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Coagulase-negative staphylococcal bacteremia in critically ill children: risk factors and antimicrobial susceptibility

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Coagulase-negative staphylococci (CoNS) are the most common microorganisms isolated from blood cultures in childern, and determining whether there is true bacteremia or merely contamination is a clinical dilemma. A total of 67 episodes of CoNS-positive blood cultures in pediatric and neonatal intensive care units were evaluated during a 3-year period in order to find the possible risk factors involved and the antimicrobial susceptibility of CoNS isolates. In this study, 37 episodes were judged to be infections as opposed to 30 that were not. In comparison with individuals without infection, patients with true infection of CoNS stayed longer in the hospital (32 ± 32.9 vs 10.7 ± 9.3 days, p=0.001), had more surgical procedures (32.4% vs 6.7%, p=0.014), received more antibiotic treatments in the recent 2 weeks (37.8% vs 0%, p<0.001), underwent more central venous catheter insertions (86.4% vs 10%, p<0.001), received more parenteral nutrition (37.8% vs 3.3%, p=0.001), had higher C-reactive protein profiles (4.8 ± 5.4 vs 0.6 ± 0.9 mg/dL, p<0.001), and had higher neutrophil proportion (58.1% vs 44.3%, p=0.001). However, there were no significant differences in corticosteroid therapy, hemoglobin level, total leukocyte count, and platelet count. All strains of the infection group were resistant to cefazolin, cefotaxime, penicillin, and erythromycin. Nonetheless, all isolates were susceptible to vancomycin. The percentage of multiple-resistant CoNS in the infection group was 96.9%. Empirical therapy with vancomycin for CoNS bacteremia in critically ill children is therefore recommended.

Key words: Antimicrobial susceptibility, bacteremia, coagulase-negative staphylococci, risk factors

Coagulase-negative staphylococci (CoNS), formerly regarded as harmless inhabitants of the skin and mucosal linings, are now recognized as a major cause of nosocomial bloodstream infections in critically ill patients, especially those in intensive care units, that leads to morbidity and even mortality [1-4]. They may represent up to 76% of positive blood cultures obtained from neonatal intensive care units [5]. Because CoNS are ubiquitous on the skin, they frequently contaminate blood cultures. Whether a positive blood culture isolate reflects true bacteremia or just a contaminant remains a question. However, clinicians should differentiate between the two in order to make the appropriate treatment. Moreover, no single supplementary test for the identification of true CoNS bacteremia had been found to be reliable [6]. The predisposing factors that had been identified include prematurity, low birth weight, the use of intravascular catheters (especially central venous catheters), presence of cerebrospinal fluid shunts, previous administration of antibiotics, long hospital stays, surgery during admission, multiple antibiotic resistance, C-reactive protein (CRP), white blood cell (WBC) count, platelet count, and white cell morphology [2,7-12].

We conducted a retrospective study to evaluate clinical and laboratory findings for positive blood cultures of CoNS in pediatric and neonatal intensive care units. The purpose of this study was to investigate the potential risk factors of CoNS bacteremia of these patients and the antimicrobial susceptibility of these isolates.

Materials and Methods

Patients

Patients from the neonatal and pediatric intensive care units of Taipei Veterans General Hospital who had blood culture positive for CoNS between July 1998 and June 2001 were enrolled in this study. Patients were excluded if they had polymicrobial blood culture findings. Coagulase-negative staphylococci isolated from the same patient more than 2 weeks apart were considered independent episodes.

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Data collection

Medical records of the enrolled cases were retrospectively reviewed. The possible risk factors of CoNS studied were as follows: duration of hospital stay, presence of central venous catheterization or cerebral fluid shunting, administration of antibiotics 2 weeks before obtaining blood culture, previous steroid therapy, parenteral nutrition, and surgery during admission. Laboratory data evaluated were as follows: hemoglobin, WBC, differential count, platelet count, and CRP level.

Bacterial isolation and identification

All blood specimens were incubated and monitored through the BACTEC 9240 series with continuous blood culture monitoring system using pediatric bottles (Becton-Dickinson Microbiology System, Sparks, MD, US). Each blood culture bottle containing 1 to 3 mL of blood was inoculated. Bottles were incubated at 37°C.

Bacterial identification and antimicrobial susceptibility were performed using the AutoSCAN-4 (Microscan Microbiology Autoanalyzer system, Baxter Healthcare Corp., CA, US) identification system. Microorganisms that resisted to 5 or more antibiotics were defined as multiple-antibiotic resistant.

Criteria used for the definition of CoNS bacteremia

On the basis of literature review [15,16], a true bacteremia was defined as either the growth of the same strain of CoNS in sequential blood cultures or a positive blood culture accompanied by clinical signs of sepsis. The clinical signs of sepsis in children were described as any 2 of the followings: temperature instability, hypotension, irritability, acute respiratory distress and change of consciousness. On the other hand, contaminant was defined as a positive blood culture without any accompanying clinical sign of sepsis.

Data analysis

Comparison between groups was made through the Mann-Whitney *U* test for nonparametric variables. Categorical analyses were performed using chi-square test, or the Fisher's exact test when cell sizes were less than 5. Statistical significance was defined as $p<0.05$.

Results

Epidemiological findings

A total of 67 episodes of CoNS bacteremia were isolated from 60 patients enrolled in this study, accounting for 36.8% of the total number of positive blood cultures in neonatal and pediatric intensive care units during this study period (182 episodes). *Staphylococcus epidermidis* was the major species, accounting for 44 (65.7%) episodes of isolates. *Staphylococcus capitis* accounted for 10 (15.9%) episodes; *Staphylococcus haemolyticus*, 3 (4.4%) episodes; *Staphylococcus simulans*, 3 (4.4%) episodes; *Staphylococcus warneri*, 2 (2.9%) episodes; *Staphylococcus hominis*, 2 (2.9%) episodes; *Staphylococcus cohnii*, 2 (2.9%) episodes; and *Staphylococcus auricularis*, 1 (1.5%) episode. Thirty-seven episodes of CoNS positive blood culture were considered true infections while 30 episodes were considered contaminations.

Demographic, clinical, and laboratory findings

The clinical findings, demographic, and laboratory data were summarized in Table 1. There were no significant differences in terms of sex distribution and mean age

Table 1. Characteristics of children with positive coagulase-negative staphylococci in blood culture

Clinical characteristics/laboratory data	Infection group n = 37 (%)	Non-infection group n = 30 (%)	*p*
Age (mo)	52.2 ± 47.0	34.3 ± 33.2	NS
Sex (M/F)	20/17	16/14	NS
Duration of hospital stay before positive culture (days)	32.0 ± 32.9	10.7 ± 9.3	0.001
Surgery during this admission	12 (32.4)	2 (6.7)	0.014
Antibiotic therapy in recent 2 weeks	14 (37.8)	0	<0.001
Steroid therapy during this admission	4 (10.8)	0	0.086
Central venous catheters in place	32 (86.4)	3 (10.0)	<0.001
Parenteral nutrition	14 (37.8)	1 (3.3)	0.001
Hemoglobin (mg/dL)	12.2 ± 2.5	12.2 ± 2.3	NS
Leukocyte count ($x10^3$ /mm^3)	13.0 ± 6.0	11.9 ± 5.9	NS
Platelet count ($x10^3$ /mm^3)	256 ± 122	310 ± 138	NS
CRP (mg/dL)	4.8 ± 5.4	0.6 ± 0.9	<0.001

Abbreviations: NS = not significant; CRP = C-reactive protein

between infection and non-infection groups. Days of hospital stay before positive blood culture of the infection group was longer than the non-infection group (32 ± 32.9 vs 10.7 ± 9.3 days, p=0.001). In comparison with the non-infection group, patients with true CoNS infection underwent more surgical procedure (32.4% vs 6.7%, p=0.014), received more antibiotic treatment in the past 2 weeks (37.8% vs 0%, p<0.001), had more central venous catheter insertions (86.4% vs 10%, p <0.001), and received more parenteral nutrition (37.8% vs 3.3%, p=0.001). However, in this study, although the infection group seemed to have a longer history of previous corticosteroid therapy than the non-infection group, there was no significant difference (10.8% vs 0%, p=0.086).

Laboratory data shows that the infection group had a higher CRP profile (4.8 ± 5.4 vs 0.6 ± 0.9 mg/dL, p <0.001) and proportionally more neutrophils (58.1% vs 44.3%, p=0.001). However, there were no significant differences in hemoglobin level, leukocyte count, and platelet count.

Antimicrobial susceptibility

The antimicrobial susceptibility profile of CoNS isolated from 67 episodes is shown in Table 2. All strains of the infection group were resistant to cefazolin, cefotaxime, penicillin, and erythromycin. All isolates were susceptible to vancomycin. The percentage of multiple-resistant CoNS was 96.9% in the infection group and 80.1% in the non-infection group. There was no significant difference in terms of multiple resistance rates between the 2 groups.

Discussion

Coagulase-negative staphylococci are now being recognized as the most common cause of nosocomial infections in intensive care units, even though not all positive blood cultures of CoNS represent true bacteremia because CoNS in the skin flora commonly causes contamination of blood cultures [13,14]. This makes the evaluation of a positive blood culture difficult in individual patients. Nonetheless, differentiating between true infection and contamination remains important since treatment of CoNS septicemia may be expensive and complicated.

Several studies have used subjective or objective criteria to determine whether specific bloodstream isolates of CoNS were contaminations or represented bloodstream infections [15-19]. Nataro *et al* [19] proposed that an isolate be considered an infection if the same CoNS strain was isolated from 2 or more blood culture specimens, at least one of which was a peripheral percutaneous specimen. On the other hand, all strains isolated from only one blood culture when more than one specimen was drawn was defined as contamination. Herwaldt *et al* [16] proposed a definition of coagulase-negative staphylococcal bloodstream infection in adults, which included a temperature of higher than 38°C on the day of the first positive blood culture specimen, treatment with vancomycin, or the removal of a potentially infected foreign body. Furthermore, the episode was required to meet the attending physician's implicit definition of infection based on the University of Iowa Hospitals and Clinics criteria for nosocomial bloodstream infection. The latter documented a positive predictive value of 26% for true infection.

Based the definitions on previous studies [6,15,16], sequential blood cultures growing the same strain of CoNS, or a positive blood culture accompanied by clinical signs of sepsis were defined as true infections. In contrast, contaminants were defined as positive blood cultures without any accompanying clinical signs of sepsis. Fifty-five percent of isolates met our strict definition of bloodstream infection. This true infection

Table 2. Antimicrobial susceptibility profile of coagulase-negative staphylococci

Antimicrobial agent	No. of resistant isolates	
	Infection group n = 37 (%)	Non-infection group n = 30 (%)
Ampicillin	36 (97.2)	27 (90.0)
Cefazolin	37 (100)	30 (100)
Cefotaxime	37 (100)	30 (100)
Clindamycin	27 (72.9)	13 (43.3)
Erythromycin	37 (100)	28 (93.3)
Gentamicin	34 (91.8)	24 (80.0)
Oxacillin	36 (97.2)	20 (66.6)
Penicillin	37 (100)	27 (90.0)
Tetracycline	26 (70.2)	22 (73.3)
Trimethoprim/sulfamethoxazole	15 (40.5)	12 (40.0)
Vancomycin	0	0

rate was higher than the findings of Herwaldt *et al*. But in another study, the investigators suggested that no more than 2% of cultures were likely to represent contaminants with CoNS in the neonatal intensive care unit population [20].

The present findings were consistent with the data of other investigators in detailing specific host risk factors for CoNS nosocomial infections in children. Children with CoNS bacteremia were more likely to have central lines in place [21,22]. Central venous catheters may serve as a portal for the introduction of skin flora CoNS. In addition, several authors have demonstrated that CoNS adhere to catheter surfaces and produce extracellular substances, including slime, thus making them inaccessible to phagocytes and antibiotics [15,23].

Avila-Figueroa *et al* [24] demonstrated intravenous lipid emulsions were the more important risk factors for CoNS bacteremia (adds ratio, 9.4). In contrast, the relative importance of intravenous catheters as independent risk factors had declined. The administration of lipids and parenteral nutrition through central catheters may serve as a growth medium and allow rapid bacterial proliferation.

This study suggests that surgery might be a risk factor of CoNS bacteremia in children. In the infection group, 10 patients (12 episodes) received surgery, including tracheostomy, cardiac surgery, cerebral fluid shunting, operation for necrotizing enterocolitis, and thoracotomy. In previous studies, CoNS were important causative agents in postoperative sepsis. There was perioperative invasion of the bloodstream by bacteria but the symptoms were seldom noted until a long time had elapsed postoperatively [25].

Some investigators showed that the administration of corticosteroids served as a risk factor for CoNS bacteremia [26]. However, there was no statistically significant difference in our data. This may be due to the small sample size evaluated.

Previous studies had reported the usefulness of complete blood cell count, differential count, and platelet count in the identification of infected children [27]. Some investigators found the association of thrombocytopenia with CoNS septicemia [28]. Baumgart *et al* [29] reported increased immature/total neutrophil ratio in infants infected with CoNS, whereas other studies found that hematological values are likely to be normal in CoNS infected infants [19]. Lyytikainen *et al* [30] evaluated clinical and laboratory findings in leukemic patients with blood cultures positive for *S. epidermidis* and showed that increased CRP over 24 h from the first positive blood culture was significantly higher in true bacteremia than in contaminants. Noel *et al* [31] showed a correlation between assumed CoNS sepsis and a CRP of more than 30 mg/L, a leukocytosis or leukopenia (WBC <4000 or >12 000 /mm^3), and thrombocytopenia (platelet <100 000 /mm^3). Kite *et al* [32] studied the comparison of 5 tests used in the diagnosis of neonatal bacteremia: the neutrophil count, immature/total neutrophil ratio, CRP, nitroblue tetrazolium test, and an acridine orange leukocyte cyto spin test. No single test gave satisfactory sensitivity, specificity, and positive predictive accuracy. Huang *et al* [9] showed that abnormal white cell count and abnormal white cell morphology correlated with CoNS bacteremia. In this study, CRP and neutrophil proportion are better indicators of CoNS bacteremia than total leukocyte count and platelet count.

In previous studies, patients whose central venous catheters remained in place were 2.9 times more likely to experience a recurrence than those whose catheters were removed. Catheter retention might result in a significantly higher risk for the recurrence of bacteremia [12]. Thus, unless necessary for the patient's condition, central venous catheters must be removed as soon as possible.

Patients with CoNS bacteremia were usually nosocomially infected. These isolates were usually resistant to multiple antibiotics [19]. The present findings revealed high resistance to β-lactam antibiotics. In cases of multiply resistant strains of CoNS, antibiotic treatment with vancomycin or teicoplanin is recommended.

In summary, CoNS are the important nosocomial pathogens in intensive care units, especially in neonatal intensive care units. Central venous catheter *in situ*, administration of parenteral nutrition, prolonged hospital stay, surgery during admission, and previous antibiotic administrations are the potential risk factors of CoNS bacteremia in children. The emergence of multiresistant strains of CoNS is a critical problem that clinical practitioners should be concerned about.

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