Coagulase Negative Staphylococci in the Neonatal Intensive Care Unit: Are We Any Smarter?

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Drs Nash, Chu, Bhatti, Alexander, Schreiber, and Hageman have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gaps

1. Distinction between definitions and subsequent management of true coagulase negative staphylococcus infections versus contamination or colonization needs to be established.
2. Evidence of the potential clinical impact (ie, neurodevelopmental outcome) of coagulase negative staphylococcus infections in the neonatal population is lacking and further study is needed.

Abstract

Coagulase negative staphylococci are increasingly common organisms isolated in the evaluation of neonates with sepsis. However, there is a lack of consensus on the definition of true infection and the criteria for treatment. This article presents clinically useful methods to distinguish true infection from contamination. Additionally, we describe clinically relevant virulence factors contributing to the pathogenicity of various species. Knowing these virulence factors may help to stratify patient risk for serious infection. There are inconsistent data regarding the clinical importance of coagulase negative staphylococcal infections in the neonatal population. This inconsistency highlights the importance of establishing a consensus for the diagnosis and treatment of these infections in both the clinical and research arenas.

Objectives

After completing this article, readers should be able to:

1. Propose clinically useful definitions of true infection with coagulase negative staphylococcus.
2. Use definitions of coagulase negative staphylococcal infection as a guide for a more standard approach to diagnosis and treatment.
3. Describe the virulence factors of coagulase negative staphylococcus and their clinical importance in pathogenicity.
4. Highlight treatment and prevention strategies for coagulase negative staphylococcal infections.

Abbreviations

CFU:	colony-forming unit
CoNS:	coagulase negative staphylococci
CRP:	C-reactive protein
CSF:	cerebrospinal fluid
MALDI-TOF:	matrix-assisted laser desorption/ionization time of flight mass spectrometry
PIA:	polysaccharide intercellular adhesin
TPN:	total parenteral nutrition
TTP:	time to positivity

Introduction

Coagulase negative staphylococci (CoNS) are a commonly identified group of bacteria encountered in clinical sepsis evaluation of neonates. However, the true significance of isolating these organisms in neonates is frequently a matter of debate. There are barriers clouding accurate assessment of sepsis in the neonatal population. One of the largest

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barriers is the lack of a uniform definition of neonatal sepsis among care providers. This makes evaluation, diagnosis, and treatment course potentially different among providers, institutions, and clinical studies. Additionally, there is no consensus on how to determine whether CoNS isolates are true pathogens versus contaminants, and whether to treat. As CoNS are generally agreed upon as relatively innocuous organisms, some practitioners argue for limited or no treatment without clear evidence of infection. However, some researchers suggest evidence of deleterious neurodevelopmental outcomes associated with isolation of CoNS in sepsis evaluation, which supports more aggressive treatment. Even if the organism is felt to be a true pathogen, the mechanisms by which CoNS lead to unfavorable neurodevelopmental outcomes are unclear. These uncertainties continue to confound diagnosis and treatment approaches despite microbiological diagnostic advances. These advances include more rapid bacterial detection, improved species identification, and recognition of distinctive virulence characteristics among CoNS species.

This article will review the microbiology, virulence factors, and epidemiologic trends of CoNS within the neonatal population. Suggestions for a standard diagnostic and treatment approach will be proposed and applied to those studies addressing possible detrimental neurodevelopmental outcomes of neonatal sepsis.

Epidemiology

Coagulase-negative staphylococcal species are aerobic and facultatively anaerobic gram-positive organisms. There are over 30 species of CoNS, including *S capitis*, *S haemolyticus*, *S hominis*, *S lugdunensis*, *S saccharolyticus*, and *S saprophyticus*. CoNS are found as part of normal skin microbiota, colonizing primarily moist body surfaces such as the anterior nares, axillae, and groin area. *S epidermidis* is the most predominant species, found consistently in nearly three quarters of clinical isolates. (1) Other clinically relevant CoNS species include *S saprophyticus*, a pathogen in the genitourinary tract and *S lugdunensis*, a causative agent of endocarditis and sepsis.

CoNS are generally regarded as nonpathogenic skin commensals. They are largely attributed to the presence of foreign material (eg, central venous catheters or ventriculoperitoneal shunts) when found in sterile sites such as the blood or cerebrospinal fluid (CSF) in both immunocompetent and immunocompromised hosts. (2) Although CoNS are most commonly isolated in the blood, there are infrequent reports of isolation in tracheal, peritoneal, urine, and CSF cultures. The identification of CoNS in these normally sterile fluids likely results from the breakdown of normal physical barriers to bacterial entry. (3) CoNS are one of the most common agents causing nosocomial infection in all patients, including neonates. They are also one of the most common contaminants of clinical cultures. Consequently, determining their clinical significance poses a challenge, particularly in the neonatal population in which accurate assessment of bloodstream infection often proves difficult. Nosocomial infection represents infection acquired in a hospital or health-care setting that was not present or incubating at the time of admission, usually with onset of symptoms more than 48 hours after admission. (2)

According to the Centers for Disease Control and Prevention National Healthcare Safety Network, CoNS contribute to over 30% of hospital-wide central-line associated bloodstream infections, the most common type of nosocomial infection attributed to CoNS. (4) This is a change from previous trends of nosocomial infections. During the 1970s through 2000, there was a shift from gram-negative infections being most common, to gram-positive infections isolated more often, along with *Candida* spp and multidrug-resistant gram-negative organisms. This epidemiologic shift made CoNS the most commonly isolated organisms in the hospital setting, inclusive of pediatric and neonatal patients. (5) In the mid 1980s, the National Healthcare Safety Network reported that CoNS contributed to 10% and 31% of all general pediatric and NICU nosocomial infections, respectively. (6)

The increased frequency of CoNS nosocomial infection is concurrent with the changing hospitalized neonatal population. With advances in neonatal medicine and technology, there are now more premature infants surviving at younger gestational ages and at lower birth weights. In the 21st century, CoNS continue to be the most commonly isolated organisms attributed to late-onset sepsis in the NICU, particularly in very low birth weight neonates. (7)(8)(9)(10) It is believed that increased risk of nosocomial infection in this population is due to host factors such as relative immaturity of their immune system, along with dependence on technology, particularly the use of indwelling catheters, and prolonged hospital stays. As early as the 1970s, immunocompromised patients or those with an indwelling catheter were found to be the common variable in identified CoNS infection. (11)

True Pathogen or Not

Although CoNS have become an emerging player in nosocomial disease, the difficulty of how to distinguish true

infection from contamination when CoNS are isolated in neonatal patients remains. This dilemma results largely from inherent characteristics of the organism itself, specific difficulties in caring for and identifying sepsis in the neonatal patient population, and lack of consensus among neonatal providers. These factors interplay such that the inconsistency and confusion potentially leads to misdiagnosis and inappropriate treatment. (3)

Clinical Manifestations, Definitions, and Diagnosis of CoNS Infection

Clinical manifestations of CoNS sepsis can be subtle and are often nonspecific. They are often indistinguishable from sepsis caused by other organisms and even other disease entities. (12) Common clinical manifestations include temperature instability, hypoxemia, apnea, bradycardia, lethargy, and feeding intolerance. (13)(14) Once clinical features of sepsis are present and evaluation is undertaken, distinguishing CoNS skin colonization and contaminants from those causing true infection continues to be a challenge. There is no standard methodology by which cultures are appropriately collected and assessed. Further, the distinction between central line colonization versus bacteremia versus sepsis is often blurred. Clinicians define CoNS infection in varying ways: a single positive culture drawn after 72 hours of age; two positive cultures from blood samples drawn within 2 days of each other; or one positive culture drawn from a patient with an intravascular line, in the presence of clinical sepsis. (9)(15)(16)(17) None of these definitions differentiate contamination from true infection. The potential result of these varying definitions and practices is overrepresentation of CoNS as true pathogens. (13)

To address this problem, Craft and Finer (18) proposed a CoNS assessment algorithm. The algorithm provides clear definitions of bacteremia or "true infection," line colonization, and contamination. They defined bacteremia as positive blood cultures from a peripheral site and central line (if present) with the same organism and greater than 50 colony-forming units (CFU)/mL. Line colonization is defined as positive blood culture through central line with concurrent negative peripheral culture or less than 30 CFU/mL. Contamination is defined as a positive peripheral blood culture with less than 30 CFU/mL and concurrent negative central line blood culture. All cultures optimally contain at least 1 mL of blood. Accurate assessment is confirmed by repeating both the central line and peripheral culture, only the central line culture, or only the peripheral culture, based on what the initial set of cultures reveal (Fig 1). (18) More stringent adherence to this algorithm serves to decrease unwarranted antibiotic use.

There can be difficulty adhering to this algorithm as clinicians do not routinely obtain quantitative cultures, and instead commonly rely on automated continuous-monitoring blood culture systems. Haimi-Cohen et al (19) proposed an alternative by using time to positivity (TTP), which is the amount of time a blood culture bottle incubates before microbial activity is detected by the system. The incubation TTP correlates to level of bacterial density as TTP is inversely proportional to the inoculated bacterial concentration. A shorter TTP indicates a higher initial colony count. It was found that TTP with densities greater than 50 CFU/mL was less than 15 hours, whereas TTP with densities less than 10 CFU/mL was greater than 20 hours. (19) Several studies have also demonstrated that in neonates, a single blood culture with greater than 50 CFU/mL is indicative of infection, whereas a single blood culture with less than 5 to 10 CFU/mL suggests contamination. (20)(21)(22) Without relying on quantitation, one can employ TTP when following the Craft algorithm, such that TTP serves as an indicator of bacterial density and the likelihood of a true infection.

The difficulty in simply obtaining blood cultures further complicates the already existing challenges of uniformly defining neonatal sepsis and assessing blood culture results. In such small patients with inaccessible vasculature, it is often not feasible to obtain more than one blood culture. Collection of greater than or equal to two blood cultures during a neonatal sepsis evaluation has proven superior to only one blood culture. (22)(23)(24) Investigators demonstrated 31% increased frequency of CoNS infection diagnoses and 8.2% increased total use of vancomycin with the use of one blood culture versus two. More than one blood culture is optimal for establishing the diagnosis of bacteremia, line colonization, or contamination. However, even repeatedly positive blood cultures can signify contamination; multiple different CoNS species may falsely represent "persistent" bacteremia. (25) Consequently, there is no perfect culture method, though most evidence demonstrates that greater than or equal to two cultures of adequate blood volume (1 mL) is optimal. (14)(26)

Inflammatory markers, such as C-reactive protein (CRP), may provide additional information, particularly when trended, as to the likelihood of true infection versus contamination secondary to CoNS. A significantly or persistently elevated CRP level from a patient's previous level may be more indicative of true infection, in addition to

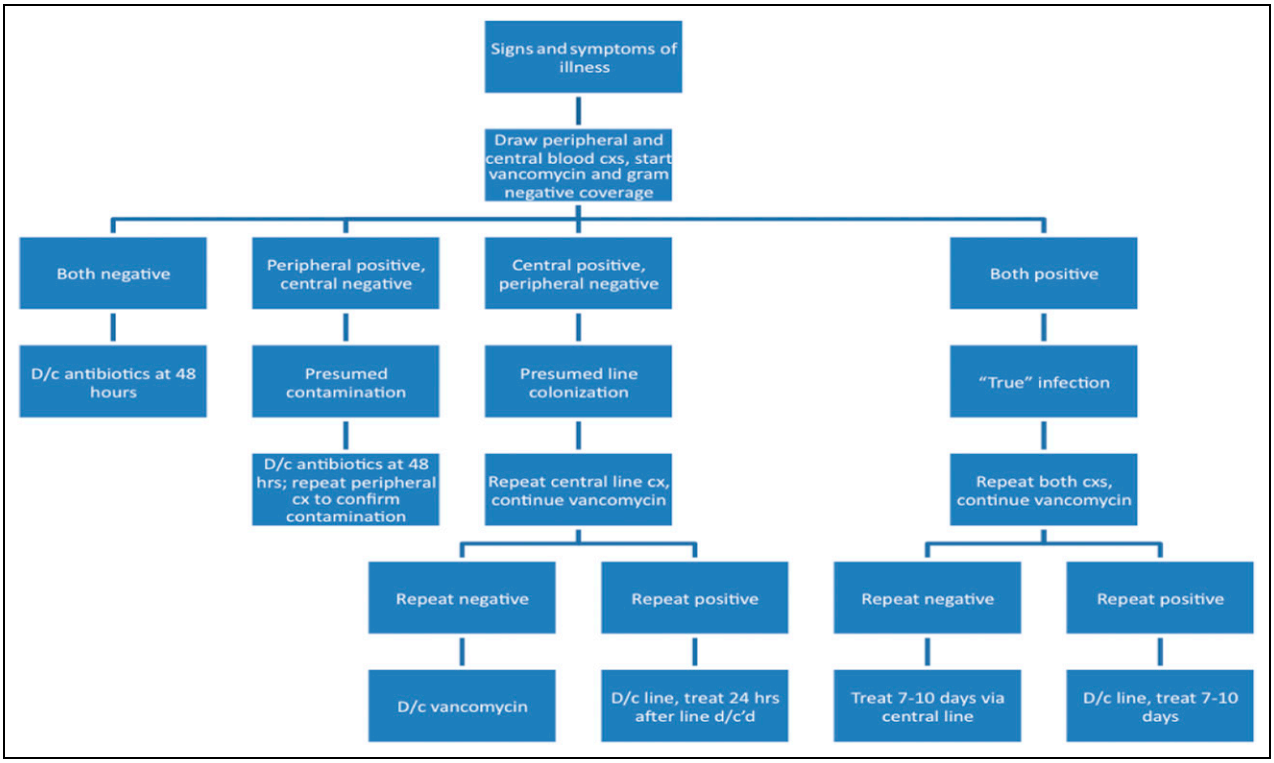

Figure 1. CoNS management algorithm. A decision tree for the management of CoNS diagnosis and treatment in the neonate, based on the type of culture(s) (peripheral versus central) and if there is culture growth. Adapted by permission from Macmillan Publishers Ltd.: Craft A, Finer N. Nosocomial coagulase negative staphylococcal (CoNS) catheter-related sepsis in preterm infants: definition, diagnosis, prophylaxis, and prevention. *J Perinatol*. 2001;21(3):186–192, copyright 2001.

a noted change in clinical status. (14)(18) Other inflammatory markers, such as interleukin-6 and procalcitonin, are less commonly used in the NICU, but are more recently discussed as possible more widely used markers of infection. (18) Elevated CRP may be helpful in the initial evaluation of neonatal sepsis; however, there is no one value that provides a clear confirmation of true infection, particularly in the face of inconsistently virulent CoNS.

CoNS Virulence Factors and Microbiological Advances

Advances in microbiologic detection of CoNS have allowed further speciation and opportunity to risk-stratify patients based on the known species. As we gain more knowledge about CoNS virulence factors, it may be beneficial to further identify the species in order to predict pathogenicity. The dilemma of persistent positive cultures potentially representing contamination with different CoNS species highlights one of the potential benefits of further speciation once CoNS are isolated.

Over the past several years, molecular diagnostic methods have allowed identification of the most prevalent molecular CoNS types causing sepsis and persistent infection via polymerase chain reaction and gel electrophoresis. Many CoNS types are found within NICUs, in the air, among health-care staff, and patients. Many fewer types are found in patients and health-care workers, suggesting cross-contamination and possible mechanism of persistence. (27)(28) However, Krediet et al (28) found that by examining CoNS isolates over an 11-year period, the majority of strains causing sepsis were attributable to very few molecular clusters, with one cluster responsible for more than 30% of infections. They also found among the most common molecular clusters a high rate of *mecA* gene carriage, which is responsible in part for β-lactam (methicillin) resistance, and may also select for persistence of a sepsis-causing CoNS strain. (28)

One of the more recent advances utilized for rapid bacterial identification is matrix-assisted laser desorption/ionization time of flight mass spectrometry, or MALDI-TOF. Using biomarkers and cellular protein content,

MALDI-TOF can speciate organisms grown in culture often in under an hour. *S epidermidis* is the most commonly isolated CoNS species across patient populations, and is the species most often associated with infection. *S haemolyticus*, *S lugdunensis*, *S warneri*, and *S hominis* are other more commonly isolated species proven to cause significant infection. (10)(12)(29) The pathogenic potential of a particular species or a species-specific epidemic may be identified if there is routine species identification. However, MALDI-TOF operational machinery is very expensive and requires a trained technician, making its routine use cost-prohibitive in some microbiology laboratory settings.

Several virulence factors have been identified among CoNS involving adhesion, aggregation, and biofilm production. Adhesion is the first step of bacterial entry into the host, whether by adherence to the host itself via the skin, or adherence to foreign material such as an intravascular catheter. By way of adhesin, bacteria can effectively bind to their host. (12) Production of biofilm follows adherence as the next most important virulence factor. The key elements of biofilm production are polysaccharides, termed polysaccharide intercellular adhesin (PIA) and capsular polysaccharide adhesin. (12)(30) PIA has hemagglutinin activity that prevents bacterial phagocytosis and killing. (31) Studies have demonstrated that CoNS' ability to produce slime, and the quantity of slime production, predicts infection severity. (32) Biofilm production is also found to impede T lymphocyte function and proliferation and to lessen the host inflammatory response. (10)(33)(34) When foreign material is present, plasma and extracellular matrix proteins come in contact with its surface, which later promotes bacterial colonization and biofilm production. (12) Biofilm production and its ability to efficiently adhere to polymer surfaces make treatment difficult without removal of the coated foreign material (Fig 2). (34)

Host Risk Factors

The most important host risk factors for CoNS infection in the neonatal population are prematurity and very low birth weight. In a recent retrospective study, the primary determinants of true CoNS sepsis (defined as two or more positive blood cultures with the same species and susceptibility profiles, and at least one clinical parameter of neonatal sepsis) were gestational age less than 34 weeks and birth weight less than 2000 g. (13) Infants with lower birth weight were also more likely to have repeated episodes of CoNS sepsis. (13)

Premature infants are particularly at risk for clinical deterioration with CoNS infections because of their immature immune system. Several suboptimal immune functions of premature infants have been described including the following: low C3 and IgG levels, reduced neutrophilic phagocytosis, impaired opsonic activity and intracellular killing, insufficient complement deposition, and poor cytokine response to CoNS. (10)(35)(36)(37)

As the presence of biofilm is a significant bacterial virulence factor, the presence of foreign material as a host risk factor augments this pathogenic potential. A study done by Healy et al (13) revealed that the number of central venous catheters inserted since birth, as opposed to the duration of one catheter, was most significant in determining real infection. The greater number of breaks in the skin for catheter insertion was a significant predictor of CoNS sepsis. (13)

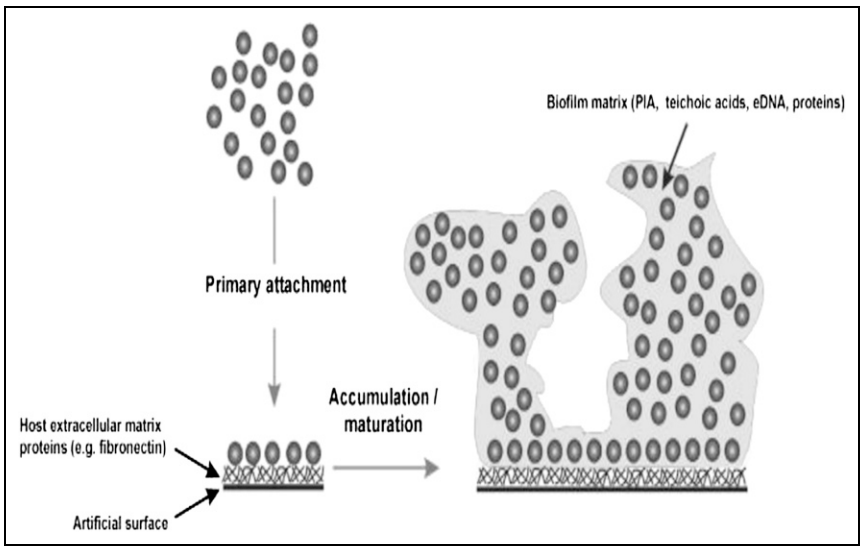

Figure 2. Representation of *S epidermidis* biofilm formation. Schematic representation of *S epidermidis* biofilm production. Primary attachment occurs as bacteria contact the surface in association with extracellular matrix proteins. *S epidermidis* then proceeds through the accumulative phase by using intercellular adhesive surface properties, namely PIA, forming a multilayered biofilm matrix composed of extracellular DNA (eDNA), proteins, and techoic acids. Rohde H, Frankenberger S, Zähringer U, Mack D. Structure, function and contribution of polysaccharide intercellular adhesin (PIA) to Staphylococcus epidermidis biofilm formation and pathogenesis of biomaterial-associated infections. Adapted from *European Journal of Cell Biology*. 89(1), 103–111, Copyright 2010, with permission from Elsevier.

There is also an association of increased risk of CoNS infection with the use of total parenteral nutrition (TPN), which some theorize is secondary to further immune system dysfunction from components within TPN. (38) Okada et al (39) found that whole blood and neutrophil bactericidal activity against CoNS was decreased in neonates who had received TPN for greater than or equal to 10 days. An overall increased risk of sepsis and persistent CoNS infection associated with TPN use, with or without a central venous catheter, has been demonstrated. (40)

Treatment

Antibiotics are the mainstay of therapy for CoNS, but because of the high rates of methicillin resistance, β-lactam antibiotics are not the first drugs of choice. Methicillin resistance conferred by the *mecA* gene is found in up to 90% of isolates. (10)(35) Consequently, the glycopeptide vancomycin is the first-line treatment choice for CoNS. Persistent infections may require combination therapy with another agent, such as rifampin. (41) Other agents, such as the aminoglycosides, linezolid, quinupristin and dalfopristin, and clindamycin, may have a role in organisms with alternative susceptibility profiles or more persistent organisms.

In addition to antimicrobial therapy, the presence of a central line and its removal becomes important, especially in those with persistent infection. Several studies have revealed that persistent culture positivity greatly affects morbidity and mortality with greater than or equal to four positive cultures and a central line still in place. (42)(43) Evidence of increased end-organ damage and mortality has been seen in neonatal patients with central access and more than three positive cultures. However, the same studies also revealed a nearly 50% rate of clearing infections without removal of central venous catheters. (43) This remains important in clinical practice when establishing access in very small infants proves difficult. It is recommended that if there are more than three positive cultures taken from a central line, it must be removed without further salvage attempts.

Prevention is also an important consideration. The efficacy of antibiotic and ethanol central line locks and continuous antibiotic infusions in neonatal patients with longstanding central catheters has been demonstrated in several studies. Garland et al (44) found that in patients with a central line in place for more than 2 weeks, using vancomycin line locks decreased the incidence of catheter-related bloodstream infections from 30% in those who did not receive line locks, to 5% in those that did receive them. Garland et al also found no increased vancomycin resistance with this prevention strategy, a concept that supports line locks over continuous low-dose infusion, or prophylaxis. Vancomycin prophylaxis has also shown to decrease the incidence of catheter-related bloodstream infections, but has more unclear risk of creating antibiotic resistance, and has not shown to be superior to line locks. (10)(18)(45) Ethanol locks have shown similar and sometimes better efficacy to vancomycin locks for CoNS line infection prevention and biofilm eradication. (46) Other prevention methods include antibiotic impregnated central lines and line dressings. Amidst these newer technologies, the foundation of all infection prevention efforts must include the following: vigorous hand hygiene, appropriate use of protective personal equipment, and sterile procedural techniques.

Clinical Impact/Future Implications

It remains controversial whether CoNS infections are associated with increased morbidity, including neurodevelopmental impairment. In one study of 16,629 infants, infants with clinical sepsis and CoNS-positive isolates actually had lower mortality rates than infants with clinical sepsis and negative blood cultures. (17) In contrast, two large cohort studies previously revealed a significant association between neurodevelopmental impairment and CoNS sepsis. (47)(48)

One US cohort study revealed that infants with sepsis secondary to CoNS and other microbiological agents had a statistically significant higher risk of poor physical disability scores on Bayley testing, and higher risk of cerebral palsy and visual impairment, compared with uninfected infants. (47) However, the definition of sepsis relied on one positive blood culture (from an unspecified source) and antibiotic therapy for greater than or equal to 5 days. Evaluating one CoNS-positive culture without knowledge of repeat culture, clinical status of the patient, or presence of central access makes it difficult to draw conclusions about whether true CoNS infection is present. Consequently, it is difficult to infer causality that neonatal CoNS infection causes detrimental neurodevelopmental outcomes.

Another large, multicenter cohort study of Swiss neonates also revealed an increased risk of cerebral palsy in infants with CoNS infection versus uninfected infants. (48) A more stringent definition of neonatal sepsis was employed; sepsis was defined as one or more positive blood or CSF cultures in an infant with clinical signs of infection and treated with greater than or equal to 5 days of antibiotics. (48) One runs into the same difficulties in

interpretation of true CoNS infection in this neonatal patient population. Without using a consistent diagnostic approach, appropriate interpretation of the presence of true CoNS infection is problematic.

CoNS cause a spectrum of disease, not only neonatal sepsis, but also central line colonization and bacteremia. Would clinicians consider all these diagnoses the same in terms of treatment and potential neurodevelopmental outcome? Many would suggest this is not the case. There is need for an algorithm similar to that mentioned above, wherein confirmation of true CoNS infection is sought out by a consistent definition of sepsis and culture collection (Fig 1). (18) When evaluating the above two studies, one does not have a uniform definition of neonatal sepsis, sepsis related to CoNS or other information to appropriately determine possible contamination.

If in fact CoNS infection does contribute to poor neurodevelopmental outcomes, the mechanisms by which this phenomenon occurs are unknown. On a cellular level, some groups hypothesize that bacterial products, even of low virulence, elicit a cytokine storm as part of a systemic inflammatory response. These cytokines directly damage the vulnerable, premature brain. This theory is clinically supported by studies that demonstrate magnetic resonance imaging changes of white matter injury in premature infants with bacterial infections and necrotizing enterocolitis. (49)(50) Additionally, impaired neurodevelopment postinfection may also be explained physiologically. The host inflammatory response may also affect the expression of vasoactive regulatory signals resulting in decreased cerebral blood flow. Not only could this lead to poor brain perfusion but also reperfusion injury and reactive oxygen species causing further brain parenchymal damage. (48)

Going forward, the neonatal medical community would benefit from a clear, working definition and management algorithm of neonatal CoNS sepsis by which providers reliably employ treatment plans. This will most accurately promote treatment for those patients with true CoNS infection. It will also avoid unnecessary treatment in those without true infection. In the future with any invasive neonatal infection including CoNS, it will be important to further clarify the role of true sepsis in neurodevelopmental outcome. Not only are clinical standards of assessment needed for CoNS diagnosis and treatment, but also for future neonatal research. It will help us glean more accurately the trends and outcomes of true neonatal CoNS infection. This information will allow other neonatal clinical providers to more accurately diagnose and appropriately treat neonates, allowing for the best outcome possible.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the infectious agents that cause neonatal sepsis.
- Know the epidemiology, prevention, and pathogenesis of neonatal infection with Staphylococcus aureus and Staphylococcus epidermidis.
- Know the clinical manifestations and diagnostic features of neonatal infections with Staphylococcus aureus and Staphylococcus epidermidis.
- Know the management, including understanding of antibiotic resistance, and complications of neonatal infection with Staphylococcus aureus and Staphylococcus epidermidis.
- Know the effective techniques for control of nosocomial infection in the nursery, neonatal intensive care unit, and obstetrical unit.

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NeoReviews Quiz
New minimum performance level requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit*™. In order to successfully complete 2013 *NeoReviews* articles for *AMA PRA Category 1 Credit*™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

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1. A 21-day-old, 29-weeks'-gestational-age female is on continuous positive airway pressure support and has advanced to 80ml/kg per day of enteral feeds and is receiving parenteral nutrition of 80ml/kg per day through a right upper extremity peripherally inserted central catheter. Over the past 24 hours, she has developed increased apnea and bradycardia, and an evaluation for sepsis is completed including blood, urine, and cerebrospinal fluid cultures. The blood culture grows coagulase negative staphylococcus. Which of the following factors would lead you most strongly to consider that this positive culture is a true infection and not a contaminated specimen?
   A. The culture shows a bacterial density of 5 CFU/ml.
   B. The time to positivity for the blood culture was at 14 hours after the culture was obtained.
   C. There were two cultures obtained, of which a peripheral blood culture was positive, whereas a culture obtained from the central line was negative.
   D. A C-reactive protein level obtained at the same time as the culture is not elevated.
   E. The same blood culture contains 2 different organisms, one with density of 5 CFU/ml, and the second with density of 10 CFU/ml.

2. A 3-week-old, 27-weeks'-gestational-age male has had clinical deterioration and two blood cultures (one peripheral and one from a central line) are positive for coagulase negative staphylococcus. He is re-intubated due to worsening respiratory status and he is placed on dopamine for hypotension. What is an appropriate concurrent step in management for this patient?
   A. The patient should be started on vancomycin.
   B. The patient should receive methicillin until sensitivities are confirmed.
   C. A third culture should be obtained prior to starting antibiotic therapies.
   D. All central lines should be removed and a new blood culture obtained. A new central line should be placed and antibiotics can be withheld unless the new culture is also positive.
   E. All other patients in the same room should undergo an evaluation for sepsis.

3. A 24-weeks'-gestational-age female develops coagulase negative staphylococcus (CoNS) infection at 4 weeks of age. The parents ask how this infection may impact her. Which of the following is true regarding the relationship between CoNS infection and short- and long-term outcomes?
   A. CoNS infection has been shown definitively to cause cerebral palsy for infants born before 28 weeks' gestational age.
   B. Compared with infections with positive blood cultures of other bacteria, CoNS infections are associated with significantly increased mortality in the neonatal period.
   C. One potential limitation in interpretation of studies that have shown an association of CoNS infection with neurodevelopmental delay is the lack of a consistent definition that demonstrates evidence of true clinical CoNS infection.
   D. One main reason that the possibility of potential brain injury arising from CoNS infection is unlikely is that there is no good theory as to the pathophysiology of how such an infection might lead to white matter injury.
   E. CoNS infections are unlikely to have any clinical impact as the large majority of positive cultures reflect contamination, particularly when a central line is in place.

4. The parents further ask why their child may have developed the CoNS infection. Which of the following is true regarding risk factors for developing CoNS infection?
   A. Any patient being cared for in the hospital is at similar risk for CoNS infection as it is a common hospital-based pathogen.
   B. For premature infants, particularly those born very early such as this 24-week-gestational-age infant, one episode of CoNS infection should lead to immunity, and she is unlikely to have another infection during her hospital course.
   C. Although parents as well as healthcare workers are advised to use precautions such as hand hygiene and sterile procedural techniques, those preventive therapies are primarily aimed at gram negative species and would be unlikely to have any role in preventing CoNS infection.
   D. Longer use of parenteral nutrition, both with or without use of a central line, has been associated with increased risk of CoNS infection.
   E. As length of line placement is more likely to confer higher risk than number of lines placed, a policy of removing and re-inserting central lines every 1-2 weeks may decrease the risk of developing CoNS infection.

5. You are discussing the care of patients with CoNS infection during rounds. A pediatrics resident asks you what differences exist amongst various CoNS species. Which of the following is true?
   A. Staph haemolyticus is the most commonly isolated CoNS species and most commonly associated with infection.
   B. Although there have been many CoNS species identified, each having differing characteristics with in vitro testing, there are no differences from a clinical standpoint in terms of source of infection or virulence.
   C. Staph lugdunensis can be a causative agent of endocarditis and sepsis.
   D. Staph epidermidis is most commonly found as a pathogen in the genitourinary tract.
   E. Infections with all species of CoNS have continued to decline in the past four decades with the routine use of antenatal prophylaxis with antibiotics for most mothers in preterm labor.

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