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ORIGINAL ARTICLE

Distinguishing true coagulase-negative *Staphylococcus* infections from contaminants in the neonatal intensive care unit

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Objective: To characterize true coagulase-negative *Staphylococcus* (CoNS) infections in infants receiving neonatal intensive care.

Study Design: Retrospective cohort study of neonatal intensive care unit (NICU) infants with clinical sepsis and CoNS isolated from ⩾2 blood cultures (BCs) *or* one BC *and* a sterile site (proved infection) *or* CoNS isolated from one BC *and* deemed significant after blinded data review (probable infection).

Result: In all, 98% of 40 proved and 96% of 55 probable infections occurred in infants with birth weight (BW) <2000 g and gestation <34 weeks. Total central lines (CLs) placed, but not CL duration or presence *in situ*, predicted proved (odds ratio (OR) 3.5, 95% confidence interval (CI) 1.4 to 8.3; $P = 0.005$) and probable infection (OR 2.7, 95% CI 1.3 to 5.6; $P = 0.007$) by multivariate analysis as did lethargy and gastric residuals.

Conclusion: True CoNS infection is unlikely in infants with BW >2000 g and gestation >34 weeks. Total CL required for care, lethargy and gastric residuals predicted true CoNS infection.
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Keywords: coagulase-negative *Staphylococcus*; neonate; sepsis; late-onset sepsis; blood culture contaminants

Introduction

Over the past 50 years, advances in neonatal intensive care have resulted in improved survival of increasingly preterm, lower birth weight (BW) infants. One consequence of increased survival is an increased risk for sepsis because of the many manipulations required for infant's management.[1,2] Case-fatality rates have varied according to neonatal characteristics and pathogen, ranging from 0 to 74% in contemporary series of neonatal sepsis.[3–10] The diagnosis of sepsis in the neonatal intensive care unit (NICU) setting is difficult as clinical features are non-specific, but sepsis can rapidly progress and even be fatal before the infecting pathogen has been identified.[3,4,8,9]

Coagulase-negative staphylococci (CoNS) are commensal skin flora but these organisms account for up to one-half of reported bloodstream infections in very low birth weight (<1500 g) infants.[3,4,7–9,11] CoNS present a particular dilemma because their isolation from a single blood culture (BC) in an NICU patient can reflect contamination rather than true bacteremia. The difficulty inherent in distinguishing true infections from culture contaminants potentially results in over-representation of CoNS in NICU sepsis incidence data, despite attempts to define infection using clinical and laboratory parameters or duration of antimicrobial therapy.[3,12–15] These issues lead to considerable variation in practice among neonatologists.[16] The aim of our study was to define factors that would distinguish true CoNS bloodstream infection from BC contamination.

Methods

The study cohort was taken from a larger group of infants evaluated for invasive staphylococcal disease in a NICU during the 30-month period from 1 January 2000 through 30 June 2002.[6] Woman's Hospital of Texas serves women with uncomplicated and high-risk pregnancies and has had >8000 deliveries annually since 1999. The NICU consists of a 40-bed level III and 80-bed level II unit staffed by 10 full-time neonatologists. Ill term or near term infants with complex surgical problems (for example, congenital heart disease) are transferred to a tertiary care children's hospital. The study was approved by the Institutional Review Boards for Human Research of Baylor College of Medicine and Woman's Hospital of Texas.

All neonates admitted to NICU who had CoNS isolated from any site during the study period were identified through microbiology laboratory records. Infants with CoNS isolated from a sterile body site (blood, cerebrospinal fluid (CSF), pleural or joint fluid, bone, abscess material or soft tissue aspirate, excluding urine and tracheal aspirate) and whose medical record was available for review were included. Infants whose only isolate was from a non-sterile site or

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urine were excluded. Data from medical records were entered onto a standardized form. Data entered included demographics, antenatal history, mode of delivery, complications of prematurity, hyperalimentation, central line (CL) use, clinical presentation of episodes where CoNS was isolated, anti-infective use during the clinical episode as well as indication and duration, laboratory test results, history of prior CoNS colonization, diagnostic imaging results, therapeutic interventions, and clinical outcome.

Proved CoNS infection was defined as $\geqslant 1$ clinical sign of neonatal sepsis (temperature instability, cardio-respiratory signs, gastrointestinal disturbance, lethargy or irritability) in infants who had isolation of CoNS (same species and/or identical antimicrobial susceptibility results) from two or more BC, *or* from one BC (CL or peripheral vessel) *and* usually sterile body site.[9,17] Molecular typing of CoNS isolates was not performed. Probable infection was defined as isolation of CoNS from a single BC or usually sterile body site culture where it was deemed a probable pathogen after independent review of all clinical and laboratory data by at least two of three pediatric infectious disease specialists. Episodes associated with contaminants were defined as isolation of CoNS from a single blood or usually sterile site culture where criteria for probable infection were not met. Proved meningitis was defined as a positive CSF culture and BC, because although CSF cultures can be positive in the absence of bacteremia in this population, acceptance of a less strict definition would lead to misclassification of culture contaminants when the infecting organism is CoNS. Skin, soft tissue and bone or joint complications were defined by clinical signs with supporting culture or radiographic findings (for example, osteomyelitis). Peritonitis was defined by positive peritoneal cultures. Endocarditis was presumptively diagnosed if vegetations and/or thrombi were detected in the heart or great vessels by two-dimensional echocardiography. Mortality was classified as CoNS related if the infant had a positive blood or CSF culture within 48 h of death or if the likely etiology of death or sequelae (for example, multiorgan failure) was a direct result of the infant developing CoNS infection.

Statistical analyses were performed using SPSS 13 for Windows (SPSS, Chicago, IL, USA). Where CoNS was isolated during more than one episode of evaluation for sepsis in a single infant, only the first episode was analyzed and descriptive statistics were performed for multiple episodes. Proved and probable CoNS infections and episodes associated with contaminants were compared for maternal and neonatal characteristics, clinical features at onset, laboratory data, therapy and outcome. Proved and probable infections were compared and each was compared with contaminant episodes. Statistical significance for dichotomous outcomes was determined by χ^2 and Fisher's exact tests. Normally distributed data were assessed by mean values and the Student *t*-test; where positive or negative skewing of data occurred, statistical significance was assessed by median values and the Mann–Whitney *U*-test. When appropriate, multiple logistic regression analysis, where variables with a *P*-value of $\leqslant 0.2$ on univariate testing were included in further analysis, assessed the significance of variables.

Results

Incidence of CoNS

From 1 January 2000 through 30 June 2002, 2785 neonates, 579 (21%) of whom were very low birth weight (<1500 g), were admitted to the level II or III NICU. CoNS was isolated from blood or a usually sterile body site culture in 134 infants (4.8%) on one, 13 (0.5%) on two and 2 (0.1%) on three occasions during hospitalization. Of 149 first episodes of CoNS, 40 (27%) were proved, 55 (37%) probable and 54 (36%) contaminants. Infants from whom CoNS was isolated had a mean BW of 1391 g (range 400 to 3870) and gestation at birth of 29.57 weeks (range 22.14 to 41.57); 69 (47%) were white, 45 (30%) black, 25 (17%) Hispanic, 5 (3%) Asian and 5 (3%) were other ethnicity.

Infants with lower BW were more likely to have multiple episodes where CoNS was isolated ($\leqslant 750$ g, 20%; 751 to 1000 g, 13%; 1001 to 1250 g, 4%; >1250 g, 0; $P = 0.006$). The median interval between multiple episodes was 51 days (range 14 to 137). Five (33%) second episodes were proved, 6 (40%) probable and 4 (27%) contaminants; one-third episode was probable and one was a contaminant. There was no relationship between the clinical or laboratory characteristics of first episodes and likelihood of developing multiple episodes ($P = 0.67$). The remainder of the analysis is for first episodes only.

Maternal and infant characteristics

Proved and probable CoNS infections occurred most often in very low birth weight infants (proved 93%, probable 91%, contaminant 50%; $P<0.001$); 98% of 40 proved and 95% of 55 probable infections occurred in infants with BW <2000 g and gestation at birth <34 weeks (Figure 1). In addition to BW and gestational age (GA), use of antenatal steroids, mode of delivery and some underlying conditions of prematurity (Table 1) predicted proved or probable CoNS infection by univariate but not by multivariate analysis.

Risk factors for infection

Most proved (95%) and probable (98%) CoNS infections occurred at >72 h of age compared with 52% for contaminants ($P \leqslant 0.001$). Fifty-eight percent of infants did not have a CL at sepsis evaluation. Potential factors increasing risk for proved and probable infection were evaluated by univariate analysis as summarized in Table 2.[1–3,17–19] By a multivariate model that evaluated risk factors for infection and also accounted for BW and GA, an increasing number of CLs before infection predicted proved CoNS infection (odds ratio (OR) 3.5, confidence interval (CI) 1.4 to 8.3 for each additional CL; $P = 0.005$) and having a CL *in situ* at the time of sepsis did not (OR 0.1, CI 0.01 to 0.7; $P = 0.03$). Number of CLs

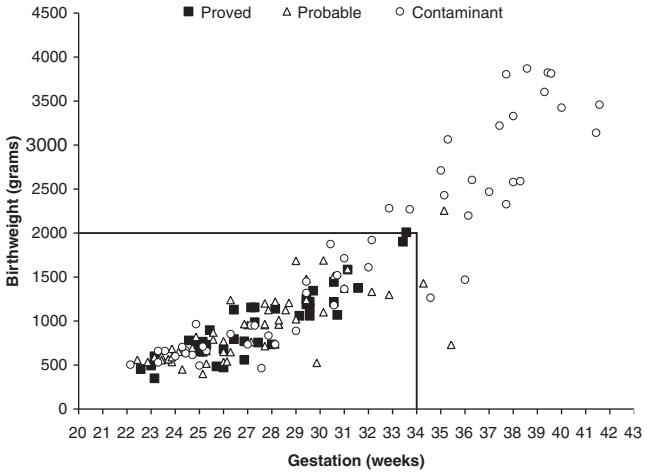

Figure 1 Distribution of 149 infants with proved and probable coagulase-negative *Staphylococcus* (CoNS) infections or contaminated sterile site cultures associated with birthweight (BW) and gestation. The majority of proved and probable infections occurred in infants of BW <2000 g and gestation at birth <34 weeks.

also predicted probable infection (OR 2.7, CI 1.3 to 5.6; $P = 0.007$) but having a CL *in situ* at evaluation did not (OR 0.11, CI 0.02 to 0.72; $P = 0.02$).

Description of clinical syndromes

The most frequent clinical findings prompting sepsis evaluations in all infants, regardless of infection category, were hypoxia, apnea and bradycardia, and lethargy (Table 3). By multivariate analysis, however, only lethargy (OR 8.5, CI 2.1 to 34.5, $P = 0.003$ for proved vs. contaminant; OR 6.1, CI, 1.6 to 23.3, $P = 0.009$ for probable vs. contaminant) and gastric residuals (OR 7.4, CI 1.3 to 41.1, $P = 0.02$ for proved vs. contaminant; OR 6.5, CI 1.2 to 35.3, $P = 0.03$ for probable vs. contaminant) independently predicted CoNS infection.

CoNS was isolated from the bloodstream of 130 (87%) infants overall. The mean duration of bacteremia was 2.9 days (range 1 to 5) for proved infection, 26 (65%) had involvement of other organs or body sites. Three infants had endocarditis; the mean duration of vancomycin for these patients was 33.5 days and all recovered. Two

Table 1 Mother-infant characteristics for proved and probable CoNS infections in NICU infants

Characteristics	*Proved (N = 40)*	*Probable (N = 55)*	*Contaminant (N = 54)*	*P-value*[a]		
				Proved vs. Contaminant	*Probable vs. Contaminant*	*Proved vs. Probable*
Maternal						
Gravidity[b]	2.4 (1–8)	2.2 (1–6)	2.5 (1–6)	0.759	0.191	0.199
Parity[b]	0.7 (0–5)	0.6 (0–3)	0.7 (0–5)	0.391	0.693	0.599
Multiple gestation[c]	27 (68)	22 (40)	12 (22)	0.346	0.063	0.522
Antenatal steroids[c]	32 (80)	41 (75)	25 (46)	0.001	0.002	0.8
Antenatal antibiotics[c]	25 (63)	38 (69)	44 (81)	0.058	0.183	0.518
Vaginal delivery[c]	9 (22)	11 (20)	25 (46)	0.029	0.004	0.796
Infant						
Birthweight (g)[b]	954 (350–2009)	929 (400–2255)	1784 (465–3870)	<0.001	<0.001	0.76
Gestational age (weeks)[b]	27.4 (22.6–33.6)	27.3 (22.4–35.4)	31.7 (22.1–41.6)	<0.001	<0.001	0.96
Male	17 (43)	31 (56)	29 (54)	0.304	0.848	0.216
Respiratory distress syndrome[c]	39 (98)	51 (93)	33 (61)	<0.001	<0.001	0.394
Chronic lung disease[c]	29 (73)	42 (76)	21 (39)	0.001	<0.001	0.99
Hypotension[c]	34 (85)	50 (91)	28 (52)	0.001	<0.001	0.518
Patent ductus arteriosis[c]	19 (48)	27 (49)	17 (31)	0.136	0.079	0.99
Patent ductus arteriosis ligation[c]	16 (40)	21 (38)	14 (26)	0.658	0.99	0.445
Steroids[c]	18 (45)	31 (56)	19 (35)	0.396	0.035	0.304
Intraventricular hemorrhage[c]	8 (20)	16 (29)	8 (15)	0.584	0.105	0.349
Necrotizing enterocolitis[c]	10 (25)	16 (29)	10 (19)	0.458	0.262	0.816
Retinopathy of prematurity[c]	37 (93)	47 (85)	21 (39)	<0.001	<0.001	0.727

Abbreviations: CoNS, coagulase-negative *Staphylococcus*; NICU, neonatal intensive care unit.
[a]Univariate analysis.
[b]Mean (range).
[c]No. (%).

Table 2 Risk factors for proved and probable CoNS infections in NICU infants

All infants	*Proved (N = 40)*	*Probable (N = 55)*	*Contaminant (N = 54)*	*P-value*[a]		
				Proved vs. Contaminant	*Probable vs. Contaminant*	*Proved vs. Probable*
Age (days)[b]	16 (1–100)	12 (2–59)	4 (0–115)	<0.001	<0.001	0.153
Intravascular catheter						
In situ[c]	16 (40)	25 (45)	22 (41)	0.99	0.7	0.677
Previously[c]	39 (98)	51 (93)	28 (52)	<0.001	<0.001	0.394
Number of catheters[b]	2 (0–6)	3 (0–4)	1 (0–4)	<0.001	<0.001	0.961
Catheter days[b]	11 (0–73)	8 (0–39)	0.5 (0–114)	<0.001	<0.001	0.156
Total parenteral nutrition						
At time of infection[c]	33 (83)	42 (76)	22 (41)	<0.001	<0.001	0.612
Previously[c]	39 (98)	51 (93)	26 (48)	<0.001	<0.001	0.99
TPN days[b]	12.5 (0–55)	9.5 (0–54)	0 (0–80)	<0.001	<0.001	0.147
Previously colonized[c]	8 (20)	11 (20)	2 (4)	0.017	0.015	0.99
Subset with late-onset sepsis	*Proved (N = 39)*	*Probable (N = 54)*	*Contaminant (N = 28)*	*Proved vs Contaminant*	*Probable vs Contaminant*	*Proved vs Probable*
Age (days)[b]	17 (6–100)	12.5 (4–59)	11 (4–115)	0.018	0.286	0.059
Intravascular catheter						
In situ[c]	15 (38)	24 (44)	16 (57)	0.145	0.353	0.671
Previously[c]	38 (97)	50 (93)	23 (82)	0.075	0.262	0.395
Number of catheters[b]	2 (0–6)	3 (0–4)	2 (0–4)	0.069	0.07	0.934
Catheter days[b]	11.5 (0–73)	8 (0–39)	6 (0–114)	0.032	0.224	0.126
Total parenteral nutrition						
At time of infection[c]	33 (85)	41 (76)	22 (79)	0.538	0.99	0.435
Previously[c]	39 (100)	50 (93)	26 (93)	0.171	0.28	0.99
TPN days[b]	13 (4–55)	10 (0–54)	6.5 (0–80)	0.002	0.023	0.121
Previously colonized[c]	8 (21)	11 (20)	2 (7)	0.174	0.20	0.99

Abbreviations: CoNS, coagulase-negative *Staphylococcus*; NICU, neonatal intensive care unit; TPN, total parenteral nutrition.
[a]Univariate analysis.
[b]Median (range).
[c]No. (%).

infants had bone or joint infection (septic arthritis, hip; left ulna osteomyelitis).

Meningitis was diagnosed in six infants. One of three infants with proved and each of three with probable infection had an intraventricular hemorrhage. Isolation of CoNS was not associated with CSF pleocytosis.

Additional laboratory parameters

The complete blood count was not helpful in defining infants with proved or probable CoNS infection. Hemoglobin and hematocrit were lower in these infants compared with those with contaminants (hemoglobin, proved 11.3 g dl^{-1}, probable 12.5 g dl^{-1}, contaminant 14.3 g dl^{-1}, $P = 0.009$; hematocrit, proved 32.8%, probable 36.9%, contaminant 41.5%, $P \leqslant 0.001$) but there were no differences in either white cell or platelet counts ($P = 0.76$ and $P = 0.14$, respectively). C-reactive protein determination was not routinely performed during sepsis evaluation.

Thirty-one infants had more than one organism isolated during the CoNS illness. There was no significant difference in the proportion of infants in each group who had polymicrobial infections (15% proved, 20% probable, 26% contaminants, $P = 0.428$). Infants with polymicrobial proved or probable infections had similar GA, BW and clinical features to those with proved or probable CoNS infection alone (data not shown).

Treatment

All infants with proved or probable infection and 31 of 54 (57%) with contaminants received vancomycin in combination with gentamicin for initial therapy. The median duration of vancomycin therapy for proved and probable infection was 13 and

Table 3 Clinical findings and sites of involvement in proved and probable CoNS infections in NICU infants[a]

All infants	*Proved (N = 40)*	*Probable (N = 55)*	*Contaminant (N = 54)*	*P-value*[b]		
				Proved vs. Contaminant	*Probable vs. Contaminant*	*Proved vs. Probable*
Clinical findings						
Hypoxia	31 (78)	36 (65)	21 (39)	<0.001	0.012	0.257
Temperature instability	9 (23)	7 (13)	6 (11)	0.162	0.99	0.269
Apnea and bradycardia	24 (60)	28 (51)	15 (28)	0.001	0.019	0.4
Hypotension	8 (20)	17 (31)	14 (26)	0.624	0.672	0.25
Emesis	3 (8)	3 (5)	0	0.074	0.342	0.694
Abdominal distension	17 (43)	16 (29)	10 (19)	0.02	0.262	0.196
Gastric residuals[c]	15 (38)	12 (22)	3 (6)	<0.001	0.024	0.111
Diarrhea/blood in stool	3 (8)	1 (2)	1 (2)	0.309	0.99	0.307
Lethargy[c]	18 (45)	18 (33)	4 (7)	<0.001	0.002	0.285
Irritability	2 (5)	0	0	0.178	0.99	0.175
Disease expression						
Bacteremia	40 (100)	51 (93)	39 (72)	<0.001	0.006	0.136
Skin and soft tissue	19 (48)	12 (22)	5 (9)	<0.001	0.112	0.014
Endocarditis/endocarditis equivalent[d]	3 (8)	0	0	0.074	0.99	0.071
Meningitis	3 (8)	3 (5)	5 (9)	0.99	0.489	0.69
Bone or joint infection	2 (5)	0	0	0.178	0.99	0.175
Peritonitis	1 (3)	4 (7)	2 (4)	0.99	0.679	0.394

Abbreviations: CoNS, coagulase-negative *Staphylococcus*; NICU, neonatal intensive care unit.
[a]No. (%).
[b]Univariate analysis.
[c]$P<0.05$ on multivariate analysis.
[d]Endocarditis equivalent: portal vein thrombosis.

12 days, respectively, and 3 days for contaminants ($P \leqslant 0.001$ for each analysis). Twenty infants (37%) with contaminants received vancomycin for 5 or more days.

When a CL was *in situ* at the time of sepsis evaluation, the CL was removed more often in those infants with proved than other categories of infection (12/16 (75%) proved, 4/25 (16%) probable, 3/18 (16%) contaminant; $P \leqslant 0.001$); the median duration of bacteremia after CL removal was 2 days (range 0 to 5). Surgical drainage was uncommon, required in nine (eight skin/soft tissue, one bone and joint) proved and seven probable infections.

Outcome

In all, 15 infants (10%) with CoNS isolated during a sepsis evaluation died (4 (10%) proved, 7 (13%) probable and 4 (7%) contaminant). CoNS infection contributed to deaths of two (5%) infants with proved infection. One 1070 g BW, 30 weeks GA infant developed CoNS bacteremia associated with necrotizing enterocolitis, intestinal perforation and multiorgan failure; bacteremia persisted for 4 days and peritoneal fluid cultures only grew CoNS. The other infant (655 g BW, 25 weeks GA) developed CoNS bacteremia on day of life 8 resulting in prolonged respiratory and renal insufficiency until her death some weeks later.

Discussion

CoNS are ubiquitous commensals that colonize the skin and gastrointestinal tract of up to 99% of newborn infants by day 3 of life.[20,21] Since colonization precedes invasion, it is not surprising that the developmentally immature immune system of preterm infants is vulnerable to invasive CoNS infection. Our investigation focused on the spectrum of illness that occurs when CoNS is isolated from blood or other usually sterile sites, excluding urine. We identified clinical features that support and others that, in some instances unexpectedly, are not helpful in differentiating true bloodstream infection from BC contamination. Our most important finding is that virtually all proved or probable invasive CoNS infection occurred among infants with BW <2000 g and GA <34 weeks at birth. To correctly define CoNS bloodstream infection assumes great importance in era of increasing antimicrobial resistance, where inappropriate prescribing of antibiotics, in particular vancomycin, should be avoided.[22] Lack of randomized

prospective studies of CoNS infection in preterm infants where only a single culture is available for assessment is problematic. Decisions made on the basis of a single culture rely heavily on data such as serum concentrations of inflammatory markers (for example, C-reactive protein) where non-infectious disorders often confound interpretation, or on length of therapy received by infants where criteria for treatment and clinical practice varies greatly.[3,15,16]

Our findings, although limited by retrospective design, provide potentially useful data for clinicians evaluating need for vancomycin use in NICU infants. First, among our 149 infants, proved and probable CoNS infection occurred almost exclusively in infants with BW and GA <2000 g and 34 weeks at birth, respectively (Figure 1), suggesting that when these demographic characteristics are absent, isolation of CoNS most likely reflects contamination of the culture specimen. This observation is consistent with the known developmental immaturity of more preterm infants' innate and adaptive immune function added to concomitant medical conditions that require invasive procedures allowing CoNS to invade skin, respiratory and gastrointestinal barriers.[23–26] Second, many factors predisposing infants to late-onset sepsis[1–3,18] predicted CoNS infection by univariate analysis, but having a CL at evaluation did not. Having CL *in situ* increases suspicion for sepsis and prompts evaluation. However, the number of CLs inserted since birth rather than duration was the significant factor differentiating between proved/probable bloodstream infections and BC contaminants. While the need for increasing numbers of CLs undoubtedly was a surrogate for increased medical complexity in infants, our findings suggest that each breach of the skin barrier more than doubles the likelihood that isolation of CoNS from a BC reflects true infection. This finding may reflect increased opportunity for infection to become established or define a subset of infants even more immunocompromised within the already vulnerable study cohort or a combination of both. Third, while signs of proved and probable CoNS infection are non-specific, the presence of lethargy or gastric residuals appear useful in defining proved CoNS whereas potentially more ominous clinical findings such as hypotension were of limited value.

While our demographic, risk factor and clinical findings provide a framework to assist in determining the implication of a single BC isolate growing CoNS, they do not replace sufficient culture data. Obtaining two BCs from separate sites at sepsis evaluation remains the 'gold standard' for diagnosing CoNS infection.[14] One noteworthy finding was that despite the perception of CoNS bloodstream infection as 'benign'[3,7,8,27,28] these infections have potential in the NICU infant to cause profound illness and even death.[6,10] Not only did some CoNS-infected infants present with findings associated with severe sepsis, but 67% of those in whom the diagnosis was proved had involvement of multiple body sites, 25% required surgical intervention (predominantly for skin and soft tissue complications) and 5% had CoNS-attributable mortality. Prolonged antibiotic courses were needed for endocarditis (8%) and for the rare bone and joint complications more typically associated with *Staphylococcus aureus*.[29] The report by Khashu *et al*.[30] of persistent CoNS bacteremia and thrombocytopenia in preterm infants is consistent with our findings. Overestimation of CoNS infections through misclassification of blood or sterile site culture contaminants contributes to a misperception that CoNS infection is benign and this emphasizes the importance of evaluating potentially infected infants with at least two BCs as well as obtaining culture of focal sites (for example, abscesses) if present. We conclude that routine collection of two BCs from separate sites would eliminate a substantial proportion of cases where there is diagnostic confusion and would facilitate timely discontinuation of vancomycin therapy. Empirical therapy could be provided until optimal culture data are available, but in the circumstance of negative or a single BC growing CoNS in infants >34 weeks' gestation and BW >2000 g, vancomycin could be discontinued, resulting in substantial reduction in vancomycin use.

Conflict of interest

Dr Healy is the recipient of research grants from Sanofi Pasteur and Novartis Vaccines and Diagnostics and is on an advisory board for Novartis Vaccines and Diagnostics. Dr Palazzi has received research grants from Merck and Astellas Pharma, serves on a data safety monitoring board for Pfizer and on a speaker's bureau for Sanofi Pasteur. Dr Edwards is a consultant for Novartis Vaccines and Diagnostics.

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