NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

Volume 1 / Issue 5
September 2006

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NEONATOLOGY TODAY
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ANTIBIOTICS USED IN THE NICU

FROM THE PEDIATRIX-OBSTETRIX CENTER FOR RESEARCH AND EDUCATION

By Reese H. Clark, MD; Alan R. Spitzer, MD

Introduction

The suspicion of sterile-site (blood, spinal fluid, urine and lung) infection is the most common cause for neonatal admission to the NICU. In addition, nosocomial infections are common among neonates who require extended neonatal intensive care and are associated with an increase in mortality, morbidity, and prolonged length of hospital stay. Most authors describe neonatal infection by the terms "early-onset" and "late-onset" infection. Early-onset infections are confirmed infections that occur in the first three days of life, whereas late-onset infections occur after the third day. This distinction is important, as the organisms causing early infections are different from those that cause late infections.(1) In neonates, the most common sterile source from which a pathogen is isolated is the blood stream (sepsis). Meningitis, urinary tract infections and pneumonia are less common.

Diagnosis and management of newborns with infections is challenging and several recent articles remind us that our choices (who to treat, with what antibiotic, and for how long) are critical to the well being of our patients.(2-7) The goal of this paper is to review antibiotics used in the NICU and present suggestions for improving the use of these important medications.

What are We Treating in the NICU?

Early Infections

Most (98%) sterile-site cultures obtained from neonates admitted during the first three days after birth will not grow any organisms, and the most common bacteria found, Coagulase Negative Staphylococcus (CONS), is often considered a contaminant (Figure 1). The most frequently encountered pathogens in the early-onset infections are group B streptococci and Escherichia coli (E. coli).(8)

There is evidence that the pattern of infection in very low birth weight neonates is changing. When very low birth weight neonates born between 1991-1993 were compared to neonates born between 1998-2000, there was a marked reduction in group B streptococcal sepsis (from 5.9 to 1.7 per 1000 live births, P <0.001) and an increase in E. coli sepsis (from 3.2 to 6.8 per 1000 live births, P = 0.004).(9) The overall incidence of neonatal sepsis in very low birth weight neonates has not changed. The antibiotic sensitivity pattern also appears to be changing. In a recent study, 59% of patients infected with E. coli were infected with an ampicillin-resistant strain.(10) Monitoring the changes in organism that cause infection

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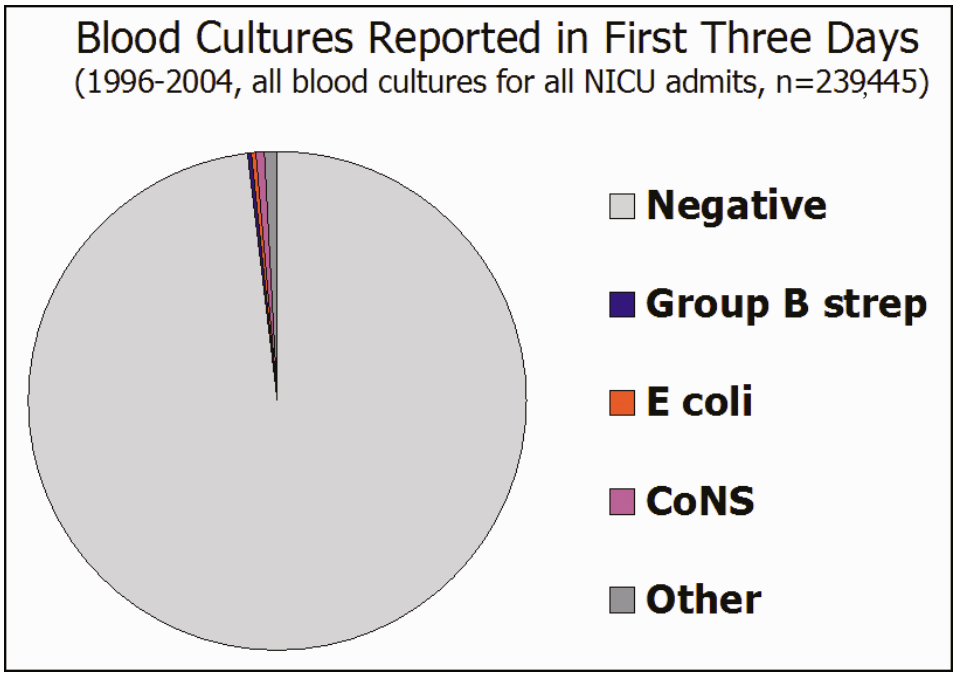

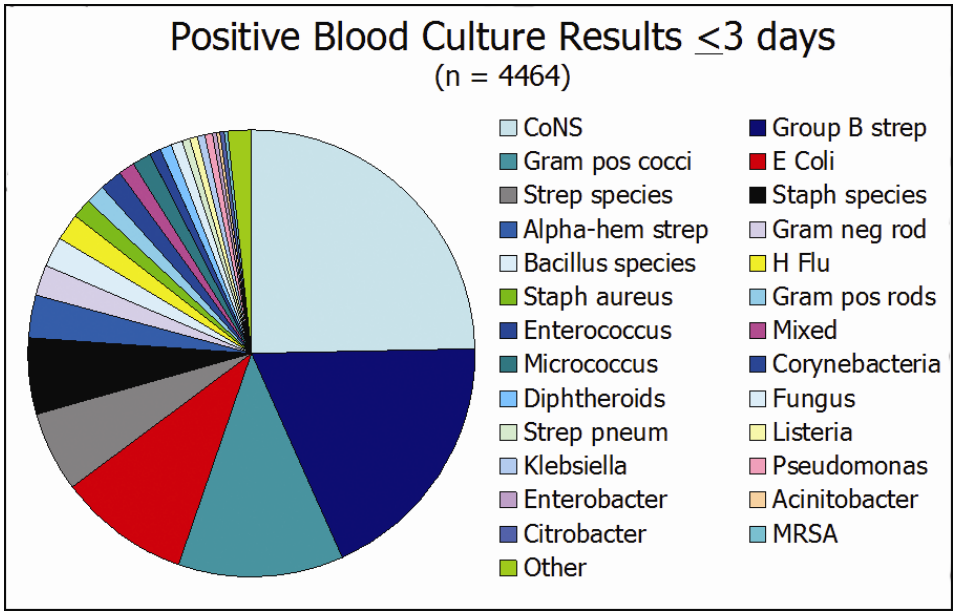

Figure 1: The upper panel shows the results of all the blood cultures obtained during the first three days after birth on neonates admitted between 1997 and 2004 (Data from the Pediatrix Medical Group Clinical Data Warehouse). Most are negative. The lower panel is from the same data set but only shows the positive results.

and their sensitivity patterns are essential in the management of neonatal infections.

Early infections, or more precisely, suspected early infections impact a much larger number of neonates than late infections. It is particularly important that we carefully manage the processes that dictate "who gets treated and for how long".

Late Infections

Neonates who remain in the NICU for more than three days are more often premature and critically ill. This subpopulation of neonatal intensive care patients is at high risk for infection. Cultures obtained after the first three days following birth are more often positive than cultures obtained during the first three days after birth (Figure 2). The organisms that grow from cultures obtained after three days are also different from those obtain before three days.

The most common organisms that cause late infections in neonates are coagulase-negative Staphylococci, E. coli, Klebsiella, and Fungus (Figure 3).(11;12) In addition to the pathogens that are easily grown in blood-culture media, other organisms that are fastidious organisms (e.g., Mycoplasma and Ureaplasma species) may be missed.

The neonatal intensive care unit (NICU) nosocomial infection rate has increased over the past decade.(1;13) The total number of neonates who develop nosocomial infection per admission varies from 6.2%(14) to 33%(15). The variability in infection rates depends on the gestational age, distribution of the infants surveyed for the report, and on the specific environment and care practices.(16) Even when statistical correction has been made for case mix, the variability between centers generally remains and understanding why some units have more late infections is important.(15;17)

Presentation

The type of organism can often be suspected from the clinical presentation. Both of the pathogens causing early infections (group B streptococcus and E. Coli) typically present with rapid and life threatening deterioration and most infants with sepsis caused by these two organisms will be clinically symptomatic.(18) The dominant presenting features of septicemia include: respiratory distress; feeding intolerance or poor feeding, hypotension or shock, lethargy, and hypotonia.

The presenting signs and symptoms in neonates with late infection are different and depend on the organism. Gram-negative nosocomial sepsis often presents with a more rapid clinical deterioration and is commonly associated with shock and coagulation problems.(19)

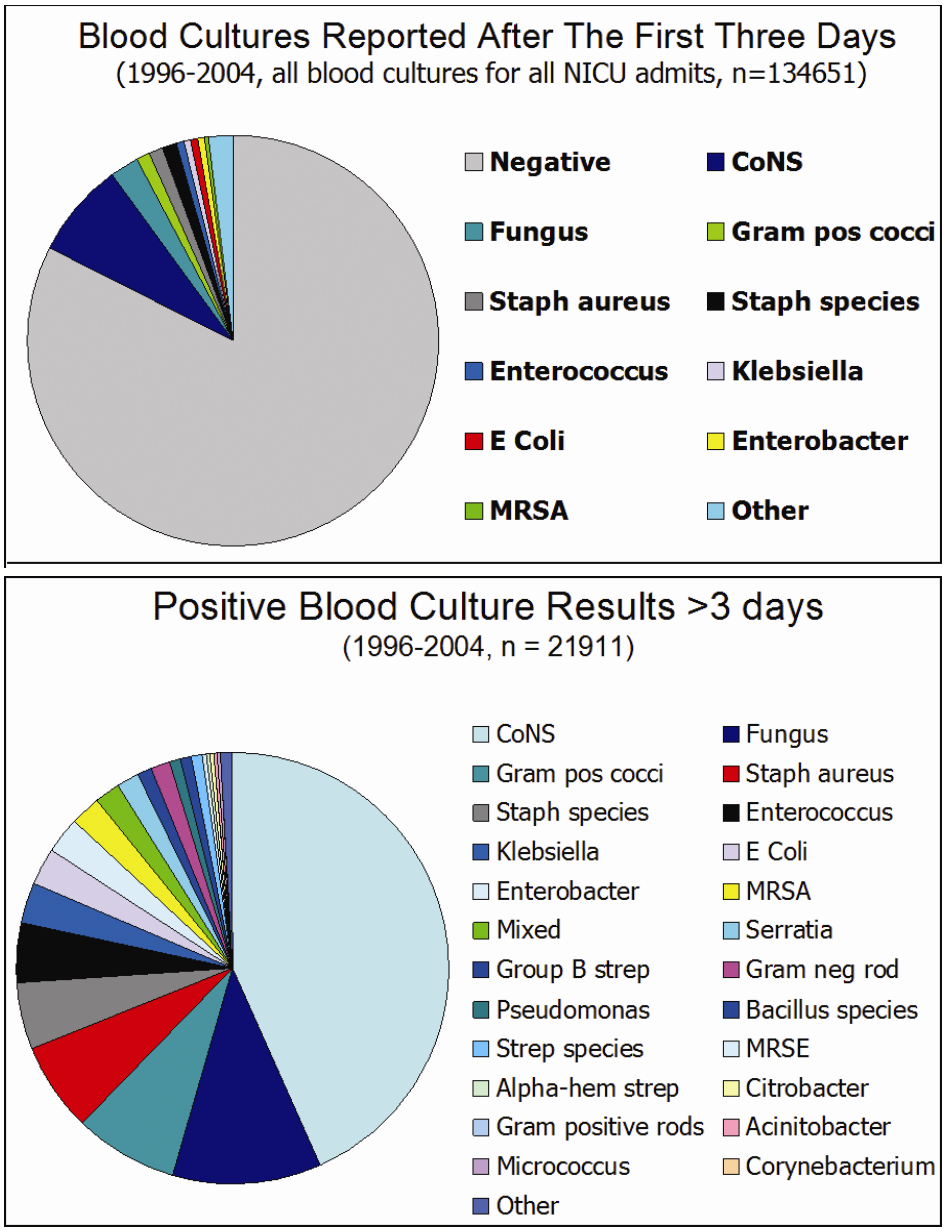

Figure 2: The upper panel shows the results of all the blood cultures obtained after the first three days on neonates admitted between 1997 and 2004 (Data from the Pediatrix Medical Group Clinical Data Warehouse). Most are negative but the proportion of positive cultures is larger compared to the very small proportion of positive cultures found during the first 3 days. The lower panel is from the same data set but only shows the positive results.

Furthermore, the pathogens associated with fulminant (lethal within 48 hours) late-onset sepsis are most often Gram-negative organisms. The frequency of fulminant sepsis is highest for Pseudomonas sp., 20 of 36 (56%; 95% CI: 38%-72%), and lowest for coagulase-negative Staphylococci, 4 of 277 (1%; 95% CI: 0%-4%).(19) Fungal sepsis is more indolent than Gram-negative sepsis and more fulminant than coagulase-negative Staphylococci. It is commonly associated with thrombocytopenia and occurs more often in extremely-low-birth-weight infants (birth weight <0.750 kg) and very premature neonates (estimated gestational age <26 weeks). Nosocomial fungal sepsis is associated with significant morbidity.(20) These data highlight the importance of monitoring culture results and choosing the appropriate antibiotic in the treatment of infections.

Antibiotics Used in the NICU

Antibiotics are the most common medications reported to be used in the NICU.(2;21) The Pediatrix Medical Group Clinical Data Warehouse shows that most (70%) of the neonates admitted to an NICU are treated empirically with antibiotics. This finding is particularly true for premature neonates (Figure 3). In addition, many (32%) of the neonates admitted for intensive care have been exposed to antibiotics before birth, either for prevention of Group B Streptococcal infection or as a part of treatment of premature labor. This treatment can influence the risk for late infections.(22)

The most commonly used antibiotics are listed in Table 1. Ampicillin and Gentamycin are the antibiotics most commonly used to treat neonates suspected of having early infections. In contrast, vancomycin, aminoglycosides, and cefotaxime are the most common antibiotics used to treat late infections.(23)

Choosing the Right Treatment

Determining whom to treat and for how long are difficult clinical problems and there is no consensus on how to establish which patient may have life-threatening septicemia. While some authors report that complete blood cell counts (24), inflammatory markers [interleukin-6 (25-27); interleukin-8 (28-35); and C-reactive protein (25;36-41)] change with acquired infection, most also agree that no one specific test excludes or confirms a diagnosis of sepsis.(24) The gold standard for the diagnosis of sepsis remains the finding of a positive blood culture for a known pathogen. The best way to confirm sepsis is to obtain an adequate volume of blood in culture specimens (1 ml is generally considered the ideal volume in a neonate).(42-44)

Early Infections

Who Should Be Treated

As data from the Pediatrix Data Warehouse and the data from other large data sets demonstrate, the risk of blood

culture proven sepsis with a pathogen is low (1-4/1000 live births), even in neonates admitted to a neonatal intensive care unit for evaluation of sepsis.(2;45) Since most of the neonates admitted within the first 3 days for evaluation of suspected (not proven) sepsis will have negative cultures, the best way to limit unnecessary use and prolonged duration of antibiotic therapy is to establish a unit-specific policy about the appropriate use of antibiotics. While establishing the policy is relatively easy, implementing and monitoring are essential if the policy is to be enforced.

The Centers for Disease Control define criteria for the evaluation of neonates who are considered at risk for early group B streptococci infection(46;47) and these guidelines generally apply to the management of early infections. The key components of the recommendations determining who to treat are:

- "If a woman is suspected of having chorioamnionitis, her newborn should have a full diagnostic evaluation and receive empiric broad spectrum therapy (e.g., ampicillin and gentamicin) pending culture results, regardless of the infant's clinical condition at birth or gestational age.
- When a neonate has clinical signs of sepsis, a full diagnostic evaluation should include a lumbar puncture, if feasible. If the lumbar puncture has been deferred and the therapy is continued more than 48 hours because of suspected infection, cerebrospinal fluid should be obtained for routine studies and culture.
- In addition to penicillin or ampicillin, IAP (Intrapartum antibiotic prophylaxis) with cefazolin at least four hours before delivery is considered adequate, because cefazolin achieves bactericidal concentrations against GBS in amniotic fluid three hours after an IAP dose. The effectiveness of other antimicrobial agents in preventing GBS is unknown.
- Hospital discharge as early as 24 hours after birth may be reasonable under certain circumstances, specifically when the infant is born after four or more hours of maternal intra-partum antibiotics, is 38 weeks' gestation or more, appears healthy, and meets all discharge criteria, including care by an individual able to comply fully with instructions for home observation."(46)

Antibiotic Choice

A specific antibiotic choice must be driven by hospital-specific guidelines based on the major causes of sepsis and organism susceptibility patterns in that specific hospital. However, it is equally important to recognize that the choice of antimicrobial agents influences subsequent presentations of neonatal sepsis and antibiotic resistance patterns within a NICU.(48) De Man, et al., showed that the relative risk for colonization with strains resistant to the empirical therapy was 18 times higher for the amoxicillin-cefotaxime regimen compared with the penicillin-tobramycin regimen (95% CI 5.6-58.0, p <0.01). The authors concluded that a regimen avoiding amoxicillin and cefotaxime reduces the resistance problem.(48)

Our choices about what antibiotics to use may also influence outcome. We recently reported that in neonates receiving ampicillin, the concurrent use of cefotaxime during the first 3 days after birth may be associated with an increased risk of death, compared with the concurrent use of gentamicin.(2) The cause for this association remains unclear. Another recent study suggests that antibiotic practice (in particular, the choice of third-generation cephalosporins in very low birth weight neonates) may contribute to increasing the risk for candidiasis as a late infection.(49)

Based on these studies, ampicillin and gentamycin remain the best choice of coverage for low-risk (asymptomatic, near-term) neonates being evaluated for suspected early sepsis.

Late infections

Who Should Be Treated

The likelihood of finding a pathogen is greater in neonates who remain in the neonatal intensive care unit for more than 3 days, and the organisms that cause sepsis are different from those causing early infections. The presentation of sepsis is often subtle, especially for CoNS. Premature patients with increasing apnea, infants with the new onset of feeding intolerance, and neonates with intravenous lines who are receiving parenteral nutrition, are particularly susceptible to CoNS. As with early infections, there are no laboratory tests that can conclusively confirm or exclude infection, and a carefully obtained blood culture is again the gold standard for diagnosing sepsis and deciding how to initiate treatment of the patient.

Antibiotic Choice

The most common organisms that cause late infections in neonates who remain in the NICU are coagulase-negative Staphylococci, E. coli, Klebsiella, and Fungus (Figure 3).(11;12) Antibiotics used for late infections must target these organisms.

A common problem in the NICU is the overuse of vancomycin.(23;50) Stoll et

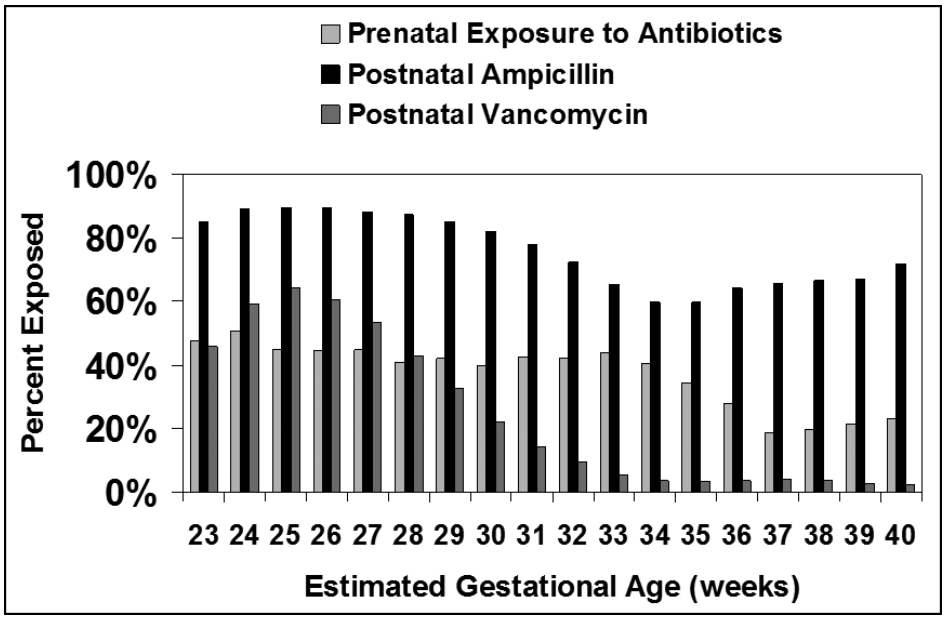

Figure 3: The reported rate of antibiotic utilization in neonates admitted for neonatal intensive care unit (Data from the Pediatrix Medical Group Clinical Data Warehouse).

al. (23), studying very-low-birth-weight neonates (401–1500 grams), found that 56% of 6215 infants received at least one course of antibiotics started after day 3 of birth and 44% were treated with a course of vancomycin. Vancomycin use was inversely related to birth weight (401–500 grams, 78%; 501–750 grams, 75%; 751-1000 grams, 60%; 1001–1250 grams, 36%; 1251–1500 grams, 18%). The question that remains to be answered is whether it is safe NOT to prescribe vancomycin at the time of the initial work-up, and before the culture results establish the organism causing the infection. Can we use other safer antibiotics as empiric coverage until we know the culture results?

Karlowicz, et al., showed that coagulase-negative Staphylococcus is rarely fulminant (19) and the mortality rate among neonates with coagulase-negative Staphylococci is no different from uninfected neonates.(23) The Centers for Disease Control and Prevention and others have recommended avoiding empiric vancomycin therapy in patients with suspected (not yet proven) sepsis to reduce the emergence of vancomycin resistant strains.(23) It may be reasonable to consider treating stable neonates with oxacillin or nafcillin instead of vancomycin for the 24 to 48 hours that it takes to identify a positive culture for coagulase-negative Staphylococci, but this approach should be subjected to prospective study.(19)

An equally important issue is which antibiotics should be chosen to cover for the Gram-negative organisms – amikacin, gentamicin, tobramycin, or cephalosporin. Overuse of cephalosporin has been associated with the emergence of resistant organisms (48) and higher rates of fungal infections (49;51).The current recommendation is to use an aminoglycoside as Gram-Negative coverage for neonates with suspected and not-yet-proven sepsis. This recommendation must be taken in the context of ongoing evaluation of site specific resistant patterns.

Duration of Treatment (Applies to both Early and Late Infection)

Improved culture media and new technology integrated into blood culture systems have shortened the incubation time required to detect positive blood cultures (the gold standard for the diagnosis of infection). Investigators have shown a 97% to 100% yield at 48 hours for positivity of blood cultures.(52-59) These data suggest that in the absence of overt clinical signs of sepsis, which would suggest that the blood culture is falsely negative, antibiotics can be safely stopped after 48 hours of treatment, if the blood culture is negative.

The best way to reduce the overuse of antibiotics in the NICU is to establish protocols that lead to the appropriate cessation of antibiotic therapy in neonates whose cultures are negative and who have no ongoing evidence of sepsis after a 48-hour course of therapy.

Appropriate Follow-Up of Culture Results (Applies to Both Early and Late Infection)

When a culture is sent, it must be followed; and when the culture is positive our treatment plan must be reevaluated. In many hospitals, MRSA has become a common cause for gram-positive bacterial species associated with serious hospital-acquired infections, particularly within intensive care units.(5) A recent study showed that as many as 40% of the hospitalized infants can become colonized with MRSA during their stay in MRSA endemic NICUs and colonization increases the risk of development of serious MRSA infections.(60) In adults (and very likely in neonates), inappropriate antimicrobial treatment of a patient with culture proven MRSA infection is associated with an increased risk of hospital mortality.(5) Once a positive culture is identified, it should be treated with the antibiotics most likely to clear the infection.

Even more disturbing are increasing reports that some infants on early culture are beginning to manifest MRSA colonization, suggesting increasing community prevalence of MRSA. MRSA no longer appears to be only a hospital-acquired organism.(3)

Methods for Improvement

As with many areas of medicine, the best way to improve the process of care is to pay close attention to that

Table 1: Antibiotics Use in the NICU and the Demographics of the Neonates in Which They are Used

ANITBIOTIC	% of ICU Patients Treated	Estimated Gestational Age (wks) (Median 25-75th)	Birth Weight (kg) (Median 25-75th)	Age At Start (days) (Median 25-75th)	Duration of Use (Median 25-75th)
Ampicillin	69.3%	35 (32-38)	2.5 (1.7-3.2)	0 (0-0)	3 (2-6)
Gentamicin	57.5%	35 (32-38)	2.4 (1.7-3.2)	0 (0-0)	3 (2-6)
Cefotaxime	18.3%	34 (29-38)	2.2 (1.2-3.1)	0 (0-3)	3 (2-7)
Vancomycin	9.9%	29 (26-33)	1.2 (0.8-1.8)	11 (7-17)	5 (2-9)
Tobramycin	2.8%	30 (26-35)	1.4 (0.9-2.3)	8 (0-20)	4 (2-7)
Ceftazidime	1.7%	27 (25-31)	0.9 (0.7-1.4)	19 (10-33)	6 (3-10)
Clindamycin	1.6%	29 (26-34)	1.2 (0.8-2)	12 (6-25)	6 (3-9)
Amikacin	0.9%	29 (27-33)	1.2 (0.9-1.9)	12 (8-20)	3 (2-7)
Penicillin G	0.8%	38 (34-40)	2.9 (2-3.4)	1 (0-3)	7 (3-10)
Nafcillin	0.7%	29 (26-35)	1.2 (0.8-2.3)	15 (6-28)	5 (2-7)
Oxacillin	0.7%	29 (26-34)	1.1 (0.8-1.9)	18 (10-33)	4 (2-7)

process. Carefully outlined and standardized plans that are implemented by thoughtful leaders within the neonatal intensive care unit can improve the health care we provide.(61;62) With regards to antibiotic utilization, the most important steps are:

1. The most important way to decrease antibiotic use in the NICU is to prevent infections. Several papers describe the process for decreasing infections in the neonatal intensive care unit.(63-66)
2. Treat only neonates with defined risk factors for sepsis. Neonates delivered prematurely for maternal reasons (e.g. abruption and preeclampsia) and who have no risk factors for infection do not need to be treated with antibiotics.
3. Define and use antibiotic ordering procedures that limit the time of treatment to 48 hours for asymptomatic low-risk neonates in whom the sterile site cultures are negative.
4. Clearly communicate and document the need and reason for using antibiotics and why you are treating for the prescribed duration.
5. Start antibiotic treatment with the safest antibiotics that cover the bacteria most likely to be causing the infection and adjust therapy as soon as the culture results are finalized.

Summary

Managing neonates with suspected early and late infection is a common neonatal intensive care problem. Identifying who has a serious infection is difficult and important; sepsis and other infections increase neonatal mortality, morbidity, and prolong the length of hospital stay. Similarly, picking the right course of treatment is important; medication errors and inappropriate treatment of infections can increase morbidity among neonates admitted to the neonatal intensive care unit. Developing process plans that direct the care of this important neonatal problem can improve the treatment of infections and reduce the errors associated with the treatment of infections.

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www.kenes.com/europaediatrics/

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Oct. 19-21, 2006; Columbus, OH
www.columbuschildrens.com/conferences

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www.nann.org/i4a/pages/index.cfm?pageid=803

30th Annual Neonatal International Symposium –Neonatology 2006
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neonatology.med.miami.edu/conference/default.htm

4th Annual Advances in Perinatal Cardiology Conference
Nov. 16-18, 2006; St. Petersburg, FL
www.allkids.org/conferences/cme/conferences/perinatalcard2006/conference.htm

2006 Annual Meeting and 7th Annual Quality Congress in Neonatology - Vermont Oxford Network
Dec. 2-3, 2006; Washington, DC
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Jun. 22-23, 2007; Chicago, IL
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NEONATOLOGY TODAY

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Printed in U.S.A. IMK111-00249 2/05