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Antimicrobial Therapy and Late Onset Sepsis

Alison Chu, MD,* Joseph R. Hageman, MD,† Michael Schreiber, MD,* Kenneth Alexander, MD, PhD§

Educational Gaps
1. In an infant with a positive blood culture with coagulase-negative Staphylococci, how does the clinician distinguish a true infection from a likely contaminant?
2. What is the evidence behind the use of certain antimicrobial agents in late onset sepsis?

Abstract
Late onset sepsis infections contribute a significant proportion of the morbidity and mortality of hospitalized infants, especially in very low birth weight infants. Although it is fairly clear which infants are at higher risk of developing sepsis, it is less clear whether a standard for diagnostic evaluation exists and is being used consistently across institutions. In the current setting of changing epidemiology and emergence of antibiotic-resistant organisms, it is important to evaluate the antimicrobial agents used for empirical therapy and to emphasize the importance of antimicrobial stewardship. In addition, it is imperative to evaluate possible methods for prevention of these infections.

Objectives After completing this article, readers should be able to:
1. Recognize risk factors for late onset sepsis in hospitalized neonates.
2. Describe some important causative organisms causing late onset sepsis.
3. Recognize that there are controversies in the diagnostic evaluation in late onset sepsis.
4. Understand the principles underlying antibiotic choice in empirical antibiotic therapy.

Introduction
Late onset sepsis (LOS) is a common clinical challenge for neonatologists. Although advances in neonatal practice have led to improved infant survival, infections continue to account for a significant proportion of morbidity and mortality in newborns, especially very low birth weight (VLBW) infants (≤1500 g). (1) VLBW infants who develop LOS are significantly more likely to die and to have impaired neurodevelopmental outcomes than those who are not infected. (2) The evolving epidemiology and the continuing emergence of antibiotic resistance among organisms that cause LOS require ongoing evaluation of the antibiotics used to treat suspected LOS. This article provides an overview of the risk factors associated with, etiologic agents identified in, diagnostic evaluation of, and antibiotic therapy for LOS. In this context, we focus the rest of our discussion of LOS within the population of hospitalized, primarily premature, infants.
Background and Definitions
The gold standard test for sepsis in neonates has been a positive blood culture along with clinical signs and symptoms of sepsis. A single positive blood culture in an asymptomatic infant may be a false positive and, depending on the organism, may have little clinical significance. LOS has varying definitions, with some groups including infections occurring 48 hours after birth, (3) 72 hours after birth, (2) or anytime 4 to 7 days after birth (4) with or without clinical symptoms. (5) On the other end, some clinicians define LOS up to 30 days of life, whereas others may include any infections occurring before discharge from the hospital. Whereas early onset sepsis (EOS) is assumed largely to be due to vertical transmission, LOS has been attributed to nosocomial or horizontal acquisition.

Risk Factors for LOS
Neonates in general are at increased risk for infection because of their immature immune defenses, including fragile cutaneous barriers, and relative immune tolerance. (1) Among hospitalized infants, certain risk factors confer greater risk for LOS and comprise a cycle of increased susceptibility to infection (Fig).

Birth Weight and Gestational Age
Many studies have verified that the rate of neonatal infection varies inversely with gestational age (GA) and birth weight of the infant. (2) The increased risk of LOS seen in VLBW infants holds true across countries and over the past decade. In 2007, the reported incidence of LOS in VLBW infants in the United States was near 20%, whereas EOS in VLBW infants was ~2%. (6) A large study of infants born in Israel from 1995 through 1998 showed similar rates of LOS. (5) Additional stratification revealed that 56% of infants born at a GA of 24 to 25 weeks, compared with 9% of infants with a GA >34 weeks, had at least 1 episode of LOS, and 53% of neonates with birth weight <750 g had ≥1 episodes of LOS, compared with close to 17% of those born weighing 1250 to 1500 g.

Comorbidities and Invasive Care
Smaller infants are usually at greater risk for developing complications of their prematurity. Many investigators have found increased risk of LOS in infants with patent ductus arteriosus, necrotizing enterocolitis, and chronic lung disease. (2,5) Infants with these clinical problems often require more invasive care during their hospitalization. Several studies have found an increased risk for LOS in VLBW infants who required prolonged periods of mechanical ventilation, central catheter use, and parenteral nutrition. (2,4) In contrast, a case-control study performed in the United Kingdom in 2011 concluded that, when controlled for GA, the only independent risk factor for Gram-negative LOS was the duration of parenteral nutrition administration. (7) Other investigators, after controlling for birth weight and other interventions, found an increased risk of Candida infection in infants born at younger gestational ages (<26 weeks) or who had abdominal surgery. (8)

Genetics
Little is known about the contribution of genetics to liability for neonatal LOS. A retrospective study spanning 10 years compared sepsis concordance rates between monozygotic and dizygotic twins. By logistic regression analysis, it was determined that almost half of variance in risk of LOS was due to genetic factors alone, with the remaining half attributable to residual environmental factors. These authors also cite investigations that demonstrate positive associations between polymorphisms in the genes encoding proinflammatory cytokines, for example, tumor necrosis factor α and β, interleukin-6, and susceptibility to and severity of sepsis. (9) Studies like this suggest a significant role of genetic susceptibility to infection and impart a strong impetus for further research.

Causative Organisms
When choosing empirical antibiotic agents in suspected sepsis, clinicians must balance concern for the most
prevalent organisms against concern for the less commonly identified Gram-negative bacteria and fungal organisms, which have higher associated mortality rates. (2) With this in mind, we discuss aspects of some of the important organisms to consider in LOS (Table).

Selected Strains of Gram-Positive Bacteria
The majority (45%–75%) of pathogens responsible for LOS are Gram-positive bacteria. (10) The most common organism isolated in LOS, coagulase-negative Staphylococci (CoNS), is also the overall least virulent. (4) Groups from England, Israel, and the United States have all reported similar rates (47%–54%) of LOS infections secondary to CoNS in the past decade. (2,3,5) However, given the low virulence of CoNS, and its ubiquity in the environment, it is frequently difficult to distinguish true infection from specimen contamination. The diagnosis of a true CoNS bacteremia relies on 2 cultures obtained from different sites within 24 hours growing the same organism with the same sensitivities, although this is rarely done in practice. (11) In response to this problem, members of the Vermont Oxford Network used their database to create criteria for CoNS sepsis. (12) However, even using criteria such as these, published studies may overestimate the true infection rate. In a study of 629 infants, those classified as having CoNS were no more likely to die than patients who were uninfected. (2) In another study of 16,629 infants, infants with clinical sepsis in combination with culture-positive CoNS infection had lower mortality rates than infants with clinical sepsis but negative blood cultures. (13) This lack of CoNS-related mortality might be interpreted to suggest either that most CoNS “infections” are not true infections or that true CoNS infections are not associated with mortality.

Methicillin-resistant Staphylococcus aureus (MRSA) has recently emerged as another increasingly prevalent organism identified in LOS. A study using data from the National Nosocomial Infections Surveillance system from 1995 to 2004 showed that, of all reported S. aureus infections, 23% were MRSA. This study also showed that the incidence of MRSA LOS increased from 0.7 per 10,000 patient days in 1995 to 3.1 in 2004, a 308% increase. (14)

Gram-Negative Bacteria
LOS due to Gram-negative organisms is associated with higher mortality. (2) Increasing antibiotic resistance is also

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<td>Gram-positive organisms</td>
<td>70.2%</td>
<td>47.9%</td>
<td>55.4%</td>
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<td>Staphylococcus, coagulate negative</td>
<td>47.9%</td>
<td>54%</td>
<td>47.4%</td>
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<tr>
<td>S. aureus</td>
<td>7.8%</td>
<td>18%</td>
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<td>Enterococcus spp.</td>
<td>3.3%</td>
<td>16%</td>
<td>2.9%</td>
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<td>Group B Streptococcus</td>
<td>2.3%</td>
<td>8%</td>
<td>0.3%</td>
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<tr>
<td>Other</td>
<td>8.9%</td>
<td>—</td>
<td>1.1%</td>
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<td>Gram-negative organisms</td>
<td>17.6%</td>
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<td>4.9%</td>
<td>13%</td>
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<td>4.0%</td>
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<td>Serratia</td>
<td>2.2%</td>
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<td>Acinetobacter</td>
<td>—</td>
<td>2%</td>
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<tr>
<td>Other</td>
<td>1.4%</td>
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<td>Fungal organisms</td>
<td>12.2%</td>
<td>9%¹</td>
<td>11.1%</td>
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<td>C. albicans</td>
<td>5.8%</td>
<td>—</td>
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<td>Candida parapsilosis</td>
<td>4.1%</td>
<td>—</td>
<td>1.9%</td>
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<tr>
<td>Other</td>
<td>2.3%</td>
<td>—</td>
<td>6.6%</td>
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<tr>
<td>Mixed organisms</td>
<td>—</td>
<td>—</td>
<td>1.8%</td>
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A dash (—) indicates a value not specifically reported in the study. Study population: Stoll (2): VLBW infants (401–1500 g); average age of first LOS infection = 22 days of age; LOS defined as infection after 3 days old. Vergagno (3): preterm and term infants; median age at first LOS infection = 18 days of age (range 3–368 days); LOS defined as infection after 48 hours old. Makhoul (5): VLBW infants (<1500 g); no data provided on age at first LOS infection; LOS defined as infection after 72 hours.
¹Values are reported as the percentage of all culture proven LOS infections in each cohort.

*Reported as Candida species.
an increasing problem in gram negative bacteria causing LOS. In the United States, *Escherichia coli* has been reported to be the most common Gram-negative rod causing LOS (Table 1). However, a longitudinal study of infections showed that the proportion of LOS cases due to *E coli* has declined steadily since 1958. (4) Other Gram-negative organisms commonly reported in LOS from studies outside the United States include *Klebsiella, Enterobacter, and Serratia*. Although less common, LOS caused by *Pseudomonas aeruginosa* carries the highest mortality risk among premature infants, with reported rates of 45% to 74%. (10)

**Yeasts**

Yeasts account for 7% to 20% of LOS infections. (5) Although less common than bacterial infections, bloodstream infections due to yeast carry significant mortality risk, and should, therefore, be considered in ill infants as a possible etiology for LOS. *Candida* species, most often *Candida albicans* and, *C parapsilosis*, are the most commonly encountered fungal organisms affecting premature infants diagnosed with LOS. (4)

**Aspects of the Diagnostic Evaluation of LOS**

**Blood Cultures**

Neonatologists use the positive blood culture to confirm the diagnosis of sepsis. Although no consensus guidelines exist for the number of blood cultures that should be obtained before initiation of empirical antibiotic therapy, 83% of clinicians polled on their practices reported that they only drew one blood culture when no central venous catheter or a catheter without blood return was present. (15) One study examining the utility of one versus two blood cultures (drawn from two peripheral sites, drawn within 15–30 minutes of each other and inoculated into aerobic bottles) obtained 269 pairs of blood cultures in the evaluation of sepsis in neonates. These investigators found that of the 9% of infants diagnosed with culture-proven sepsis, every single episode had two positive blood cultures with the same organism and sensitivities. The authors concluded that a single blood culture drawn with ≥1 mL of blood resulted in no loss of accuracy in the diagnosis of sepsis in neonates. (16) However, the use of more than one blood culture can be used to differentiate between true CoNS infection from contamination. (11)

**Use of C-Reactive Protein**

The use of C-reactive protein (CRP) to differentiate true infection from contamination, especially with positive CONS blood cultures, is still debated. Approximately 30% of NICU clinicians reported drawing a CRP at initial evaluation, >12 hours after initial evaluation, or serially in a survey of treatment practices from 2002. (15) We discuss the utility of and evidence behind using CRP in the evaluation of sepsis in the final paper of this series.

**Lumbar Punctures**

Whereas lumbar puncture (LP) may be more routinely completed as part of the febrile neonate workup in previously healthy full-term infants, there are no standardized guidelines for when to perform LP in hospitalized VLBW infants with suspected LOS. In a retrospective study of infants treated with antibiotics after 72 hours of age, the safety of using a clinical algorithm in determining whether an LP should be done was evaluated. The authors suggested that, in sick infants with presumed LOS, neurologic signs, a positive blood culture, the lack of localizing signs of infection with the presence of risk factors (eg, mechanical ventilation, presence of a central catheter, VLBW) are all reasons to perform an LP. Using these criteria in infants with suspected LOS, this study found that 71% of evaluations included an LP, and late onset meningitis was diagnosed in <2% of all evaluations. No significant differences in short- or long-term morbidity were found between infants who did and did not receive LP, including infants with diagnosed meningitis. However, it is not stated whether the study was powered to detect differences in outcomes, especially given the low incidence of meningitis in this cohort. (17) It should also be noted that in the scenario of a positive blood culture, the importance of performing an LP may be dependent on the organism identified, given that isolates such as group B *Streptococcus* or *Candida* portend such poor outcomes if spread to the CSF.

**Treatment**

Because a thorough review of the mechanisms and coverage of commonly used antibiotics is presented in the accompanying article in this issue, which concerns EOS, we focus on a discussion of how empirical antibiotic therapy differs in LOS.

**Empirical Antibiotic Therapy**

The goal of antibiotic use before the identification of the infectious microbe, or empirical antibiotic therapy, is to eradicate harmful organisms as early in the clinical course as possible. However, the life-saving potential of antibiotic use in infants at high risk for infection must be balanced against the possible negative consequences of widespread use in low-risk infants. Antibiotic therapy can alter the neonatal microbiome, potentially making
the infant more susceptible to opportunistic infection, and lead to increased incidence of antibiotic-resistant organisms. In a retrospective cohort study, the administration of prolonged initial empirical antibiotic therapy (≥5 days; negative cultures) in the first week of life in VLBW infants was associated with an increase in LOS. Therefore, the choice of antibiotic therapy for suspected sepsis should be tailored for the most likely organisms with the highest mortality risk, with consideration to local resistance patterns. No consensus guidelines exist as to specific antibiotic regimens. (19)

Vancomycin is commonly used in LOS, likely because the majority of LOS infections are caused by CoNS and the concern for rising rates of β-lactamase antibiotic resistance in LOS isolates including MRSA. One large multicenter study reported that 44% of VLBW infants were treated with vancomycin after day 3, and perhaps more importantly, 30% of babies without proven infection received this drug. (2) The Centers for Disease Control and Prevention and others have recommended against empirical vancomycin therapy to prevent the emergence and spread of vancomycin-resistant strains. (20) Given the relatively low reported virulence of Gram-positive organisms in LOS (21) and lack of data to suggest decreased rates of fulminant sepsis with the use of vancomycin, (22) this seems to represent a reasonable approach. (2,16) A recent quality improvement initiative using a guideline to reduce vancomycin use in 2 NICUs with low MRSA infection rates demonstrated significant reduction in vancomycin exposure without an increase in attributable morbidity or mortality. (23) However, the widespread use of vancomycin may be explained by the concern for impaired neurodevelopmental outcomes reported in infants with CoNS LOS. (24) As a result, the decision as to whether to include vancomycin as part of empirical therapy pending culture results rests with the clinician.

The temptation to use third-generation cephalosporins seems unwarranted on the basis of recent literature. Data published in 2011 from the British Health Protection Agency’s surveillance program showed that 95% of organisms in LOS were susceptible to gentamicin with either flucloxacinil or amoxicillin and that only 79% were susceptible to cefotaxime monotherapy. (25) Although cefotaxime has been frequently considered for empirical therapy with its broader spectrum of coverage, it actually provides less coverage for the relevant disease-causing organisms and has greater potential to promote antibiotic resistance and increase the risk for fungal infections. An important caveat to this rule would be in suspected meningitis, in which cefotaxime has superior cerebrospinal fluid penetration.

Antifungal Therapy
The rationale for treatment of Candida infections in neonates is largely based on data in adults, because there is a lack of well-designed studies on antifungal therapy in neonates. The most commonly used agents are amphotericin B, which binds to ergosterol, leading to altered cell permeability inducing pore formation and cell death, and fluconazole, which binds and inhibits production of ergosterol. The safety and efficacy of newer antifungals such as echinocandins are being studied in neonates. (26) Caspofungin is an echinocandin in which the principal mechanism of action is the noncompetitive inhibition of β-(1,3)-D-glucan synthase, an essential enzyme responsible for fungal cell wall synthesis.

Duration of Empirical Antibiotic Therapy
Although no actual guidelines exist on duration of empirical therapy, a 2002 survey of treatment practices revealed that the majority of clinicians would discontinue antibiotics after 2 to 3 days of negative cultures. (15) This practice seems reasonable on the basis of published studies examining the time to positive cultures in LOS. One study found that of positive cultures in LOS evaluations, 98% had a time to detection ≤48 hours. Of those that were positive later than 48 hours in this study, 7 of 8 grew CoNS, and 4 were contaminants. (27) A more recent study in Belgium found that the median time to positive cultures in LOS was 21 hours and that the median time to positive cultures for Gram-negative and Gram-positive organisms was 11 hours and close to 24 hours, respectively. (28) However, in a critically ill infant, prolonged courses of antibiotics are often used. It is important in these cases of presumed “culture-negative sepsis” to avoid erroneous attribution and to reevaluate the infant for possible noninfectious etiologies for their clinical worsening.

Antimicrobial Stewardship
On the basis of this evidence, it is critical to emphasize the rational use of antibiotics. It seems that oxacillin/nafcillin plus gentamicin is a reasonable regimen for empirical antibiotic therapy in LOS, although the specific agents chosen should take into account local resistance patterns. The use of vancomycin should be initiated if, in the judgment of the clinician, the infant is critically ill and the postulated infecting organism may be a methicillin-resistant strain of a Gram-positive organism. Third-generation cephalosporin use should be discouraged outside of suspected meningitis. Antibiotic therapy should be narrowed as much as possible once an organism is identified. In addition to careful selection of what agent to use, duration
of empirical antibiotic therapy should be limited to 2 to 3 days if cultures are negative. It is also important to avoid treating colonization (positive endotracheal cultures without evidence of pneumonia) and prophylactic antibiotic use for invasive devices. (21,29)

Preventions to Decrease LOS Rate
Despite being well studied and the only established means for preventing transmission of infectious organisms among hospitalized patients, hand hygiene is poorly adhered to, with recently reported rates of 70% in NICUs. (30) Other potentially promising interventions are being studied, and here we report recent literature on the use of antimicrobial agents in prevention of LOS and a multicenter trial therapy with intravenous polyvalent immunoglobulin G (IgG).

Antimicrobial Prophylaxis
As emphasized earlier, Gram-positive infections constitute a large portion of LOS infections. On the basis of studies in pediatric oncology patients, a recent evaluation of 85 VLBW infants has demonstrated the efficacy of vancomycin catheter locks in reducing the incidence of infection from 42% to 17%. (31) Given this and other studies, there seems to be some reduction in the incidence of CoNS LOS without increase in resistant organisms, but there is no evidence of a decrease in morbidity or mortality with vancomycin prophylaxis. (32) Antifungal prophylaxis has also been studied for prevention of Candida infections. Although topical nystatin and prophylactic fluconazole appear to provide significant reduction in Candida LOS, this strategy should be balanced against the low reported rates of invasive candidiasis in VLBW infants. (10,26)

Intravenous Immunoglobulin
The previously reported benefits of intravenous infusion of IgG in the prevention and treatment of neonatal sepsis in premature infants resulted in a multicenter, prospective, randomized trial of more than 3400 infants. The investigators randomized infants receiving antibiotics for suspected or proven infection to either receiving two infusions of polyvalent IgG or matching placebo infusions 48 hours apart. This study demonstrated no differences between groups in death or major disability at age 2 years; no significant differences in rates of EOS or LOS were reported. (33)

Conclusions
LOS in the neonate continues to contribute significantly to the morbidity and mortality of hospitalized infants worldwide. Risk factors for LOS include prematurity, low birth weight, invasive interventions, as well as comorbid conditions of prematurity. The predominant etiologic agents of LOS include coagulase-negative Staphylococcus, MRSA, methicillin-sensitive Staphylococcus aureus, E coli, and Candida. Although diagnostic practices vary, antibiotics remain the mainstay of treatment, but the regimen of empirical therapy is debated and ever evolving. Institutions should establish epidemiologic surveillance programs and partner with their infectious disease colleagues to devise appropriate empiric antibiotic regimens specific to each NICU. Several studies have evaluated the possible use of antimicrobials as preventative strategies for LOS. Because there is significant cost resulting from sometimes inappropriate antimicrobial use, it is important to develop and implement antimicrobial stewardship programs.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the clinical manifestations, laboratory features, and differential diagnosis of neonatal sepsis.
- Understand the treatment and complications of sepsis.
- Know the infectious agents that cause neonatal sepsis.
- Know the maternal, perinatal, and neonatal risk factors for neonatal sepsis.
- Know the epidemiology, prevention, and pathogenesis of neonatal infection 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.

References


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 2012 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. Starting with 2012 NeoReviews, AMA PRA Category 1 Credit™ can be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. Late onset sepsis, attributed to nosocomial or horizontal transmission, is common among very low birth weight (VLBW) infants (<1500g). Of the following, according to the National Institutes of Child Health and Human Development Neonatal Research Network, the incidence of late onset sepsis among VLBW infants in the United States, is closest to
   A. 10 percent
   B. 20 percent
   C. 30 percent
   D. 40 percent
   E. 50 percent

2. The risk of late onset sepsis from gram-negative microorganisms is increased among VLBW infants who require invasive care during their hospitalization. Of the following, according to a case-control study performed in the United Kingdom in 2011, the only independent risk factor for gram-negative late onset sepsis after controlling for gestational age is the duration of
   A. Chest tube placement
   B. Ductus arteriosus ligation
   C. Intravascular catheterization
   D. Mechanical ventilation
   E. Parenteral nutrition

3. A 28-day-old preterm infant, who has chronic lung disease and need for support with mechanical ventilation, is suspected to have late onset sepsis. In choosing the antibiotics for treatment, you review the profile of microorganisms likely to cause late onset sepsis in preterm infants in your nursery. Of the following, the most common microorganism isolated in late onset sepsis is
   A. Candida albicans
   B. Coagulase negative Staphylococcus
   C. Enterococcus spp
   D. Escherichia coli
   E. Group B Streptococcus

4. A 14-day-old preterm infant, who weighed 650g at birth at an estimated gestational age of 24 weeks, is suspected to have late onset sepsis. The infant has clinical evidence of rapidly worsening shock. The blood culture is positive for gram-negative microorganisms. Of the following, the gram-negative microorganism that carries the highest mortality risk among preterm infants is
   A. Acinetobacter baumannii
   B. Enterobacter cloacae
   C. Klebsiella pneumoniae
   D. Pseudomonas aeruginosa
   E. Serratia marcescens

5. A 6-week-old preterm infant, who weighed 1,520g at birth at an estimated gestational age of 32 weeks, is brought to the emergency department after an acute life-threatening event. The infant is suspected to have
late onset sepsis and meningitis. You choose to treat with an antibiotic that has superior cerebrospinal fluid penetration. Of the following, the antibiotic most likely to provide effective coverage for suspected meningitis is

A. Cefotaxime
B. Fluconazole
C. Gentamicin
D. Nafcillin
E. Vancomycin
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