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Coagulase-negative Staphylococcal Infections in the Neonatal Intensive Care Unit

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Abstract

Background—Coagulase-negative staphylococci (CoNS) are the most commonly isolated pathogens in the neonatal intensive care unit (NICU). CoNS infections are associated with increased morbidity including neurodevelopmental impairment.

Objective—Describe the epidemiology of CoNS infections in the NICU. Determine mortality among infants with definite, probable, or possible CoNS infections.

Methods—We performed a retrospective cohort study of all blood, urine, and cerebrospinal fluid cultures from infants <121 postnatal days.

Setting—248 NICUs managed by the Pediatrix Medical Group from 1997 to 2009.

Results—We identified 16,629 infants with 17,624 episodes of CoNS infection: 1734 (10%) definite, 3093 (17%) probable, and 12,797 (73%) possible infections. Infants with lower gestational age and birth weight had a higher incidence of CoNS infection. Controlling for gestational age, birth weight, and 5-minute Apgar score, infants with definite, probable, or possible CoNS infection had lower mortality—OR=0.74 (95% confidence interval; 0.61, 0.89), OR=0.68 (0.59, 0.79), and OR=0.69 (0.63, 0.76)—compared to infants with negative cultures ($P<0.001$). No significant difference in overall mortality was found in infants with definite CoNS infection compared to those with probable or possible CoNS infection—OR=0.93 (0.75, 1.16) and OR=0.85 (0.70, 1.03), respectively.

Conclusions—CoNS infection was strongly related to lower gestational age and birth weight. Infants with clinical sepsis and culture-positive CoNS infection had lower mortality rates than

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POTENTIAL CONFLICTS OF INTEREST

Naomi Jean-Baptiste: None.

Daniel K. Benjamin Jr.: Disclosures may be viewed at www.dcri.duke.edu/research/coi.jsp.

Michael Cohen-Wolkowicz: None.

Vance G. Fowler Jr.: Consultant for Aprida, Astellas, Cubist, Inhibitex, Johnson & Johnson, Leo, Merck, Theravance; principal investigator for Astellas, Cerexa, Cubist, Inhibitex, Merck, Nabi, Theravance.

Matthew Laughon: Consultant for Nycomed, Astellas, Pfizer.

Reese H. Clark: Employee of Pediatrix-Obstetrix Center for Research and Education.

P. Brian Smith: Disclosures may be viewed at www.dcri.duke.edu/research/coi.jsp.

MANUSCRIPT PREPARATION

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infants with clinical sepsis and negative blood culture results. No difference in mortality between infants diagnosed with definite, probable, or possible CoNS infection was observed.

Keywords

nosocomial infection; infant; prematurity; *Staphylococcus*

Coagulase-negative staphylococci (CoNS) are the most commonly isolated pathogens in the neonatal intensive care unit (NICU).^{1–3} CoNS typically demonstrate low virulence^{1,2} but are associated with morbidities in the premature infant, including chronic lung disease and adverse neurodevelopmental outcomes.^{2, 4–9} CoNS infections are also associated with prolonged hospital stay and increased hospital costs.¹⁰

These organisms are skin commensals, and isolation in culture may reflect culture contamination. Several definitions of CoNS sepsis exist. Repeated isolation of CoNS from blood cultures may represent contamination if samples are obtained >1 day after institution of appropriate antibiotic therapy.¹¹ Some investigators have defined CoNS infection as either two positive blood cultures drawn within two days of each other or one positive blood culture and observed elevated C-reactive protein within two days of the CoNS positive culture.² For patients <1 year of age, the Centers for Disease Control and Prevention defines CoNS infection as the presence of clinical sepsis (e.g., hyperthermia, hypothermia, apnea, or bradycardia) and isolation of CoNS organisms, either cultured from two or more blood cultures drawn on separate occasions or obtained from at least one blood culture in a patient with an intravascular line, where the physician begins appropriate antimicrobial therapy.¹² The common objective of these various definitions is to distinguish CoNS infection from CoNS contaminant.

In the following study, we sought to describe the epidemiology of CoNS infection in the NICU and determine the mortality for infants with definite, probable, or possible CoNS infection in a large cohort of infants. We hypothesized that infants with definite CoNS infection would have lower gestational age, lower birth weight, and higher mortality than infants with probable or possible CoNS infection.

METHODS

Study Design and Setting

We identified all blood, cerebrospinal fluid (CSF), and urine cultures obtained from a cohort of infants <121 postnatal days admitted to 248 NICUs in the United States managed by the Pediatrix Medical Group between 1997 and 2009. The database was created using a computer-assisted tool that generates clinical progress notes. We collected demographic information as reported in the clinical progress note including: birth weight, gestational age, sex, maternal race/ethnicity, 5-minute Apgar score, maternal age, method of delivery (vaginal vs. Cesarean section), place of delivery (inborn vs. outborn), presence of mechanical ventilation, use of antenatal steroids, and exposure to antenatal antibiotics. Cultures were processed according to the protocols at each hospital's clinical microbiology laboratory. We included urine cultures obtained by any method of collection (suprapubic tap, in-and-out catheterization, bag specimen).

Definitions

Using previously reported criteria, we defined CoNS infection in one of three ways: *definite* CoNS infection as two positive cultures drawn on the same day¹¹; *probable* CoNS infection as two positive cultures within a four-day period, three positive cultures within a seven-day

period, or four positive cultures within a ten-day period; and *possible* CoNS infection as a culture positive for CoNS that did not meet criteria for definite or probable CoNS infection.²

We defined separate episodes of CoNS infection as positive CoNS cultures obtained >21 days following the previous positive CoNS culture. During data analysis, we defined patients with multiple episodes of CoNS infection by their highest-ranking CoNS episode. For example, a patient with one definite episode of CoNS and one possible episode of CoNS infection was defined as having definite CoNS infection. We defined mortality as death that occurred prior to discharge from the NICU.

Statistical Methods

The unit of observation used for analysis was the infant. We used univariable and multivariable logistic regression with backward selection (*P* value for removal of 0.2) to examine potential risk factors for definite or probable CoNS infection. We used logistic regression to compare the risk of death between infants with CoNS infection and those with negative blood cultures, and to evaluate the relationship between duration of CoNS infection and mortality adjusting for gestational age, birth weight, and 5-minute Apgar score. STATA 10 (College Station, TX) was used to perform all statistical analyses. Significance for all tests was established at a *P* value of <0.05. Permission to conduct this analysis was provided by the Duke University Institutional Review Board.

RESULTS

Study Population

From 1997 through 2009, the Pediatrix Medical Group cared for a total of 527,518 infants. Of these, 388,331 infants had at least one blood, urine, or CSF culture, and 34,851 (9%) of these infants had at least one positive blood, CSF, or urine culture. Of these infants, 16,629 (48%) had a total of 17,624 episodes of CoNS infection: 1734 (10%) definite, 3093 (17%) probable, and 12,797 (73%) possible CoNS infections (Figure 1).

Demographics

Infants with definite, probable, or possible CoNS infection had lower gestational ages and birth weights compared to infants with negative cultures (Table 1). Episodes of CoNS infection decreased with increasing gestational age (Figure 2). The cumulative incidence of definite, probable, or possible CoNS infection decreased from 5.4/1000 patient days at 23 weeks' gestational age to 0.8/1000 patient days at 34 weeks' gestational age. For birth weight, the cumulative incidence of definite, probable, or possible CoNS infection decreased from 4.5/1000 patient days in infants with birth weights of 600–699 g to 1.7/1000 patient days in infants with birth weights of 1400–1499 g (Figure 3). The development of definite or probable CoNS infection was strongly associated with lower birth weights (Table 2). On multivariable analysis, gestational age and birth weight <750 g were associated with development of definite or probable CoNS infection (Table 3). We found that infants with higher birth weights had a decreased incidence of definite and probable CoNS infection—OR=0.40 (95% confidence interval; 0.35, 0.46).

Onset of CoNS Infection

In this population, large numbers of possible CoNS infection were noted at birth but decreased between day of life 0 and postnatal day 3 (Figure 4). The number of definite and probable episodes of CoNS infection was highest between postnatal day 7 and postnatal day 14. The duration of positive cultures during episodes of CoNS infection ranged from one to 28 days; the median (10th, 90th percentile) duration of positive cultures in infants with

definite, probable, or possible CoNS infection was 3 days (1, 14), 3 days (2, 12), and 1 day (1, 1), respectively.

The majority of definite, probable, or possible episodes of CoNS infection were isolated bloodstream infections (Table 4). Isolation of CoNS from blood and urine in the same episode occurred in 11.5% of the episodes of definite CoNS infection. Diagnosis of definite or probable CoNS infection from only urine, CSF, or a combination of both urine and CSF was unusual; $\leq 1\%$ of the episodes of definite or probable CoNS infection had only positive urine, CSF, or a combination of both urine and CSF.

Mortality

The overall mortality for infants with definite, probable, and possible CoNS infection was 148/1500 (10%), 245/2588 (9%), and 643/10,575 (6%), respectively. After adjusting for gestational age, birth weight, and 5-minute APGAR score, we found no difference in overall mortality between infants with definite CoNS infection compared to those with probable (OR=0.93 [0.75, 1.16]) or possible CoNS infection (OR=0.85 [0.70, 1.03]). We also found that, compared to infants with negative cultures, infants with definite, probable, or possible CoNS infection had lower mortality—OR=0.74 (0.61, 0.89), OR= 0.68 (0.59, 0.79), and OR=0.69 (0.63, 0.76), respectively. Infants with positive CoNS cultures for >14 days had increased mortality relative to infants with shorter durations of positive CoNS cultures (OR=1.38 [1.08, 1.75]).

DISCUSSION

In this study, we found a strong association between CoNS infections and lower gestational age and lower birth weight. This finding is consistent with previous studies.^{2,5} Preterm, low-birth-weight infants are more likely to require prolonged use of central catheters, prolonged use of parenteral nutrition, and mechanical ventilation—all risk factors for CoNS infection. We found that episodes of CoNS infection increased in the second postnatal week, and we found no difference in mortality between infants with definite, probable, or possible CoNS infection. Most surprisingly, we found lower mortality in infants diagnosed with CoNS compared to infants with negative cultures.

Consistent with our hypothesis, infants with the lowest gestational ages and birth weights had the highest incidence of CoNS infection. Interestingly, we observed a slightly higher incidence in CoNS infections in term infants (37–42 weeks' gestation) compared to infants born near-term (34–36 weeks' gestation). Most of the observed increase was due to the presence of possible CoNS infection. It is believed that this observation may be attributable to the underlying reason for the infant's admission to the NICU. Infants in the NICU at 34 weeks' gestational age are there primarily for feeding and growth, but, beyond this gestational age, the more likely it is that the infant has a serious underlying issue (e.g., a congenital anomaly, respiratory difficulties) that may increase his/her susceptibility to CoNS infection.

In our study, the highest incidence of CoNS infection was observed between postnatal day 7 and 14. This observation is consistent with findings from prior research⁴ and with the status of CoNS as one of the primary pathogens isolated in late-onset sepsis.^{1,2, 13} CoNS infection has been equated to a disease of medical advancement.¹⁴ The emergence of CoNS as a nosocomial infection has coincided with the use of life-extending measures such as intravascular catheters and mechanical ventilators, devices through which CoNS gains access to normally sterile body fluids.¹⁵ In our study, the vast majority of CoNS infections were isolated bloodstream infections, and only a small fraction of definite or probable CoNS infections were attributed to urine or CSF culture. One explanation for this observation is

that diagnosis of CoNS infection was made primarily through blood cultures with lumbar punctures, and urine cultures are not always performed in infants with suspected infection in the NICU.¹⁶ It is possible that we have underestimated the true incidence of urinary tract infections, as not all infants had urine obtained.

The similarity in mortality between infants with definite, probable, or possible CoNS sepsis in our study may be attributed to the low virulence of CoNS. Specifically, CoNS may be virulent enough to lead to increased morbidity,^{2, 4-9} but the organism is not sufficiently virulent to cause mortality unless the bacteremia (organism burden) is prolonged. Previous studies have documented an association between persistent recovery of pathogens from normally sterile body sites and adverse outcomes including death.¹⁷⁻¹⁹ Prolonged infections have been attributed to inappropriate antibiotic therapy or the delay in removal of contaminated in-dwelling catheters.²⁰ Although the mortality attributed to CoNS infection compared to more virulent organisms historically has been significantly lower,^{1,2,21, 22} we observed a higher mortality for infants with persistently positive culture (>14 days); this is consistent with previous studies. Mortality is similar between CoNS and non-CoNS pathogens (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas* spp., *Enterococcus* spp. *Enterobacter cloacae*) for prolonged infections.¹⁸

The finding that infants with CoNS infection had lower mortality than infants with negative cultures may be attributable to an overestimation of the number of CoNS infections in this cohort of infants. Although we used published criteria to define CoNS infection, we may have overestimated the incidence of CoNS infection, particularly in the probable and possible categories, as many neonatologists only obtain a single blood culture.²³ Additionally, the small amount of blood (often <1 mL) obtained from infants for culture increases the risk for false-negative blood culture results for other infections.²⁴ Missing true infections associated with increased mortality (Gram-negative rods and *Candida*) may also account for the finding of increased mortality in infants with negative cultures compared to those with CoNS infection.

Although several researchers have proposed algorithms for distinguishing between true CoNS infections and contaminants,^{11, 25-28} no gold standard exists. Because presenting signs are usually nonspecific, definitive diagnosis of CoNS infection in infants is difficult.²⁹ Further complicating the diagnosis is the fact that CoNS are a component of normal skin flora and thus can potentially contaminate blood cultures drawn peripherally or through venous catheters.³⁰ The inability to distinguish between infection and contamination can lead to more laboratory tests, longer hospital stays, and unnecessary antibiotic exposures.^{26, 31} As proposed by Zaidi et al., a possible solution would be to obtain two peripheral blood cultures at the time of every sepsis evaluation.¹¹

A strength of this study was the large sample size and diversity of NICUs included. We had access to contemporary culture data from blood, urine, and CSF, allowing us to evaluate the contributions of these cultures to the diagnosis of CoNS infection. This study was limited by precise documentation of the timing and dosage of antimicrobial therapy. We also lacked information about clinical signs of infection in the infant and the presence and removal of central venous catheters. Collection of urine via bag method may have also increased the risk of contamination relative to samples collected by in-and-out catheterization or suprapubic tap. We made no attempt to relate CSF cultures to CSF parameters (glucose, protein, white blood cell count) or urinalysis results and acknowledge that some positive cultures may have represented skin contamination. Finally, we lacked information on site-specific practices on skin disinfection (i.e., alcohol, chlorhexidine).

In summary, we found that CoNS infection was strongly related to lower gestational age and birth weight. We found no difference in mortality between infants diagnosed with definite, probable, and possible CoNS infection. We also found lower mortality in infants with clinical sepsis and CoNS positive cultures compared to infants with clinical sepsis and negative cultures. Future studies focusing on the differences in morbidities between infants with definite, probable, or possible CoNS infection are needed to further explore the long-term effect of CoNS infection in infants in the NICU.

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Figure 1.
Study population. CoNS, coagulase-negative staphylococcus; NICU, neonatal intensive care unit.

Figure 2. Coagulase-negative staphylococcal infection rates by gestational age—infants 23–42 weeks per 1000 patient days. CoNS, coagulase-negative staphylococcus.

Figure 3. Coagulase-negative staphylococcal infections by birth weight—infants 600–1499 g per 1000 patient days. CoNS, coagulase-negative staphylococcus.

Figure 4. Coagulase-negative staphylococcal infection by day of life. CoNS, coagulase-negative staphylococcus.

Table 1

Infant Characteristics

	Definite CoNS sepsis	Probable CoNS sepsis	Possible CoNS sepsis	Negative cultures
Number of patients	1725	3004	11,900	370,538
Gestational age, n (%)				
<26 weeks	588 (32)	929 (31)	2185 (18)	8465 (2)
26–28 weeks	570 (33)	1037 (35)	3070 (26)	19,004 (5)
29–33 weeks	379 (22)	682 (23)	3175 (27)	91,810 (25)
34–36 weeks	102 (6)	138 (5)	1269 (11)	111,301 (30)
≥37 weeks	115 (7)	216 (7)	2180 (18)	139,541 (38)
Birth weight, n (%)				
<750 g	564 (33)	952 (32)	2223 (19)	8438 (2)
750–1000 g	461 (27)	778 (26)	2305 (19)	12,751 (3)
1001–1500 g	382 (22)	710 (24)	2648 (22)	36,696 (10)
1501–2000 g	115 (7)	208 (7)	1258 (11)	62,336 (17)
2001–3500 g	169 (10)	286 (10)	2633 (22)	196,821 (53)
>3500 g	33 (2)	67 (2)	810 (7)	52,770 (14)
Race/ethnicity, n (%)				
White	795 (47)	1337 (46)	5349 (46)	187,544 (53)
African American	422 (25)	681 (23)	2462 (21)	60,800 (17)
Hispanic	396 (23)	778 (27)	3171 (28)	90,054 (25)
Other	82 (5)	114 (4)	524 (5)	17,642 (5)
Sex, n (%)				
Male	947 (55)	1604 (53)	6786 (57)	209,067 (56)
5-minute Apgar score, n (%)				
<3	95 (6)	147 (5)	420 (4)	5384 (1)
4–6	368 (22)	609 (21)	1754 (15)	23,141 (6)
7–10	1235 (73)	2195 (74)	9432 (81)	334,190 (92)
Mechanical ventilation day of life 1, n (%)	1268 (79)	2189 (80)	6632 (64)	75,186 (22)
Cesarean delivery, n (%)	1167 (68)	2058 (69)	7488 (64)	198,688 (54)
Inborn, n (%)	1343 (79)	2291 (78)	9080 (78)	312,222 (86)
Maternal age, n (%)				
10–19 years	274 (16)	410 (14)	1681 (14)	44,921 (12)
20–29 years	868 (51)	1523 (51)	6005 (51)	186,062 (50)
30–39 years	517 (30)	965 (32)	3803 (32)	126,113 (34)
≥40 years	57 (3)	97 (3)	355 (3)	11,845 (3)
Antenatal steroids, n (%)	1148 (67)	1983 (66)	6264 (53)	108,397 (29)
Antenatal antibiotics, n (%)	729 (42)	1316 (44)	4612 (39)	135,130 (36)

NOTE. CoNS, coagulase-negative staphylococcus.

Table 2

Association of Birth Weight with Development of Definite or Probable CoNS Infection

Birth weight (g)	Odds ratio (95% confidence interval)
<750	51.2 (47.0–55.8)
750–1000	30.0 (27.5–32.8)
1001–1500	14.4 (13.1–16.0)
1501–2000	6.6 (5.9–7.5)
>2000	1.0*

NOTE. CoNS, coagulase-negative staphylococcus;

*
reference.

TABLE 3

Risk Factors for CoNS Sepsis

	Univariable analysis Odds ratio (95% CI)	Multivariable analysis Odds ratio (95% CI)
Birth weight (g)		
≥1500	1.00 (REF)	1.00 (REF)
1250–1499	6.62 (5.87, 7.46)	
1000–1249	14.43 (13.06, 15.96)	
<u>750–999</u>	30.05 (27.52, 32.82)	
<750	51.23 (47.04, 55.80)	1.56 (1.49, 1.63)
Gestational age (weeks)	0.71 (0.70, 0.71)	0.87 (0.86, 0.89)
Sex		
Female	1.00 (REF)	1.00 (REF)
Male	0.91 (0.85, 0.96)	1.06 (0.99, 1.14)
5-minute APGAR score		
0–3	1.00 (REF)	
4–6	0.94 (0.82, 1.09)	
7–10	0.24 (0.21, 0.27)	
Ventilator on day 1		
No	1.00 (REF)	1.00 (REF)
Yes	12.35 (11.48, 13.29)	2.28 (2.06, 2.54)
Birth method		
Vaginal birth	1.00 (REF)	1.00 (REF)
Caesarean section	1.84 (1.73, 1.96)	1.12 (1.04, 1.22)
Antenatal steroids		
No	1.00 (REF)	1.00 (REF)
Yes	4.57 (4.30, 4.86)	1.21 (1.11, 1.31)
Antenatal antibiotics		
No	1.00 (REF)	1.00 (REF)
Yes	1.32 (1.25, 1.40)	1.47 (1.05, 2.06)
Premature rupture of membranes		
No	1.00 (REF)	1.00 (REF)
Yes	0.36 (0.33, 0.38)	0.86 (0.79, 0.93)
Race/ethnicity		
White	1.00 (REF)	1.00 (REF)
Black	1.58 (1.47, 1.70)	
Hispanic	1.14 (1.06, 1.22)	1.23 (1.14, 1.33)
Other	0.98 (0.84, 1.13)	

Table 4

Site of CoNS Infection

	Definite sepsis N (%)	Probable sepsis N (%)	Possible sepsis N (%)
Blood only	1469 (84.7)	2927 (94.6)	11,756 (91.9)
Urine only	3 (0.2)	30 (1.0)	764 (6.0)
CSF only	7 (0.4)	32 (1.0)	216 (1.7)
Urine/CSF	1 (0.1)	1 (0.0)	1 (0.0)
Blood/urine	199 (11.5)	58 (1.9)	42 (0.3)
Blood/CSF	55 (3.2)	45 (1.5)	18 (0.1)

NOTE. CSF, cerebrospinal fluid; CoNS, coagulase-negative staphylococcus.