Washington University School of Medicine
Digital Commons@Becker

Open Access Publications

2004

Antimicrobial use and the influence of inadequate empiric antimicrobial therapy on the outcomes of nosocomial bloodstream infections in a neonatal intensive care unit

Anucha Apisarnthanarak
Thammasat University Hospital

Galit Holzmann-Pazgal
Washington University School of Medicine in St. Louis

Aaron Hamvas
Washington University School of Medicine in St. Louis

Margaret A. Olson
Washington University School of Medicine in St. Louis

Victoria J. Fraser
Washington University School of Medicine in St. Louis

Follow this and additional works at: http://digitalcommons.wustl.edu/open_access_pubs

Part of the Medicine and Health Sciences Commons

Author(s): Anucha Apisarnthanarak , MD, Galit Holzmann-Pazgal , MD, Aaron Hamvas , MD,
Margaret A. Olsen , PhD, MPH, Victoria J. Fraser , MD
Reviewed work(s):

ANTIMICROBIAL USE AND THE INFLUENCE OF INADEQUATE EMPIRIC ANTIMICROBIAL THERAPY ON THE OUTCOMES OF NOSOCOMIAL BLOODSTREAM INFECTIONS IN A NEONATAL INTENSIVE CARE UNIT

Anucha Apisarnthanarak, MD; Galit Holzmann-Pazgal, MD; Aaron Hamvas, MD; Margaret A. Olsen, PhD, MPH;
Victoria J. Fraser, MD

ABSTRACT

OBJECTIVE: To evaluate antimicrobial use and the influence of inadequate empiric antimicrobial therapy on the outcomes of nosocomial bloodstream infections (BSIs).

DESIGN: Prospective cohort study with nested case–control analysis.

SETTING: Neonatal intensive care unit (NICU).

METHODS: All patients weighing 2,000 g or less were enrolled. Data collection included risk factors for nosocomial BSI, admission severity of illness, microbiology, antimicrobial therapy, and outcomes. Inadequate empiric antimicrobial therapy was defined as the use of antibiotics for more than 48 hours after the day that blood cultures were performed that did not cover the microorganisms causing the bacteremia or administration of antibiotics that failed to cover resistant microorganisms.

RESULTS: Two hundred twenty-nine patients were enrolled. Forty-five developed nosocomial BSIs. The BSI rates were 11.2, 2.8, and 0 per 1,000 catheter-days for patients weigh-

ing 1,000 g or less, between 1,001 and 1,500 g, and between 1,501 and 2,000 g, respectively. After adjustment for severity of illness, the mortality in patients with nosocomial BSI receiving inadequate empiric antimicrobial therapy was higher than in those receiving adequate therapy (adjusted odds ratio [AOR], 5.3; 95% confidence interval [CI_{95}], 1.2–23.2). By multivariate analysis, nosocomial BSI attributed to *Candida* species (AOR, 6.3; CI_{95}, 1.4–28.0) and invasive procedure prior to onset of BSI (AOR, 6.4; CI_{95}, 1.0–39.0) were associated with administration of inadequate empiric antimicrobial therapy.

CONCLUSIONS: Administration of inadequate empiric antimicrobial therapy among NICU patients with nosocomial BSI was associated with higher mortality. Additional studies on the role of inadequate empiric antimicrobial therapy and the outcomes of BSIs among NICU patients are needed (*Infect Control Hosp Epidemiol* 2004;25:735-741).

Inadequate antimicrobial therapy for infections has been defined in multiple ways, including (1) microbiological documentation of an infection that was not being effectively treated at the time of its identification; (2) absence of antimicrobial agents directed against a specific class of microorganisms; and (3) administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant.[1,2] In addition, the absence of antimicrobial therapy for a confirmed infection is also considered to represent inadequate antimicrobial therapy.[1]

Several studies have demonstrated a correlation between adequate empiric antimicrobial therapy for bloodstream infection (BSI) and low mortality rates in adult patients.[3-6] Identified risk factors for the administration of inadequate empiric antimicrobial therapy in patients with BSI include prior administration of antibiotics, presence of central venous catheters, infection due

to *Staphylococcus aureus,* and infections due to antibiotic-resistant pathogens (*Candida* species, methicillin-resistant, vancomycin-resistant *Enterococcus*, and coagulase-negative staphylococci).[6-8] However, there are no data on the relationship between the adequacy of empiric antimicrobial therapy and the outcomes of nosocomial BSIs in neonatal patients. Because neonates and adults have different anatomies, physiologies, and underlying diseases, as well as patterns of antibiotic use and antimicrobial resistance, specific studies of the outcomes of inadequate empiric antimicrobial therapy in neonates are needed.

We performed a prospective cohort study to determine the rates and microbiology of nosocomial BSI, patterns of antibiotic use, and relationship between the adequacy of prescribed empiric antimicrobial therapy for nosocomial BSI and clinical outcomes in a neonatal intensive care unit (NICU).

METHODS

Setting and Empiric Antimicrobial Therapy

St. Louis Children's Hospital is a 235-bed, tertiary-care center affiliated with Washington University School of Medicine. St. Louis Children's Hospital has a level-III, 52-bed NICU with 700 to 750 admissions per year and an average census of 50 patients. The NICU staff includes 3 neonatologists, 2 newborn medicine fellows, and 5 pediatric house staff and nurse practitioners. The estimated patient-to-nurse ratio is 2 to 1. In this NICU, ampicillin and aminoglycosides are generally used for empiric treatment of patients with clinically suspected sepsis within the first 7 days of life. Vancomycin and aminoglycosides are administered to patients with clinically suspected sepsis after the first 7 days of life. For patients who were previously infected with specific pathogens, empiric antimicrobial therapy was modified to cover for those pathogens in addition to the standard spectrum of antimicrobial coverage within or after the first 7 days of life.

Patients

From October 1, 2000, to July 31, 2001, all patients with a birth weight of 2,000 g or less admitted to the NICU for longer than 48 hours were included in the study. Patients transferred to the NICU from an outside hospital were included as long as their birth weight was 2,000 g or less, even if their weight on admission to the NICU was more than 2,000 g. The development of nosocomial infection was monitored from the day of admission until discharge from the NICU. If the patients were discharged to another St. Louis Children's Hospital location or to the nursery of an affiliated university hospital (Barnes–Jewish Hospital), they were observed for an additional 48 hours. Approval was obtained from the institutional review boards of Washington University and St. Louis Children's Hospital prior to the initiation of the study.

Study Design and Data Collection

A prospective cohort study design was used with a subsequent nested case–control study. Patients with nosocomial BSIs were classified according to the adequacy of their empiric antimicrobial therapy, with NICU mortality as the main outcome variable. Another outcome measured was the length of stay in the NICU. For the purposes of this investigation, inadequate empiric antimicrobial therapy for nosocomial BSI was defined as the use of antibiotics for longer than 48 hours following the day that the blood cultures were performed that did not have efficacy against the identified microorganisms. Inadequate antimicrobial therapy included the absence of antimicrobial agents directed at the specific class of recovered microorganisms or administration of ineffective antimicrobial agents due to the microorganisms' drug resistance patterns. One of the authors (AA), an infectious diseases fellow, reviewed medical records to confirm that these neonates had received inadequate empiric antimicrobial therapy for longer than 48 hours.

Medical records, including charts, daily flow sheets, and laboratory and radiographic reports, were prospectively reviewed by one of the investigators (GH-P). For all study patients, the following characteristics were prospectively recorded: gender, race, estimated gestational age, underlying diseases, administration of therapeutic antibiotics, placement of central venous and arterial catheters, ventilator use, invasive procedures, microbiology data (microorganisms and their susceptibility results), length of stay in the NICU, concurrent nosocomial infections, and mortality. Severity of illness on admission was calculated using the Score for Neonatal Acute Physiology–Perinatal Extension (SNAP–PE) derived from the first 24 hours of NICU admission according to the method of Richardson et al.[9,10] Invasive procedures included patent ductus arteriosus ligation, laparotomy, and chest tube placement. Specific processes of medical care that were examined included the administration of corticosteroids, antacids, and histamine type-2 blockers.

Definitions

A nosocomial infection was defined as an infection not present or incubating at the time of NICU admission, with onset after 48 hours of NICU stay.[11] Isolation of a high-grade pathogen (eg, *Pseudomonas aeruginosa* or *Staphylococcus aureus*) in one or more blood culture specimens was considered definitive evidence of bacteremia. In our NICU, only a single blood culture was routinely performed for neonates with intravenous catheters. Therefore, we developed more stringent criteria for the isolation of organisms commonly associated with skin contamination from a single positive blood culture, such as coagulase-negative *Staphylococcus*. This criterion for primary bacteremia required a diagnosis of sepsis by an attending physician in the NICU if only one positive blood culture was performed prior to the initiation of antibiotics. Secondary BSI was defined as bacteremia due to the presence of a localized infection at another site that occurred within 1 week before the development of the bacteremia or simultaneously.

A bacteremic episode was included as a new episode if a new microorganism was isolated from a blood culture or when the original microorganism was recovered again more than 2 weeks after the first episode with negative blood cultures in the interim. Empiric therapy was considered to be present when antimicrobials were prescribed for fever or other systemic signs of infection such as hypothermia or leukocytosis before identification of the causative microorganisms. Early-onset bacteremia was defined as bacteremia occurring within the first 7 days of life, and late-onset bacteremia was defined as bacteremia occurring after 7 days of life. Crude mortality related to nosocomial BSI was defined as patient death occurring within 7 days of the bacteremia and during treatment for nosocomial BSI.

To identify factors for BSI-related mortality, risk factors were evaluated from the time of NICU admission until the occurrence of the last episode of nosocomial BSI.

TABLE 1
PATIENT CHARACTERISTICS

Characteristic	Patients in Entire Cohort (n = 229)	Patients Who Developed BSI (n = 45)	Patients Who Did Not Develop BSI (n = 184)	P*
Demographic				
Female	114 (50%)	24 (53%)	90 (49%)	.59
White	113 (49%)	20 (44%)	93 (51%)	.46
Median SNAP–PE score (range)†	16 (2–70)	40 (6–70)	14 (2–70)	< .001
Birth weight, g				
< 1,000	85 (37%)	31 (69%)	54 (29%)	< .001
1,000 to 2,000	144 (63%)	14 (31%)	130 (71%)	< .001
Median estimated gestational age, wk (range)†	29 (22–39)	26 (22–34)	29 (22–39)	< .001
Invasive procedure‡				
Patent ductus arteriosus ligation	10 (4%)	5 (11%)	5 (3%)	.02
Chest tube placement	7 (3%)	2 (4%)	5 (3%)	.54
Laparotomy	4 (2%)	2 (4%)	2 (1%)	.12
Underlying disease				
Congenital heart diseases§	28 (12%)	10 (22%)	18 (10%)	.02
Patent ductus arteriosus	73 (32%)	21 (47%)	52 (28%)	< .001
Bronchopulmonary dysplasia	63 (28%)	30 (67%)	33 (18%)	< .001
Respiratory distress syndrome	200 (87%)	34 (76%)	166 (90%)	.008
Medication‖				
Dexamethasone	74 (32%)	37 (82%)	37 (20%)	< .001
Surfactant	196 (86%)	34 (76%)	162 (88%)	.03
Histamine type-2 receptor blockers	64 (28%)	27 (60%)	37 (20%)	< .001
Intravenous gamma globulin	18 (8%)	10 (22%)	8 (4%)	< .001
Indomethacin	48 (21%)	24 (53%)	24 (13%)	< .001
Outcome				
Total median NICU stay, d (range)	30 (3–361)	96 (4–312)	30 (3–361)	< .001
Death	24 (11%)	12 (27%)	12 (7%)	< .001

BSI = bloodstream infection; SNAP–PE = Score for Neonatal Acute Physiology–Perinatal Extension; NICU = neonatal intensive care unit.
*Analyzed by chi-square or Fisher's exact test, as appropriate, unless otherwise noted.
†Analyzed by Mann–Whitney test.
‡All invasive procedures were performed prior to the first episode of bacteremia.
§Includes any anatomy other than normal four-chamber heart with left ventricle and excludes patent foramen ovalae and patent ductus arteriosus.
‖All medications were administered prior to the first episode of bacteremia.

To identify risk factors for receipt of inadequate empiric antimicrobial therapy, risk factors were evaluated from admission until the first episode of bacteremia for patients who received inadequate empiric antimicrobial treatment, and from admission until the last episode of bacteremia for patients who received adequate empiric antimicrobial treatment.

Statistical Analysis

A nested case–control method was used to analyze risk factors and outcomes of inadequate antimicrobial therapy. SPSS software (version 10.0; SPSS, Inc., Chicago, IL) was used to analyze the data. Proportions were compared using chi-square or Fisher's exact test as appropriate. Continuous variables were compared by use of the Mann–Whitney U test. All P values were two-tailed. A P value of .05 or less was considered statistically significant. Adjusted odds ratios (ORs) and 95% confidence intervals (CI$_{95}$) were computed for categorical variables. Multivariate logistic regression was performed to assess the predictive association of inadequate empiric antimicrobial therapy with crude mortality. To identify independent risk factors for inadequate empiric antimicrobial therapy, backward stepwise logistic regression was performed. Variables that were present in more than 10% of the population with a P value of less than .20 or that had a priori clinical significance were entered into the models. Significant variables that were thought to co-vary were grouped, and only one variable from each group was chosen for entry into the model. The final model was chosen on the basis of biological plausibility and by selecting the logistic regression model with the lowest -2 log-likelihood function.

TABLE 2
MICROORGANISMS ASSOCIATED WITH THE BLOODSTREAM INFECTIONS

Pathogen	Total No. of BSI Episodes (n = 90)	BSI Within the First 7 Days of Life (n = 13)	BSI After 7 Days of Life (n = 77)
Coagulase-negative Staphylococcus	39 (43%)	10 (77%)	29 (38%)
Staphylococcus aureus	7 (8%)	1 (8%)	6 (8%)
Enterococcus species	3 (3%)	0 (0%)	3 (4%)
Alpha-hemolytic Streptococcus	5 (6%)	0 (0%)	5 (7%)
Escherichia coli	9 (10%)	2 (15%)	7 (9%)
Klebsiella pneumoniae	5 (6%)	0 (0%)	5 (7%)
Enterobacter species	5 (6%)	0 (0%)	5 (7%)
Pseudomonas species	4 (4%)	0 (0%)	4 (5%)
Candida species	13 (14%)	0 (0%)	13 (17%)

BSI = bloodstream infection.

TABLE 3
EMPIRIC ANTIBIOTIC REGIMENS FOR THE BLOODSTREAM INFECTIONS

Regimen	Frequency (%)*
Early-onset bacteremia (n = 13 episodes)[†,‡]	
Ampicillin and aminoglycosides	13 (100)
Late-onset bacteremia (n = 77 episodes)[§,‖]	
Vancomycin and aminoglycosides	62 (81)
Vancomycin and ceftazidime[¶]	6 (8)
Vancomycin and extended-spectrum penicillin[#]	3 (4)
Vancomycin and ceftriaxone[**]	2 (3)
Vancomycin, ceftazidime, and fluconazole[††]	2 (3)
Vancomycin, ceftriaxone, and fluconazole[‡‡]	1 (1)
Vancomycin, extended-spectrum penicillin, and fluconazole[§§]	1 (1)

*Total bacteremic episodes.
[†]Bloodstream infection that occurred within the first 7 days of life.
[‡]Ampicillin was changed to vancomycin in 8 episodes of early-onset bacteremia to cover for coagulase-negative Staphylococcus bacteremia.
[§]Bloodstream infection that occurred after the first 7 days of life.
[‖]Amphotericin B was added on 7 episodes of late-onset bacteremia to cover for candidemia.
[¶]These patients had evidence of Pseudomonas species infections prior to onset of bacteremia.
[#]These patients had evidence of Enterobacter species infections prior to onset of bacteremia.
[**]These patients had evidence of Escherichia coli infections prior to onset of bacteremia.
[††]These patients had evidence of Pseudomonas species and Candida infections prior to onset of bacteremia.
[‡‡]These patients had evidence of Escherichia coli and Candida species infections prior to onset of bacteremia.
[§§]These patients had evidence of Enterobacter species and Candida species infections prior to onset of bacteremia.

RESULTS

Cohort Characteristics

Forty-five (20%) of 229 patients who were enrolled in the study developed nosocomial BSI. Two (4%) of the patients were transferred to our institution from outside hospitals prior to the onset of BSI on their second day of life. The median birth weight was 740 g (range, 420 to 1,705 g) and the median gestational age was 26 weeks (range, 22 to 34 weeks). Thirty-four (76%) of the patients had primary BSI only, 5 patients (11%) had secondary BSI only, and 6 patients (13%) had both primary and secondary BSI. Sources of secondary BSI were the respiratory tract (6 of 11; 55%) and urinary tract (5 of 11; 45%). The median rates of BSI were 11.2, 2.8, and 0 per 1,000 catheter-days for patients weighing 1,000 g or less, 1,001 to 1,500 g, and 1,501 to 2,000 g, respectively. The median duration from admission to the first onset of nosocomial BSI was 15 days (range, 2 to 52 days). Twenty-three (51%) of the 45 patients had more than one BSI episode (range, 2 to 5 episodes). Nine patients had invasive procedures performed prior to the first onset of BSI. The median duration from invasive procedure to the first onset of nosocomial BSI was 18 days (range, 5 to 53 days). Demographics and clinical characteristics for the cohort of patients are summarized and compared in Table 1.

There were 90 bacteremic episodes, which occurred in 45 patients. Thirteen episodes (14%) occurred within the first 7 days of life, and 77 (86%) occurred after 7 days of life. Coagulase-negative Staphylococcus (39 of 90; 43%), Candida species (13 of 90; 14%), and Escherichia coli (9 of 90; 10%) were the most common microorganisms isolated from the blood cultures. The distribution of microorganisms according to the time of onset is presented in Table

2. Fifteen patients had nosocomial infections other than BSIs. Of these patients, 11 developed pneumonia or urinary tract infection due to Pseudomonas species (n = 6), Enterobacter species (n = 3), or Escherichia coli (n = 2), whereas 4 patients developed pneumonia or urinary tract infection due to Pseudomonas species (n = 2), Enterobacter species (n = 1), or Escherichia coli (n = 1) together with candidal urinary tract infection (n = 4). Eleven (73%) of these 15 patients developed secondary BSIs, including 2 (50%) of 4 patients who had candidemia in association with urinary tract infections. The median duration from prior nosocomial infection to onset of secondary BSI was 5 days (range, 1 to 7 days).

Treatment Given and the Adequacy of Therapy

The empiric antimicrobial regimens used in the 90 episodes of BSI are listed in Table 3. The median duration of antimicrobial therapy for each bacteremic episode was 14 days (range, 4 to 28 days). BSI caused by coagulase-negative Staphylococcus occurred in 18 (40%) of the 45 patients. There was no difference in characteristics or crude mortality among patients who developed BSI due to coagulase-negative Staphylococcus versus non–coagulase-negative microorganisms (P = .56), or among patients who developed early-onset versus late-onset nosocomial BSI (P > .99).

Twenty-one (47%) of the patients had 21 episodes of inadequate empiric antimicrobial therapy. Each patient had one episode of inadequate empiric antimicrobial ther-

TABLE 4
REASONS FOR INADEQUATE ANTIMICROBIAL TREATMENT

Reason	Frequency (%)*
Early-onset bacteremia (n = 10 episodes)†	
Absence of antimicrobial agents directed at a specific class of microorganisms	
Coagulase-negative *Staphylococcus* species	10 (100)
Late-onset bacteremia (n = 11 episodes)‡	
Absence of antimicrobial agents directed at a specific class of microorganisms	
Candida species	7 (64)
Administration of antibiotic to resistant microorganisms	
Pseudomonas species§	2 (18)
Enterobacter species§	1 (9)
Escherichia coli§	1 (9)

*Total episodes of inadequate empiric antimicrobial treatment.
†Bloodstream infection that occurred within the first 7 days of life.
‡Bloodstream infection that occurred after the first 7 days of life.
§This organism was resistant to third-generation cephalosporins, extended-spectrum penicillin, or both.

TABLE 5
CHARACTERISTICS AMONG NONSURVIVORS VERSUS SURVIVORS OF BLOODSTREAM INFECTION IN THE NEONATAL INTENSIVE CARE UNIT

Characteristic*	Nonsurvivors (n = 12)	Survivors (n = 33)	P†
Demographic			
Female	8 (67%)	16 (48%)	.28
White	5 (42%)	15 (45%)	1.00
Median SNAP–PE score (range)‡	46 (10–70)	33 (6–41)	.44
Birth weight, g			
≤ 1,000	8 (67%)	23 (70%)	1.00
1,001 to 2,000	4 (33%)	10 (30%)	1.00
Median estimated gestational age, wk (range)‡	26 (23–33)	26 (22–34)	.83
Underlying disease			
Congenital heart disease§	3 (25%)	7 (21%)	1.00
Patent ductus arteriosus	6 (50%)	15 (45%)	.79
Bronchopulmonary dysplasia	8 (67%)	22 (67%)	1.00
Respiratory distress syndrome	10 (83%)	24 (73%)	.69
Invasive procedure‖	4 (33%)	5 (15%)	.21
Medication¶			
Dexamethasone	10 (83%)	27 (82%)	.69
Surfactant	10 (83%)	24 (73%)	.69
Histamine type-2 receptor antagonist	7 (58%)	20 (61%)	.71
Intravenous gamma globulin	3 (25%)	7 (21%)	1.00
Indomethacin	6 (50%)	18 (55%)	.78
Episodes of inadequate antimicrobial therapy	9 (75%)	12 (36%)	.02
Outcome			
Median NICU stay, d (range)‡	138 (4–240)	99 (15–312)	.22

SNAP–PE = Score for Neonatal Acute Physiology–Perinatal Extension; NICU = neonatal intensive care unit.
*All risk factors were evaluated from the time of NICU admission until the occurrence of the last episode of bloodstream infection.
†Analyzed by chi-square or Fisher's exact test, as appropriate.
‡Analyzed by Mann-Whitney test.
§Includes any anatomy other than normal four-chamber heart with left ventricle and excludes patent foramen ovalae and patent ductus arteriosus.
‖All invasive procedures were performed prior to the last episode of bacteremia.
¶All medications were administered prior to the last episode of bloodstream infection.

apy for nosocomial BSI. The reasons for inadequate empiric antimicrobial treatment and the microorganisms associated with it are listed in Table 4. Twelve patients had delayed receipt of adequate antimicrobial therapy; the median delay was 2 days (range, 2 to 3 days). There was no difference in crude mortality between patients who received delayed versus adequate empiric antimicrobial treatment (OR, 2.6; 5 [42%] of 12 vs 7 [21%] of 33; *P* = .25).

Effect of Inadequate Empiric Antimicrobial Therapy

Twelve patients with nosocomial BSI died. Four (33%) of the 12 deaths occurred during therapy for early-onset bacteremia, and 8 (67%) of the deaths occurred during therapy for late-onset bacteremia. Nine (75%) of the 12 patients had received inadequate empiric antimicrobial therapy. The reasons for inadequate empiric antimicrobial therapy in these patients were absence of antimicrobial agents directed at a specific class of recovered microorganisms on the day that blood cultures were performed (6 of 9; 67%) and institution of antimicrobial treatment that failed to cover antibiotic-resistant microorganisms (3 of 9; 33%). There were 11 microorganisms associated with death in 9 patients (coagulase-negative *Staphylococcus* [n = 4], *S. aureus* [n = 2], *Escherichia coli* [n = 2], *Enterobacter* species [n = 1], and *Candida* species [n = 2]). Two patients had two microorganisms that grew from blood cultures (coagulase-negative *Staphylococcus* [n = 2] together with *Escherichia coli* [n = 2]). All deaths in patients with coagulase-negative *Staphylococcus* BSI occurred during the early-onset bacteremia. There was no difference in the crude mortality among patients who developed candidemia versus those who did not (OR, 1.3;

4 [31%] of 13 vs 8 [25%] of 32; *P* = .98]. The median duration from the last BSI episode until death was 4 days (range, 1 to 7 days).

The clinical characteristics among survivors versus nonsurvivors of BSI in the NICU are listed in Table 5. On univariate analysis, inadequate empiric antimicrobial therapy was the only factor associated with mortality (OR, 5.25; 9 [75%] of 12 vs 12 [36%] of 33; *P* = .02). Because severity of illness was considered to be a potentially important confounder, logistic regression was used to estimate the effect of inadequate antimicrobial therapy on mortality and to adjust for severity of illness.

TABLE 6

RISK FACTORS FOR INADEQUATE EMPIRIC ANTIMICROBIAL THERAPY FOR BLOODSTREAM INFECTION AMONG PATIENTS IN THE NEONATAL INTENSIVE CARE UNIT ON UNIVARIATE ANALYSIS

Dichotomous Variable*	Inadequate Antimicrobial Therapy (n = 21)[†]	Adequate Antimicrobial Therapy (n = 24)	P[‡]
Candidemia	10 (48%)	3 (13%)	.02
Estimated gestational age < 24 wk[§]	5 (24%)	5 (21%)	1.00
Invasive procedure	7 (33%)	2 (8%)	.06
SNAP–PE score > 32[§]	14 (67%)	12 (50%)	.36
Prior BSI	5 (24%)	9 (38%)	.35
Prior antibiotic use	11 (52%)	14 (58%)	.70
Prior nosocomial infections excluding BSI	6 (29%)	5 (21%)	.55
Antibiotics > 18 d[§]	4 (19%)	5 (21%)	1.0
NICU stay prior to BSI > 75 d[§]	7 (33%)	6 (25%)	.74

SNAP–PE = Score for Neonatal Acute Physiology–Perinatal Extension; BSI = bloodstream infection; NICU = neonatal intensive care unit.
*All risk factors were abstracted prior to the first episode of inadequate empiric antimicrobial therapy for BSI in patients who received inadequate empiric antimicrobial treatment vs the last episode of BSI in patients who received adequate empiric antimicrobial treatment.
[†]Twenty-one patients each had one episode of inadequate empiric antimicrobial treatment.
[‡]Analyzed by chi-square or Fisher's exact test, as appropriate, unless otherwise noted.
[§]The number represents the 75th percentile.

Inadequate empiric antimicrobial therapy remained significant after adjustment for severity of illness (adjusted OR, 5.3; CI_{95}, 1.2 to 23.2; P = .04). We also examined the potentially confounding effects of length of stay in the NICU prior to the onset of BSI and gestational age; they did not materially affect the estimate of the effect (ORs).

Risk Factors for Inadequate Antimicrobial Therapy

The only significant risk factor associated with the administration of inadequate empiric antimicrobial treatment on univariate analysis was nosocomial BSI attributed to *Candida* species (OR, 6.3; CI_{95}, 1.4 to 28.0; P = .02) (Table 6). Multivariate logistic regression was used to identify independent risk factors for inadequate empiric antimicrobial treatment. The final model included candidemia (adjusted OR, 7.1; CI_{95}, 1.5 to 33.7; P = .01) and invasive procedure prior to the onset of BSI (adjusted OR, 6.4; CI_{95}, 1.0 to 39.0; P = .04). On univariate analysis, prior BSI was the only significant risk factor associated with candidemia (OR, 8.0; CI_{95}, 1.6 to 45.2; P = .003). Due to the limitation of the sample size, logistic regression was not performed for candidemia as an outcome.

DISCUSSION

Our study is the first to describe antibiotic use, antimicrobial resistance, and the influence of inadequate empiric antimicrobial therapy on outcomes of nosocomial BSIs in patients in the NICU. This study demonstrated that critically ill patients with BSI in the NICU who received inadequate empiric antimicrobial therapy were significantly more likely to die during their hospitalization compared with those receiving adequate empiric antimicrobial therapy. We also identified BSI caused by *Candida* species and invasive procedures prior to the onset of BSI as potential risk factors for the administration of inadequate empiric antimicrobial therapy.

According to the data of the National Nosocomial Infections Surveillance System, median BSI rates are 12, 7.3, and 4.7 per 1,000 catheter-days for neonates weighing 1,000 g or less, 1,001 to 1,500 g, and 1,501 to 2,500 g, respectively.[12] In the literature, coagulase-negative *Staphylococcus* is the predominant organism in all studies, whereas the proportions of other microorganisms vary greatly in each study.[13-19] In our study, the median rates of nosocomial BSI were similar to those of the National Nosocomial Infections Surveillance System for patients weighing 1,000 g or less, between the 10th and 25th percentile for patients weighing 1,001 to 1,500 g, and at the 0th percentile for patients weighing 1,501 to 2,500 g. The distribution of the microorganisms in our study was similar to that reported by Beck-Sague et al.[14]

Several studies of adults have shown a significant reduction in mortality associated with adequate empiric antibiotic treatment,[4,20-23] whereas others failed to identify this association.[24-27] The varying outcomes in these studies might be due to the definitions used for adequacy of empiric antimicrobial therapy. Our results confirmed the association of inadequate antimicrobial therapy with adverse outcomes.

Risk factors for the administration of inadequate empiric antimicrobial therapy to adult patients with BSI are well recognized,[6-8] but little has been published regarding neonatal patients. The role of invasive procedures prior to the onset of bacteremia is not entirely clear, although this factor may reflect greater severity of illness, which may predispose to colonization and infection with antibiotic-resistant organisms. We confirmed candidemia as a risk factor associated with inadequate empiric antimicrobial therapy, as has been consistently shown in previous adult studies.[6-8] Although there are no current recommendations for empiric antifungal therapy in neonates, there may be specific groups of patients identified in the future who would benefit from such an approach.[28]

There are several limitations to this study. Because it was conducted at a tertiary-care hospital that uses guidelines for empiric antimicrobial therapy for suspected sepsis, our results may not be applicable to other hospitals with lower rates of BSI caused by *Candida* species or hospitals that do not have guidelines for empiric antimicrobial therapy. Our sample size was not large enough to exclude the possibility of characteristics unique to patients depending on the causative agents of bacteremias or to identify other risk factors associated with inadequate empiric antimicrobial therapy and outcomes. In addition,

the large confidence intervals of the ORs make it difficult to estimate the true effect size between risk factors and outcomes. Because all of our patients had a single blood culture performed from a central venous catheter, it was difficult to ascertain whether coagulase-negative staphylococci episodes represented true bacteremias. Most of the patients in our NICU developed late-onset BSI (median onset, 15 days); thus, it is likely that the SNAP–PE score on admission was not as informative as a SNAP–PE score immediately before the onset of BSI. Finally, the observational nature of this investigation did not allow us to detect an absolute causal relationship between the administration of inadequate empiric antimicrobial treatment and specific clinical outcomes including hospital mortality.

Our data suggest that inadequate empiric antimicrobial therapy was associated with adverse outcomes in patients in the NICU. Physicians in the NICU should be able to balance the need to provide adequate empiric antimicrobial therapy with the risk of selecting for resistant microorganisms. Studies on the role of inadequate antimicrobial therapy and outcomes in patients in the NICU are needed.

REFERENCES

1. Kollef MH. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clin Infect Dis* 2000;31(suppl 4):S131-S138.
2. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999;115:462-474.
3. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998;244:379-386.
4. Weinstein MP, Towns ML, Quartey SM, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. *Clin Infect Dis* 1997;24:584-602.
5. Vidal F, Mensa J, Almela M, et al. Epidemiology and outcome of *Pseudomonas aeruginosa* bacteremia, with special emphasis on the influence of antibiotic treatment: analysis of 189 episodes. *Arch Intern Med* 1996;156:2121-2126.
6. Chow JW, Fine MJ, Shlaes DM, et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991;115:585-590.
7. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. *Crit Care Med* 1999;27:887-892.
8. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000;118:146-155.
9. Richardson DK, Phibbs CS, Gray JE, McCormick MC, Workman-Daniels K, Goldmann DA. Birth weight and illness severity: independent predictors of neonatal mortality. *Pediatrics* 1993;91:969-975.
10. Richardson DK, Gray JE, McCormick MC, Workman K, Goldmann DA. Score for Neonatal Acute Physiology: a physiologic severity index for neonatal intensive care. *Pediatrics* 1993;91:617-623.
11. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;16:128-140.
12. National Nosocomial Infections Surveillance (NNIS) System. National Nosocomial Infections Surveillance (NNIS) System report: data summary from January 1992-April 2000, issued June 2000. *Am J Infect Control* 2000;28:429-448.
13. Baltimore RS. Neonatal nosocomial infections. *Semin Perinatol* 1998;22:25-32.
14. Beck-Sague CM, Azimi P, Fonseca SN, et al. Bloodstream infections in neonatal intensive care unit patients: results of a multicenter study. *Pediatr Infect Dis J* 1994;13:1110-1116.
15. Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. *Pediatrics* 1996;98(part 1):357-361.
16. Freeman J, Goldmann DA, Smith NE, Sidebottom DG, Epstein MF, Platt R. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *N Engl J Med* 1990;323:301-308.
17. Stoll BJ, Gordon T, Korones SB, et al. Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. *J Pediatr* 1996;129:63-71.
18. Stoll BJ, Hansen N, Fanaroff AA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. *N Engl J Med* 2002;347:240-247.
19. Nambiar S, Singh N. Change in epidemiology of health care-associated infections in a neonatal intensive care unit. *Pediatr Infect Dis J* 2002;21:839-842.
20. Leibovici L, Samra Z, Konigsberger H, Drucker M, Ashkenazi S, Pitlik SD. Long-term survival following bacteremia or fungemia. *JAMA* 1995;274:807-812.
21. Jones GR, Lowes JA. The systemic inflammatory response syndrome as a predictor of bacteraemia and outcome from sepsis. *QJM* 1996;89:515-522.
22. Meyers BR, Sherman E, Mendelson MH, et al. Bloodstream infections in the elderly. *Am J Med* 1989;86:379-384.
23. Gransden WR, Eykyn SJ, Phillips I, Rowe B. Bacteremia due to *Escherichia coli*: a study of 861 episodes. *Rev Infect Dis* 1990;12:1008-1018.
24. Bryan CS, Reynolds KL, Brenner ER. Analysis of 1,186 episodes of gram-negative bacteremia in non-university hospitals: the effects of antimicrobial therapy. *Rev Infect Dis* 1983;5:629-638.
25. Ispahani P, Pearson NJ, Greenwood D. An analysis of community and hospital-acquired bacteraemia in a large teaching hospital in the United Kingdom. *QJM* 1987;63:427-440.
26. McCue JD. Improved mortality in gram negative bacillary bacteremia. *Arch Intern Med* 1985;145:1212-1216.
27. Watanakunakorn C, Jura J. *Klebsiella* bacteremia: a review of 196 episodes during a decade (1980-89). *Scand J Infect Dis* 1991;23:399-405.
28. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. *N Engl J Med* 2001;345:1660-1666.