration ($\pm$ SD) of CVC use was shorter during the second study period (3 ± 2.9 vs 7 ± 5.7 CVC-days; $P = .043$), as was the mean duration ($\pm$ SD) of arterial catheterization (3 ± 3 vs 0.6 ± 3.5 arterial catheter–days; $P = .001$). Transfusion was also slightly more common among patients during the second study period (36% vs 32%; $P = .015$). We conclude that the findings of multivariate analysis involving a larger sample size and a longer period are more robust and less subject to variation in qualitative, unmeasured aspects of catheter care, such as adherence to barrier precautions during catheter insertion. The robustness of the findings for the larger sample is supported by goodness-of-fit statistics from the multivariate model.

In the 2-year cohort analysis, packed red blood cell transfusion was more common among patients with BSIs caused by coagulase-negative staphylococcal species, compared with patients with BSIs caused by other organisms. Factors associated with coagulase-negative staphylococcal BSIs were similar to those associated with gram-negative bacterial BSIs. Packed red blood cell transfusion and genetic syndrome have not been previously described as risk factors for nosocomial BSI in pediatric patients. In our previously published analysis, patients with BSIs received transfusions more often than uninfected patients, but the association did not hold in multivariate analysis.[4]

Arterial catheter use is a biologically plausible risk factor for BSI, because such catheters are not always placed under sterile conditions, they are accessed frequently, and they are left in place for long periods because accessing arteries is difficult in small patients. In addition, care of the arterial catheter site is often not standardized. We noted a moderately substantial effect size and a dose response, also supporting a causal relationship. The finding that arterial catheter use increases the risk of nosocomial primary BSI in PICU patients contrasts with findings reported in the literature for adult ICU patients. Several prospective studies involving adult ICU patients demonstrated low rates of BSIs at catheter-related insertion sites[18] and showed that BSIs associated with arterial catheters occurred in less than 1% of arterial catheters, with rates of 1.5 BSIs/1,000 arterial catheter–days.[19,20] In our PICU, arterial catheters are left in place until they are no longer indicated, they malfunction, or they become infected. This is likely the practice in other PICUs, because children are small, and accessing arteries is technically difficult. Only 2 prospective studies of arterial catheter–related infections have been performed in pediatric populations. Furfara et al.[21] found that only 3% of 340 arterial catheters placed in PICU patients were either locally infected or associated with BSI; culture data were not available for 18% of catheters. Ducharme et al.[22] found no cases of local or systemic infection associated with arterial catheters in 68 children. The current rates of arterial catheter colonization warrant further study, because advances in technology during the past 15 years may have changed the composition of the PICU patient popula-

TABLE 3. Results of Univariate Analysis of Risk Factors for and Characteristics of Patients With Nosocomial Primary Bloodstream Infection (BSI), by Causal Pathogen

Variable	CoNS	Gram-negative organism	Gram-positive organism
Risk factor, crude OR (95% CI)			
Male sex	NS	NS	2.7 (1.1-6.8)
Transfer from another hospital	4.2 (2.0-8.8)	2.9 (1.3-6.8)	3.8 (1.6-8.8)
Congenital heart disease	2.4 (1.1-4.9)	4.7 (2.0-11.2)	NS
Arterial catheter use	1.8 (0.9-3.9)	2.1 (0.9-5)	1.1 (0.5-2.6)
Central vascular catheter use	1.7 (0.8-3.5)	0.8 (0.7-2.1)	2.8 (1.2-6.5)
History of burns	21.3 (5.7-80)	NS	NS
Failure to thrive	2.9 (1.0-8.4)	3.8 (1.3-11.2)	NS
Neonate status	3.2 (1.4-7.7)	2.8 (1.0-7.7)	3.0 (1.1-8.2)
Prednisone use	4.6 (2.5-8.5)	3.9 (2.1-7.0)	3.8 (2.1-6.8)
Total parenteral nutrition use	212 (59-757)	154 (38-622)	88 (18-419)
Transfusion			
Packed RBCs	11.5 (5.4-24.3)	7.4 (3.2-17)	NS
Platelets	11.9 (5.4-26.4)	12.1 (5.0-29.3)	NS
Fresh frozen plasma	9.4 (4.0-21.8)	10.8 (4.3-26.8)	NS
Cryoprecipitate	NS	25.2 (9.8-65)	5.8 (1.3-25.5)
Characteristic, mean value ± SD			
Age, y	3.4 (6.0)	2.4 (4.2)	2.4 (5.0)
PRISM score	10.5 (8.2)	10.7 (8.8)	9.6 (7.5)
No. of arterial catheter–days	11.9 (13.7)	11.4 (13.4)	9.6 (13.8)
No. of CVC-days	10.7 (14.1)	11.9 (15.1)	10.7 (10.8)

NOTE. Uninfected patients were used as the reference group. CI, confidence interval; CoNS, coagulase-negative *Staphylococcus* species; CVC, central vascular catheter; NS, not significant; OR, odds ratio; PRISM, Pediatric Risk of Mortality III; RBC, red blood cell.

tion, such that more patients with complex congenital heart disease, patients with genetic syndromes, and transplant recipients are living longer. Arterial catheter use (as well as packed red blood cell transfusion) may be a marker of ongoing severity of illness, and thus might be driving the association between BSI and arterial line use through a different mechanism. However, data on PRISM scores obtained closest to the onset of BSI actually reveal that PRISM scores decrease over time (mean admission PRISM score [±SD] for patients with BSI 10.2 ± 8 days [median, 8 days] vs mean PRISM score at infection 6.4 ± 6.3 [median, 5]; $P < .001$). This makes it unlikely that ongoing severity of illness is driving risk of infection through an undefined mechanism.

Transfusion of packed red blood cells is also a biologically plausible risk factor for BSI, with several possible mechanisms of BSI onset. Transfusion may be inherently immunosuppressive. Proposed mechanisms for this immunosuppressive effect include the induction of suppressor T cells and anti-idiotypic antibodies, deletion of naive T cells, and decreased natural killer cell activity.[23-29] Previous investigators have observed that, in adult populations that have undergone cardiovascular or colorectal surgery, the risk of surgical site infection increases 7%-14% with each unit of packed red blood cells transfused.[23-29] Transfusion may also be a marker for frequent access of arterial catheters and CVCs.

Finally, we identified genetic syndrome as a predictor of nosocomial primary BSI. Patients with a genetic syndrome

may have recognized or unrecognized associated primary immunodeficiencies, placing them at increased risk for infection. Half of our patients with a genetic syndrome had recognized associated immunodeficiencies. Six of the 13 patients without a documented immunodeficiency had Down syndrome. Patients with Down syndrome may have defects in humoral immunity that predispose them to infection. Differences in morbidity and mortality associated with nosocomial infection that are based on single-nucleotide polymorphisms in the promoter of the gene encoding TNF-α, in the gene encoding TNF-β, and in the gene encoding cell marker CD14 (ie, the lipopolysaccharide receptor) have been identified in adult trauma patients.[30-33] O'Keefe et al.[32] demonstrated that pa-

TABLE 4. Multivariate Analysis of Factors Associated With Nosocomial Primary Bloodstream Infection (BSI) in a Pediatric Intensive Care Unit

Risk factor	aOR (95% CI)	P
Genetic syndrome	4.7 (1.8-12)	.001
High number of arterial catheter–days	5.7 (3.4-9.8)	<.001
High number of packed RBC transfusions	1.2 (1.1-1.4)	<.001

NOTE. The final model had a χ^2 statistic of 529.574, a P value of less than .001, a -2_{log} likelihood of 211.516, a Naegelkerke R^2 value of 0.747, a Hosmer-Lemeshow goodness-of-fit statistic of 5.888 (with a P value of .660), and an overall correct classification of 99.1% (78.2% for patients with BSI and 99.9% for uninfected patients). aOR, adjusted odds ratio; CI, confidence interval; RBC, red blood cell.

tients with single-nucleotide polymorphisms at the −308 position in the TNF-α promoter have an OR of 2.5 for sepsis after shock or organ failure and a 2-fold increased risk of death. Majetschhak et al.[33] demonstrated that homozygosity for the TNF-β allele was associated with a 3-fold increased risk for sepsis after shock or organ failure.

Our study had several limitations. PRISM scores were created by research personnel. Other investigators have noted wide variability in the generation of PRISM scores, particularly when such scores are created by nonintensivists without training.[34] However, van Keulen et al.[35] demonstrated that training and use of written guidelines increased the consistency of PRISM score determination among a group that included nonintensivists, with intraclass correlation coefficients for nonintensivists of 0.24 before training and 0.73 after training. In addition, scores determined by the nonintensivists correlated well with those determined by the intensivists after training (intraclass correlation coefficient, 0.8). We lacked a sufficient number of cases of BSIs due to gram-positive organisms and cases due to gram-negative organisms to perform multivariate analysis to determine independent predictors for these infections. This sample size had a power of 80% to detect a 10-fold difference in risk with a confidence of 95%.

In summary, we found 2 independent risk factors for nosocomial primary BSI in PICU patients that were related to process of care, as well as a third risk factor unique to pediatric patients that, to our knowledge, has not been previously reported. Future interventions to decrease nosocomial primary BSI rates among PICU patients should focus on improving the process of arterial catheter care, as well as the processes of CVC insertion and care. More studies are needed to test the specific mechanisms by which transfusion and genetic syndrome increase the risk of nosocomial primary BSI in PICU patients.

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