

Commentary

Nosocomial Coagulase Negative Staphylococcal (CoNS) Catheter-Related Sepsis in Preterm Infants: Definition, Diagnosis, Prophylaxis, and Prevention

Alissa Craft, DO
Neil Finer, MD

Nosocomial infections with coagulase negative staphylococcus (CoNS) are a frequent and significant cause of morbidity in the preterm infant. Infections diagnosed after the first 72 hours of life are arbitrarily deemed to be “nosocomial.” There are many difficulties encountered in efforts to evaluate and compare nosocomial sepsis in the NICU. An issue of primary concern is the lack of uniformity in the definition of sepsis in the NICU. Based on the frequency of positive blood cultures in infants less than 1000 g, it appears reasonable to evaluate methods for the prevention of nosocomial sepsis. These include prophylactic antibiotic administration, antiseptic impregnated catheters, and the use of an antibiotic lock technique.

Journal of Perinatology 2001; 21:186–192.

INTRODUCTION

Nosocomial infections are a frequent and significant cause of morbidity in the preterm infant. Infections diagnosed after the first 72 hours of life are arbitrarily deemed to be “nosocomial,” and are often associated with clinical deterioration, including increased apnea, temperature instability, abdominal distension, lethargy, septic shock, necrotizing enterocolitis, meningitis, and death. Preterm infants are at higher risk of infection than more mature infants because of immature immune responses, such as reduced phagocytosis, opsonisation and intracellular killing,^{1,2} decreased immunoglobulin concentrations,³ and poor skin⁴ and gut barrier function.⁵ The risk of sepsis is further increased by the use of central venous catheters to administer parenteral nutrition⁶ and lipids.⁷ Freeman et al.,⁸ in a case cohort study, demonstrated that infants with CoNS were 5.8 times as likely as controls to have received intravenous lipids, and that 56.6% of all of the cases of nosocomial bacteremia could be attributed to lipid administration. Infants with CoNS were also 3.5 times as likely as controls to have had a percutaneously inserted central venous catheter (attributable risk, 14.9%). This group repeated their evaluation in a more current

cohort of premature infants and reported, using conditional logistic regression to adjust for indicators of severity of illness, two factors, intravenous lipid and central catheters, were independently associated with subsequent risk of CoNS bacteremia at any time during hospitalization. The highest odds ratio (OR) = 9.4 [95% confidence interval (CI) 1.2 to 74.2] was found for lipid use; the OR for central lines was 2.0 (95% CI 1.1 to 3.9).⁹ They additionally reported that 85% of bacteremias were attributable to lipid therapy and that the time to infection was much shorter when intravenous lipid was used.

There are many difficulties encountered in efforts to evaluate and compare nosocomial sepsis in the NICU. An issue of primary concern is the lack of uniformity in the definition of sepsis in the NICU. If we are to encourage the development of a consistent approach to management of neonatal nosocomial infection, a uniform definition is needed. Based on the frequency of positive blood cultures in infants less than 1000 g, it appears reasonable to evaluate methods for the prevention of nosocomial sepsis. These include prophylactic antibiotic administration, antiseptic impregnated catheters, and the use of an antibiotic lock technique.

DEFINITION

Coagulase negative staphylococci (CoNS) have emerged as the most common cause of late bacteremia in the neonatal intensive care unit.^{10–13} There are difficulties in the diagnosis of CoNS septicemia as the organism is a common skin commensal, which often results in contamination of blood cultures, either at the time of blood draw or during the blood-handling process. Common diagnostic schemes, such as that of the National Nosocomial Infections Surveillance System,¹⁴ have as one of many definitions of sepsis, the presence of clinical signs of sepsis with a single positive blood culture to confirm the diagnosis. However, clinical signs are often subtle and blood cultures are rarely drawn in the absence of clinical signs. Additional diagnostic schemas have been developed by the NICHD Neonatal Research Network and the Vermont Oxford Network. The NICHD employs a definition of one positive blood culture drawn after 72 hours of age, in the presence of signs of infection.¹⁵ The Vermont Oxford Network defines CoNS sepsis as one positive blood culture with signs of generalized infection in a neonate, greater than 72 hours of age, and treated with at least 5 days of antibiotic therapy.¹⁶ Although more stringent requirements do exist for the diagnosis of “true

Neonatal Specialists, Ltd., Phoenix, AZ.

Address correspondence and reprint requests to Alissa Craft, DO, Neonatal Specialists, Ltd., 1111 East McDowell Road, Anc 1, Phoenix, AZ 85006.



sepsis," they often involve the use of two positive blood cultures.¹⁷ Usual practice in most neonatal intensive care units is to obtain only a single blood culture, minimizing both blood volume removed and skin punctures to the infant.

None of these definitions adequately differentiates between true CoNS sepsis, catheters colonized with CoNS, and contaminated blood cultures. Therefore, decisions regarding the need to treat and the length of treatment of a positive blood culture for CoNS remain empiric, at best.

DIAGNOSIS

The diagnosis of septicemia, as opposed to line colonization or culture contamination, can be aided through the use of ancillary tests, such as white blood cell counts. Although blood cultures remain the gold standard, the culture results are affected by the volume of blood in the culture bottle, the length of time allowed for the culture to grow, and the site of culture.

As many as 60% of culture results will be falsely negative if only 0.5 ml of blood is obtained for culture in low colony count sepsis.¹⁸ With the blood-culture systems currently available in most hospital laboratories, 48 hours of incubation will result in growth of approximately 98% of all cultures that will become positive.¹⁹

The site from which the blood culture is drawn continues to be a source of significant controversy. In a study by Atela et al.,²⁰ of 45 catheters studied, 138 isolates of 27 different species were obtained from the catheter hub. Only 11 catheters had negative quantitative cultures from the hub. Therefore, positive blood cultures drawn through a central line may reflect bacteremia, line colonization, or contamination of the culture. Peripherally drawn blood cultures also may represent bacteremia or culture contamination.

In hospitalized critically ill patients, line colonization may be as important to treat as bacteremia, if the line is to remain in place. For this reason, it is recommended that when a central venous catheter is present, a blood culture should be obtained both from the line and using a peripheral stick.²¹ Positive blood cultures for the same organism through both sites almost certainly represents "true infection," whereas a positive peripheral blood culture for CoNS with a negative central line culture is more likely to represent skin contamination. A positive central line culture for CoNS with a negative peripheral blood culture may represent contamination of the culture at the time of the blood draw, or colonization of the central line, which may require treatment or line removal.

The sensitivity and specificity of the blood culture can be increased using quantitative cultures. St. Geme et al.²² found greater than 50 cfu/ml from a quantitative culture was consistently associated with sepsis, where sepsis was defined as >2 positive blood cultures with identical antibiotic susceptibilities in an infant with clinical signs of illness. However, some neonates with fewer colony-forming units and a central venous line still met the definition of sepsis applied in this article. Therefore, it becomes prudent to consider the report by Ruderman et al.²³ which defined contamination as any blood culture, regardless of the site or organism, with less than 30 cfu/ml.

Neonatologists frequently rely on one or more ancillary tests to guide them in differentiating a "true infection" from contamination or colonization. In a study evaluating the use of the neutrophil count to determine the presence of bacteremia, Kite et al.²⁴ found the neutrophil count to be 70.6% sensitive and only 57.8% specific. The same study found the immature to total neutrophil ratio to be 29.4% sensitive and 82.5% specific, with a positive predictive value of 27%. Thrombocytopenia has been found a useful marker for bacteremia, with much greater accuracy in Gram-negative sepsis as opposed to Gram-positive infections, such as CoNS.²⁵ An elevated mean platelet volume and high platelet distribution width have high specificity for detecting bacteremia and good negative predictive value.²⁶

Between 24 and 48 hours after the onset of clinical symptoms, the C-reactive protein appears to be a reasonable marker of bacteremia with a sensitivity of 84% and a specificity of 96%.²⁷ The same study demonstrated that interleukin-6 had the highest sensitivity and a negative predictive value of 91%. Interleukin-6 levels, like tumor necrosis factor levels, are rarely available in hospital laboratories, leaving neonatologists with the ongoing dilemma of how to differentiate a "true infection," while subjecting the infants to the smallest amount of bloodletting possible.

TREATMENT

The majority of infants with CoNS sepsis are treated with vancomycin, as the sensitivity pattern typically demonstrates resistance to other agents. Specifically, many hospital-acquired CoNS are methicillin resistant. Thus, many preterm infants experience substantial exposure to vancomycin. Newer alternatives, such as teicoplanin, are not currently widely used.²⁸

Good outcomes have been demonstrated with very restricted use of vancomycin, where infants with cultured CoNS, sensitive only to vancomycin, demonstrated clinical improvement without vancomycin therapy.²⁹ These findings lend further credence to the belief that not every positive blood culture represents "true infection" requiring therapy. It is crucial, however, to address the issue of line colonization. Although a positive blood culture from a central line may not represent bacteremia, it either represents line colonization or contamination during sampling. In the preterm infant, where the central line may be the only means of vascular access, it may be necessary to treat the "line colonization" to prevent a future bacteremia, if the catheter will not immediately be removed.

The ongoing difficulty in determining when treatment is necessary, along with the appropriate length of time to treat, suggests the need for more relevant definitions of sepsis and line contamination and consideration toward the prevention of nosocomial CoNS sepsis in the neonate.

PREVENTION

Precautions During Insertion of Central Lines

Central venous catheter hubs may become colonized with CoNS within 24 hours of insertion. This makes the insertion process

critical in the prevention of nosocomial infection, despite most infections occurring greater than 7 days after insertion of the line. Raad et al.³⁰ demonstrated that the use of maximal sterile barrier precautions for insertion of central venous catheters minimized infections. Maximal precautions include sterile gown, gloves, cap, and mask.

Preparation and Use of Intravenous Fluids for Central Administration

Intravenous fluids for administration using central venous catheters should be prepared in a sterile environment to prevent contamination of the fluid. This is especially crucial with intravenous lipid preparations. A prospective study of contamination of infusion sets for hyperalimentation compared infusion sets changed every 24, 48, or 72 hours.³¹ The bacteriologic examination of the infusion set was always negative in sets changed every 24 hours, but contaminated 6.7% of the time when changed every 72 hours. Based on these findings, it is recommended that infusion sets be changed every 24 hours when administering total parenteral nutrition.

Vancomycin Prophylaxis

Five prospective randomized trials of vancomycin for prophylaxis against neonatal nosocomial sepsis have been published in the past 10 years.^{32–36} Three of the five studies administered vancomycin as a continuous infusion of 25 µg/ml in hyperalimentation.^{23–25} The remaining two studies evaluated the administration of 5 mg/kg of vancomycin twice a day through the central venous catheter.^{26,27}

All five studies noted a decrease in the incidence of both overall sepsis events and CoNS sepsis events in neonates receiving prophylactic vancomycin.³⁷ The meta-analysis of the five studies demonstrated a decrease in overall sepsis, RR 0.11 (95% CI 0.05,0.24) and CoNS sepsis, RR 0.33 (95% CI 0.19,0.59).³⁶ There was no effect on mortality or length of hospital stay, and no toxic effects of vancomycin were reported. Although there is a concern regarding the theoretical development of resistant organisms with the administration of prophylactic antibiotics, there is insufficient evidence available to determine the risk of development of resistant organisms. However, for this reason, the routine use of prophylactic vancomycin cannot be routinely recommended until a randomized controlled trial is completed that properly assesses for the development of resistant organisms.

Impregnated Catheters

Multiple studies in adults have demonstrated that catheters impregnated with antibiotics and/or antibacterials reduce nosocomial catheter-related infections. A study by Maki et al.³⁸ randomized adults to receive either a standard triple lumen polyurethane catheter or one impregnated with chlorhexidine and silver sulfadiazine. Patients with antiseptic impregnated catheters were five-fold less likely to have bacteremia and seven-fold less likely to develop line colonization. A similar trial by Raad et al.³⁹ demonstrated a reduction

in catheter colonization from 26% to 8% using a catheter impregnated with tridodecylmethyl-ammonium chloride and minocycline and rifampin. Unfortunately, antibiotic- and antiseptic-coated catheters have not yet become a viable option in the neonate.

Antibiotic Lock Techniques

Another approach to the prevention of catheter colonization and resultant bloodstream infection is the antibiotic flush or antibiotic lock technique. The use of a heparin and vancomycin flush (25 µg/ml of vancomycin) for prevention of sepsis was initially described by Schwartz et al.⁴⁰ in immunosuppressed pediatric patients. Not only was the incidence of sepsis decreased from 20% in the control group to none in the study group; the study patients had fewer septic evaluations as well. A similar study by Carratala et al.⁴¹ in adult patients with malignancies demonstrated a complete elimination of catheter colonization and catheter-related bacteremia in the study group receiving a 25 µg/ml flush of vancomycin plus heparin. Most recently, Henrickson et al.⁴² evaluated the use of a vancomycin/ciprofloxacin/heparin flush solution in immune compromised pediatric oncology patients. Both vancomycin and heparin and vancomycin/ciprofloxacin/heparin flush solution significantly decreased the incidence of Gram-positive, Gram-negative, and total line infections. No antibiotic could be detected in the patient after the flush was completed and there was no increased incidence of vancomycin resistant organisms causing colonization or disease.

The benefit of the antibiotic lock technique over prophylactic administration of vancomycin is the avoidance of any concentration of antibiotic appearing in the patients. By administering only enough vancomycin plus heparin solution to flush the catheter, levels of vancomycin would be undetectable in even the smallest infant. Therefore, the risk of the development of resistant organisms should be eliminated. Prospective trials of the antibiotic lock technique should be conducted in the high-risk population in the NICU.

Avoidance of Central Lines

The most certain way to avoid catheter colonization and subsequent infection is to minimize the use of central venous catheters. There is a certain reluctance to encourage enteral feedings in the extremely low-birth-weight infant (<1000 g), yet it is precisely these infants at greatest risk of nosocomial infection. The benefits of early, aggressive enteral nutrition and the avoidance of prolonged use of central venous catheters must be assessed against the risk of necrotizing enterocolitis (NEC). There is, however, no evidence to suggest that a more rapid feeding advancement is associated with increased risk of necrotizing enterocolitis.⁴⁰ In fact, the most recent randomized trial of “slow versus rapid” feeding in neonates was not associated with an increased risk of NEC⁵¹ in keeping with results of previous randomized trials.^{44,45} There does remain literature to the contrary, The association of more rapid feeding advancement with an

Figure 1: CoNS Management Decision Tree

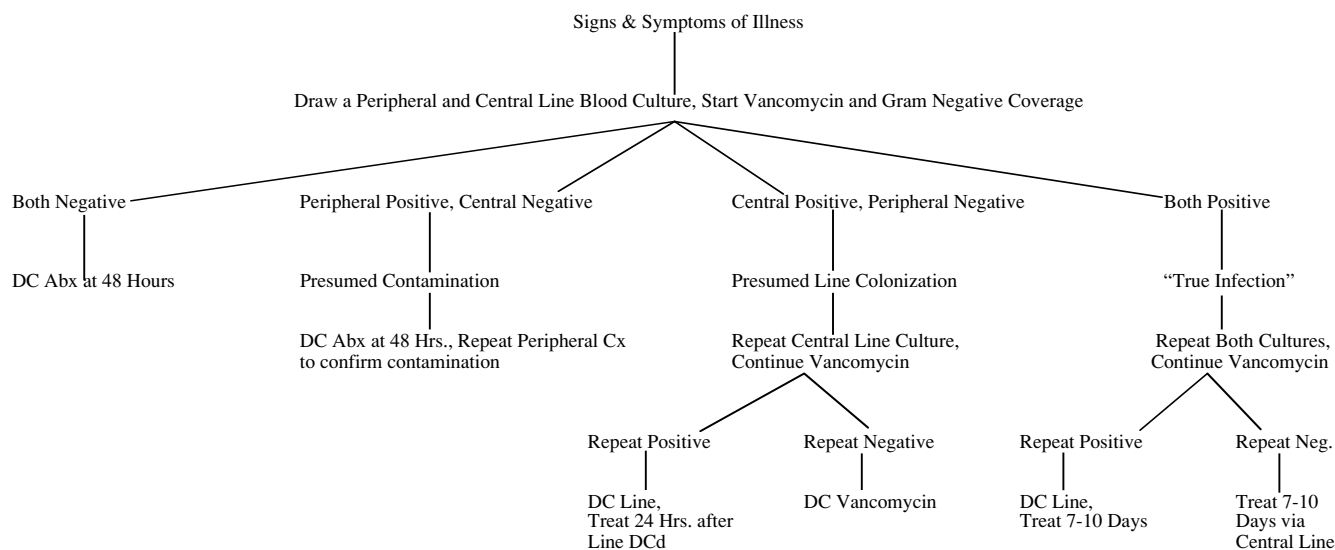


Figure 1. A proposed decision tree for the diagnosis and treatment of nosocomial CoNS sepsis in preterm infants.

increased risk of NEC has been reported in retrospective case cohort and chart review studies.^{46–48} A more recent meta-analysis reviewing the rate of feeding advancement demonstrated a reduction in days to full enteral feeds and days to regain birth weight with a more rapid feeding-advancement schedule. There was no increase in necrotizing enterocolitis.⁵⁰

DISCUSSION

Based on a thorough review of the available literature, in combination with consideration for the difficulty in effecting change in the NICU environment, we have proposed a diagnostic scheme and suggested a treatment paradigm for presumed CoNS sepsis (Figure 1). Diagnosis of “true infection” is based on the clinical presentation, and the results of blood cultures after a 48-hour incubation period. Blood cultures should always contain 1 ml of blood and be drawn from both the central line, if present, and a peripheral site. The following definition for CoNS positive blood cultures is therefore proposed:

Bacteremia, or “true infection”: Simultaneous positive blood cultures for the same organism through the central line and a peripheral site. If colony counts are available, greater than 50 cfu/ml is significant.

Line colonization: A positive blood culture through the central venous line, with a simultaneous negative peripheral blood culture, or fewer than 30 cfu/ml, if colony counts are available. This applies to an infant who appears stable at the time of the culture result, without other clinical and laboratory evidence to suggest ongoing infection, such as continuing thrombocytopenia or neutropenia.

Contaminated blood culture: A positive peripheral blood culture, with a colony count < 30 cfu/ml if available, and a simultaneous negative central line blood culture. This applies to an infant who appears stable

at the time of the culture result, without other clinical and laboratory evidence to suggest ongoing infection such as continuing thrombocytopenia or neutropenia.

This diagnostic scheme eliminates the need for ancillary tests, which lack a great deal of sensitivity and specificity, and often serve to only increase the amount of blood withdrawn from the neonate. However, ancillary tests may be useful in the infant who remains ill despite negative blood cultures, and in whom other sources of infection are being considered (i.e., osteomyelitis, necrotizing enterocolitis).

Treatment of the neonate pending blood culture results should include broad-spectrum antibiotics, with coverage for CoNS. The antibiotic therapy for suspected central venous line infection should always be administered through the central line. This empiric therapy is necessary only for 48 hours, or the return of a positive blood culture, whichever occurs first. At the time the culture become positive, a repeat blood culture should be obtained based on the following:

Bacteremia (two positive cultures): Repeat both the central line culture and the peripheral blood culture.

Line colonization (positive central line culture): Repeat only the central line culture.

Contamination (positive peripheral blood culture): Repeat a peripheral blood culture to verify that it is negative.

Treatment is also based on the culture results as follows:

Bacteremia: Continue antibiotic coverage against CoNS pending the results of the second set of blood cultures. If the second set remains positive, discontinue the central venous line, and treat for a total of 7 to

10 days. If the second set is negative, treat through the central line a total of 7 to 10 days.

Line Colonization: Continue antibiotic coverage against CoNS pending the results of the second set of blood cultures. If the second set remains positive, discontinue the central venous line, and treat for 24 hours following discontinuation of the line. A peripheral blood culture should be obtained following the short course of therapy to confirm adequacy of therapy. If the second set of cultures is negative, discontinue therapy.

Contamination: Discontinue therapy when the 48-hour incubation results of the blood cultures are available.

At this time, we do not recommend prophylactic use of vancomycin in the hyperalimentation fluids. Studies of a modified antibiotic lock technique in neonates are indicated. In an effort to reduce nosocomial CoNS bacteremia, the following techniques are recommended, based on a critical review of the literature:

1. Use of good hand-washing techniques, preferably with chlorhexidine products.⁵²
2. Maximal sterile barrier precaution for insertion of central venous lines.⁵³
3. Sterile preparation of fluids administered through central venous catheters.³¹
4. Minimize the duration of intravenous lipid administration, preferably discontinuing this caloric source when the infant tolerates 80 to 100 calories/kg per day enterally.⁸⁹
5. Minimize the need for central venous access through early aggressive enteral nutrition and early extubation to noninvasive forms of ventilatory support.⁵⁴
6. Use an umbilical venous catheter for up to 7 to 10 days, as opposed to placing a peripherally inserted central catheter (PICC) for a brief period of time. This avoids exposing the neonate to multiple central venous lines. A retrospective chart review recently demonstrated an increased incidence of infection in PICC lines, when compared to UVCs left in place for up to 7 days.⁵⁵

CONCLUSION

Neonatal nosocomial sepsis remains a persistent and perplexing problem for neonatologists. Each episode of sepsis impacts on mortality, morbidity, and significantly increases length of stay in the neonatal intensive care unit. Unfortunately, nosocomial CoNS sepsis has become so prevalent in infants less than 1000 g that some see infection as an entitlement, not a complication.

The variety of definitions of nosocomial sepsis, combined with differing criteria for performing sepsis evaluations, suggests that neonatologists have little comfort in establishing a diagnosis of "true infection." This discomfort impacts on treatment policies, potentially exposing neonates to unnecessary and excessive antibiotic therapy.

The goal of the neonatal community should be the establishment of a method to distinguish contamination from "true infection" and a definition for line colonization and catheter-related bacteremia. This requires diagnostic tests with

both high specificity and sensitivity with a minimal amount of blood withdrawal. After a uniform definition of neonatal nosocomial sepsis has been established further studies can be performed to evaluate the most effective treatment strategies, including the potential use of antibiotic prophylaxis or antibiotic lock techniques.

References

1. Drossou V, Kanakoudi F, Tzimouli V, et al. Impact of prematurity, stress and sepsis on neutrophil respiratory burst activity of neonates. *Biol Neonate* 1997;72:201–9.
2. Kallman J, Schollin J, Schalen C, Erlandsson A, Kihlstrom E. Impaired phagocytosis and opsonization towards group B streptococci in preterm neonates. *Arch Dis Child Fetal Neonat Ed* 1998;78:F46–50.
3. Ballow M, Cates KL, et al. Development of the immune system in very low birth weight (less than 1500 g) premature infants: concentrations of plasma immunoglobulins and patterns of infections. *Pediatr Res* 1986;20:899–904.
4. Rutter N. The immature skin. *Eur J Pediatr* 1996;155 (Suppl 2):S18–20.
5. Insoft RM, Sanderson IR, Walker WA. Development of immune function in the intestine and its role in neonatal diseases. *Pediatr Clin North Am* 1996;43:551–71.
6. Johnson-Robbins LA, El-Mohandes AE, Simmens SJ. Staphylococcus epidermidis sepsis in the intensive care nursery: a characterization of risk associations in infants < 1000 g. *Biol Neonate* 1996;69:249–56.
7. Nataro JP, Corcoran L, Zirin S, et al. Prospective analysis of coagulase negative staphylococcal infection in hospitalized infants. *J Pediatr* 1994;125:798–804.
8. Freeman J, Goldmann DA, Smith NE, Sidebottom DG, Epstein MF, Platt R. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *N Engl J Med* 1990 Aug 2;323(5):301–8.
9. Avila-Figueroa C, Goldmann DA, Richardson DK, Gray JE, Ferrari A, Freeman J. Intravenous lipid emulsions are the major determinant of coagulase-negative staphylococcal bacteremia in very low birth weight newborns. *Pediatrics* 1998 Jan;17(1):10–7.
10. Patrick CC. Coagulase negative staphylococci: pathogens with increasing clinical significance. *J Pediatr* 1990;116:497.
11. Ronnestad A, Abrahamsen TG, Gaustad P, Finne PH. Blood culture isolates during 6 years in a tertiary neonatal intensive care unit. *Scand J Infect Dis* 1998;30(3):245–51.
12. Vermont CL, Hartwig NG, Fleer A, et al. Persistence of clones of coagulase-negative staphylococci among premature neonates in neonatal intensive care units: two-center study of bacterial genotyping and patient risk factors. *J Clin Microbiol* 1998 Sep;36(9):2485–90.
13. Kallman J, Kihlstrom E, Sjoberg L, Schollin J. Increase of staphylococci in neonatal septicaemia: a fourteen-year study. *Acta Paediatr* 1997 May;86(5):533–38.
14. Gaynes RP, Horan TC. Definitions of nosocomial infections. In: Mayhall CG, editor. *Hospital Epidemiology and Infection Control*. Baltimore, MD: Williams and Wilkins; 1995. chap. 77, A1.
15. Stoll BJ, Gordon T, Korones SB, et al. Late onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. *J Pediatr* 1996;129:63–71.

16. Horbar JD, Lucey JF, Soll RF, et al. Vermont Oxford Network Database Manual of Operations, Release 3.3; 1997. p.19.
17. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions of sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864–74.
18. Schelonka RL, et al. Volume of blood required to detect common neonatal pathogens. *J Pediatr* 1996;129:275–8.
19. Rowley AH, Wald ER. Incubation period necessary to detect bacteremia in neonates. *Pediatr Infect Dis* 1986;5:590–1.
20. Atela I, Coll P, Rello J, et al. Serial surveillance cultures of skin and catheter hub specimens from critically ill patients with central venous catheters: molecular epidemiology of infection and implications for clinical management and research. *J Clin Microbiol* 1997;35:1784–90.
21. Blot F, Nitenberg E, et al. Diagnosis of catheter related bacteremia: a prospective comparison of the time to positivity of hub blood versus peripheral blood cultures. *Lancet* 1999;354:1071–77.
22. St Geme JW, Bell LM, Baumgart S, et al. Distinguishing sepsis from blood culture contamination in young infants with blood cultures growing coagulase negative staphylococci. *Pediatrics* 1990;86:157–62.
23. Ruderman JW, Morgan MA, Klein AH. Quantitative blood cultures in the diagnosis of sepsis in infants with umbilical and Broviac catheters. *J Pediatr* 1988;122:748–51.
24. Kite P, Millar MR, Gorham P, Congdon P. Comparison of five tests used in diagnosis of neonatal bacteraemia. *Arch Dis Child* 1988;63:639–43.
25. Modanlou H, Ortiz OB. Thrombocytopenia in neonatal infection. *Clin Pediatr (Philadelphia)* 1981;20:402–7.
26. Patrick CH, Lazarchick J. The effect of bacteremia on automated platelet measurements in neonates. *Am J Clin Pathol* 1990;93:391–4.
27. Ng PC, Cheng SH, Chui KM, et al. Diagnosis of late onset neonatal sepsis with cytokines, adhesion molecule, and C-reactive protein in preterm very low birth weight infants. *Arch Dis Child* 1997;77:F221–7.
28. Moller JC, Nelskamp I, Jensen R, et al. Comparison of vancomycin and teicoplanin for prophylaxis of sepsis with coagulase negative staphylococci in very low birth weight infants. *J Perinat Med* 1997;25:361–7.
29. Matrai-Kovalkis Y, Greenberg D, Shinwell ES, Fraser D, Dagan R. Positive blood cultures for coagulase negative staphylococci in neonates: does highly selective vancomycin usage affect outcome? *Infection* 1998;26:85–92.
30. Raad II, Hohn DC, Gilbreath J, et al. Prevention of central venous catheter related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol* 1994;15:231–8.
31. Pacifici A, Manieri R, De Medici M. Total parenteral nutrition: a study of the microbial contamination of the bags and the infusion lines. *Ann Ital Chir* 1992;63:89–91.
32. Baier RJ, Bocchini JA, Brown EG. Selective use of vancomycin to prevent coagulase negative staphylococcal nosocomial bacteremia in high risk very low birth weight infants. *Pediatr Infect Dis J* 1998;17:179–83.
33. Kacica MA, Horgan, MJ, Ochoa L, Sandler R, Lepow ML, Venezia RA. Prevention of gram positive sepsis in neonates weighing less than 1500 grams. *J Pediatr* 1994;125:253–8.
34. Spafford PS, Sinkin RA, Cox C, Reubens L, Powell KR. Prevention of central venous catheter related coagulase negative staphylococcal sepsis in neonates. *J Pediatr* 1994;125:259–63.
35. Cooke RWI, Nycyk JA, Okuonghae H, Shah V, Damjanovic V, Hart CA. Low dose vancomycin prophylaxis reduces coagulase negative staphylococcal bacteremia in very low birthweight infants. *J Hosp Infect* 1997;37:297–303.
36. Moller JC, Rossa M, Nachtrodt G, Richter A, Tegtmeier FK. Preventive antibiotikagabe zur verhinderung nosokomialer septikamien bei sehr kleinen fruhgeborenen (VLBW infants). *Klin Paediatr* 1993;205:140–4.
37. Craft AP, Finer NN, Barrington KJ. Vancomycin for prophylaxis against sepsis in preterm neonates (Cochrane Review). In: *The Cochrane Library, Issue 1*. Oxford: Update Software; 2000.
38. Maki DG, Stoltz SM, Wheeler S, Mermel IA. Prevention of central venous catheter related bloodstream infection by use of an antiseptic impregnated catheter. *Ann Intern Med* 1997;127:257–66.
39. Raad I, Darouiche R, Dupuis J, et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter related colonization and bloodstream infections. *Ann Surg* 1996;223:363–9.
40. Schwartz C, Henrickson KJ, Roghmann K, Powell K. Prevention of bacteremia attributed to luminal colonization of tunneled central venous catheters with vancomycin susceptible organisms. *J Clin Oncol* 1990;8:1591–7.
41. Carratala J, Niubo J, Fernandez-Sevilla A, et al. Randomized double blind trial of an antibiotic lock technique for prevention of gram positive central venous catheter related infection in neutropenic patients with cancer. *Antimicrob Agents Chemother* 1999;43:2200–4.
42. Henrickson KJ, Axtell RA, Hoover SM, et al. Prevention of central venous catheter related infections and thrombotic events in immunocompromised children by the use of vancomycin/ciprofloxacin/heparin flush solution: a randomized, multicenter, double-blind trial. *J Clin Oncol* 2000;18:1269–78.
43. Rayyis SF, Ambalavanan N, Wright L, Carlo WA. Randomized trial of “slow” versus “fast” feed advancements on the incidence of necrotizing enterocolitis in very low birth weight infants. *J Pediatr* 1999;134:293–7.
44. Book LS, Herbst JJ, Jung AL. Comparison of fast- and slow-feeding rate schedules to the development of NEC. *J Pediatr* 1976;89:463–6.
45. Caple, JJ, Armentrout DC, Huseby VD, Halbrdier BM, Garcia J, Sparks JW. The effect of feeding volume on clinical outcome of premature infants. *Pediatr Res* 1997;41:229A.
46. Anderson DM, Kliegman RM. The relationship of neonatal alimentation practices to the occurrence of endemic necrotizing enterocolitis. *Am J Perinatol* 1991;8:62–7.
47. McKeown RE, Marsh TD, Amarnath U, Garrison CZ, Addy CL, Thompson SJ. Role of delayed feeding and of feeding increments in necrotizing enterocolitis. *J Pediatr* 1992;121:764–70.
48. Goldman HI. Feeding and NEC. *Am J Dis Child* 1980;134:553–5.
49. LaGamma EF, Browne LE. Feeding practices for infants weighing less than 1500 grams at birth and the pathogenesis of necrotizing enterocolitis. *Clin Perinatol* 1994;21:271–306.
50. Kennedy KA, Tyson JE, Chamnanvanakij S. Rapid versus slow rate of advancement of feedings for promoting growth and preventing necrotizing enterocolitis in parenterally fed low-birth-weight infants (Cochrane Review). In: *The Cochrane Library, Issue 2*. Oxford: Update Software; 2000.
51. Kennedy KA, Tyson JE, Chamnanvanakij S. Rapid versus slow rate of advancement of feedings for promoting growth and preventing necrotizing enterocolitis in parenterally fed low-birth-weight infants (Cochrane

- Review). In: The Cochrane Library, Issue 2. Oxford: Update Software; 2000.
52. Doebbeling BN, Stanley GL, Sheetz CT, et al. Comparative efficacy of alternative handwashing agents in reducing nosocomial infections in intensive care units. *N Engl J Med* 1992;327:88–93.
53. Agee KR, Balk RA. Central venous catheterization in the critically ill patient. *Crit Care Clin* 1992;8:677–86.
54. Cordero L, Sananes M, Ayers LW. Failure of systemic antibiotics to eradicate gram negative bacilli from the airway of mechanically ventilated very low birthweight infants. *Am J Infect Control* 2000;28:286–90.
55. Tuttle D, Leef K, Moore G, et al. Increased risk of line sepsis associated with peripherally inserted central venous catheters in premature infants. *Pediatr Res* 2000;47:279A.