CHAPTER OUTLINE

**Bacteriology**
- Group B Streptococci
- Group A Streptococci
- *Streptococcus Pneumoniae*
- Other Streptococci
- Enterococcus Species
- *Staphylococcus Aureus* and Coagulase-Negative Staphylococci
- *Listeria Monocytogenes*
- *Escherichia Coli*
- Klebsiella Species
- *Enterobacter and Cronobacter* Species
- *Citrobacter* Species
- *Serratia Marcescens*
- *Pseudomonas Aeruginosa*
- *Salmonella* Species
- *Neisseria Meningitidis*
- *Haemophilus Influenzae*
- Anaerobic Bacteria
- Neonatal Tetanus
- Mixed Infections
- Uncommon Bacterial Pathogens

**Epidemiology**
- Incidence of Sepsis and Meningitis
- Characteristics of Infants who Develop Sepsis
- Nursery Outbreaks or Epidemics

**Pathogenesis**
- Host Factors Predisposing to Neonatal Bacterial Sepsis
- Infection in Twins
- The Umbilical Cord as a Focus of Infection
- Administration of Drugs to the Mother Before Delivery
- Administration of Drugs other than Antibiotics to the Neonate

**Pathology**
- Clinical Manifestations
- Fever and Hypothermia
- Respiratory Distress
- Jaundice
- Organomegaly
- Gastrointestinal Signs
- Skin Lesions
- Neurologic Signs

**Diagnosis**
- Maternal History
- Microbiologic Techniques
- Laboratory Aids

**Management**
- Choice of Antimicrobial Agents
- Current Practice
- Continuation of Therapy when Results of Cultures are Available
- Management of the Infant whose Mother Received Intrapartum Antimicrobial Agents
- Treatment of the Infant whose Bacterial Culture Results are Negative
- Management of the Infant with Catheter-Associated Infection
- Treatment of Neonatal Meningitis
- Management of the Infant with a Brain Abscess
- Treatment of the Infant with Meningitis whose Bacterial Culture Results are Negative
- Treatment of Anaerobic Infections
- Adjunctive Therapies for Treatment of Neonatal Sepsis

**Prognosis**

**Prevention**
- Obstetric Factors
- Chemoprophylaxis
- Maternal Factors
- Immunoprophylaxis
- Decontamination of Fomites
- Epidemiologic Surveillance

**Sepsis in the Newborn Recently Discharged From the Hospital**
- Congenital Infection
- Late-Onset Disease
- Infections in the Household
- Fever in the First Month of Life
Bacterial sepsis in the neonate is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteremia in the first month of life. Meningitis in the neonate usually is a sequela of bacteremia and is discussed in this chapter because meningitis and sepsis typically share a common cause and pathogenesis. Infections of the bones, joints, and soft tissues and of the respiratory, genitourinary, and gastrointestinal tracts can be accompanied by bacteremia, but the cause, clinical features, diagnosis, and management of these infections are sufficiently different to warrant separate discussions. Bloodstream and central nervous system (CNS) infections caused by group B streptococci (GBS), Staphylococcus aureus, and coagulase-negative staphylococci (CoNS), Neisseria gonorrhoeae, Listeria monocytogenes, Salmonella spp., and Mycobacterium tuberculosis are described in detail in other individual chapters. Chapter 2 describes the features of neonatal sepsis and meningitis in developing regions.

The two patterns of disease, early-onset and late-onset, have been associated with systemic bacterial infections during the first month of life (Table 6-1). Early-onset disease typically presents as a fulminant, systemic illness during the first 24 hours of life (median age of onset approximately 6 hours), with the large majority of other cases presenting on the second day of life. Infants with early-onset disease can have a history of one or more obstetric complications, including premature or prolonged rupture of maternal membranes, preterm onset of labor, chorioamnionitis, and peripartum maternal fever, and many of the infants are premature or of low birth weight (LBW). Bacteria responsible for early-onset disease are acquired hours before delivery from the birth canal during delivery after overt or occult rupture of membranes. The mortality rate varies from 3% to as high as 50% in some series, especially with gram-negative pathogens. Late-onset disease has been variably defined for epidemiologic purposes as occurring after 72 hours to 6 days (e.g., GBS) of life. Very-late-onset infection caused by GBS (disease in infants older than 3 months) is discussed in Chapter 12. Term infants with late-onset infections can have a history of obstetric complications, but these are less characteristic than in early-onset sepsis or meningitis. Bacteria responsible for late-onset sepsis (LOS) and meningitis include those acquired from the maternal genital tract and organisms acquired after birth from human contacts or, infrequently, from contaminated hospital equipment or materials, where prolonged intensive care is needed for a neonate. The mortality rate usually is lower than that for early-onset sepsis but can vary between 2% and 40%, with the latter figure typically for very-low-birth-weight (VLBW) infants with gram-negative sepsis. Because different microorganisms are responsible for disease according to age at onset, the choice of antimicrobial agents also differs. Some organisms, such as Escherichia coli, groups A and B streptococci, and L. monocytogenes, can be responsible for early- and late-onset infections, whereas others, such as S. aureus, CoNS, and Pseudomonas aeruginosa, rarely cause early-onset and typically are associated with late-onset disease. The survival of VLBW infants with prolonged stays in the neonatal intensive care unit (NICU)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early Onset*</th>
<th>Late Onset†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset (days)</td>
<td>0-6</td>
<td>7-90</td>
</tr>
<tr>
<td>Complications of pregnancy or delivery</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Source of organism</td>
<td>Mother’s genital tract</td>
<td>Mother’s genital tract; postnatal environment</td>
</tr>
<tr>
<td>Usual clinical presentation</td>
<td>Fulminant</td>
<td>Slowly progressive or fulminant</td>
</tr>
<tr>
<td>Mortality rate (%)</td>
<td>3-50</td>
<td>2-40</td>
</tr>
</tbody>
</table>

*Many studies define early-onset sepsis as that which occurs in the first 72 hours of life; others in the first 5 or 6 days of life.
†Very small premature infants may have late-onset sepsis beyond 90 days of life.
‡Higher mortality rates in earlier studies.

has been accompanied by increased risk for nosocomial or hospital-associated infections and for very-late-onset disease† (see Chapter 35).

**Bacteriology**

The changing pattern of organisms responsible for neonatal sepsis is well illustrated in a series of reports by pediatricians at the Yale–New Haven Hospital covering the period 1928 to 2003 (Table 6-2). Before development of the sulfonamides, gram-positive cocci, including S. aureus and β-hemolytic streptococci, caused most cases of neonatal sepsis. With the introduction of antimicrobial agents, gram-negative enteric bacilli, particularly E. coli, became the predominant cause of serious infection in the newborn. Reports for the periods of 1966 to 1978 and 1979 to 1988 document the rise to importance of GBS and E. coli as agents of neonatal sepsis. In the most recent analysis from 1989 to 2003, CoNS species, predominantly Staphylococcus epidermidis, emerged as the single most commonly identified agent of neonatal sepsis, with GBS, E. coli, Enterococcus faecalis, S. aureus, and Klebsiella spp. also occurring at substantial frequency. The latest reports also document the problem of sepsis in very premature and LBW infants who have survived with the aid of sophisticated life-support equipment and advances in neonatal intensive care; it is these infants for whom CoNS are particularly threatening. Emerging data from the same center indicate that intrapartum antibiotic prophylaxis protocols, although reducing the overall incidence of early-onset sepsis, may be influencing a higher proportion of septicemia attributable to ampicillin-resistant E. coli.9

The etiologic pattern of microbial infection observed at Yale Medical Center also has been reported in studies of neonatal sepsis carried out at other centers during the same intervals. Studies indicate that GBS and gram-negative enteric bacilli, predominantly E. coli, were the most frequent pathogens for sepsis, but other organisms were prominent...
in some centers. *S. aureus* was an important cause of sepsis in the mid-1980s in Finland and East Africa and a more recently significant pathogen in Connecticut and southern Israel. *S. epidermidis* was responsible for 53% of cases in Liverpool and CoNS account for 35% to 48% of all LOS in VLBW infants across the United States and in Israel, and *Klebsiella* and *Enterobacter* spp. were the most common bacterial pathogens in Tel Aviv. Sepsis and focal infections in neonates in developing countries are further discussed in Chapter 2.

The Yale data also provide information about the microorganisms responsible for early- and late-onset bacterial sepsis (Table 6-3). GBS were responsible for most early-onset disease. CoNS, *S. aureus*, *E. coli*, *Enterococcus* spp., and *Klebsiella* spp. were the major pathogens of late-onset disease: a wide variety of gram-positive cocci and gram-negative bacilli are documented as causes of bacterial sepsis in the infant after age 30 days.

The mortality rates for neonatal sepsis over time are documented in the Yale Medical Center reports. In the pre-antibiotic era, neonatal sepsis usually was fatal. Even with the introduction of penicillins and aminoglycosides in the reports from 1944 to 1965, death resulted from sepsis in most infants. Concurrent with the introduction of NICUs and technologic support for cardiorespiratory and metabolic functions beginning in the early 1970s, the mortality rate was reduced to 16%. By 1989 to 2003, mortality from neonatal sepsis in this academic medical center was a rare event, occurring in only 3% of cases. A decline in the incidence of early-onset sepsis, commonly associated with more virulent pathogens, coupled with an increase in late and “late-late”–onset sepsis from CoNS and other commensal species (which together now account for nearly half of all cases), has contributed to the improved survival figures, along with continued advances in care and monitoring of the critically ill infant.

From 2005 to 2008, 658 cases of neonatal early-onset sepsis were reported to the Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance (ABCs) sites in four states (California, Connecticut, Georgia, Minnesota), for an incidence of approximately 77 cases per 1000 live births (95% confidence interval [CI], 0.72 to 0.84) associated with a 10.9% mortality rate (Table 6-4). The five most commonly reported pathogens were GBS (37.8%), *E. coli* (24.2%), viridans streptococci (17.9%), *S. aureus* (4.0%), and *Haemophilus influenzae* (4.0%). *E. coli* infections had the highest case fatality rate at 24.5%. Black preterm infants had the highest disease incidence (5.14 cases/1000 live births) and case fatality ratio (24.4%), whereas nonblack term infants had the lowest incidence (0.40 cases/1000 live births) and case fatality ratio (1.6%). *E. coli* was the most common infection (1.18 cases/1000 live births) with the highest case fatality ratio (32.1%) among preterm infants, whereas GBS were the leading pathogens among term infants (0.22 cases/1000 live births), with no reported deaths.

The incidence of neonatal sepsis showed a strong inverse correlation to birth weight in the latest Yale cohort: greater than 2000 g (0.2%), 1500 to 1999 g (2.5%), 1000 to 1499 g (9.4%), 750 to 999 g (14.8%), and less than 750 g (34.8%). Survival of VLBW infants (<1500 g) has been accompanied by an increased risk for invasive, nosocomial, or health care–associated bacterial infection as a cause of morbidity and mortality. The danger of sepsis is documented in a multicenter trial that enrolled 2416 VLBW infants in a study of the efficacy of intravenous immunoglobulin in

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**Table 6-2** Bacteria Causing Neonatal Sepsis at Yale–New Haven Hospital, 1928-2003

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Hemolytic streptococci</td>
<td>15</td>
<td>18</td>
<td>11</td>
<td>8</td>
<td>86</td>
<td>83</td>
<td>155</td>
</tr>
<tr>
<td>Group A</td>
<td>16</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group B</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>76</td>
<td>64</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Group D (<em>Enterococcus</em>)</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>9</td>
<td>19</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Viridans streptococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>11</td>
<td>4</td>
<td>8</td>
<td>2</td>
<td>12</td>
<td>14</td>
<td>70</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Haemophilus spp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>10</td>
<td>11</td>
<td>23</td>
<td>33</td>
<td>76</td>
<td>46</td>
<td>106</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
<td>0</td>
<td>13</td>
<td>11</td>
<td>5</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>Klebsiella and Enterobacter spp.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>28</td>
<td>25</td>
<td>97</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>6</td>
<td>4</td>
<td>9</td>
<td>21</td>
<td>38</td>
<td>54</td>
</tr>
<tr>
<td>Total no. of cases</td>
<td>39</td>
<td>44</td>
<td>62</td>
<td>73</td>
<td>239</td>
<td>270</td>
<td>784</td>
</tr>
<tr>
<td>Mortality rate for years</td>
<td>87%</td>
<td>90%</td>
<td>67%</td>
<td>45%</td>
<td>26%</td>
<td>16%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Data from Dunham EC: Septicemia in the newborn, Am J Dis Child 45:229, 1933.
### Table 6-3 Microbiology of Neonatal Sepsis at Yale–New Haven Hospital, 1989-2003

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>0-4</th>
<th>5-30</th>
<th>&gt;30</th>
<th>Transformed Infants</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>8</td>
<td>18</td>
<td>20</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>6</td>
<td>119</td>
<td>42</td>
<td>81</td>
<td>248</td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>53</td>
<td>12</td>
<td>7</td>
<td>14</td>
<td>86</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>5</td>
<td>21</td>
<td>23</td>
<td>33</td>
<td>82</td>
</tr>
<tr>
<td>Viridans streptococci</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Stomatococcus spp.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bacillus spp.</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>25</td>
<td>27</td>
<td>12</td>
<td>41</td>
<td>106</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>0</td>
<td>20</td>
<td>9</td>
<td>18</td>
<td>47</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>0</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Enterobacter aerogens</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Enterobacter agglomerans</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>0</td>
<td>6</td>
<td>10</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2</td>
<td>14</td>
<td>4</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Bacteroides spp.</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Other gram-negative rods</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Candida and other fungi/yeast</td>
<td>3</td>
<td>41</td>
<td>16</td>
<td>18</td>
<td>78</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td>304</td>
<td>169</td>
<td>277</td>
<td>862</td>
</tr>
</tbody>
</table>


preventing nosocomial infections. Sixteen percent of the VLBW infants developed septicemia at a median age of 17 days, with an overall mortality rate of 21% and a hospital stay that averaged 98 days; infants without sepsis had an overall mortality rate of 9% and 58-day average length of stay. Stoll and colleagues reported recent patterns of pathogens causing early-onset sepsis in VLBW infants (400–1500 g) in the centers participating in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (Table 6-5). Compared with earlier cohorts, a marked reduction in GBS infections (from 5.9–2.08/1000 live births) and an increase in E. coli infections (3.2–5.09/1000 live births) were noted, although the overall incidence of neonatal sepsis in this population did not change.

Organisms responsible for bacterial meningitis in the newborn are listed in Table 6-6, which summarizes data collected from 1932 to 1997 at neonatal centers in the United States, The Netherlands, Great Britain, and Israel. Gram-negative enteric bacilli and GBS currently are responsible for most cases. Organisms that cause acute bacterial meningitis in older children and adults—Streptococcus pneumoniae, Neisseria meningitidis, and type b and nontypeable Haemophilus influenzae—are relatively infrequent causes of meningitis in the neonate. A nationwide survey of causative agents of neonatal meningitis in Sweden between 1976 and 1983 indicated a shift from bacterial to viral or unidentified microorganisms, with lower attributable mortality rates.

### GROUP B STREPTOCOCCI

Group B β-hemolytic streptococci were implicated in human disease shortly after the precipitin-grouping technique was described. For the past 3 decades, GBS has been the most common pathogen causing invasive disease in neonates throughout the United States and western Europe (see Chapter 12).

Streptococcus agalactiae, the species designation of GBS, has a characteristic colonial morphology on suitable solid media. The organism produces a mucoid colony with a narrow zone of β-hemolysis on sheep blood-agar media. The GBS can be differentiated immunochemically on the basis of their type-specific polysaccharides. Ten capsular types—Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX—have been characterized, and most invasive human isolates can be classified as one of these types, with serotypes Ia, III, and V the most prevalent in many recent epidemiologic surveys.

GBS have been isolated from various sites and body fluids, including throat, skin, wounds, exudates, stool, urine, cervix, vagina, blood, joint, pleural or peritoneal fluids, and cerebrospinal fluid (CSF). The organisms frequently are found in the lower gastrointestinal and genital tracts of adult women and men and in the lower gastrointestinal and upper respiratory tracts of newborns. Patterns of early-, late-, and very-late-onset disease have been associated with GBS (see Table 6-1). Early-onset disease presents as a multisystem illness, with rapid onset typically during the first day or two of life and is frequently characterized by severe respiratory distress. The pathogenesis is presumed to be similar to that of other forms of early-onset sepsis of neonates. The mortality rate is estimated at 8% but was previously as high as 50% in the 1970s.

Clinical manifestations of late-onset neonatal sepsis are more insidious than those of early-onset disease, and meningitis is frequently a part of the clinical picture. However, some infants with meningitis have a fulminant onset with rapid progression to centrally mediated apnea. Many of the infants are products of a normal pregnancy and delivery and have no problems in the nursery. It is uncertain whether GBS infection was acquired at the time of birth and carried until disease developed, was acquired after delivery from the mother or other household contacts, or was acquired from other infants or personnel in the nursery. In late-onset infection, a majority of strains belong to serotype III. The mortality rate, estimated at 3%, is lower than that for early-onset disease. With increasing survival of extremely-low-birth-weight (ELBW) (<1000 g) infants, very-late-onset disease (>89 days) has been described in the past decade.

In addition to sepsis and meningitis, other manifestations of neonatal disease caused by GBS include pneumonia,
Table 6-4  Invasive Early-Onset* Neonatal Sepsis Cases and Deaths, Centers for Disease Control Active Bacterial Core Surveillance, 2005-2008

<table>
<thead>
<tr>
<th></th>
<th>TOTAL</th>
<th>BLACK PRETERM</th>
<th>BLACK TERM</th>
<th>NONBLACK PRETERM</th>
<th>NONBLACK TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (Rate)</td>
<td>658 (0.77)</td>
<td>131 (5.14)</td>
<td>120 (0.89)</td>
<td>158 (2.27)</td>
<td>249 (0.040)</td>
</tr>
<tr>
<td>Deaths (CFR)</td>
<td>72 (10.9)</td>
<td>32 (24.4)</td>
<td>2 (1.7)</td>
<td>34 (21.5)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td></td>
<td>249 (0.29)</td>
<td>40 (1.57)</td>
<td>75 (0.55)</td>
<td>38 (0.55)</td>
<td>96 (0.15)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>159 (0.19)</td>
<td>46 (1.81)</td>
<td>16 (0.12)</td>
<td>66 (0.95)</td>
<td>31 (0.05)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>81 (0.09)</td>
<td>31 (1.22)</td>
<td>3 (0.02)</td>
<td>31 (0.45)</td>
<td>16 (0.03)</td>
</tr>
<tr>
<td>Viridans</td>
<td>118 (0.14)</td>
<td>16 (0.63)</td>
<td>16 (0.12)</td>
<td>18 (0.26)</td>
<td>68 (0.11)</td>
</tr>
<tr>
<td>Streptococci</td>
<td>26 (0.03)</td>
<td>2 (0.08)</td>
<td>5 (0.04)</td>
<td>1 (0.01)</td>
<td>18 (0.03)</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>26 (0.03)</td>
<td>10 (0.39)</td>
<td>0 (0)</td>
<td>12 (0.17)</td>
<td>4 (0.006)</td>
</tr>
<tr>
<td>aureus</td>
<td>26 (0.03)</td>
<td>17 (0.67)</td>
<td>8 (0.06)</td>
<td>23 (3.3)</td>
<td>32 (0.05)</td>
</tr>
<tr>
<td>Other pathogens</td>
<td>80 (0.09)</td>
<td>17 (0.67)</td>
<td>4 (17.4)</td>
<td>4 (0.006)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>


*Occurring in infants the first 72 hours of life.

empyema, facial cellulitis, ethmoiditis, orbital cellulitis, conjunctivitis, necrotizing fascitis, osteomyelitis, suppurrative arthritis, and impetigo. Bacteremia without systemic or focal signs of sepsis can occur. GBS infection in pregnant women can result in peripartum infections, including septic abortion, choioamnionitis, peripartum bacteremia, septic pelvic thrombophlebitis, meningitis, and toxic shock syndrome.32

**GROUP A STREPTOCOCCI**

Streptococcal puerperal sepsis has been recognized as a cause of morbidity and mortality among parturient women since the 16th century.33-35 Neonatal group A streptococcal (GAS) infection now is reported infrequently but can occur rarely in epidemic form in nurseries.36-39 The reemergence of virulent GAS infections during the last 4 decades, including invasive disease and toxic shock syndrome, has been reflected in more case reports of severe disease in the pregnant woman and the newborn.33-35

GAS disease in the mother can affect the fetus or newborn in two clinical patterns. Maternal streptococcal bacteremia during pregnancy can lead to in utero infection resulting in fetal loss or stillbirth, or alternatively, acquisition of GAS from the maternal genital tract can cause early-onset neonatal sepsis similar to early-onset GBS disease. In the first form of disease, previously healthy pregnant women with influenza-like signs and symptoms have been reported. This presentation rapidly progressed to disseminated intravascular coagulopathy and shock, with high mortality and risk to the fetus or newborn.45-47

The features of 38 cases of neonatal invasive GAS infection from the literature were recently catalogued.48 Overall mortality rate in neonatal invasive GAS infection was significantly high, at 31%. Most of these infants presented with early-onset infection (62%), with many occurring in the first 48 hours of life. A specific focus of GAS infection was documented in three quarters of cases; 42% of neonates had pneumonia, sometimes complicated by empyema, and 17% had a toxic-shock–like syndrome presentation. Among the cases of early-onset GAS infection, puerperal sepsis or toxic shock–like syndrome in the mother during the peripartum period was an associated factor in 62% of cases. In late-onset cases of neonatal GAS infection reviewed in this series, soft tissue infections, meningitis, and pneumonia were among the reported clinical manifestations. An earlier review by Greenberg and colleagues49 on 15 cases of GAS neonatal infection yielded similar statistics on clinical presentations and mortality.

In addition to sepsis, meningitis, and toxin-mediated disease in the neonate, focal infections, including cellulitis,38 osteoarthritis, pneumonia, empyema,39 osteomyelitis, and parotitis,35 have been reported. Because all GAS are susceptible to β-lactam antibiotics, the current strategy for prevention or treatment of infections caused by GBS also could apply to infections caused by GAS.

**STREPTOCOCCUS PNEUMONIAE**

Although pneumococcal infections in the neonate are unusual occurrences, they are associated with substantial morbidity and mortality.50-53 Malhotra and colleagues54 recently reported four infants with invasive neonatal pneumococcal infections that developed within the first 24 hours of life, with all four having clinical and radiologic features of pneumonia and a pattern of disease rather indistinguishable from typical severe early-onset GBS sepsis. One of the infants was a 33-week premature infant, and one of the mothers had choioamnionitis before delivery. All four infants survived, with varying levels of supportive care,
including extracorporeal membrane oxygenation in a child who also developed meningitis. Two infants were expected to suffer significant long-term sequelae. In another report, fatal pneumococcal bacteremia in a mother 4-weeks post-partum and the same disease and outcome in her healthy term infant who died at 6 weeks of age suggested an absence of protective antibody in mother and child.55

Hoffman and colleagues,51 from the United States Multicenter Pneumococcal Surveillance Group, identified 20 cases of neonatal S. pneumoniae sepsis or meningitis in a review of 4428 episodes of pneumococcal infection at eight children’s hospitals from 1993 to 2001. Ninety percent of the infants were born at term, with a mean age at the onset of infection of 18.1 days. Only two of the mothers had clinically apparent infections at the time of delivery. Eight neonates had meningitis and 12 had bacteremia; 4 of the bacteremic neonates also had pneumonia. The most common infecting pneumococcal serotypes were 19 (32%), 9 (18%), and 18 (11%). Penicillin and ceftriaxone nonsusceptibility were observed in 21.4% and 3.6% of isolates, respectively. Three deaths (15%) occurred, all within 36 hours of presentation. A case report of peripartum transmission of penicillin-resistant S. pneumoniae underlines concern that the increasing use of peripartum ampicillin to prevent GBS disease in the neonate may result in an increase in neonatal infections caused by β-lactam–resistant organisms.52 A case of purulent pneumococcal pericarditis in a neonate has recently been reported.56

OTHER STREPTOCOCCI

Human isolates of group C and G streptococci form large β-hemolytic colonies that closely resemble those of GAS and share many virulence genes, including those encoding surface M proteins and the cytotoxin streptolysin S. Group C streptococci have been associated with puerperal sepsis, but neonatal sepsis or meningitis related to these organisms is rare.57-60 Likewise, group G streptococci are an infrequent cause of neonatal sepsis and pneumonia.61-63 Maternal intrapartum transmission was the likely source for most

### Table 6-5  Characteristics and Mortality Rate of 389 U.S. Infants With Early-Onset Sepsis

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 389)</th>
<th>Preterm (22-36 wk) with GBS or E. coli</th>
<th>Term (37+ wk) with GBS or E. coli</th>
<th>Overall with GBS or E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth Weight (G)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>401-1500</td>
<td>142 (37%)</td>
<td>27 (63)</td>
<td>66 (76)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1501-2500</td>
<td>51 (13%)</td>
<td>11 (26%)</td>
<td>20 (23%)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>&gt;2500</td>
<td>196 (50%)</td>
<td>5 (12)</td>
<td>1 (1)</td>
<td>114 (97)</td>
</tr>
<tr>
<td><strong>Infant Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>205 (53)</td>
<td>22 (51)</td>
<td>47 (54)</td>
<td>57 (49)</td>
</tr>
<tr>
<td>Female</td>
<td>184 (47)</td>
<td>21 (49)</td>
<td>40 (46)</td>
<td>60 (51)</td>
</tr>
<tr>
<td><strong>Delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>181 (47)</td>
<td>18 (43)</td>
<td>29 (33)</td>
<td>63 (54)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>204 (53)</td>
<td>25 (57)</td>
<td>58 (67)</td>
<td>54 (46)</td>
</tr>
<tr>
<td>ROM &gt; 18 hr PTD</td>
<td>127 (33)</td>
<td>19 (44)</td>
<td>54 (62)</td>
<td>17 (15)</td>
</tr>
<tr>
<td>SROM &lt; 37 wk of gestation</td>
<td>157 (40)</td>
<td>30 (70)</td>
<td>75 (86)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Symptoms &lt; 72 hr PTD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal temperature &gt; 38.0° C</td>
<td>102 (26)</td>
<td>3 (7)</td>
<td>27 (32)</td>
<td>42 (36)</td>
</tr>
<tr>
<td>Uterine or abdominal tenderness</td>
<td>56 (15)</td>
<td>6 (14)</td>
<td>26 (31)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Maternal tachycardia (&gt;100 bpm)</td>
<td>150 (30)</td>
<td>14 (33)</td>
<td>36 (42)</td>
<td>30 (26)</td>
</tr>
<tr>
<td>Fetal tachycardia (&gt;160 bpm)</td>
<td>120 (31)</td>
<td>11 (26)</td>
<td>34 (40)</td>
<td>40 (34)</td>
</tr>
<tr>
<td><strong>Placental Pathology Performed</strong></td>
<td>248 (65)</td>
<td>33 (77)</td>
<td>72 (85)</td>
<td>49 (43)</td>
</tr>
<tr>
<td><strong>Histologic Chorioamnionitis</strong></td>
<td>190 (77)</td>
<td>30 (91)</td>
<td>63 (88)</td>
<td>32 (65)</td>
</tr>
<tr>
<td><strong>Infant Mortality n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Deaths</td>
<td>61 (16)</td>
<td>13 (30)</td>
<td>33 (38)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Time of Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 days</td>
<td>35 (57)</td>
<td>7 (54)</td>
<td>21 (64)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>4-7 days</td>
<td>12 (20)</td>
<td>1 (8)</td>
<td>7 (21)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>8-14 days</td>
<td>3 (5)</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>&gt;14 days</td>
<td>11 (18)</td>
<td>5 (38)</td>
<td>3 (9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>


bpm, Beats per minute; E. coli, Escherichia coli; GBS, group B streptococci; NA, not available; PTD, prior to delivery; ROM, rupture of membranes; SROM, spontaneous rupture of membranes.
cases, and concurrent endometritis and bacteremia in the mother and sepsis in the neonate have been reported. Recently, a case of neonatal toxic streptococcal shock syndrome attributed to maternal transmission of a group C streptococcus was reported.

Viridans streptococci are a heterogeneous group of α-hemolytic and nonhemolytic streptococci that are constituents of the normal flora of the respiratory and gastrointestinal tracts of infants, children, and adults. There are several classification schemes for these streptococci, and they may bear different designations in the literature. Streptococcus bovis is capable of causing neonatal sepsis and meningitis that is clinically similar to sepsis caused by GBS. Rare cases of fulminant neonatal sepsis or meningitis caused by Streptococcus mitis, Streptococcus gallolyticus, and Streptococcus alactolyticus have been reported.

Viridans streptococci accounted for 23% of isolates from cultures of blood and CSF obtained from neonates at the Jefferson Davis Hospital, Houston; only GBS were more common (28%) as a cause of neonatal sepsis. In this series, most infants had early-onset infection with clinical features similar to those of sepsis caused by other pathogens, but 22.6% had no signs of infection. One infant had meningitis. The case-fatality rate was 8.8%. Sepsis related to viridans streptococci also has been reported from Finland, Liverpool, Indianapolis, and Montreal. Among ventilated neonates in a NICU in Ankara, Turkey, the most prominent bacteria in bronchioalveolar lavage cultures were multidrug-resistant viridans streptococci (66%), and these were also one of the most common bloodstream isolates (29%) in the same population. It is clear from these studies that isolation of viridans streptococci from the blood culture of a neonate suspected to have sepsis cannot be considered a contaminant, as is the case in many other patient populations.

**ENTEROCOCCUS SPECIES**

Members of the genus Enterococcus (E. faecalis and E. faecium) were formerly classified as group D streptococci; but in the mid-1980s, genomic DNA sequence analysis revealed that taxonomic distinction was appropriate, and a unique genus was established. Enterococci are differentiated from nonenterococci by their ability to grow in 6.5% sodium chloride broth and to withstand heating at 60°C for 30 minutes.
Most cases of enterococcal sepsis in the neonate are caused by *E. faecalis*, with a smaller number caused by *E. faecium* \(^6,7,74-80\). In the 4 years beginning in 1974, 30 neonates with enterococcal sepsis occurred among 30,059 deliveries at Parkland Memorial Hospital in Dallas. \(^76\) During this period, enterococci were second only to GBS (99 cases) and were more common than *E. coli* (27 cases) as a cause of neonatal sepsis. The clinical presentation in most cases was similar to that of early-onset sepsis of any cause. \(^78\) Among infants with respiratory distress as a prominent sign of infection, the chest radiographs were similar to those demonstrating the hyaline membrane–appearing pattern of GBS infection. Enterococcal bacteremia during the 10 years beginning January 1977 was reported in 56 neonates from the Jefferson Davis Hospital in Houston, Texas. \(^81\) Patients were segregated among three clinical syndromes: early-onset disease was a mild illness with respiratory distress or diarrhea; late-onset infection often was severe with apnea, bradycardia, shock, and increased requirement for oxygen and mechanical ventilation; and many cases were nosocomial. \(^81\) A large series of 100 cases of enterococcal bacteremia in neonates over a 20-year period at New York Hospital–Cornell Medical Center was evaluated by McNeely and colleagues. \(^77\) Common characteristics were the presence of a central venous catheter (77%) or a diagnosis of necrotizing enterocolitis (NEC; 33%).

In general, *Enterococcus* spp. are resistant to cephalosporins, are only moderately susceptible to penicillin G and ampicillin, and require the synergistic activity of penicillin, at high dosage, and an aminoglycoside for maximal bactericidal action; nonenterococcal strains are susceptible to penicillin G, ampicillin, and most cephalosporins. Vancomycin-resistant (VRE) *Enterococcus* has been reported from NICUs, causing illnesses clinically indistinguishable from vancomycin-sensitive strains. \(^77\) yet raises concerns about the efficacy of antimicrobial agents currently approved for use in neonates. \(^82\) Use of high doses of ampicillin is one option, but other drugs, including daptomycin \(^83\) and the oxazolidinone linezolid, \(^84\) may be required depending on the susceptibility pattern (see Chapter 37).

**STAPHYLOCOCCUS AUREUS AND COAGULASE-NEGATIVE STAPHYLOCOCCI**

*S. aureus* and CoNS, especially *S. epidermidis*, colonize skin and mucosa. Isolation of *S. aureus* from tissue, blood, or other body fluids usually is clearly associated with disease. Most episodes of sepsis caused by *S. aureus* are hospital acquired, and mortality can be high (23% among 216 Swedish neonates with *S. aureus* bacteremia during 1967 to 1984), with LBW as the most important risk factor. \(^85\) Recently, reports of pneumonia and other severe nosocomial infection in neonates caused by community-acquired methicillin-resistant *S. aureus* (CA-MRSA) strains, including the epidemic USA300 clone, have been documented. \(^86-88\) Molecular epidemiologic techniques have established direct transmission of CA-MRSA between postpartum women \(^89\) and among NICU patients. \(^90\) CoNS include more than 30 different species. *S. epidermidis* is the dominant species of CoNS responsible for neonatal sepsis, but other species, including *Streptococcus capitis*, *Streptococcus hemolyticus* and *Streptococcus hominis*, have been identified as causes of sepsis in the newborn. \(^91\) A well-documented increased incidence of CoNS sepsis \(^8,15,16,92\) has accompanied the increased survival of VLBW and ELBW infants with developmentally immature immune systems and prolonged stay in NICUs. The CoNS infections have been associated with the introduction of invasive procedures for maintenance and monitoring of the infants, in particular long-term vascular access devices. Levels of serum complement and transplacental anti-CoNS immunoglobulin G (IgG) are inversely correlated with gestational age, and this relative deficiency in preterm infants contributes to their suboptimal opsonization and impaired bacterial killing of CoNS. \(^93,94\) Because CoNS are present on the skin, isolation of these organisms from a single culture of blood can represent skin contamination but also can indicate bloodstream invasion. Collection of two cultures of blood at separate sites can assist in differentiating skin or blood-culture–bottle contamination from bloodstream invasion in the infant with suspected late-onset sepsis. \(^95\) and adoption of a standard two-blood-culture practice can reduce the number of neonates diagnosed with CoNS and exposed to intravenous antibiotic therapy. \(^96-97\) The significance of a positive blood culture yielding CoNS is discussed in “Microbiologic Techniques.”

Many episodes of sepsis caused by CoNS are associated with the use of vascular catheters. *S. epidermidis* and other CoNS species can adhere to and grow on surfaces of synthetic polymers used in the manufacture of catheters. Strains obtained from infected ventricular shunts or intravenous catheters produce a mucoid substance (i.e., slime or glycocalyx) that stimulates adherence of microcolonies to various surfaces in the environment and on epithelial surfaces, ultimately leading to establishment of a biofilm. \(^98,99\) In addition to this adhesin function, the slime may protect staphylococci against antibiotics and host defense mechanisms, such as macrophage phagocytosis, \(^100\) predisposing to persistent infection. \(^101\) Parenteral nutrition with a lipid emulsion administered through a venous catheter having organisms adherent to the polymer provides nutrients for growth of the bacteria, leading to invasion of the bloodstream when the organisms reach an inoculum of sufficient size. \(^102\) Disease in newborn infants caused by *S. aureus* and CoNS is discussed in detail in Chapter 14.

**LISTERIA MONOCYTOGENES**

The potential of *L. monocytogenes* to contaminate food products and the resultant danger to immunocompromised patients and pregnant women was reconfirmed in a 2002 outbreak involving 46 patients in eight states. This outbreak resulted in seven deaths of adults and miscarriages or stillbirths in three pregnant women. \(^103\) *Listeria* can be found in unprocessed animal products, including milk, meat, poultry, cheese, ice cream, and processed meats, and on fresh fruits and vegetables. The organism possesses several virulence factors that allow it to infect the fetal placental unit, survive and replicate within human cells, and achieve cell-to-cell spread. \(^104\) Although most people exposed to *L. monocytogenes* do not develop illness, pregnant women can suffer
fetal loss, and the neonate can develop early- or late-onset sepsis and meningitis. Neonatal disease caused by *Listeria* is discussed in detail in Chapter 13.

**ESCHERICHIA COLI**

*Escherichia coli* is second only to GBS as the most common cause of both early- and late-onset neonatal sepsis and meningitis.\(^8,105-107\) Coliform organisms are prevalent in the maternal birth canal, and most infants are colonized in their lower gastrointestinal or respiratory tracts during or just before delivery. The antigenic structure of *E. coli* is complex; members of this species account for more than 145 different somatic (O) antigens, approximately 50 flagellar (H) antigens, and 80 different capsular (K) antigens. Although there is a wide genetic diversity of human commensal isolates of *E. coli*, strains causing neonatal pathology are derived from a limited number of clones.\(^108\) One of these, the O18:K1:H7 clone, is distributed globally; meanwhile, others such as O83:K1 and O45:K1 are restricted to a smaller subset of countries.\(^109\) The presence of a 134-kDa plasmid encoding iron acquisition systems and other putative virulence genes is characteristic of several of these clones, and loss of the plasmid reduces the virulence more than 100-fold in a neonatal rat model of *E. coli* meningitis.\(^110\) In a recent analysis comparing *E. coli* with other agents of early-onset neonatal sepsis, infants with *E. coli* sepsis (n = 19) were more likely to be premature, of VLBW (<1500 g), and to have been associated with the intrapartum characteristics of fever, premature or prolonged rupture of membranes, antibiotic use, and presentation in the first 24 hours of life.\(^111\) Fifteen of the 19 *E. coli* isolates in this study (79%) were ampicillin resistant, and three (16%) were gentamicin resistant; antepartum or intrapartum antibiotic exposure was associated with ampicillin-resistant *E. coli* sepsis.\(^111\)

The K1 capsular antigen present in certain strains of *E. coli* is uniquely associated with neonatal meningitis.\(^112,113\) The K1 antigen is polysialic acid that is immunochemically identical to the capsular antigen of group B *N. meningitidis*. McCracken and coworkers\(^114\) found K1 strains in the blood of CSF of most (65/77) neonates with meningitis related to *E. coli*. These strains also were cultured from the blood of some infants (14/36) and adults (43/301) with sepsis but without meningitis. The K1 capsular antigen was present in 88% of 132 strains from neonates with *E. coli* meningitis reported from The Netherlands.\(^25\) Infants with meningitis caused by K1 strains had significantly higher mortality and morbidity rates than did infants with meningitis caused by non-K1 *E. coli* strains.\(^112\) The K1 strains have been present in the birth canal of mothers and subsequently in cultures from their newborns, indicating that these newborn infants acquired the organisms vertically from their mothers.\(^115,116\) However, high rates of carriage of K1 strains by nursery personnel indicate that postnatal acquisition of the K1 strains in the nursery also may occur.\(^112,115\)

The pathogenesis of *E. coli* K1 infection is hypothesized to begin with bacterial penetration of the gastrointestinal epithelium to enter the circulation, and efficient transcytosis of gastrointestinal epithelial cell monolayers by the pathogen has been demonstrated in tissue culture.\(^117\) Next, the organisms can establish high-grade bacteremia in the immune-susceptible neonate through the complement resistance properties of its O lipopolysaccharide and K1 capsule–mediated impairment of opsonophagocytic killing.\(^118\) Finally, the pathogen possesses a series of surface protein determinants (OmpA, IbeA-C, CNF1, etc.) that mediate binding to and invasion of brain endothelial cells, as demonstrated in human tissue culture experiments and the neonatal rat model of meningitis.\(^111\)

**KLEBSIELLA SPECIES**

*Klebsiella* is a genus of Enterobacteriaceae that has emerged as a significant nosocomial pathogen in neonates.\(^119,120\) The four recognized species include *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella terrigena*, and *Klebsiella planticola*. *K. pneumoniae*, the most common human pathogen, and *K. oxytoca* cause neonatal infections of the bloodstream, urinary tract, CNS, lung, skin, and soft tissues.\(^121-123\) Previously thought to be a nonpathogenic organism inhabiting soil and water, *K. planticola* has been implicated as a cause of neonatal sepsis.\(^124,125\)

In a 4-year retrospective study from Israel,\(^126\) *Klebsiella* spp. caused 31% of late-onset neonatal sepsis. Greenberg and colleagues\(^12\) performed an 8-year prospective study of neonatal sepsis and meningitis at Soroka University Medical Center in Israel during 1986 to 1994; 49 (20%) of 250 cases were caused by *K. pneumoniae*, with a mortality rate of 29%. *Klebsiella* was also the most common single agent in recent reviews of sepsis in Jamaican\(^127\) and Indian\(^128\) neonates. Risk factors for infection included preterm, VLBW, prolonged rupture of membranes (>24 hours), and cesarean section or instrument delivery. *Klebsiella* spp. appear to be among the more common causes of liver abscess complicating bacteremia in the neonate.\(^129\)

The reservoirs for transmission of *Klebsiella* infections include the hands of health care workers and the gastrointestinal tracts of hospitalized infants. Multidrug resistance, in the form of extended-spectrum β-lactamase production, of *Klebsiella* strains causing neonatal infections and nursery outbreaks has become a substantial problem in some nurseries and is associated with increased morbidity and mortality.\(^130-132\) Enhanced infection-control measures and changes in use of routine broad-spectrum antibiotics can reduce the frequency of these serious infections.

**ENTEROBACTER AND CRONOBACTER SPECIES**

Among the *Enterobacter* spp., *Enterobacter cloacae*, *Enterobacter sakazakii*, and *Enterobacter hormaechei* have caused sepsis and a severe form of necrotizing meningitis in neonates.\(^113-115\) In 2008, the taxonomy of *E. sakazakii* was revised, resulting in identification of five species belonging to a new genus, *Cronobacter*.\(^116\)

*Enterobacter* septicemia was the most common nosocomial infection in neonates at the Ondokuz Mayis University Hospital in Samsun, Turkey, from 1988 to 1992.\(^137\) Willis and Robinson\(^138\) reviewed 17 cases of neonatal meningitis caused by *E. sakazakii*; cerebral abscess or cyst formation developed in 77% of the infants, and 50% of the infants died. Bonadio and colleagues\(^139\) reviewed 30 cases of *E. cloacae* bacteremia in children, including 10 infants younger than 2 months. Of importance was the high frequency of multidrug resistance among isolates from patients in the...
NICUs that was attributed to routine extended-spectrum cephalosporin use. In a recent review of Enterobacter sepsis in 28 neonates from Taiwan, thrombocytopenia (66%) and increased band-form neutrophils (41%) were common laboratory features, with a reported clinical outcome of 11% mortality, 14% meningitis, and 7% brain abscess.

In addition to the gastrointestinal tracts of hospitalized infants and hands of health care personnel, sources and modes of transmission of Enterobacter infections in the neonate include contaminated infant formula, contaminated total parenteral nutrition fluid, bladder catheterization devices, and contaminated saline. Effective infection-control measures require reinforcement of procedures, including proper hand hygiene, aseptic technique, isolation protocols, and disinfection of environmental surfaces.

Citrobacter spp. are an emerging group of opportunistic gram-negative pathogens that typically affect LBW neonates, causing life-threatening meningitis, sepsis, and NEC. An outbreak of C. sakazakii in a French NICU in 1994 involved 17 cases, including 7 neonates with NEC, 1 case of sepsis, and 1 case of meningitis; 8 infants were colonized but asymptomatic; there were three deaths. Four separable pulse types of C. sakazakii were identified, but the deaths were attributable to only one. C. sakazakii infection in vulnerable infants has often been linked to the consumption of contaminated powdered infant formula.

**CITROBACTER SPECIES**

Organisms of the genus Citrobacter are gram-negative bacilli that are occasional inhabitants of the gastrointestinal tract and are responsible for disease in neonates and debilitated or immunocompromised patients. The genus has undergone frequent changes in nomenclature, making it difficult to relate the types identified in reports of newborn disease over the years. For example, in 1990, Citrobacter koseri replaced Citrobacter diversus.

Citrobacter spp. are responsible for sporadic and epidemic clusters of neonatal sepsis and meningitis, and C. koseri is uniquely associated with brain abscesses. Neonatal disease can occur as early- or late-onset presentations. Brain abscesses caused by C. koseri have been reported in a pair of twins.

Outbreaks of C. koseri in NICUs resulting in sepsis and meningitis, septic arthritis, and skin and soft tissue infections were reviewed by Doran. Other focal infections in neonates caused by Citrobacter spp. include bone, pulmonary, and urinary tract infections.

From 1960 to 1980, 74 cases of meningitis caused by Citrobacter spp. were reported to the CDC of the U.S. Public Health Service. In 1999, Doran reviewed an additional 56 cases of neonatal meningitis caused by Citrobacter spp. Combining results from the two studies, brain abscess developed in 73 (76%) of 96 patients for whom information was available. The pathogenesis of brain abscess caused by C. koseri is uncertain; cerebral vasculitis with infarction and bacterial invasion of necrotic tissues is one possible explanation. Studies in the neonatal rat model suggest that the ability of C. koseri to survive phagolysosome fusion and persist intracellularly within macrophages could contribute to the establishment of chronic CNS infection and brain abscess. Such persistence of C. koseri in the CNS is well illustrated by a case report of recovery of the organism from the CSF during a surgical procedure 4 years after treatment of neonatal meningitis. The mortality rate for meningitis caused by Citrobacter spp. was about 30%; most of the infants who survived had some degree of mental retardation. A review of 110 survivors of Citrobacter meningitis revealed only 20 infants who were believed to have structurally intact brains and development that was age appropriate.

Citrobacter spp. usually are resistant to ampicillin and variably susceptible to aminoglycosides. Serial neuroimaging is critical for the diagnosis of cerebral abscess in infants with Citrobacter meningitis. Surgical drainage has been used in some cases with variable success. Choosing antimicrobial agents with the most advantageous susceptibility pattern and selected surgical drainage appears to be the most promising approach to therapy. High neutrophil and CNS penetration and favorable toxicity profiles suggest ciprofloxacin and meropenem as potential antibiotic treatment options for systemic infection or meningitis caused by C. koseri. Plasmid profiles, biotypes, serotypes, and chromosomal restriction endonuclease digests are useful as epidemiologic markers for the study of isolates of C. koseri. Morris and colleagues used these markers to investigate an outbreak of six cases of neonatal meningitis caused by C. koseri in three Baltimore hospitals between 1983 and 1985. Identification of a specific outer membrane protein associated with strains isolated from CSF but uncommon elsewhere can provide a marker for virulent strains of C. koseri according to some investigators.

**SERRATIA MARCESCENS**

Like other members of Enterobacteriaceae, Serratia marcescens increasingly is associated with hospital-acquired infections among infants in the NICU. Late-onset sepsis has occurred in infants infected from health care equipment, the hands of health care workers, milk bottles, aqueous solutions such as theophylline, hand hygiene washes, and lipid parenteral feeds. The gastrointestinal tract of hospitalized infants provide a reservoir for transmission and infection. Investigation of an outbreak of multidrug-resistant S. marcescens in NICU identified exposure to inhalational therapy as an independent risk factor for acquisition. Recently, three consecutive outbreaks caused by genetically unrelated S. marcescens clones occurred in a NICU over a 3-year period, with administration of total parenteral nutrition the only statistically significant risk factor identified by logistic regression.

In a review of neonatal bacteremia and meningitis caused by S. marcescens by Campbell and colleagues, 11 of 29 (29%) of 38 infants had meningitis as a complication of their bacteremia. Mean gestational age and birth weight were 28 weeks and 1099 g, respectively. All patients required mechanical ventilation. 90% had central venous catheters in situ, 90% had received prior antibiotics, 50% had a prior intraventricular hemorrhage, 40% had a hemodynamically significant patent ductus arteriosis treated medically or surgically, and 20% had NEC with perforation. All patients were treated for a minimum of 21 days with combination antimicrobial therapy that included a third-generation cephalosporin or an aminoglycoside, typically...
gentamicin. Three of 10 patients died. Four of the 7 survivors developed severe hydrocephalus requiring ventriculoperitoneal shunt placement and had poor neurologic outcome. Poor neurologic outcome also was documented in a report of *S. marcescens* brain abcess, resulting in multicytic encephalomalacia and severe developmental retardation. Combination therapy with high-dose amikacin and meropenem was associated with clinical improvement in a case of *S. marcescens* brain abcess in a 34-week premature neonate.

**PSEUDOMONAS AERUGINOSA**

*Pseudomonas aeruginosa* usually is a cause of late-onset disease in infants who are presumably infected from their endogenous flora or from equipment, from aequous solutions, or occasionally from the hands of health care workers. An outbreak of *P. aeruginosa* sepsis in a French NICU was associated with contamination of a milk bank pasteurizer. Stevens and colleagues reported nine infants with *Pseudomonas* sepsis, four of whom presented in the first 72 hours of life. In three of these infants, the initial signs were those of respiratory distress, and chest radiographs were consistent with hyaline membrane disease. Noma (i.e., gangrenous lesions of the nose, lips, and mouth) in a neonate has been associated with bacteremia caused by *P. aeruginosa*.

A retrospective review of sepsis in infants admitted over the 10-year period from 1988 through 1997 to the NICU at Children’s Hospital of the King’s Daughters in Norfolk, Virginia, identified 825 cases of LOS. Infants with *Pseudomonas* sepsis had the highest frequency of clinically fulminant onset (56%), and 20 (56%) of the 36 (56%) infants with *Pseudomonas* sepsis died within 48 hours of blood-culture collection.

*P. aeruginosa* conjunctivitis in the neonate is a danger because it is rapidly destructive to the tissues of the eye and because it may lead to sepsis and meningitis. Shah and Gallagher reviewed the course of 18 infants at Yale–New Haven Hospital NICU who had *P. aeruginosa* isolated from cultures of the conjunctiva during the 10 years beginning in 1986. Five infants developed bacterial meningitis, including 3 with meningitis, and 2 infants died. A cluster of four fatal cases of *P. aeruginosa* pneumonia and bacteremia among neonates was traced by genotypic fingerprinting to their shared exposure to a health care worker experiencing intermittent otitis externa. A case of fatal multidrug-resistant *Pseudomonas* sepsis with ethyema gangrenosum was recently reported in a premature neonate, shortly after the infant was discharged after a prolonged course of empirical antibiotic therapy secondary to maternal chorioamnionitis.

**SALMONELLA SPECIES**

Non-Typhi *Salmonella* infection is an uncommon cause of sepsis and meningitis in neonates, but a significant proportion of cases of *Salmonella* meningitis occur in young infants. The CDC observed that approximately one third of 290 *Salmonella* isolates from CSF reported during 1968 to 1979 were from patients younger than 3 months, and more than one half were from infants younger than 1 year. A 21-year review of gram-negative enteric meningitis in Dallas, beginning in 1969, identified *Salmonella* as the cause in 4 of 72 cases. Investigators from Turkey reported 7 cases of neonatal meningitis caused by *Salmonella* during 1995 to 2001. Two of the five survivors developed communicating hydrocephalus, and one had a subdural empyema. Cases of neonatal meningitis caused by *Salmonella enterica* ser. *Ancona*, in which the pathogen was isolated simultaneously from the newborn’s CSF, parental fecal samples, and the mother’s breast milk; *S. enterica* ser. *Arizona* meningitis in a 13-day-old girl; and septicemia caused by *S. Paratyphi* B were recently reported.

Reed and Klugman reviewed 10 cases of neonatal typhoid that occurred in a rural African hospital. Six of the infants had early-onset sepsis with acquisition of the organism from the maternal genital tract, and 4 had late-onset infection with acquisition from a carrier or an environmental source. Two neonates developed meningitis, and 3 died. Recurrent *S. enteritidis* meningitis in a neonate after a 3-week course of ceftriaxone and ciprofloxacin was recently described.

**NEISSERIA MENINGITIDIS**

Although *Neisseria meningitidis* is a leading cause of bacterial sepsis and meningitis among children and adolescents, it rarely is associated with invasive infection in neonates. N. meningitidis may colonize the female genital tract and has been associated with pelvic inflammatory disease. The infant can be infected at delivery by organisms present in the maternal genital tract, or intrauterine infection can result during maternal meningococemia. Meningococcal sepsis is rare in the neonate, but more than 50 cases (including 13 from the preantibiotic era) have been described. Early- and late-onset forms of meningococcal sepsis in neonates have been reported. Purpura similar to that of meningococcemia in older children has been observed in a 15-day-old and a 25-day-old infant.

Shepard and colleagues from the CDC reported 22 neonates with invasive meningococcal disease from a 10-year active, population-based surveillance of 10 states with diverse populations and more than 31 million persons. The average annual incidence was 9 cases per 100,000 people (vs. 97.3, 8/100,000 for GBS). Sixteen patients had meningitis, and 6 of these also had meningococcosis. Six patients had early-onset disease. The overall mortality rate was 14%. Ten isolates were serogroup B, 4 were serogroup C, 3 were serogroup Y, 1 was nongroupable, and 4 were unavailable for analysis. Cases of meningococcal meningitis in infants successfully treated with no evidence of neurologic sequelae have been described.

**HAEMOPHILUS INFLUENZAE**

Because of the introduction of *H. influenzae* type b conjugate vaccines in 1988, there has been a substantial decrease in the incidence in *H. influenzae* type b disease in infants and children in the United States and many other countries. Given the estimated proportion of individuals that are completely immunized, the decrease in *H. influenzae* type b invasive disease has exceeded expectations. The reduction in *H. influenzae* carriage associated with
vaccination and the consequent decreased transmission from immunized children to unimmunized infants and children likely explains this effect.\textsuperscript{199,200}

Despite increased reporting of invasive infections caused by nontypeable \textit{H. influenzae} in adults and older children,\textsuperscript{201} such infections in neonates remain uncommon.\textsuperscript{202-205} Five clinical syndromes have been associated with neonatal disease caused by \textit{H. influenzae}: sepsis or respiratory distress syndrome, pneumonia, meningitis, soft tissue or joint infection, and otitis media or mastoiditis. The overall mortality rate was 5.5\% for 45 cases reviewed by Friesen and Cho;\textsuperscript{206} the mortality rate was 90\% for 20 infants with a gestation lasting less than 30 weeks. Clinical and epidemiologic characteristics were similar to those of neonatal disease caused by GBS, including early- (within 24 hours of birth) and late-onset presentations, signs simulating respiratory distress syndrome, and a high mortality rate. Autopsy of infants with bacteremia related to nontypeable \textit{H. influenzae} and signs of respiratory distress syndrome revealed hyaline membranes with gram-negative coccobacilli within the membranes, similar to findings of hyaline membranes caused by GBS.\textsuperscript{207} Examination of placentas from mothers of infants with sepsis caused by nontypeable \textit{H. influenzae} revealed acute chorioamnionitis and acute villitis in some.\textsuperscript{203} \textit{H. influenzae} also has been responsible for maternal disease, including bacteremia, chorioamnionitis,\textsuperscript{208} acute or chronic salpingitis, and tubo-ovarian abscess.\textsuperscript{204}

Recently, a cluster of 8 cases of early-onset infections over 53 months caused by \textit{\beta-lactamase negative, nontypeable H. influenzae} was reported from a NICU in Israel.\textsuperscript{209} In this series, a presentation resembling pneumonia, rather than classical respiratory distress syndrome, characterized the infants’ respiratory problems.

Neonatal sepsis caused by \textit{Haemophilus parainfluenzae}\textsuperscript{210} and \textit{Haemophilus aphrophilus}\textsuperscript{211} have also been reported.

ANAEROBIC BACTERIA

Improvements in techniques for isolation and identification of the various genera and species of anaerobic bacteria have provided a better understanding of the anaerobic flora of humans and their role in disease.\textsuperscript{212} With the exception of \textit{Clostridium tetani} and \textit{Clostridium botulinum}, all of the anaerobic bacteria belong to the normal flora of humans. Anaerobes are present on the skin, in the mouth, in the intestines, and in the genital tract. They account for the greatest proportion of the bacteria of the stool. All are present in the intestines and have been isolated from the external genitalia or vagina of pregnant and nonpregnant women.\textsuperscript{213} Newborns are colonized with these organisms during or just before delivery. A literature review by Brook in 1990, on neonatal bacteremia caused by anaerobic bacteria, included 179 cases, with a mortality rate of 26\%. \textit{Bacteroides} and \textit{Clostridium} spp. were the most common isolates. Predisposing factors for infection included premature rupture of membranes, preterm delivery, and NEC.

Anaerobic bacteria have been isolated from the blood of newborns with sepsis,\textsuperscript{215-217} from various organs at autopsy,\textsuperscript{218} from an infant with an adrenal abscess,\textsuperscript{219} and from infants with necrotizing fasciitis of the scalp associated with placement of a scalp electrode.\textsuperscript{221} Feder \textsuperscript{222} reviewed meningitis caused by \textit{Bacteroides fragilis}; seven of nine reported cases occurred in neonates.

The incidence of neonatal sepsis caused by anaerobic bacteria remains uncertain, but recent data are available from some surveys that suggest the incidence is low (<5\%).\textsuperscript{12,14,214} Noel and colleagues\textsuperscript{216} identified 29 episodes of anaerobic bacteremia in neonates in the intensive care unit (ICU) at New York Hospital during 18 years. Chow and coworkers\textsuperscript{218} analyzed 59 cases of neonatal sepsis associated with anaerobic pathogens and classified them into four groups: transient bacteremia after premature rupture of membranes and maternal amnionitis, sepsis after postoperative complications, fulminant septicemia (in the case of clostridial infections), and intrauterine death associated with septic abortion. The mortality rate associated with neonatal anaerobic sepsis reported in the literature ranges from 4\% to 38\%.\textsuperscript{218,222,224}

Serious infections of the bloodstream or CNS of neonates caused by \textit{Bacillus cereus} have been reported,\textsuperscript{219,227} and in certain cases have proven intractable and refractory to antibiotic therapy.\textsuperscript{222,223} Magnetic resonance imaging of \textit{B. cereus} meningocencephalitis reveals a pattern of hemorrhage and early cavitation accompanied by selective white matter destruction.\textsuperscript{230} An outbreak of \textit{B. cereus} infections in a NICU was traced to contamination of balloons used in mechanical ventilation.\textsuperscript{211} \textit{Bacteroides fragilis} has been identified as a cause of pneumonia, sepsis, or meningitis in the immediate newborn period.\textsuperscript{212,213,234}

Infections caused by \textit{Clostridium} spp. can be localized, as in the case of omphalitis,\textsuperscript{235} cellulitis, and necrotizing fasciitis;\textsuperscript{236} or can manifest as sepsis or meningitis.\textsuperscript{217} Disease in neonates has been related to \textit{Clostridium perfingens}, \textit{Clostridium septicum}, \textit{Clostridium sordellii}, \textit{Clostridium butyricum}, \textit{Clostridium tertium}, and \textit{Clostridium paraputrificum}.\textsuperscript{218} The presenting signs usually are similar to those of other forms of bacterial sepsis. Chaney reported a case of bacteremia caused by \textit{C. perfingens} in mother and child in which the neonate had classic features of adult clostridial sepsis, including active hemolysis, hyperbilarubinemia, and hemoglobinuria. Motz and colleagues reviewed five cases of clostridial meningitis caused by \textit{C. butyricum} and \textit{C. perfingens}. Clostridial sepsis is accompanied by a high mortality rate.\textsuperscript{237}

NEONATAL TETANUS

Neonatal tetanus is caused by the gram-positive anaerobic spore-forming bacillus, \textit{C. tetani}. The organism is present in soil and can be present in human and animal feces. Infection usually occurs after contamination of the umbilical stump. Maternal and neonatal tetanus are important causes of mortality in developing countries, claiming an estimated 180,000 lives annually.\textsuperscript{240} In the United States, tetanus in the newborn is exceedingly rare.\textsuperscript{241} Since 1984, only three cases of neonatal tetanus have been reported.\textsuperscript{241-243} The most recent case, reported from Montana in 1998, was an infant born to an unimmunized mother; the parents used a \textit{C. tetani}–contaminated clay powder to accelerate drying of the umbilical cord. The use of this product had been promoted on an Internet site on “cord care” for use by midwives.\textsuperscript{244}
In many developing countries, both the incidence and mortality of neonatal tetanus remain startlingly high. Mustafa and colleagues conducted a retrospective neonatal tetanus survey among rural and displaced communities in the East Nile province in the Sudan and observed an incidence of neonatal tetanus of 7.1 cases per 1000 live births, more than double that reported from the stable rural community (3.2/1000). In both communities, coverage with two doses of tetanus toxoid was about 58%. Mortality attributable to neonatal tetanus in Djakarta in 1982 was 6.9 deaths per 1000 live births, and in the island provinces of Indonesia, it was 10.7 deaths per 1000 live births. Among 62 cases of neonatal tetanus in Ethiopia, 90% were born at home and 70% lacked antenatal care. Three quarters of infants in this series died in hospital, and risk factors for fatal outcome included an incubation period of less than 1 week, onset of symptoms at less than 48 hours, tachycardia, and fever. The mortality rate for neonates with tetanus in Peru was 45% and was not improved with use of intrathecal tetanus antitoxin. However, a meta-analysis of intrathecal therapy in tetanus suggested benefit in adults but not in neonates. A recent systematic review of prognostic factors in neonatal tetanus indicated that LBW and age of onset less than or equal to 5 to 7 days were crucial factors increasing the odds of death.

Application of contaminated materials to the umbilical cord is associated with deep-rooted customs and rituals in developing countries. A case-control study to identify risk factors for neonatal tetanus in rural Pakistan identified application of ghee (i.e., clarified butter from the milk of water buffaloes or cows) to the umbilical cord as the single most important risk factor. Although commercial ghee is available in Pakistan, the ghee used in rural areas is made at home from unpasteurized milk. Oudesluys-Murphy observed that application of some materials, including ghee and a stone wrapped in wet cloth, increased the risk of neonatal tetanus among Yoruba women but that other practices of cord care decreased the incidence, including searing of the cord with heat in China during the Ming dynasty and use of a candle flame to scar the cord in Guatemala.

Neonatal tetanus is a preventable disease; use of hygienic techniques at delivery and a program of tetanus toxoid immunization of children and young adults, particularly of pregnant women, are effective in eliminating this lethal disease. A systematic review of interventions to reduce neonatal tetanus mortality found vaccination of pregnant women with tetanus toxoid to be the key factor; in resource-poor countries such as Pakistan, this single intervention coupled with regular effective antenatal checkups and clean delivery practices effectively reduces neonatal tetanus.

**MIXED INFECTIONS**

Multiple organisms frequently are present in brain, liver, or lung abscesses; lung aspirate after pneumonia; or pleural empyema, but multiple organisms are found infrequently in cultures of blood or CSF. When several species are found, the significance of each is uncertain because it is possible that one or more of the organisms in a mixed culture is a contaminant.

Bacteremia with more than one organism occurs in patients with immunodeficiency, major congenital abnormalities, or contamination of a body fluid with multiple organisms, as is present in peritonitis, typically as a sequela of severe NEC in the VLBW infant. Neonatal meningitis caused by *S. pneumoniae* and *Acinetobacter calcoaceticus* and sepsis caused by *P. aeruginosa* and *Yersinia enterocolitica* have been reported. Although included in a series of cases of neonatal sepsis by some investigators, mixed cultures are not identified by most. Mixed infections were reported by Tessin and coworkers in 5% of 231 Swedish neonates, by Vesi-kari and associates in 4% of 377 Finnish infants, and by Bruun and Paerregaard in 7% of 81 Danish neonates. Faix and Kovarik reviewed the records of 385 specimens of blood or CSF submitted to the microbiology laboratories at the University of Michigan Medical Center from September 1971 to June 1986. More than one organism was present in 38 specimens from 385 infants in the NICU; 15 (3.9%) infants had multiple pathogens associated with clinical signs of sepsis or meningitis. The mortality was high (60%). Factors predisposing to mixed infection included prolonged rupture of membranes (>24 hours), total parenteral nutrition, NEC, presence of an intravascular catheter or ventriculostomy, and entities associated with multiple pathogens, including peritonitis, pseudomembranous colitis, and hepatic necrosis. Chow and colleagues reported polymicrobial bacteremia in eight newborns with anaerobic co-isolates or aerobic and anaerobic organisms in combination. An outbreak of polymicrobial bacteremia caused by *K. pneumoniae* and *E. cloacae* associated with use of a contaminated lipid emulsion was reported by Jarvis and colleagues.

Mixed infections also can include bacteria and viruses or bacteria and fungi, typically *Candida*, in the situation of intravascular central catheter or peritoneal infections associated with bowel perforation. Sierra and Pacini reported mixed viral-bacterial meningitis in five patients, including neonates with CSF isolates of enterovirus and GBS in a 10-day-old child and enterovirus and *Salmonella* in a 12-day-old child.

**UNCOMMON BACTERIAL PATHOGENS**

A large number of additional bacterial pathogens have been identified as rare or uncommon causes for neonatal sepsis and meningitis. These are listed in Table 6–7 with references, and were reviewed by Giacoia.

**Epidemiology**

**INCIDENCE OF SEPSIS AND MENINGITIS**

The reported incidence of neonatal sepsis varies from less than 1 to 8.1 cases per 1000 live births. The increased use of intrapartum antibiotic prophylaxis for women with GBS colonization, with or without other risk factors associated with neonatal GBS disease, has been associated with a 70% reduction in the incidence of early-onset GBS sepsis to 0.44 per 1000 live births in 1999, a rate comparable to that of LOS (see Chapter 12).

*References 12, 18, 20, 119, 126, 260, 267–270.*
ARTICLE

**Table 6-7 Unusual Pathogens Responsible for Neonatal Sepsis and Meningitis**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achromobacter spp.</td>
<td>743-745</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>746-750</td>
</tr>
<tr>
<td>Bacillus anthracis</td>
<td>751</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>226, 228, 231, 752</td>
</tr>
<tr>
<td>Borellia (relapsing fever)</td>
<td>753, 754</td>
</tr>
<tr>
<td>Brucella spp.</td>
<td>755, 756</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>757-759</td>
</tr>
<tr>
<td>Burkholderia pseudomallei</td>
<td>760</td>
</tr>
<tr>
<td>Campylobacter spp.</td>
<td>725, 761</td>
</tr>
<tr>
<td>Capnocytophaga spp.</td>
<td>762-764</td>
</tr>
<tr>
<td>Corynebacterium spp.</td>
<td>765, 766</td>
</tr>
<tr>
<td>Edwardsiella tarda</td>
<td>767-769</td>
</tr>
<tr>
<td>Escherichia hermanii</td>
<td>770, 771</td>
</tr>
<tr>
<td>Chryseobacterium (Flavobacterium) spp.</td>
<td>772, 773</td>
</tr>
<tr>
<td>Gardnerella vaginalis</td>
<td>774, 775</td>
</tr>
<tr>
<td>Helicobacter cinaedi</td>
<td>776</td>
</tr>
<tr>
<td>Lactobacillus spp.</td>
<td>777-778</td>
</tr>
<tr>
<td>Leptospira spp.</td>
<td>779, 780</td>
</tr>
<tr>
<td>Leuconostoc spp.</td>
<td>781, 782</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>783-785</td>
</tr>
<tr>
<td>Mycoplasma hominis</td>
<td>786</td>
</tr>
<tr>
<td>Ochrobactrum anthropi</td>
<td>787</td>
</tr>
<tr>
<td>Pantoaea agglomerans</td>
<td>788</td>
</tr>
<tr>
<td>Pasteurella spp.</td>
<td>792, 789, 790</td>
</tr>
<tr>
<td>Plesiomonas spp.</td>
<td>791-793</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>794-796</td>
</tr>
<tr>
<td>Pseudomonas pseudomallei</td>
<td>797</td>
</tr>
<tr>
<td>Psychrobacter immobilis</td>
<td>798</td>
</tr>
<tr>
<td>Raistonia picketti</td>
<td>799</td>
</tr>
<tr>
<td>Rothia dentocariosa</td>
<td>800</td>
</tr>
<tr>
<td>Shigella sonnei</td>
<td>801-803</td>
</tr>
<tr>
<td>Staphylococcus capitis</td>
<td>804</td>
</tr>
<tr>
<td>Stomatococcus mucilaginosis</td>
<td>805</td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td>806, 807</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>808, 809</td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td>810</td>
</tr>
</tbody>
</table>

The incidence of meningitis usually is a fraction of the number of neonates with early-onset sepsis. During the 8-year period from 1986 to 1994 at the Soroka University Medical Center in southern Israel, Greenberg and colleagues found incidences of neonatal bacterial sepsis and meningitis of 3.2 and 0.5 cases per 1000 live births, respectively. Certain pathogens that cause bloodstream invasion, such as GBS, *E. coli*, and *L. monocytogenes*, are more likely to be accompanied by meningeal invasion than others (e.g., *S. aureus*). Meningitis is more frequent during the first month of life than in any subsequent period.

**CHARACTERISTICS OF INFANTS WHO DEVELOP SEPSIS**

Host susceptibility, socioeconomic factors, obstetric and nursery practices, and the health and nutrition of mothers are important in the pathogenesis of neonatal sepsis and meningitis. Infants who develop sepsis, particularly early-onset disease, usually have a history of one or more risk factors associated with the pregnancy and delivery that significantly increase the risk for neonatal infection. These factors include preterm delivery or LBW, premature rupture of membranes (i.e., rupture before the onset of labor), prolonged time of rupture of membranes, maternal peripartum infection, septic or traumatic delivery, and fetal hypoxia.

**Birth Weight**

The factor associated most significantly with enhanced risk for bacterial sepsis and meningitis in neonates is LBW [12,18,20,27] (see Table 6-5). Infection is the most common cause of death in VLBW infants [271,272]; the diagnosis of early-onset sepsis in this population is associated with a threefold increase in mortality. However, with the exception of infection caused by GBS, it is unusual for a term infant to develop early-onset sepsis after an uneventful pregnancy and delivery. In a U.K. study, neonates born weighing less than 2000 g acquired meningitis six times more frequently than did infants weighing greater than 2000 g. The lower the infant’s birth weight, the higher is the incidence of sepsis (see Table 6-5). An Israeli study of 5555 VLBW infants documented the increased risk of LOS with decreasing birth weight: LOS occurred in 16.8% of neonates with a birth weight of 1250 to 1500 g, 30.6% of neonates weighing 1000 to 1249 g, 46.4% of those weighing 750 to 999 g, and 53% of those weighing less than 750 g at birth. In NICHD prospective disease surveillance from 2006 to 2009, the incidence of infection per 1000 live births was 0.57 for infants with birth weight greater than 2500 g, 1.38 for infants with birth weight 1500 to 2500 g, and 10.96 for infants of birth weight 400 to 1500 g.

**Risk Factors of Infant and Mother**

The relative importance of other factors associated with systemic infection in the newborn is more difficult to define. Greenberg and coworkers [12] found that certain conditions were common in their prospective study of 229 infants with sepsis and meningitis: 130 (57%) were premature (<37 weeks of gestation), 64 (28%) were delivered by cesarean section or instrumental delivery, 43 (19%) had an Apgar score of less than 7 at 5 minutes, and 27 (2%) had a prolonged (>24 hours) interval after rupture of maternal membranes. Investigators in Pakistan [274] found that maternal urinary tract infection and maternal fever, vaginal discharge, and vaginal examinations during labor were maternal factors significantly associated with neonatal early-onset sepsis, whereas low Apgar scores at birth and the need for endotracheal intubation were significant neonatal risk factors. Attack rates for early-onset sepsis are affected by birth weight, duration of rupture of membranes, and occurrence of maternal peripartum fever. Uterine or abdominal tenderness and/or maternal or fetal tachycardia are other suggestive signs (see Table 6-5).

**Maternal Fever**

Maternal fever during or after delivery suggests a concurrent infectious event in mother and infant, but noninfectious events may be responsible for maternal fever. Use of epidural analgesia for pain relief during labor is associated with increases in maternal temperature. Intrapartum fever of greater than 38°C (100.4°F) occurred an average of 6 hours after initiation of the epidural anesthesia in 14.5% of women receiving an epidural anesthetic, compared with 1.0% of women not receiving an epidural agent; the rate of fever increased from 7% in women with labors of less than 6 hours to 36% for labors lasting longer than 18 hours. There was no difference in the incidence of neonatal sepsis in the infants born to 1045 women who received epidural analgesia (0.3%), compared with infants born to women who did not have epidural analgesia (0.2%). Petal core temperature may be elevated during maternal temperature...
elevation, and increased temperature may be present transiently in the neonate after delivery.

**Ethnicity**

The Collaborative Perinatal Research Study provides historical information on 38,500 pregnancies\(^{276}\); selected data for white and black women are presented in Tables 6–4 and 6–8. Black women had a higher rate of premature rupture of membranes lasting more than 24 hours (21.4%), compared with white women (10.8%); black women had a higher rate of puerperal infection (4.1%), compared with white women (3.6%); and more black infants weighed less than 2500 g at birth (13.4%), compared with white infants (7.1%).

Recent published data concurs with that observed 30 years ago. The National Center for Health Statistics reports continued disparities between blacks and whites in maternal and infant health indicators.\(^{277}\) In 2010, significant differences were found between non-Hispanic blacks and the general population in terms of neonatal mortality (11.46 vs. 6.14 deaths/1000 live births), LBW (13.6% vs. 7.7%), and preterm delivery less than 37 weeks’ gestation (17.1% vs. 12.0%).

An earlier review of the literature from 1966 to 1994 reported significantly increased rates of severe histologic chorioamnionitis, maternal fever during labor, prolonged rupture of membranes, and early neonatal mortality from sepsis in blacks compared with whites.\(^{278}\)

In a study of GBS disease in infants from the Atlanta metropolitan area,\(^{268}\) black infants had a higher incidence than nonblack infants of early-onset disease; the risk of late-onset disease was 35 times greater in black infants than in white infants. Thirty percent of early-onset disease and 92% of late-onset disease could be attributed to black race, after controlling for other significant risk factors, such as LBW and maternal age younger than 20 years. The increased incidence of GBS disease in blacks of all ages was observed in a survey by the CDC in selected counties in California, Georgia, and Tennessee and the entire state of Oklahoma. The rate of disease of 1.3 cases per 100,000 blacks was significantly higher than the 4.5 cases per 100,000 whites. In neonates with early-onset infection, 2.7 cases per 1000 live births occurred in blacks and 1.3 cases per 1000 live births occurred in whites.\(^{279}\)

Maternal factors, such as socioeconomic status, nutrition, recently acquired sexually transmitted diseases, or racial differences in maternally acquired protective antibodies, may result in the increased risk of GBS disease among blacks.

**Gender**

Historical data have suggested that there is a predominance of male neonates affected by sepsis and meningitis but not by in utero infections\(^{280,281}\) (Table 6–9). This difference partially may reflect the fact that female infants had lower rates of respiratory distress syndrome (i.e., hyaline membrane disease) than did male infants. Torday and colleagues\(^{282}\) studied fetal pulmonary maturity by determining lecithin-to-sphingomyelin ratios and concentrations of saturated phosphatidylcholine and cortisol in amniotic fluid of fetuses between 28 and 40 weeks of gestation. Female infants had higher indices of pulmonary maturity than did male infants. These data provide a biochemical basis for the increased risk of respiratory distress syndrome in male infants and the possible role of these factors of pulmonary maturation in the development of pulmonary infection. Later studies failed to confirm a significant increased risk for bacterial sepsis and meningitis among male infants.\(^{22,283-285}\)

**Geographic Factors**

The cause of neonatal sepsis varies from hospital to hospital and from one community to another. These differences probably reflect characteristics of the population served.

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### Table 6-8  Selected Characteristics of Women,* Their Pregnancies, and Newborns

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White Women</th>
<th>Black Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREMATURE RUPTURE OF MEMBRANES: TIME FROM RUPTURE TO ONSET OF LABOR (HR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>70.9</td>
<td>56.7</td>
</tr>
<tr>
<td>8-23</td>
<td>18.3</td>
<td>21.9</td>
</tr>
<tr>
<td>24-48</td>
<td>5.4</td>
<td>11.7</td>
</tr>
<tr>
<td>≥49</td>
<td>5.4</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>PUERPERAL INFECTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal vertex</td>
<td>91.7</td>
<td>92.4</td>
</tr>
<tr>
<td>Vaginal breech</td>
<td>3.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>4.9</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>BIRTH WEIGHT &lt; 2500 G</strong></td>
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<td></td>
</tr>
<tr>
<td>Amnion</td>
<td>7.1</td>
<td>13.4</td>
</tr>
<tr>
<td>Chorion</td>
<td>13.1</td>
<td>15.6</td>
</tr>
<tr>
<td>Umbilical vein</td>
<td>14.6</td>
<td>7.5</td>
</tr>
</tbody>
</table>

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### Table 6-9  Incidence of Fetal and Neonatal Infections by Sex

<table>
<thead>
<tr>
<th>Infection</th>
<th>NO. OF INFANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTRAUTERINE INFECTIONS</strong></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>118</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>15</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>118</td>
</tr>
<tr>
<td>Listeriosis</td>
<td>26</td>
</tr>
<tr>
<td><strong>PERINATAL SEPSIS</strong></td>
<td></td>
</tr>
<tr>
<td>Gram-negative organisms</td>
<td>82</td>
</tr>
<tr>
<td>Gram-positive organisms</td>
<td>58</td>
</tr>
<tr>
<td><strong>PERINATAL MENINGITIS</strong></td>
<td></td>
</tr>
<tr>
<td>Gram-negative organisms</td>
<td>126</td>
</tr>
<tr>
<td>Gram-positive organisms</td>
<td>45</td>
</tr>
</tbody>
</table>

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These data are based on a review of the literature and study of Johns Hopkins Hospital case records, 1930–1963. Washburn TC, Medearis DN J, Childs B. Sex differences in susceptibility to infections, Pediatrics 35:57, 1965.
including unique cultural features and sexual practices, local obstetric and nursery practices, and patterns of antimicrobial agent use. The bacteriology of neonatal sepsis and meningitis in western Europe\(^1\) and Jamaica\(^2\) is generally similar to that in the United States. In tropical areas, a somewhat different pattern can be observed.\(^{289-291}\) In Riyadh, Saudi Arabia, from 1980 through 1984, \(E.\) \(coli,\) \(Klebsiella,\) and \(Serratia\) \(spp.,\) were the dominant causes of neonatal sepsis; group B streptococci were an infrequent cause.\(^{291}\) However, later data from this geographic location revealed \(E.\) \(coli\) and \(CoNS,\) respectively, were the most common pathogens causing early-onset and LOS.\(^{292}\)

Every year four million neonatal deaths occur. About one third of the deaths are due to sepsis.\(^{293,294}\) The highest numbers of neonatal deaths are in South Central Asian countries and sub-Saharan Africa. The global perspective of neonatal sepsis is discussed in Chapter 2. The most common isolates responsible for neonatal sepsis vary by country but include a wide spectrum of gram-negative and gram-positive species, the most common of which are \(E.\) \(coli,\) \(S.\) \(aureus,\) \(Pseudomonas,\) and \(Klebsiella.\)\(^{295}\) Multidrug-resistant strains are an increasing threat to intervention programs.\(^{296,297}\) In a recent meta-analysis of 19 neonatal sepsis studies identified from 13 developing countries, \(Staphylococcus aureus,\) \(Klebsiella\) \(spp.,\) and \(Escherichia coli\) accounted for 55% (39%-70%) of culture-positive sepsis on weighted prevalence.\(^{298}\)

GBS is the most frequent cause of early- and late-onset sepsis in the United States, but the rates and risk factors for maternal and neonatal GBS colonization and disease vary in different communities.\(^{299-301}\) Amin and colleagues\(^{299}\) in the United Arab Emirates evaluated 563 pregnant women from similar socioeconomic and ethnic backgrounds and reported a GBS colonization rate of 10.1%. In Athens, Greece, maternal and neonatal colonization rates were 6.6% and 2.4%, respectively, with a vertical transmission rate of 22.5%.\(^{300}\) Middle-class women followed in the private setting were more frequently colonized with GBS than those followed in a public hospital. No association was found between colonization with GBS and maternal age, nationality, marital status, previous obstetric history, cesarean section, infant birth weight, or preterm birth.

Stoll and Schuchat\(^{301}\) reviewed data on female genital colonization with GBS from 34 reports in the literature and emphasized the importance of appropriate specimen collection and inoculation into selective (antibiotic containing) broth media in the ascertainment of accurate colonization rates. Analysis of data from studies using adequate methods revealed regional GBS colonization rates of 12% in India and Pakistan, 19% in Asian and Pacific countries, 19% in sub-Saharan Africa, 22% in the Middle East and North Africa, and 14% in the Americas. A comparison of studies that did and did not use selective broth media revealed significantly higher GBS colonization rates in the populations where selective broth media was used to assess colonization. Other reasons for varying rates of GBS colonization and disease may include socioeconomic factors or differences in sexual practices, hygiene, or nutrition.

Socioeconomic Factors

The lifestyle pattern of mothers, including cultural practices, housing, nutrition, and level of income, appears to be important in determining infants at risk for infection. The

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\(^{1}\) References 10, 13, 26, 260-262, 267, 286, 287.

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most significant factors enhancing risk for neonatal sepsis are LBW and prematurity, and the incidence of these is inversely related to socioeconomic status. Various criteria for determining socioeconomic status have been used, but no completely satisfactory and reproducible standard is available. Maternal education, resources, and access to health care can affect the risk of neonatal sepsis. A CDC report\(^{302}\) evaluating the awareness of perinatal GBS infection among women of childbearing age in the United States revealed that women with a high school education or less; women with a household income of less than $25,000; and women reporting black, Asian/Pacific Islander, or other ethnicity had lower awareness of perinatal GBS infections than other women.

Procedures

Most VLBW infants have one or more procedures that place them at risk for infection. Any disruption of the protective capabilty of the intact skin or mucosa can be associated with infection. In a multicenter study of NICU patients, increased risk of bacteremia was associated with parenteral nutrition, mechanical ventilation, peripherally inserted central catheters, peripheral venous catheters, and umbilical artery catheters.\(^{303}\)

NURSERY OUTBREAKS OR EPIDEMICS

The nursery is a small community of highly susceptible infants where patients have contact with many adults, including parents, physicians, nurses, respiratory therapists, and diagnostic imaging technicians (see Chapter 14). Siblings may enter the nursery or mothers’ hospital suites and represent an additional source of infection. In these circumstances, outbreaks or epidemics of respiratory and gastrointestinal illness, most of which is caused by nonbacterial agents, can occur. Spread of microorganisms to the infant occurs by droplets from the respiratory tracts of parents, nursery personnel, or other infants. Organisms can be transferred from infant to infant by the hands of health care workers. Individuals with open or draining lesions are especially hazardous agents of transmission.

Staphylococcal infection and disease are a concern in many nurseries in the United States (see Chapter 14). Epidemics or outbreaks associated with contamination of nursery equipment and solutions caused by \(Proteus\) \(spp.,\) \(Klebsiella\) \(spp.,\) \(S.\) \(marcescens,\) \(Pseudomonas\) \(spp.,\) and \(Flavobacterium\) also have been reported. An unusual and unexplained outbreak of early-onset GBS sepsis with an attack rate of 14 per 1000 live births occurred in Kansas City during January through August of 1990.\(^{304}\)

The availability of molecular techniques to distinguish bacterial strains provides an important epidemiologic tool in the investigation of nursery outbreaks. Previously, methods to determine strain relatedness relied on antibiotic susceptibility patterns, biochemical profiles, and plasmid or phage analysis.\(^{154,305}\) More recent techniques permit the discrimination of strains based on bacterial chromosomal polymorphisms. Pulse-field gel electrophoresis, ribotyping, multilocus sequence typing, and polymerase chain reaction (PCR)-based methods are widely used tools to assign strain identity or relatedness.\(^{306-308}\)
Antimicrobial agents play a major role in the ecology of the microbial flora in the nursery. Extensive and prolonged use of these drugs eliminates susceptible strains and allows proliferation of resistant subpopulations of neonatal flora. There is selective pressure toward colonization by microorganisms that are resistant to the antimicrobial agents used in the nurseries and, because of cross-resistance patterns, to similar drugs within an antimicrobial class.

A historical example of the selective pressure of a systemic antimicrobial agent is provided by Gezon and coworkers in their use of benzathine penicillin G to control an outbreak of GAS disease. All infants entering the nursery during a 3-week period were treated with a single intramuscular dose of penicillin. Before institution of this policy, most strains of *S. aureus* in the nursery were susceptible to penicillin G. One week after initiation of the prophylactic regimen and for the next 2 years, almost all strains of *S. aureus* isolated from newborns in this nursery were resistant to penicillin G.

During a 4-month period in 1997, van der Zwart and colleagues investigated a nosocomial nursery outbreak of gentamicin-resistant *K. pneumoniae* in which 13 neonates became colonized and 3 became infected. Molecular typing of strains revealed clonal similarity of isolates from 8 neonates. The nursery outbreak was terminated by the substitution of amikacin for gentamicin in neonates when treatment with an aminoglycoside was believed to be warranted. Development of resistance in gram-negative enteric bacilli also has been documented in an Israeli study after widespread use of aminoglycosides.

Extensive or routine use of third-generation cephalosporins in the nursery, especially for all neonates with suspected sepsis, can lead to more rapid emergence of drug-resistant gram-negative enteric bacilli than occurs with the standard regimen of ampicillin and an aminoglycoside. Investigators in Brazil performed a prospective investigation of extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* colonization and infection during the 2-year period from 1997 to 1999 in the NICU. A significant independent risk factor for colonization was receipt of a cephalosporin and an aminoglycoside. Previous colonization was an independent risk factor for infection. In India, Jain and coworkers concluded that indiscriminate use of third-generation cephalosporins was responsible for the selection of ESBL-producing, multiresistant strains in their NICU, where ESBL production was detected in 86.6% of *Klebsiella* spp., 73.4% of *Enterobacter* spp., and 63.6% of *E. coli* strains. Nosocomial infections in the nursery and their epidemiology and management are further discussed in Chapter 35.

**Pathogenesis**

The developing fetus is relatively protected from the microbial flora of the mother. However, procedures disturbing the integrity of the uterine contents, such as amniocentesis, cervical cerclage, transcervical chorionic villus sampling, or percutaneous umbilical blood sampling, can permit entry of skin or vaginal organisms into the amniotic sac, causing amnionitis and secondary fetal infection.

Initial colonization of the neonate usually takes place after rupture of the maternal membranes. In most cases, the infant is colonized with the microflora of the birth canal during delivery. However, if delivery is delayed, vaginal bacteria may ascend the birth canal and, in some cases, produce inflammation of the fetal membranes, umbilical cord, and placenta. Fetal infection can then result from aspiration of infected amniotic fluid, leading to stillbirth, premature delivery, or neonatal sepsis. The organisms most commonly isolated from infected amniotic fluid are GBS, *E. coli* and other enteric bacilli, anaerobic bacteria, and genital mycoplasmas.

There are studies reporting that amniotic fluid inhibits the growth of *E. coli* and other bacteria because of the presence of lysozyme, transferrin, immune globulins (IgA and IgG but not IgM), zinc and phosphate, and lipid-rich substances. The addition of meconium to amniotic fluid in vitro has resulted in increased growth of *E. coli* and GBS in some studies. However, in other in vitro studies of the bacteriostatic activity of amniotic fluid, there is no inhibition of the growth of GBS. Further discussion of bacterial inhibition by amniotic fluid is available in Chapter 3.

Infection of the mother at the time of birth, particularly genital infection, can play a significant role in the development of infection in the neonate. Transplacental hematogenous infection during or shortly before delivery (including the period of separation of the placenta) is possible, although it is more likely that the infant is infected just before or during passage through the birth canal. Among reports of concurrent bacteremia in mother and neonate are cases caused by *H. influenzae* type b, *H. parainfluenzae*, *S. pneumoniae*, GAS, *N. meningitidis*, *Citrobacter* spp., and *Morganella morganii*. Concur rent cases of meningitis have been reported as caused by *S. pneumoniae*, *N. meningitidis*, and GBS. Many neonates are bacteremic at the time of delivery, which indicates that invasive infection occurred antepartum. Infants with signs of sepsis during the first 24 hours of life also have the highest mortality rate. These data suggest the importance of initiating chemoprophylaxis for women with GBS colonization or other risk factors for invasive disease in the neonate at the time of onset of labor (see Chapter 12).

Microorganisms acquired by the newborn infant just before or during birth colonize the skin and mucosal surfaces, including the conjunctivae, nasopharynx, oropharynx, gastrointestinal tract, umbilical cord, and in the female infant, the external genitalia. Normal skin flora of the newborn includes CoNS, diphtheroids, and *E. coli*. In most cases, the microorganisms proliferate at the initial site of attachment without resulting in illness. On occasion, contiguous areas may be infected by direct extension (e.g., sinusitis and otitis can occasionally occur from upper respiratory tract colonization).

Bacteria can be inoculated into the skin and soft tissue by obstetric forceps, and organisms may infect these tissues if abrasions or congenital defects are present. Scalp abcesses can occur in infants who have electrodes placed during labor for monitoring of heart rate. The incidence of this type of infection in the hands of experienced clinicians, however, is generally quite low (0.1% to 5.2%). A 10-year survey of neonatal enterococcal bacteremia detected 6 of 44 infants with scalp abscesses as the probable source of their bacteremia. The investigators were unable
from the data available to deduce whether these abscesses were associated with fetal scalp monitoring, intravenous infusion, or other procedures that resulted in loss of the skin barrier.

Transient bacteremia can accompany procedures that traumatize mucosal membranes, such as endotracheal suctioning. Invasion of the bloodstream also can follow multiplication of organisms in the upper respiratory tract or other foci. Although the source of bacteremia frequently is inapparent, careful inspection can reveal a focus, such as an infected circumcision site or infection of the umbilical stump, in some neonates. Metastatic foci of infection can follow bacteremia and can involve the lungs, kidney, spleen, bones, or CNS.

Most cases of neonatal meningitis result from bacteremia. Fetal meningitis followed by stillbirth or hydrocephalus, presumably because of maternal bacteremia and transplacentally acquired infection, has been described but is exceedingly rare. Although CSF leaks caused by spiral fetal scalp electrodes do occur, no cases of meningitis have been traced to this source. After delivery, the meninges can be invaded directly from an infected skin lesion, with spread through the soft tissues and skull sutures and along thrombosed bridging veins, but in most circumstances, bacteria gain access to the brain through the bloodstream to the choroid plexus during the course of sepsis. Infants with developmental defects, such as a midline dermal sinus or myelomeningocele, are particularly susceptible to invasion of underlying nervous tissue.

Brain abscesses can result from hematogenous spread of microorganisms (i.e., septic emboli) and proliferation in tissue that is devitalized because of anoxia or vasculitis with hemorrhage or infarction. Certain organisms are more likely than others to invade nervous tissue and cause local or widespread necrosis. Most cases of meningitis related to C. koseri (formerly C. diversus) and E. sakazakii are associated with cyst and abscess formation. Other gram-negative bacilli with potential to cause brain abscesses include Proteus, Citrobacter, Pseudomonas, S. marcescens, and occasionally GBS. Volpe comments that bacteria associated with brain abscesses are those that cause meningitis with severe vasculitis.

HOST FACTORS PREDISPOSING TO NEONATAL BACTERIAL SEPSIS

Infants with one or more predisposing factors (e.g., LBW, prematurity rupture of membranes, septic or traumatic delivery, fetal hypoxia, maternal peripartum infection) are at increased risk for sepsis. Microbial factors such as inoculum size and virulence properties of the organism undoubtedly are significant. Immune function of phagocytes and decreased inflammatory and immune effector responses are characteristic of very small infants and can contribute to the unique susceptibility of the fetus and newborn (see Chapter 4).

Metabolic factors are likely to be important in increasing risk for sepsis and severity of the disease. Fetal hypoxia and acidosis can impede certain host defense mechanisms or allow localization of organisms in necrotic tissues. Infants with hyperbilirubinemia can suffer impairment of various immune functions, including neutrophil bactericidal activity, antibody response, lymphocyte proliferation, and complement functions (see Chapter 4). The indirect hyperbilirubinemia that commonly occurs with breastfeeding jaundice rarely is associated with neonatal sepsis. Late-onset jaundice and direct hyperbilirubinemia can be the result of an infectious process. In one study from Turkey, more than one third of infants with late-onset direct hyperbilirubinemia had culture-proven sepsis, with gram-negative enteric bacteria, including E. coli, the most common etiologic agents. Evidence of diffuse hepatocellular damage and bile stasis have been described in such infected and jaundiced infants.

Hypothermia in newborns, generally defined as a rectal temperature equal to or less than 35°C (95°F), is associated with a significant increase in the incidence of sepsis, meningitis, pneumonia, and other serious bacterial infections. In developing countries, hypothermia is a leading cause of death during the winter. Hypothermia frequently is accompanied by abnormal leukocyte counts, acidosis, and uremia, each of which can interfere with resistance to infection. However, the exact cause of increased morbidity in infants presenting with hypothermia remains poorly understood. In many infants, it is unclear whether hypothermia predisposes to or results from bacterial infection. For example, in a large outbreak of S. marcescens neonatal infections affecting 1.59 cases in Gaza City, Palestine, hypothermia was the single most common presenting symptom, recorded in 38% of cases.

Infants with galactosemia have increased susceptibility to sepsis caused by gram-negative enteric bacilli, in particular E. coli. Among 8 infants identified with galactosemia by routine newborn screening in Massachusetts, 4 had systemic infection caused by E. coli. Three of these 4 infants died of sepsis and meningitis; the fourth infant, who had a urinary tract infection, survived. A survey of state programs in which newborns are screened for galactosemia revealed that among 32 infants detected, 10 had systemic infection, and 9 died of bacteremia. E. coli was the infecting organism in 9 of the infants. It appears that galactosemic neonates have an unusual predisposition to severe infection with E. coli, and bacterial sepsis is a significant cause of death among these infants. Depressed neutrophil function resulting from elevated serum galactose levels is postulated to be a possible cause of their predisposition to sepsis.

The gold standard for diagnosis of classic galactosemia is measurement of galactose-1-phosphate uridyltransferase (GALT) activity in erythrocytes, and the sole therapy is galactose restriction in the diet. Shurin observed that infants became ill when serum galactose levels were high and when glucose levels were likely to be low, and that susceptibility to infection diminished when dietary control was initiated.

Other inherited metabolic diseases have not been associated with a higher incidence of neonatal bacterial infection. A poorly documented increase in the relative frequency of sepsis has been observed among infants with hereditary fructose intolerance. Infants with methylmalonic acidemia and other inborn errors of branched-chain amino acid metabolism manifest neutropenia as a result of bone marrow suppression by accumulated metabolites; however, no increased incidence of infection has been described in this group of infants.
Iron may have an important role in the susceptibility of neonates to infection, but this continues to be controversial. Iron added to serum in vitro enhances the growth of many organisms, including *E. coli*, *Klebsiella* spp., *Pseudomonas* spp., *Salmonella* spp., *L. monocytogenes*, and *S. aureus*. The siderophore IroN is a proven virulence factor for the bacteremic phase of *E. coli* K1 sepsis and meningitis in the neonatal rat infection model. Iron-binding proteins, lactoferrin and transferrin, are present in serum, saliva, and breast milk. However, the newborn has low levels of these proteins. The iron sequestering capacity of oral bovine lactoferrin supplementation may be one contributing factor to its reported efficacy in prophylaxis of bacterial sepsis in VLBW infants. 

Barry and Reeve demonstrated an increased incidence of sepsis in Polynesian infants who were treated with intramuscular iron as prophylaxis for iron-deficiency anemia. The regimen was shown to be effective in preventing anemia of infancy, but an extraordinary increase in bacterial sepsis occurred. The incidence of sepsis in newborns receiving iron was 17 cases per 1000 live births, whereas the incidence of sepsis in infants who did not receive iron was 3 cases per 1000 live births. During a comparable period, the rate of sepsis for European infants was 0.6 cases per 1000 live births. Special features of sepsis in the infants who received iron soon after birth were late onset, paucity of adverse perinatal factors, and predominance of *E. coli* as the cause of sepsis. During the period studied, *E. coli* was responsible for 26 of 27 cases of sepsis in iron-treated Polynesian infants and for none of the three cases of sepsis in the infants who did not receive iron. Results of this study were similar to the experience reported by Farmer for New Zealand infants given intramuscular iron. The incidence of meningitis caused by *E. coli* increased fivefold in infants who received iron and decreased when the use of iron was terminated. Conventional iron-supplemented human milk fortifiers, however, appear safe and do not contribute to a higher rate of sepsis in preterm infants.

### INFECTION IN TWINS

Studies have suggested a higher risk for contracting ascending intrauterine infection in the first than the second born of twins. Comparing delivery methods, no difference was observed in the incidence of neonatal sepsis in twins delivered in the vertex/vertex position when compared with cases requiring uterine manipulation (vertex/breech extraction). However, vaginal delivery of twin A, followed by cesarean delivery of twin B, may be associated with a higher rate of endometritis and neonatal sepsis when compared with cases where both twins are delivered by cesarean section.

A recent large study from the NICHD Neonatal Research Network conducted from 2002 to 2008 identified LOS occurring in 25.0% (3797/15,178) of singleton and 22.6% (1196/5294) of multiple-birth infants with VLBW (401-1500 g). CoNS accounted for 53.2% of episodes in singletons and 49.2% in multiples. A similar concordance of LOS in same-sex and unlike-sex twin pairs suggested that susceptibility to LOS among VLBW infants is not genetically determined. No difference in complications or sepsis risk exists among twin pregnancies conceived spontaneously or through in vitro fertilization.

Edwards and colleagues studied GBS infection in 12 index cases of multiple gestations. Early-onset disease occurred in both twins in one pair and in one twin in five other pairs; late-onset infection occurred in both infants in two pairs and in one twin in four other pairs. Cases of late-onset GBS disease in twin pairs occurred closely in time to one another: 19 and 20 days in one set and at 28 and 32 days of age in the other set. In another case report of late-onset GBS infection in identical twins, twin A suffered fulminant fatal meningitis whereas twin B recovered completely. The GBS isolates proved to be genetically identical; clinical variables associated with the adverse outcome in twin A were longer duration of fever before antibiotics and the development of neutropenia. In twins, the presence of virulent organisms in the environment, especially the maternal genital tract; their absence of specific maternal antibodies; and their similar genetic heritage probably contribute to the risk for invasive infection. It seems logical that twins, particularly if monochorionic, should have high rates of simultaneous early-onset infection, but it is particularly intriguing that some cases of late-onset disease occur in twins almost simultaneously. However, the incidence of infection in preterm twins co-bedding in the nursery did not differ from those cared for in separate beds.

Infections in twins, including disease related to *Toxoplasma pallidum*, echoviruses 18 and 19, and *Toxoplasma gondii*, are discussed in Chapters 16, 25, and 31, respectively. Examples of neonatal infections in twins include those caused by GAS (case report of streptococcal sepsis in a mother and infant twins), *Salmonella* spp., *C. koseri* (brain abscesses in twins), *malaria*, *coccidioidomycosis*, *cytomegalovirus* infection, and rubella.

### THE UMBILICAL CORD AS A FOCUS OF INFECTION

Historically, the umbilical cord was a particularly common portal of entry for systemic infection in the newborn, and infection by this route can still occur. The devitalized tissue is an excellent medium for bacterial growth, the recently thrombosed umbilical vessels provide access to the bloodstream, the umbilical vein is a direct route to the liver, and the umbilical artery and urachus are pathways to the pelvis. Epidemics of erysipelas, staphylococcal disease, tetanus, and gas gangrene of the umbilicus were common in the 19th century. The introduction of simple hygienic measures in cord care resulted in a marked reduction of omphalitis. In 1930, Cruickshank wrote, "in Prague, before antisepic and aseptic dressing of the cord was introduced, sepsis neonatorum was as common as puerperal sepsis..." Closure of the umbilical vessels and the subsequent aseptic necrosis of the cord begin soon after the infant takes the first breath; the umbilical arteries contract, the blood flow is interrupted, and the cord tissues, deprived of a blood supply, undergo aseptic necrosis. The umbilical stump acquires a rich flora of microorganisms. Within hours, the umbilical stump is colonized with large numbers of gram-positive cocci, particularly *Staphylococcus* spp., and shortly thereafter with fecal organisms. These bacteria can invade...
the open umbilical wound, causing a localized infection with purulent discharge and, as a result of delayed obliteration of the umbilical vessels, bleeding from the umbilical stump. From this site, infection can proceed into the umbilical vessels, along the fascial planes of the abdominal wall, or into the peritoneum.401,403,404 (Fig. 6-1).

Although umbilical discharge or an “oozing” cord is the most common manifestation of omphalitis, periumbilical cellulitis and fasciitis are the conditions most often associated with hospitalization.403 Infants presenting with fasciitis have a high incidence of bacteremia, intravascular coagulopathy, shock, and death.403 Edema of the umbilicus and peau d’orange appearance of the surrounding abdominal skin, signaling obstruction of the underlying lymphatics, can be an early warning sign, whereas the pathognomonic purplish-blue discoloration implies advanced necrotizing cellulitis.398 Septic embolization arising from the infected umbilical vessels is uncommon but can produce metastatic lesions in the kidneys, and skin.399 Such emboli can arise from the umbilical vessels and enter the umbilical vein because final closure of the ductus venosus and separation of the portal circulation from the inferior vena cava and the systemic circulation are generally delayed until day 15 to day 30 of life.405 Complications of omphalitis, now a rare infection in developed countries because of modern umbilical cord care, include a variety of infections such as septic umbilical arteritis,399,406 suppurative thrombophlebitis of the umbilical or portal veins or the ductus venosus,406-408 peritonitis,404,406,407,409 intestinal gangrene,404 pyoura-chus (infection of the urachal remnant),410 liver abscess, endocarditis, pylephlebitis,404,411 and subacute necrotizing funisitis.412 Some of these infections can occur in the absence of signs of omphalitis.399,406

ADMINISTRATION OF DRUGS TO THE MOTHER BEFORE DELIVERY

Almost all antimicrobial agents cross the placenta. Antimicrobial drugs administered to the mother at term can alter the initial microflora of the neonate and can complicate the diagnosis of infection in the neonate. Chapter 37 reviews the clinical pharmacology of antimicrobial agents administered to the mother.

It is well established that studies have shown that corticosteroid administration to mothers in preterm labor to enhance pulmonary maturation in the fetus resulted in a significant decrease in the incidence and severity of neonatal respiratory distress syndrome but an increase in maternal infection, particularly endometritis, when compared with placebo;411 however, the impacts of this practice on the risk of neonatal infection differed among early studies.413,414 However, Roberts and Dalziel415 recently performed large meta-analysis of 21 randomized controlled studies from the Cochrane Pregnancy and Childbirth Group Trials register, comprising in sum 3885 pregnant women and 4269 infants, and concluded that antenatal corticosteroid administration (betamethasone, dexamethasone, or hydrocortisone) given to women expected to deliver singleton or multiple pregnancies, whether labor was spontaneous, induced by membrane rupture, or electively induced, was associated with multiple favorable outcomes, including reduced neonatal death (risk ratio [RR], 0.69), intensive care admissions (RR, 0.80), and systemic infections in the first 48 hours of life (RR, 0.56).

Substance abuse during pregnancy can affect immune function in the neonate. Significant abnormalities in T-cell function and an apparent increased incidence of infections have been found during the first year of life among infants born to alcohol-addicted416-418 and heroin-addicted419,420 mothers. The adverse effects of cocaine and opiates on placental function, fetal growth and development, and prematurity also may predispose to a greater likelihood of neonatal infection.420,421 Unfortunately, drug abuse is a multifactorial problem; it is virtually impossible to separate the consequences of direct pharmacologic effects on the fetus from those resulting from inadequate nutrition, lack of prenatal care, and infectious medical complications encountered in addicted pregnant women.420,421

ADMINISTRATION OF DRUGS OTHER THAN ANTIBIOTICS TO THE NEONATE

Administration of indomethacin to neonates for the closure of a patent ductus arteriosus (PDA) has been associated with a higher incidence of sepsis and NEC in the indomethacin-treated groups compared with infants treated with surgery or other medications.422-424 The mechanism by which indomethacin predisposes LBW infants to sepsis is unknown. A recent meta-analysis of studies comparing ibuprofen with indomethacin for PDA closure did not identify
differences in the incidence of sepsis, mortality, or duration of hospitalization. O’Shea and colleagues described the outcomes of VLBW (500-1250 g) infants given dexamethasone at 15 to 25 days of age for the prevention of chronic lung disease. Among 61 infants treated with tapering doses of dexamethasone for 42 days, there was no increase in the incidence of sepsis or the number of sepsis evaluations in the treatment group when compared with a control population. Further trials of dexamethasone administration for chronic lung disease prophylaxis in VLBW infants confirmed a lack of increased risk for sepsis.

A strong association between intravenous lipid administration to newborns and CoNS bacteremia has been established. The role of lipid as a nutritional source for the bacteria, mechanical blockage of the catheter by deposition of lipid in the lumen, and the effect of lipid emulsions on the function of neutrophils and macrophages each might contribute to the observed increased risk for bacteremia. Avila-Figueroa and colleagues identified exposure to intravenous lipids at any time during hospitalization as the single most important risk factor (odds ratio [OR], 9.4) for development of CoNS bacteremia in VLBW infants, calculating that 95% of these bacteremias were attributable to lipid therapy. A randomized trial found that changing intravenous tubing for lipid infusion in neonates every 24 hours instead of 72 hours may reduce bloodstream infections and mortality by approximately 50%.

Recently, a surprisingly strong association between ranitidine therapy in neonates admitted to one NICU and the risk of late-onset bacterial sepsis was reported. The mechanism for such an association remains unclear but certainly merits further analysis.

Pathology

Infants with severe and rapidly fatal sepsis generally have minimal or no histologic indication of an infectious process. Findings typical of bacteremia, such as multiple disseminated abscesses of similar size, purulent vasculitis, and intravascular identification of bacteria, are evident in a minority of infants. Shock accompanying sepsis sometimes causes findings such as periventricular leukomalacia and intraventricular hemorrhage, scattered areas of nonzonal hepatic necrosis, renal medullary hemorrhage, renal cortical or acute tubular necrosis, and adrenal hemorrhage and necrosis. Evidence of disseminated intravascular coagulopathy, manifested by strands of interlacing fibrin in the vessels or by a well-demarcated subarachnoid fibrinous hematoma, also can be present. The pathology of infections of the respiratory, genitourinary, and gastrointestinal tracts and focal supplicative diseases is discussed in subsequent chapters.

The pathology of neonatal meningitis and brain abscess is similar to that in the older child and adult. The major features are ventriculitis (including inflammation of the choroid plexus), vasculitis, cerebral edema, infarction, cortical neuronal necrosis, and periventricular leukomalacia; chronic pathologic features include hydrocephalus, multicystic encephalomalacia and porencephaly, and cerebral cortical and white matter atrophy. Significant collections of purulent material can be present in the sulci and subarachnoid space, particularly around the basal cisterns, of infants with meningitis. Because the fontanelles are open, exudative material can collect around the base of the brain without a significant increase in intracranial pressure. Hydrocephalus may result from closure of the aqueduct or the foramina of the fourth ventricle by purulent exudate or by means of inflammatory impairment of CSF resorption through the arachnoid channels. Ventriculitis has been described in 20% to 90% of cases and often is the reason for persistence of bacteria in CSF when obstruction ensues and for a slow clinical recovery. Acute inflammatory cells infiltrate the ependymal and subependymal tissues, causing destruction of the epithelial lining of the ventricles. Hemorrhage, venous thrombosis, and subdural effusions often are present.

Brain abscesses and cysts in the neonate are distinguished by the relatively large size of the lesions and relatively poor capsule formation. They occur most frequently in association with meningitis caused by *C. koseris*, *E. sakazakii*, *S. marcescens*, and *Proteus mirabilis* and usually are located in the cerebrum, involving several lobes. These organisms characteristically give rise to a hemorrhagic meningoencephalitis caused by intense bacterial infiltration of cerebral vessels and surrounding tissues. The resulting vascular occlusion is followed by infarction and widespread necrosis of cerebral tissue with liquefaction and formation of multiple loculated abscesses and cysts.

CLINICAL MANIFESTATIONS

Signs of fetal distress can be the earliest indication of infection in neonates with sepsis, beginning at or soon after delivery. Fetal tachycardia in the second stage of labor was evaluated by Schiano and colleagues as a sign of infection. Pneumonia or sepsis occurred in 3 of 8 infants with marked fetal tachycardia (>180 beats/min), in 7 of 32 infants with mild tachycardia (160-179 beats/min), and in 1 of 167 infants with lower heart rates. Maternal risk factors, such as premature rupture of membranes, foul-smelling amniotic fluid, and evidence of acute placental inflammation, are associated with increased risk of neonatal sepsis and should prompt detailed evaluation of the newborn.

A low Apgar score, suggesting distress at or before delivery, also has been correlated with sepsis and associated adverse outcomes in the newborn period. Infants delivered vaginally had a 56-fold higher risk of sepsis when the Apgar score was less than 7 at 5 minutes, compared with infants with higher Apgar scores. Among infants with rupture of the amniotic membranes for 24 hours or more, St. Geme and colleagues found a significant increase in the risk for perinatal bacterial infection among those with an Apgar score of less than 6 at 5 minutes but found no association with fetal tachycardia (>160 beats/min).

The Apgar score is well characterized in term infants but less so in premature infants who have the higher attack rates for sepsis. Because low Apgar scores (<3 at 1 minute, <6 at 5 minutes) were significantly associated with LBW and shorter gestation, the use of the score is less valuable as an indicator of sepsis in premature than in term infants.
The earliest signs of sepsis often are subtle and nonspecific. Poor feeding, diminished activity, or just “not looking well” can be the only early evidence that infection is present. More prominent findings are respiratory distress, apnea, lethargy, fever or hypothermia, jaundice, vomiting, diarrhea, and skin manifestations, including petechiae, abscesses, and sclerema.445

The nonspecific and subtle nature of the signs of sepsis in newborns is even more problematic in identifying sepsis in the VLBW infant. In a study by Fanaroff and colleagues,19 the clinical signs of LOS in 325 infants weighing 501 to 1500 g at birth included increasing apnea and bradycardia episodes (55%), increasing oxygen requirement (48%), feeding intolerance, abdominal distention or guaiac-positive stools (46%), lethargy and hypotonia (37%), and temperature instability (10%). Unexplained metabolic acidosis (11%) and hypoglycemia (10%) were the most common laboratory indicators of the metabolic derangement accompanying sepsis.

Bonadio and coworkers446 attempted to determine the most reliable clinical signs of sepsis in more than 200 febrile infants from birth to 8 weeks of age. They found that changes in affect, peripheral perfusion, and respiratory status best identified those infants with serious bacterial infection. Alterations in feeding pattern, level of alertness, level of activity, and muscle tone also were present; however, these signs were less sensitive indicators. Recently, Kudawla and colleagues447 developed a scoring system for late-onset neonatal sepsis in infants weighing between 1000 and 2500 g. Clinical parameters included lethargy, tachycardia, grunting, abdominal distension, increased prefeed residual gastric aspirates, fever, and chest retractions. However, these data needed to be combined with laboratory parameters such as elevated C-reactive protein (CRP) or absolute neutrophil or band count to achieve high sensitivity and specificity.447

Focal infection involving any organ can occur in infants with sepsis, but most often (excluding pneumonia or meningitis) this occurs in neonates with late-onset rather than early-onset disease. Evaluation of infants with suspected bacteremia must include a careful search for primary or secondary foci, such as meningitis, pneumonia, urinary tract infection, septic arthritis, osteomyelitis, peritonitis, or soft tissue infection.

Serious bacterial infections are uncommon in neonates without any clinical evidence of illness;446 even among those with maternal risk factors for infection.448 On occasion, bacteremia occurs without clinical signs.449-451 Albers and associates449 described the case histories of 3 infants without signs of illness for whom blood cultures were performed as part of a nursery study involving 131 infants. Blood was obtained from peripheral veins at different times performed for infants who show no signs of sepsis.

Table 6-10 lists the common clinical signs of neonatal bacterial sepsis. Clinical signs of neonatal bacterial meningitis are given in Table 6-11. Noninfectious conditions that can present with clinical manifestations similar to those of sepsis are shown in Box 6-1.

FEVER AND HYPOTHERMIA

The temperature of the infant with sepsis may be elevated, depressed, or normal.452-458 In a multicenter survey of nearly 250 infants with early-onset GBS bacteremia, approximately 85% had a normal temperature (36° C to 37.2° C [96.8° F to 99° F]) at the time of their admission to the NICU.452 When comparing temperatures by gestational age, it was observed that term infants were more likely to have

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>Percent of Infants with Sign</th>
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<tbody>
<tr>
<td>Hyperthermia</td>
<td>51</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>33</td>
</tr>
<tr>
<td>Apnea</td>
<td>22</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>24</td>
</tr>
<tr>
<td>Jaundice</td>
<td>35</td>
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<tr>
<td>Hepatomegaly</td>
<td>33</td>
</tr>
<tr>
<td>Lethargy</td>
<td>25</td>
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<tr>
<td>Irritability</td>
<td>16</td>
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<tr>
<td>Anorexia</td>
<td>28</td>
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<tr>
<td>Vomiting</td>
<td>25</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>17</td>
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<tr>
<td>Diarrhea</td>
<td>11</td>
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<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>Percent of Infants with Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia or fever</td>
<td>62</td>
</tr>
<tr>
<td>Lethargy or irritability</td>
<td>52</td>
</tr>
<tr>
<td>Anorexia or vomiting</td>
<td>48</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>41</td>
</tr>
<tr>
<td>Bulging or full fontanelle</td>
<td>35</td>
</tr>
<tr>
<td>Seizures</td>
<td>31</td>
</tr>
<tr>
<td>Jaundice</td>
<td>28</td>
</tr>
<tr>
<td>Nuchal rigidity</td>
<td>16</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
</tr>
</tbody>
</table>

### Box 6-1 Differential Diagnosis: Clinical Signs Associated With Neonatal Sepsis and Some Noninfectious Conditions

| Respiratory Distress (Apnea, Cyanosis, Costal and Sternal Retraction, Rales, Grunting, Diminished Breath Sounds, Tachypnea) | Benign liver tumors, including hemangioma, hamartoma  
Malignant liver tumors, including hepatoblastoma, metastatic neuroblastoma, congenital leukemia |
| --- | --- |
| Transient tachypnea of the newborn  
Respiratory distress syndrome  
Atelectasis  
Aspiration pneumonia, including meconium aspiration  
Pneumothorax  
Pneumomediastinum  
Central nervous system disease: hypoxia, hemorrhage  
Congenital abnormalities, including tracheoesophageal fistula, choanal atresia, diaphragmatic hernia, hypoplastic lungs  
Congenital heart disease  
Cardiac arrhythmia  
Hypothermia (neonatal cold injury)  
Hypoglycemia  
Neonatal drug withdrawal syndrome  
Medication error with inhaled epinephrine |  |
| **Temperature Abnormality (Hyperthermia or Hypothermia)** | Gastrointestinal Abnormalities (Anorexia, Regurgitation, Vomiting, Diarrhea, Abdominal Distention)  
Gastrointestinal allergy  
Overfeeding, aerophagia  
Intestinal obstruction (intraluminal or extrinsic)  
Necrotizing enterocolitis  
Hypokalemia  
Hypercalcemia or hypocalcemia  
Hypoglycemia  
Inborn errors of metabolism, including galactosemia, urea cycle disorders, organic acidemias  
Ileus secondary to pneumonia  
Congenital adrenal hyperplasia  
Gastric perforation  
Neonatal drug withdrawal syndrome  
**Lethargy** |  |
| Altered environmental temperature  
Disturbance of central nervous system thermoregulatory mechanism, including anoxia, hemorrhage, kernicterus  
Hyperthyroidism or hypothyroidism  
Neonatal drug withdrawal syndrome  
Dehydration  
Congenital adrenal hyperplasia  
Vaccine reaction | Central nervous system disease, including hemorrhage, hypoxia, or subdural effusion  
Congenital heart disease  
Neonatal drug withdrawal syndrome  
Hypoglycemia  
Hypercalcemia  
Familial dysautonomia |
| **Jaundice** | Seizure Activity (Tremors, Hyperactivity, Muscular Twitching)  
Hypoxia  
Intracranial hemorrhage or kernicterus  
Congenital central nervous system malformations  
Neonatal drug withdrawal syndrome  
Hypoglycemia  
Hypocalcemia  
Hyponatremia, hypernatremia  
Hypomagnesemia  
Inborn errors of metabolism, including urea cycle disorders, organic acidemias, galactosemia, glycogen storage disease, peroxisomal disorders  
Pyridoxine deficiency |
| Breast milk jaundice  
Blood group incompatibility  
Red cell hemolysis, including blood group incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency  
Resorption of blood from closed space hemorrhage  
Gastrointestinal obstruction, including pyloric stenosis  
Extrahepatic or intrahepatic biliary tract obstruction  
Inborn errors of metabolism, including galactosemia, glycogen storage disease type IV, tyrosinemia, disorders of lipid metabolism, peroxisomal disorders, defective bile acid synthesis (triiodothyronic acidemia)  
Hereditary diseases, including cystic fibrosis, α1-antitrypsin deficiency, bile excretory defects (Dubin-Johnson, Rotor, Byler, Aagenaes syndrome)  
Hypothyroidism  
Prolonged parenteral hyperalimentation  
**Hepatomegaly** | Petechiae, Purpura, and Vesiculopustular Lesions  
Birth trauma  
Blood group incompatibility  
Neonatal isoimmune thrombocytopenia  
Maternal idiopathic thrombocytopenic purpura  
Maternal lupus erythematosus  
Drugs administered to mother  
Giant hemangioma (Kasabach-Merritt syndrome)  
Thrombocytopenia with absent radii (TAR) syndrome  
Disseminated intravascular coagulopathy  
Coagulation factor deficiencies  
Congenital leukemia  
Child abuse  
Cutaneous histiocytosis |
| Red cell hemolysis, including blood group incompatibility, G6PD deficiency  
Infant of a diabetic mother  
Inborn errors of metabolism, including galactosemia, glycogen storage disease, organic acidemias, urea cycle disorders, hereditary fructose intolerance, peroxisomal disorders  
Biliary atresia  
Congestive heart failure |  |
fever than preterm infants (12% vs. 1%), whereas preterm infants more frequently had hypothermia (13% vs. 3%). Phagocytes of the infant born after an uncomplicated labor can produce adult concentrations of interleukin-1 (IL-1), a potent pyrogen. The phagocytes of infants born after cesarean section have a markedly suppressed ability to produce this pyrogen.459 In the studies reviewed in Table 6-10, approximately one half of the infants had fever. Hypothermia, which was mentioned in one study, occurred in 15% of the infants.

Fever is variably defined for newborns. A temperature of 38.0° C (100.4° F) measured rectally generally is accepted as the lower limit of the definition of fever. Although some clinical studies indicate that axillary,460 skin-mattress,461 and infrared tympanic membrane thermometry462 are accurate and less dangerous than rectal measurements for obtaining core temperature, the reliability of these methods, particularly in febrile infants, has been questioned.463-465 A recent study established that statistically significant differences are present between the rectal and axillary temperatures obtained in newborns during the first 4 days of life even with the same electronic temperature device.466 Thus the current method of choice for determining the presence of fever in neonates is a rectal temperature taken at a depth of 2 to 3 cm past the anal margin. In infants with suspected sepsis without fever, it has been shown that a difference between core (rectal) and skin (sole of the foot) temperature of more than 3.5° C can be a more useful indicator of infection than measurement of core temperature alone.458

There is no study of temperatures in neonates that is prospective, assesses all infants (febrile and afebrile), includes rectal and axillary temperatures, includes preterm and term infants, and requires positive cultures of blood or other body fluids to define invasive bacterial infection. However, Voora and colleagues467 observed 100 term infants in Chicago with an axillary or rectal temperature of 37.8° C (100.1° F) or higher during the first 4 days of life and Osborn and Bolus468 conducted a retrospective review of 2656 term infants in Los Angeles. Both groups of investigators reported that temperature elevation in healthy term infants was uncommon. Approximately 1% of neonates born at term had at least one episode of fever, measured as 37.8° C (100.1° F) or higher per axilla.467 Temperature elevation infrequently was associated with systemic infection when a single evaluation occurred. None of 64 infants in these two studies who had a single episode of fever developed clinical evidence of systemic infection (cultures of blood or other body fluids were not obtained). By contrast, temperature elevation that was sustained for more than 1 hour frequently was associated with infection. Of 7 infants with sustained fever in the Osborn and Bolus study,468 5 had proven bacterial or viral infections. Of 65 infants reported by Voora and colleagues,467,469 10 had documented systemic bacterial disease. Temperature elevation without other signs of infection was infrequent. Only 1 infant (with cytomegalovirus infection) of the 5 Los Angeles infants had fever without other signs. Only 2 infants (with bacteremia caused by E. coli or GBS, respectively) of the 10 Chicago infants with fever and proven bacterial disease had no other signs of infection.

In addition to infection, fever may be caused by an elevation in ambient temperature, dehydration, retained blood or extensive hematoma, and damage to the temperature-regulating mechanisms of the CNS. Less common noninfectious causes of fever are hyperthyroidism, cystic fibrosis, familial dysautonomia, and ectodermal dysplasia. When thermoregulatory devices that monitor and modify infant temperature are introduced, the use of fever or hypothermia as a diagnostic sign of sepsis sometimes is impeded.

**RESPIRATORY DISTRESS**

Signs of respiratory distress, including tachypnea, grunting, flaring of the alae nasi, intercostal retractions, rales, and decreased breath sounds, are common and important findings in the infant suspected of having sepsis. Respiratory distress syndrome and aspiration pneumonia must be considered in the differential diagnosis. Apnea is one of the most specific signs of sepsis but usually occurs in the setting of a fulminant onset or after other nonspecific signs have been present for hours or days. Clinical signs of cardiovascular dysfunction, including tachycardia, arrhythmia, and poor peripheral perfusion, that occur in the absence of congenital heart disease are sensitive and specific signs of sepsis.

**JAUNDICE**

Jaundice is present in approximately one third of infants with sepsis and is a common finding in infants with urinary tract infection.457,469-471 It can develop suddenly or subacutely and occasionally is the only sign of sepsis. Jaundice usually decreases after institution of appropriate antimicrobial therapy. It occurs in septic infants irrespective of the type of bacterial pathogen. A fatal case of acute kernicterus secondary to glucose-6-phosphate deficiency was misdiagnosed as neonatal sepsis.472

**ORGANOMEGALY**

The liver edge is palpable in premature infants and can extend to 2 cm below the costal margin in healthy term infants. Ashkenazi and colleagues473 evaluated liver size in healthy term infants examined within 24 hours of birth and again between 72 and 96 hours. Measurements ranged between 1.6 and 4.0 cm below the costal margin, and there was no significant difference between early and late examinations. Reiff and Osborn474 suggested that determination of liver span by palpation and percussion is a more reliable technique than identifying the liver projection below the costal margin. Hepatomegaly is a common sign of in utero infections and of some noninfectious conditions such as cardiac failure and metabolic diseases, including galactosemia and glycogen storage disease. Tender hepatomegaly can be a sign of bacterial liver abscess in neonates, a potential complication of misplaced central umbilical catheters.129 Splenomegaly is less common than hepatomegaly and infrequently is mentioned in reports of bacterial sepsis of the newborn.475

Lymph nodes infrequently are palpable in newborns unless they are infected with viruses, spirochetes, or protozoa. Bamji and colleagues476 examined 214 healthy neonates in New York and identified palpable nodes at one or more sites in one third of the infants. Embree and Muriithi477 examined 66 healthy, term Kenyan neonates during
the first 24 hours of life and found palpable axillary nodes (27.7%) but no palpable inguinal nodes. Adenopathy is a sign of congenital infection caused by rubella virus, T. gondii, T. pallidum, and enteroviruses. Adenitis can occur in drainage areas involved with bacterial soft tissue infection. Although adenopathy is not an important sign of systemic bacterial infection in neonates, cellulitis-adenitis syndrome, a rare clinical manifestation of late-onset GBS infection in infants, is a condition in which local inflammation can be the only initial sign of sepsis that can include concurrent meningitis.478,479 Recently, cellulitis-adenitis syndrome was reported in a neonate with GAS sepsis.480

**GASTROINTESTINAL SIGNS**

Gastrointestinal disturbances, including poor feeding, regurgitation or vomiting, large gastric residuals in infants fed by tube, diarrhea, and abdominal distention, are common and significant early signs of sepsis. The first indications of illness can be a change in feeding pattern or lethargy during feedings.

**SKIN LESIONS**

A variety of skin lesions can accompany bacteremia, including cellulitis, abscess, petechiae, purpuric lesions, sclerema, erythema multiforme, and ecthyma.

**NEUROLOGIC SIGNS**

The onset of meningitis in the neonate is accompanied by identical signs of illness, as observed in infants with sepsis. Meningitis can be heralded by increasing irritability, alteration in consciousness, poor tone, tremors, lip smacking, or twitching of facial muscles or an extremity. Seizures were present in 31% of the infants reviewed in Table 6-11, but Volpe154 identified seizures, in many cases subtle, in 75% of infants with bacterial meningitis. Approximately one half of the seizures were focal, and at their onset, they usually were subtle. Focal signs, including hemiparesis, horizontal deviation of the eyes, and cranial nerve deficits involving the seventh, third, and sixth cranial nerves, in that order of frequency, can be identified.154 Because cranial sutures in the neonate are open and allow for expansion of the intracranial contents and for increasing head size, a full or bulging fontanelle can be absent.353,481 The presence of a bulging fontanelle is not related to gestational age. Among 72 newborns with gram-negative enteric bacillary meningitis, a bulging fontanelle was seen in 8% and 17% of term and preterm infants, respectively.24 Nuchal rigidity, an important sign in older children and adults, is uncommon in neonates.24

In addition to the physical findings observed in infants with meningitis, several investigators have reported the occurrence of fluid and electrolyte abnormalities associated with inappropriate antidiuretic hormone secretion, including hyponatremia, decreased urine output, and increased weight gain.437,443 On occasion, the onset of meningitis has been followed by a transient or persistent diabetes insipidus.483

Early clinical signs of brain abscess in the newborn are subtle and frequently unnoticed by the physician or parent. Presenting signs include those of increased intracranial pressure (e.g., emesis, bulging fontanelle, enlarging head size, separated sutures), focal cerebral signs (e.g., hemiparesis, focal seizures), and acute signs of meningitis. Of six infants with brain abscesses described by Hoffman and colleagues,434 two were febrile, two had seizures, and five had increased head size.

Other focal infections in the nervous system include pneumococcal endophthalmitis in a neonate with meningitis,482 pseudomonal endophthalmitis in a premature neonate with LOS,483 and epidural abscess caused by S. aureus.484,485

**Diagnosis**

The diagnosis of systemic infection in the newborn is difficult to establish on the basis of clinical findings alone. A history of one or more risk factors for neonatal sepsis associated with the pregnancy and delivery often is associated with early-onset infection, but there can be no clues before the onset of subtle signs in the term infant who develops LOS. The extensive list of conditions that must be considered in the differential diagnosis for the various signs that are associated with sepsis or meningitis and noninfectious conditions is given in Box 6-1. Laboratory tests to assist in the diagnosis of sepsis are discussed in Chapter 36, with recent explorations into the utility of various novel tools, such as acute phase reactants (e.g., CRP and procalcitonin), cytokines, and cell surface markers.486

**MATERNAL HISTORY**

Many infants, particularly those born prematurely, who develop systemic infection just before or shortly after delivery, are born to women who have one or more risk features for early-onset sepsis in their infants. These features include preterm labor, premature rupture of the membranes at any time during gestation, prolonged rupture of membranes, chorioamnionitis, prolonged labor, intrauterine scalp electrodes, and traumatic delivery. In 2010, the CDC revised its guidelines for the prevention of perinatal GBS disease,487 a policy endorsed by the American Academy of Pediatrics (AAP)488 and the American College of Obstetrics and Gynecology (ACOG).489

Per these recommendations, intrapartum antibiotic prophylaxis is recommended for pregnancies with

1. Previous infant with invasive GBS disease
2. GBS bacteruria during any trimester of the current pregnancy
3. Positive GBS vaginal-rectal screening culture in late gestation (35-37 weeks) during current pregnancy
4. Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following:
   a. Delivery at less than 37 weeks of gestation
   b. Amniotic membrane rupture greater than or equal to 18 hours
   c. Intrapartum temperature greater than or equal to 100.4°F (≥38.0°C)

Conversely, intrapartum GBS prophylaxis is NOT indicated for pregnancies with
1. GBS colonization or GBS bacteriuria during a previous pregnancy, unless an indication for GBS prophylaxis is present for current pregnancy
2. Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors
3. Cesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age

MICROBIOLOGIC TECHNIQUES

Isolation of microorganisms from a usually sterile site, such as the blood, CSF, urine, other body fluids (e.g., peritoneal, pleural, joint, middle ear), or tissues (e.g., bone marrow, liver, spleen) remains the most valid method of diagnosing bacterial sepsis. Infectious agents cultured from the nose, throat, external auditory canal, skin, umbilicus, or stool indicate colonization and can include organisms that cause sepsis, but isolation of a microorganism from these sites does not establish invasive systemic infection. The limited sensitivity, specificity, and predictive value of body surface cultures in a NICU was documented by Evans and colleagues using a database of 24,584 cultures from 3371 infants. These investigators strongly discouraged the use of cultures from these sites in diagnosing neonatal sepsis because of their poor correlation with the pathogen in the blood and their expense.

Culture of Blood

Isolation of a pathogenic microorganism from the blood or other body fluid is the only method to definitively establish the diagnosis of neonatal bacteremia/sepsis.

Methods. Technology has evolved from manually read, broth-based methods to continuously monitored, automated blood-culture systems that use enriched media for processing of blood-culture specimens. Automated and semiautomated systems for continuous blood-culture monitoring are standard in laboratories in the United States. Before the widespread use of automated blood-culture systems, lysis direct plating was the most often used method of isolating bacteria. Positive cultures were recognized by growth of colonies on agar and provided a rapid means to obtaining quantitative blood-culture results from pediatric patients. St. Germe and colleagues used this technique to investigate the distinction of sepsis from contamination in cultures of blood growing CoNS; true CoNS infection is unlikely in infants with birth weight greater than 2000 g and gestation greater than 34 weeks.

Time to Detection of a Positive Blood Culture. Bacterial growth is evident in most cultures of blood from neonates within 48 hours. With use of conventional culture techniques and subculture at 4 and 14 hours, only 4 of 105 cultures that had positive results (1 GBS and 3 S. aureus) required more than 48 hours of incubation. By use of a radiometric technique (BACTEC 460, Becton Dickinson, Sparks, MD), 40 of 41 cultures that grew GBS and 15 of 16 cultures with E. coli were identified within 24 hours. Controlled experiments suggest that delayed entry of the collected blood-culture bottle into the automated blood-culture machine can significantly prolong the time to positivity for common newborn pathogens.

Optimal Number of Cultures. The optimal number of cultures to obtain for the diagnosis of bacteremia in the newborn remains uncertain. A single blood culture from an infant with sepsis can be negative, but most studies suggest a sensitivity of 90% or slightly more. Sprunt suggested the use of two blood cultures “not primarily to increase the yield of organisms…” but to “minimize the insecurity and debates over the meaning of the findings.” In a study by Struthers and colleagues, it was estimated that in 5% of neonates a second blood culture failed to substantiate the presence of CoNS, leading to an 8% reduction in antibiotic use. In the high-risk neonate, there is no doubt the need to initiate therapy promptly can make this practice difficult.

Optimal Volume of Blood. The optimal volume of blood needed to detect bacteremia in neonates has not been determined. Neal and colleagues evaluated the volume of neonatal blood submitted for culture by physicians who were unaware of the study and found that the mean blood volume per patient was 1.05 mL. Dietzman and coworkers suggested that 0.2 mL of blood was sufficient to detect bacteremia caused by E. coli. The relationship between colony counts of E. coli from blood cultures from infants with sepsis and meningitis and mortality was evaluated. Meningitis occurred only in neonates with more than 1000 colonies of E. coli/mL of blood. These data of Dietzman and associates are supported by experimental results indicating that common pediatric pathogens can be reliably recovered from 0.5 mL of blood even when cultured at blood-to-broth ratios of 1:100. More recent studies have found that in the circumstance of low-inoculum bacteremia (<10 colony-forming units/mL of blood), the collection of only 0.5 mL of blood proved inadequate for the reliable detection of common pathogens. It appears that if one blood culture is to be collected before antimicrobial therapy is initiated, a volume of 1 mL or more will ensure the greatest sensitivity.

Cultures of Blood From Umbilical Vessels and Intravascular Catheters. Umbilical vessel and intravascular catheters are essential in the care of neonates in the ICU and are preferred blood-culture sampling sites. Results of cultures of blood obtained from indwelling umbilical or central venous catheters can present ambiguities in interpretation (e.g., contamination versus catheter colonization vs. systemic infection). Obtaining blood cultures from a peripheral vessel and catheters in the ill-appearing neonate is useful in the interpretation of results. A recent prospective study of semiquantitative catheter tip cultures in a Brazilian NICU found that a cutoff point of approximately 100 colony forming units was predictive of clinically significant catheter-related infections, of which CoNS accounted for 75% of cases.

Distinguishing Clinically Important Bacteremia From Blood-Culture Contamination. The increased use of intravascular catheters in neonates has resulted in an increase in the incidence of bacteremia, particularly that
caused by CoNS, and uncertainty regarding the significance of some results. Investigators have considered criteria based on clinical signs and microbiologic factors.

Yale investigators\(^6\) used the following criteria to define the role of commensal organisms in neonatal sepsis: one major clinical sign, such as apnea, bradycardia, core temperature greater than 38.0\(^\circ\) C or less than 36.5\(^\circ\) C documented at the time the blood culture was obtained, plus another blood culture positive for the same organism obtained within 24 hours of the first or an intravascular access device in place before major clinical signs occurred. Some microbiologic features can be useful in differentiating sepsis from contamination:

1. **Time to growth in conventional media**: The longer the time needed to detect growth (>2-3 days), the more likely that skin or intravascular line contamination was present.

2. **Number of cultures positive**: If peripheral and intravascular catheter specimens are positive, the presence of the organism in the blood is likely; if the catheter specimen alone is positive, intravascular line colonization may have occurred; if multiple cultures from an indwelling vascular catheter are positive or if a single culture is positive and the patient has had a clinical deterioration, a bloodstream infection must be presumed.

3. **Organism type**: Organisms that are part of skin flora (e.g., diphtheroids, nonhemolytic streptococci. CoNS) suggest contamination in certain cases as described previously, whereas known bacterial pathogens must be considered to be associated with sepsis. Contamination is more likely when multiple species grow in one blood-culture bottle, different species grow in two bottles, or only one of several cultures before or during antimicrobial therapy is positive.

4. **Clinical signs**: If the infant is well without use of antibiotics, growth of a commensal organism from a blood culture is more likely to be a contaminant.

In an attempt to resolve the question of sepsis versus contamination, investigators have used multiple-site blood cultures,\(^5\) comparisons of results of cultures of blood and cultures of skin at the venipuncture site,\(^1\) and quantitative blood cultures.\(^2\) These techniques are of investigational interest, but the results do not suggest that any one is of sufficient value to be adopted for clinical practice. Healy and colleagues\(^3\) suggest that isolation of CoNS of the same species or antimicrobial susceptibility from more than one blood culture or from one blood culture obtained from an indwelling catheter or a peripheral vessel and a normally sterile body site represents true infection if the patient is a premature infant with signs of clinical sepsis. In a recent study of premature neonates with birth weight less than 2000 g and gestation less than 34 weeks, total central lines placed, but not central line duration or presence in situ, predicted proved (OR, 3.5) and probable CoNS infection (OR, 2.7) by multivariate analysis, as did lethargy and gastric residuals.\(^4\) At present, management of the sick premature infant, especially the VLBW patient, with a positive blood culture for CoNS requires that the organism be considered a pathogen and managed with appropriate antimicrobial agents. If the infant is well, the microbiologic results given earlier should be considered in the decision to continue or discontinue use of an antimicrobial agent. Another culture of blood should be obtained when the initial culture result is ambiguous.

### Buffy-Coat Examination

The rapid diagnosis of bacteremia by identification of microorganisms in the buffy leukocyte layer of centrifuged blood is a method used for many years and has been evaluated for use in newborn infants.\(^5\) By using Gram and methylene blue stains of the buffy-coat preparation, immediate and accurate information was obtained for 37 (77\%) of 48 bacteremic, clinically septic infants in the four studies.\(^6\) Positive results were found for gram-positive and gram-negative organisms. In contrast to findings reported for adult populations,\(^7\) there were no false-positive results among almost 200 infants with negative blood cultures. Failure to identify organisms was attributed to extreme neutropenia in several patients.

The large inoculum of microorganisms in the blood of neonates with sepsis most probably explains the excellent sensitivity of leukocyte smears. Smears can be positive with as few as 50 colonies/mL of S. aureus in the peripheral blood; approximately 50\% of neonates with E. coli bacteremia have higher concentrations.\(^8\) Candida and S. epidermidis septicemia in young infants also has been diagnosed by this method.\(^9\) Strom reported that bacteria were identified in peripheral blood smears in 17 of 19 infants with septicemia. However, Rodwell and associates\(^10\) were able to identify bacteria in direct blood smears for only 4 of 24 bacteremic neonates. It is likely that the disparity in these results reflects differences in patient populations, or distribution of etiologic agents or both. The buffy-coat examination of blood smears has become infrequently used in laboratories since the introduction of automated systems for continuous blood-culture monitoring.

### Culture of Urine

Infants with sepsis can have a urinary tract origin or a concomitant urinary tract infection. The yield from culture of urine is low in early-onset sepsis and most often reflects metastatic spread to the bladder from the bacteremia, but in late-onset infection, the yield is substantially higher. Visser and Hall\(^11\) found positive cultures of urine in only 1.6\% of infants with early-onset sepsis compared with 7.4\% of infants with LOS. DiGeronimo\(^12\) performed a chart review of 146 clinically septic infants who had cultures of blood and urine. Of 11 infants with positive blood cultures, only 1 infant with GBS bacteremia had a positive urine culture. These data suggest that cultures of urine yield very limited information about the source of infection in infants with signs of sepsis before age 7 days. In contrast, it is apparent that urine should be collected for culture from infants with suspected LOS before initiation of antimicrobial therapy. Of interest, the presence of elevated leukocyte counts (≥10/ high-power field) in urine of infants younger than 90 days is an accurate predictor of urinary tract infections complicated by bacteremia.\(^13\)

Because of the difficulty in collecting satisfactory clean-voided specimens of urine from the newborn, bladder catheterization or suprapubic needle aspiration of bladder urine frequently is performed. These methods are simple and safe, and suprapubic bladder aspiration avoids the ambiguities inherent in urine obtained by other
methods. If a suprapubic aspirate cannot be performed for technical or medical reasons, catheterization is a satisfactory method of obtaining urine, although ambiguous results can occur because of contamination from the urethra, especially in VLBW neonates. Of note, application of a clinical pain scoring system using a blinded observer and video recording found suprapubic aspiration to produce more discomfort than transurethral catheterization in female and circumcised male infants younger than 2 months.

Cultures of Tracheal Aspirates and Pharynx
Because of the association of pneumonia and bacteremia, investigators have sought to determine the risk of sepsis on the basis of colonization of the upper respiratory tract. Lau and Hey found that among ventilated infants who became septic, the same organism usually was present in cultures of tracheal aspirate and blood. However, growth of a bacterial pathogen from a tracheal aspirate culture does not predict which infants will develop sepsis. Similarly, cultures of the pharynx or trachea do not necessarily predict the causative organism in the blood of a neonate with clinical sepsis. A review of the literature by Srinivasan and Vidyasagar suggest endotracheal aspirates are of poor sensitivity (≈50%), modest specificity (≈80%) and poor positive predictive value. Unless the patient has a change in respiratory status documented clinically and radiographically, routine use of cultures from the pharynx or trachea provide low diagnostic yield and seem unjustified given their expense.

Diagnostic Needle Aspiration and Tissue Biopsy
Direct aspiration of tissues or body fluids through a needle or catheter is used for the diagnosis of a wide variety of infectious and noninfectious diseases. Aspiration of an infectious focus in lung, pleural space, middle ear, pericardium, bones, joints, abscess, and other sites provides immediate and specific information to guide therapy. Biopsy of the liver or bone marrow can assist in diagnosing occult infections, but this rarely is necessary.

Autopsy Microbiology
Two factors must be considered in interpreting bacterial cultures obtained at autopsy: The frequent isolation of organisms usually considered to be nonpathogenic and the difficulty of isolating fastidious organisms such as anaerobic bacteria. To minimize these problems, it is important that specimens be collected with proper aseptic technique and as early as possible after death.

It is a common belief that organisms in the intestinal and respiratory tracts gain access to tissues after death, but it also is possible that bacteremia occurs shortly before death and is not a postmortem phenomenon. Eisenfeld and colleagues identified the same organisms in specimens obtained before and within 2 hours after death. Confusion in the interpretation of results of bacteriologic cultures often is obviated by the review of slides prepared directly from tissues and fluids. If antimicrobial treatment was administered before death, organisms can be observed on a smear even though they are not viable. Pathogens would be expected to be present in significant numbers and accompanied by inflammatory cells, whereas contaminants or organisms that invade tissues after death, if they are seen, would be present in small numbers with no evidence of an inflammatory process.

Rapid Techniques for Detection of Bacterial Antigens in Body Fluid Specimens
In the 1970s, the limulus lysate assay for detection of endotoxin produced by gram-negative bacteria based on a gelation reaction between lysates of Limulus (horseshoe crab) amebocytes and bacterial endotoxin was investigated for diagnosis of neonatal meningitis with equivocal results. Counterimmunoelectrophoresis also was used successfully for detecting the capsular polysaccharide antigens of various pathogenic bacteria, including Staphylococcus epidermidis, Neisseria meningitidis, Haemophilus influenzae, and Group B streptococci (GBS). Latex agglutination assays have been shown to be of potential benefit in early detection of bacterial antigens in the CSF of patients with acute meningitis, which may be of increased importance in the era of intrapartum antibiotic prophylaxis and its potential interference with culture yield. Among the prevalent bacterial pathogens in neonatal infections, only GBS is routinely analyzed by latex agglutination. However, Neisseria meningitidis group B shares a common capsular antigen with the neonatal meningitis pathogen Escherichia coli serotype K1, which should allow cross-identification of the latter by using a meningococcal latex reagent.

The sensitivity of latex agglutination methods for identifying infants with GBS meningitis varies between 73% and 100% for CSF and 75% and 84% for urine. Possible cross-reactions have occurred when concentrated urine was tested. The GBS cell wall antigen can occasionally cross react with those from S. pneumoniae, CoNS, enterococci, and gram-negative enteric bacteria, including Proteus mirabilis and E. cloacae. False-positive results in urine for a positive latex agglutination test for GBS often were caused by contamination of bag specimens of urine with the streptococci from rectal or vaginal colonization.

The poor specificity of GBS antigen detection methods used with urine led to the U.S. Food and Drug Administration (FDA) recommendation in 1996 that these methods not be used except for testing of CSF and serum.

Lumbar Puncture and Examination of Cerebrospinal Fluid
Because meningitis can accompany sepsis with no clinical signs to differentiate between bacteremia alone and bacteremia with meningitis, a lumbar puncture (LP) should be considered for examination of the CSF in any neonate before initiation of therapy. Up to 15% of infants with sepsis have accompanying meningitis. The overall incidence of bacterial meningitis is less than 1 case per 1000 infants, but the incidence for LBW (<2500 g) infants or premature infants is severalfold higher than that for term infants. Data from the NICHD Neonatal Research Network surveyed 9641 VLBW infants who survived 3 days or more: 30% had one or more LPs and 5% of those who had a LP had late-onset
for the diagnosis of some noninfectious CNS diseases in neonates (e.g., intracranial hemorrhage), cranial ultrasonography, and, occasionally, computed tomography or magnetic resonance imaging are the techniques of choice. For infants with hypoxic-ischemic encephalopathy, LP should be considered only for those infants in whom meningitis is a possible diagnosis.

Some investigators suggest that too many healthy term infants have a diagnostic evaluation for sepsis, including LP, based solely on maternal risk features and that the LP rarely provides clinically useful information. Other investigators have questioned the role of an admission LP in the premature infant with respiratory distress and found that the yield of the procedure is very low.\(^{531-533}\)

Of more than 1700 infants with respiratory distress syndrome evaluated for meningitis, bacterial pathogens were identified in the CSF of only 4. Three of the 4 infants with meningitis were bacteremic with the same pathogen.\(^{533}\)

A large, retrospective study assessed the value of LP in the evaluation of suspected sepsis during the first week of life and found that bacteria were isolated from 9 of 728 CSF specimens, but only 1 infant was believed to have bacterial meningitis.\(^{534}\) Fielkow and colleagues\(^ {535}\) found no cases of meningitis among 284 healthy appearing infants who had a LP performed because of maternal risk factors, whereas 2.5% of 799 neonates with clinical signs of sepsis had meningitis regardless of maternal risk factors. In summary, the value of a LP has been established for infants with clinical signs of sepsis, but LP performed because of maternal risk features in a healthy appearing neonate is less likely to be useful.

The considerations are quite different for the VLBW neonate (400-1500 g), as documented in a recent study by Stoll and colleagues\(^ {536}\) performed through the NICHD Neonatal Research Network. A full one third (45/134) of these high-risk neonates with meningitis have negative blood cultures. Lower gestational age and prior sepsis were important risk factors for development meningitis, which carried a significant risk of mortality compared with uninfected infants (23% vs. 2%). These results indicate the critical importance of LP and suggest that meningitis may be significantly underdiagnosed in the VLBW population.\(^ {536}\)

**Method of Lumbar Puncture.** Lumbar puncture is more difficult to perform in the neonate than in the older child or adult; traumatic LPs resulting in blood in the CSF are more frequent, and care must be taken in the infant who is in respiratory distress. Gleason and colleagues\(^ {537}\) suggest that the procedure be performed with the infant in the upright position or, if performed in the flexed position, be modified with neck extension. Pinheiro and associates\(^ {538}\) evaluated the role of locally administered lidocaine before LP and found that the local anesthesia decreased the degree of struggling of the infant. However, other investigators have concluded that local anesthesia failed to influence physiologic changes in the neonate undergoing LP.\(^ {539}\) Fiser and colleagues\(^ {540}\) suggest that the administration of oxygen before LP prevents most hypoxemia resulting from this procedure in infants.

The physician can choose to withhold or delay LP in some infants who would be placed at risk for cardiac or respiratory compromise by the procedure. Weisman and colleagues\(^ {541}\) observed that transient hypoxemia occurred during LP performed in the lateral position (i.e., left side with hips flexed to place knees to chest) but occurred less frequently when the infant was in a sitting position or modified lateral position (i.e., left side with hips flexed to 90 degrees). Reasons for withholding LP in older children, such as signs of increased intracranial pressure, signs of a bleeding disorder, and infection in the area that the needle will traverse to obtain CSF, are less likely to be concerns in the neonate.

Ventricular puncture should be considered in the infant with meningitis who does not respond clinically or microbiologically to antimicrobial therapy because of ventriculitis, especially with obstruction between the ventricles and lumbar CSF. Ventriculitis is diagnosed on the basis of elevated white blood cell count (>100 cells/mm\(^3\)) or identification of bacteria by culture, Gram stain, or antigen detection. Ventricular puncture is a potentially hazardous procedure and should be performed only by a physician who is an expert in the technique.

**If a Lumbar Puncture is Not Performed.** Is it sufficient to culture only blood and urine for the diagnosis of neonatal bacterial meningitis? Visser and Hall\(^ {542}\) demonstrated that the blood culture was sterile when the CSF yielded a pathogen in 6 (15%) of 39 infants with bacterial meningitis. Franco and colleagues\(^ {543}\) reported that in 26 neonates with bacterial meningitis, only 13 had a positive blood culture. In surveys from two large data bases, NICUs managed by the Pediatric Medical Group (Sunrise, FL)\(^ {544}\) and the NICHD Neonatal Research Network\(^ {545}\) results were similar: One third of infants at 34 or more weeks’ estimated gestation with meningitis and one third of VLBW neonates with meningitis had negative blood cultures. A significant number of infants with meningitis will not have this diagnosis established unless a LP is performed.

Ideally the LP should be performed before the initiation of antimicrobial therapy, but there are alternative strategies for infants who may not tolerate the procedure. If the physician believes that LP would endanger the infant with presumed sepsis and meningitis, therapy should be initiated after blood (and urine for late-onset illness) is obtained for culture. After the infant is stabilized, LP should be performed. Even several days after the start of antibiotic therapy, CSF pleocytosis and abnormal CSF chemistry assays usually should identify the presence or absence of an inflammatory reaction, although CSF culture may be sterile.

**Examination of Cerebrospinal Fluid.** The cell content and chemistry of the CSF of healthy newborn infants differ from those of older infants, children, and adults (Table 6-12). The values vary widely during the first weeks of life, and the normal range must be considered in evaluation of CSF in infants suspected to have meningitis.\(^ {546-548}\) The cell content in the CSF of a neonate is higher than that in older infants. A recent analysis calculated the median CSF leukocyte count was significantly higher in infants who were aged less than or equal to 28 days (3/µL, 95th percentile: 19/µL) than in infants who were aged 29 to 56 days (2/µL, 95th percentile: 9/µL; \(P < .0001\)).\(^ {549}\) Neutrophils often are present in the CSF of normal newborns, whereas more than a single neutrophil in the CSF of older infants or children should be
considered abnormal. Similarly, protein concentration is higher in preterm than in term infants and highest in VLBW infants\(^568\) (Table 6-13). In term infants, the total protein concentration decreases with age, reaching values of healthy older infants (\(<40\) mg/dL) before the third month of life. In LBW or preterm infants, CSF leukocyte and protein concentrations decline with postnatal age and may not fall within normal values for older infants for several months after birth.\(^570\) CSF glucose levels are lower in neonates than in older infants and can be related to the lower concentrations of glucose observed in blood. Healthy term infants can have blood glucose levels as low as 20 mg/dL.\(^568\) The physiologic basis for the higher glucose in CSF than in blood during delivery and an increased permeability of the blood-brain barrier.

The concentration of protein can be low (<30 mg/dL) or very high (≥1000 mg/dL). CSF glucose levels are lower in neonates than in older infants and can be related to the lower concentrations of glucose observed in blood. Healthy term infants can have blood glucose levels as low as 100 mg/dL in the CSF and, if clinical signs indicate, to obtain paired serum samples for serologic assays and viral cultures from body fluids or tissues for congenital CNS infections (i.e., T. gondii, rubella virus, cytomegalovirus, herpes simplex virus, human immunodeficiency virus, and T. pallidum).

In newborns with bacterial meningitis, there can be thousands of white blood cells in the CSF, and neutrophils predominate early in the course of the disease.\(^21,564\) The number of CSF leukocytes can vary greatly in infants with both gram-negative and gram-positive meningitis. The median number of cells/mm\(^3\) in the CSF of 98 infants with gram-negative meningitis was more than 1000 (range, 6-40,000), whereas the median number of cells/mm\(^3\) in 21 infants with GBS meningitis was less than 100 (range, 8 to >10,000).\(^564\) The concentration of glucose in CSF usually is less than two thirds of the concentration in blood. The concentration of protein can be low (<30 mg/dL) or very high (≥1000 mg/dL). CSF parameters observed in the healthy term neonate can overlap with those observed in the infant with meningitis.

A Gram-stain smear of CSF should be examined for bacteria, and appropriate media should be inoculated with the CSF specimen. Sarff and colleagues\(^564\) detected organisms in Gram-stain smears of CSF in 83% of infants with GBS meningitis and in 78% of those with gram-negative meningitis. After initiation of appropriate antimicrobial therapy, gram-positive bacteria usually clear from the CSF within 36 hours, whereas in some patients with meningitis caused

### Table 6-12: Hematologic and Chemical Characteristics of Cerebrospinal Fluid in Healthy Newborns: Results of Selected Studies

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of Patients</th>
<th>Age (days)</th>
<th>White Blood Cells* (mm(^3)) Mean (range)</th>
<th>Neutrophils* (mm(^3)) Mean (range)</th>
<th>Glucose* (mg/dL) Mean (range)</th>
<th>Protein* (mg/dL) Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naidoo(^513) (1968)</td>
<td>135</td>
<td>1</td>
<td>12 (0-42)</td>
<td>7 (0-26)</td>
<td>48 (38-64)</td>
<td>73 (40-148)</td>
</tr>
<tr>
<td>20</td>
<td>7</td>
<td>3 (0-9)</td>
<td>2 (0-5)</td>
<td>55 (48-62)</td>
<td>47 (27-65)</td>
<td></td>
</tr>
<tr>
<td>Sarff(^565) (1976)</td>
<td>87</td>
<td>Most &lt; 7</td>
<td>8.2 ± 7.1, median 5 (0-32)</td>
<td>61</td>
<td>52 (34-119)</td>
<td>90 (20-170)</td>
</tr>
<tr>
<td>Bonadio(^565) (1992)</td>
<td>35</td>
<td>0-4 wk</td>
<td>11.0 ± 10.4, median 8.5</td>
<td>0.4 ± 1.4, median 0.15</td>
<td>46 ± 10.3</td>
<td>84 ± 45.1</td>
</tr>
<tr>
<td>40</td>
<td>4-8 wk</td>
<td>7.1 ± 9.2, median 4.5</td>
<td>0.2 ± 0.4, median 0</td>
<td>46 ± 10.0</td>
<td>59 ± 25.3</td>
<td></td>
</tr>
<tr>
<td>Ahmed(^566) (1996)</td>
<td>108</td>
<td>0-30</td>
<td>7.3 ± 13.9, median 4</td>
<td>0.8 ± 6.2, median 0</td>
<td>51.2 ± 12.9</td>
<td>64.2 ± 24.2</td>
</tr>
</tbody>
</table>

*Expressed as mean with range (number in parentheses) or ± standard deviation unless otherwise specified.


### Table 6-13: Hematologic and Chemical Characteristics of Cerebrospinal Fluid in Healthy Very-Low-Birth-Weight Infants

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>Age (days)</th>
<th>No. of Samples</th>
<th>Red Blood Cells (mm(^3)) Mean (range)</th>
<th>White Blood Cells (mm(^3)) Mean (range)</th>
<th>Polymorphonuclear Leukocytes (%) Mean (range)</th>
<th>Glucose (mg/dL) Mean (range)</th>
<th>Protein (mg/dL) Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>0-7</td>
<td>6</td>
<td>335 (0-1780)</td>
<td>3 (1-8)</td>
<td>11 (0-50)</td>
<td>70 (41-89)</td>
<td>162 (115-222)</td>
</tr>
<tr>
<td>1000-1500</td>
<td>8-28</td>
<td>17</td>
<td>1465 (0-19,050)</td>
<td>4 (0-14)</td>
<td>8 (0-66)</td>
<td>68 (33-217)</td>
<td>159 (95-370)</td>
</tr>
<tr>
<td>29-84</td>
<td>15</td>
<td>808 (0-6850)</td>
<td>4 (0-11)</td>
<td>2 (0-36)</td>
<td>49 (29-90)</td>
<td>137 (76-260)</td>
<td></td>
</tr>
<tr>
<td>&lt;1000</td>
<td>0-7</td>
<td>8</td>
<td>407 (0-2450)</td>
<td>4 (1-10)</td>
<td>4 (0-28)</td>
<td>74 (50-96)</td>
<td>136 (85-176)</td>
</tr>
<tr>
<td>1000-1500</td>
<td>8-28</td>
<td>14</td>
<td>1101 (0-9750)</td>
<td>7 (0-44)</td>
<td>10 (0-60)</td>
<td>59 (39-109)</td>
<td>137 (54-227)</td>
</tr>
<tr>
<td>29-84</td>
<td>11</td>
<td>661 (0-3800)</td>
<td>8 (0-23)</td>
<td>11 (0-48)</td>
<td>47 (31-76)</td>
<td>122 (45-187)</td>
<td></td>
</tr>
</tbody>
</table>


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by gram-negative enteric bacilli cultures can remain positive for many days.\textsuperscript{567}

Microorganisms can be isolated from CSF that has normal white blood cell and chemistry test values. Visser and Hall\textsuperscript{561} reported normal CSF parameters (cell count <25; protein level <200 mg/dL) in 6 (15\%) of 39 infants with culture-proven meningitis. Subsequent examination of the CSF identified an increase in the number of cells and protein level. Presumably, the initial LP was performed early in the course of meningitis before an inflammatory response occurred. Other investigators reported isolation of enterovirus\textsuperscript{577} and S. pneumoniae\textsuperscript{572} from the CSF of neonates in the absence of pleocytosis.

Identification of bacteremia without meningitis, defined by the absence of pleocytosis or isolation of a pathogen from culture of CSF, can be followed by meningeal inflammation on subsequent examinations. Sarman and colleagues\textsuperscript{573} identified six infants with gram-negative bacteremia and initial normal CSF who developed evidence of meningeal inflammation 18 to 59 hours after the first examination. Although the investigators suggest that a diagnosis of gram-negative bacteremia in the neonate warrants repeat LP to identify the optimal duration of therapy, this recommendation could be broadened to include all infants with bacteremia and initial negative studies of CSF. Dissemination of the organisms from the blood to the meninges can occur after the first LP before sterilization of the blood by appropriate antimicrobial therapy occurs. This is especially likely to occur in neonates with intense bacteremia where sterilization by \(\beta\)-lactam agents (i.e., third-generation cephalosporins) is inoculum dependent.

Smith and colleagues\textsuperscript{574} recently performed a large cohort study of CSF parameters in preterm neonates with meningitis. Analysis of first LPs of 4632 neonates of less than 34 weeks of gestation found significant differences in culture-proven meningitis cases versus controls in their CSF leukocyte count (110 cells/mm\(^3\) vs. 6 cells/mm\(^3\)), total protein (217 mg/dL vs. 130 mg/dL), and glucose (43 mg/dL vs. 49 mg/dL). However the sensitivity for predicting meningitis was only 71\% for CSF leukocyte count greater than 25 cells/mm\(^3\), 61\% for CSF protein greater than 170 mg/dL, and 32\% for CSF glucose less than 24 mg/dL. The positive predictive value for each of these parameters was low (4%-10\%), emphasizing the critical need for CSF culture to establish the diagnosis of meningitis. In terms of excluding meningitis, a normal CSF protein was the most useful parameter because 96\% of premature neonates with meningitis had a CSF protein greater than 90 mg/dL.\textsuperscript{574}

Investigators have sought a sensitive and specific CSF metabolic determinant of bacterial meningitis with little success. Among products that have been evaluated and found to be inadequate to distinguish bacterial meningitis from other neurologic disease (including cerebroventricular hemorrhage and asphyxia) are \(\gamma\)-aminobutyric acid,\textsuperscript{575} lactate dehydrogenase,\textsuperscript{576} and creatine kinase brain isoenzyme.\textsuperscript{577} Cyclic-3',5'-adenosine monophosphate was elevated in the CSF of neonates with bacterial meningitis, compared with the CSF of infants who had nonbacterial meningitis or a control group.\textsuperscript{578} Elevated CSF concentrations of CRP have been reported for infants with bacterial meningitis who were older than 4 weeks\textsuperscript{579,580}; however, the test was found to be of no value in neonates.\textsuperscript{581} Current investigations of the proinflammatory cytokines IL-6 and IL-8 indicate that there is a cytokine response in the CSF after birth asphyxia and that these assays are not useful in detecting the infant with meningitis.\textsuperscript{582,583}

**The Traumatic Lumbar Puncture.** A traumatic LP can result in blood in the CSF and can complicate the interpretation of the results for CSF white blood cell count and chemistries.\textsuperscript{584} Schwersenski and colleagues\textsuperscript{554} found that 13.8\% of 712 CSF specimens obtained during the first week of life were bloody and that an additional 14.5\% were considered inadequate for testing.

If the total number of white blood cells compared with the number of red blood cells exceeds the value for whole blood, the presence of CSF pleocytosis is suggested. Some investigators have found that the observed white blood cell counts in bloody CSF were lower than would be predicted based on the ratio of white-to-red blood cells in peripheral blood; the white blood cells lyse more rapidly than red blood cells, or the number of white blood cells is decreased for other reasons.\textsuperscript{585-588} Several formulas have been used in an attempt to interpret cytologic findings in CSF contaminated by blood.\textsuperscript{589-591} However, none of the corrections applied to bloody CSF can be used with confidence for excluding meningitis in the neonate.\textsuperscript{592-594} In a cohort study of LPs performed at 150 neonatal units between 1997 and 2004, 39.5\% (2519/6374) were traumatic, and 50 of these infants turned out to have meningitis by culture. The authors found correction of the leukocyte count to account for blood contamination resulted in loss of sensitivity and only marginal gain in specificity and therefore would not aid in the diagnosis of bacterial (or fungal) meningitis.\textsuperscript{595}

Protein in CSF usually is elevated after a traumatic LP because of the presence of red blood cells. It has been estimated that an increase of approximately 2.0 mg/dL in CSF protein occurs for every 1000 red blood cells/\(\mu\)L in neonates and infants,\textsuperscript{596} whereas a value of 1.1 mg/dL per 1000 red blood cells/\(\mu\)L applies in older children.\textsuperscript{597} The concentration of glucose does not appear to be altered by blood from a traumatic LP; a low CSF glucose concentration should be considered an important finding even when associated with a traumatic LP.

Because a “bloody tap” is difficult to interpret, it can be valuable to repeat the LP 24 to 48 hours later. If the results of the second LP reveal a normal white blood cell count, bacterial meningitis can be excluded. Even if performed without trauma or apparent bleeding, CSF occasionally can be ambiguous because white blood cells can be elicited by the irritant effect of blood in the CSF.

**Brain Abscess.** Brain abscess is a rare entity in the neonate, usually complicating meningitis caused by certain gram-negative bacilli. The CSF in the infant with a brain abscess can demonstrate a pleocytosis of a few hundred cells with a mononuclear predominance and an elevated protein level. Bacteria may not be seen by Gram stain of the CSF if meningitis is not present. Sudden clinical deterioration and the appearance of many cells (>1000/mm\(^3\)), with a majority of polymorphonuclear cells, suggest rupture of the abscess into the CSF.
LABORATORY AIDS

Historically, aids in the diagnosis of systemic and focal infection in the neonate include peripheral white blood cell and differential counts, platelet counts, acute-phase reactants, blood chemistries, histopathology of the placenta and umbilical cord, smears of gastric or tracheal aspirates, and diagnostic imaging studies. New assays for diagnosis of early-onset sepsis, including serum concentrations of neutrophil CD11b, granulocyte colony-stimulating factor (G-CSF), II receptor antagonist, IL-6, IL-7, IL-8, IL-1 receptor antagonist, procalcitonin, serum amyloid A, and prohepcidin show promise for increased sensitivity and specificity compared with other laboratory assessments, such as white blood cell count, absolute neutrophil count, and acute-phase reactants. However, proinflammatory cytokines, including IL-1, II-6, and tumor necrosis factor-α (TNF-α), have been identified in serum and CSF in infants after perinatal asphyxia, raising doubts about the specificity of some of these markers.

Recently, attention has focused on the use of real-time PCR technologies, often based on the 16S ribosomal RNA sequence of leading pathogens, as a tool for the accelerated culture-independent diagnosis of neonatal sepsis. Compared with the gold standard of blood culture, the evaluation of sensitivity and specificity of these PCR technologies and their consequent clinical utility has ranged from equivocal to highly promising. A recent study of multiplexed PCR, using 100 μL neonatal blood volume, demonstrated a higher sensitivity (90.5%) compared with blood culture (71.4%), including clinical sepsis cases, even though it had a lower specificity (80.0% vs. 100.0%). Continued rapid advances in nucleic acid–based diagnostics are certain to be explored in this important clinical arena.

Management

If the maternal history or infant clinical signs suggest the possibility of neonatal sepsis, blood, CSF (all infants), and cultures of urine and other clinically evident focal sites should be collected (all infants with suspected late-onset infection). If respiratory abnormalities are apparent or respiratory status has changed, a radiograph of the chest should be performed. Because the clinical manifestations of sepsis can be subtle, the progression of the disease can be rapid, and the mortality rate remains high when compared with that for older infants with serious bacterial infection; thus empirical treatment should be initiated promptly. Many infants who have a clinical course typical of bacterial sepsis are treated empirically because of the imperfect sensitivity of a single blood culture in the diagnosis of sepsis.

CHOICE OF ANTIMICROBIAL AGENTS

Initial Therapy for Presumed Sepsis

The choice of antimicrobial agents for the treatment of suspected sepsis is based on knowledge of the prevalent organisms responsible for neonatal sepsis by age of onset and hospital setting as well as on their patterns of antimicrobial susceptibility. Initial therapy for the infant who develops clinical signs of sepsis during the first few days of life (early-onset disease) must include agents active against gram-positive cocci, particularly GBS, other streptococci, L. monocytogenes, and gram-negative enteric bacilli. Treatment of the infant who becomes septic while in the nursery after age 6 days (late-onset disease) must include therapy for hospital-acquired organisms, such as S. aureus, gram-negative enteric bacilli, CoNS (in the VLBW infant), and occasionally P. aeruginosa, as well as for maternally acquired etiologic agents.

GBS continue to demonstrate significant in vitro susceptibility to penicillins and cephalosporins. Of 3813 case isolates in active population-based surveillance conducted by the CDC between 1996 and 2003, all were sensitive to penicillin, ampicillin, cefazolin, and vancomycin. However, new reports in the United States and Japan have identified GBS strains with reduced β-lactam susceptibility and first-step mutations in the PBPs2 protein reminiscent of the emergence of β-lactam resistance in pneumococci decades ago. In the recent CDC surveillance, GBS resistance to clindamycin (15%) and erythromycin (30%) are also noted to be on the rise.

In vitro studies and experimental animal models of bacteremia and experimental animal models of pneumonia indicate that the bacterial activity of ampicillin and penicillin against GBS and L. monocytogenes is enhanced by the addition of gentamicin (synergy). Some physicians prefer to continue the combination of ampicillin and gentamicin for 48 to 72 hours, but once GBS is identified as the etiologic agent, the drug of choice for therapy is penicillin administered intravenously for the remainder of the treatment regimen. There are no clinical data to indicate that continuing an aminoglycoside in combination with a penicillin results in more rapid recovery or improved outcome for infected neonates.

Most strains of S. aureus that cause disease in neonates produce β-lactamase and are resistant to penicillin G and ampicillin. Many of these organisms are susceptible to the penicillinase-resistant penicillins, such as nafcillin, and to first-generation cephalosporins. Methicillin-resistant staphylococci that are resistant to other penicillinase-resistant penicillins and cephalosporins have been encountered in many nurseries in the United States. Antimicrobial susceptibility patterns must be monitored by surveillance of staphylococcal strains causing infection and disease in each NICU. Bacterial resistance must be considered whenever staphylococcal disease is suspected or confirmed in a patient, and empirical vancomycin therapy should be initiated until the susceptibility pattern of the organism is known. Virtually all staphylococcal strains isolated from neonates have been susceptible to vancomycin. Synergistic activity is provided by the combination of an aminoglycoside (see Chapter 14). Vancomycin- or glycopeptide-resistant S. aureus has been reported from Japan and the United States, but none of these strains has been isolated from neonates.

CoNS can cause systemic infection in VLBW infants and in neonates with or without devices such as an intravascular catheter or a ventriculoperitoneal shunt. Vancomycin is the drug of choice for treatment of serious CoNS infections.
If daily cultures from an indwelling device continue to grow CoNS, removal of the foreign material probably will be necessary to cure the infection.

*Enterococcus* species are only moderately susceptible to penicillin and highly resistant to cephalosporins. Optimal antimicrobial therapy for neonatal infections caused by *Enterococcus* includes ampicillin or vancomycin in addition to an aminoglycoside, typically gentamicin or tobramycin.

*L. monocytogenes* is susceptible to penicillin and ampicillin and resistant to cephalosporins. Ampicillin is the preferred agent for treating *L. monocytogenes*, although an aminoglycoside can be continued in combination with ampicillin if the patient has meningitis. Specific management of *L. monocytogenes* infection is discussed in Chapter 13.

The choice of antibiotic therapy for infections caused by gram-negative bacilli depends on the pattern of susceptibility for these isolates in the nursery that cares for the neonate. These patterns vary by hospital or community and by time within the same institution or community. Although isolates from neonates should be monitored to determine the emergence of new strains with unique antimicrobial susceptibility patterns, the general pattern of antibiotic susceptibility in the hospital is a good guide to initial therapy for neonates. The aminoglycosides, including gentamicin, tobramycin, netilmicin, and amikacin, are highly active in vitro against virtually all isolates of *E. coli*, *P. aeruginosa*, *Enterobacter*, *Klebsiella*, and *Proteus* spp.

**Role of Third-Generation Cephalosporins and Carbapenems**

The third-generation cephalosporins, cefotaxime, ceftriaxone, and ceftazidime, possess attractive features for therapy for bacterial sepsis and meningitis in newborns. These features include excellent in vitro activity against GBS and *E. coli* and other gram-negative enteric bacilli. Ceftazidime is highly active in vitro against *P. aeruginosa*. None of the cephalosporins is active against *L. monocytogenes* or *Enterococcus*, and activity against *S. aureus* is variable. These cephalosporins provide concentrations of drug at most sites of infection that greatly exceed the minimum inhibitory concentrations of susceptible pathogens, and there is no dose-related toxicity. Clinical and microbiologic results of studies of sepsis and meningitis in neonates suggest that the third-generation cephalosporins are comparable to the traditional regimens of penicillin and an aminoglycoside (see Chapter 37). Because ceftriaxone can displace bilirubin from serum albumin, it is not recommended for use in neonates unless it is the only agent effective against the bacterial pathogen. Meropenem is a broad-spectrum carbapenem antibiotic with extended-spectrum antimicrobial activity, including against *P. aeruginosa*, and excellent CSF penetration that appears safe and efficacious in the neonate for treatment of most nosocomial gram-negative pathogens.

The rapid development of resistance of gram-negative enteric bacilli when cefotaxime is used extensively for presumptive therapy for neonatal sepsis suggests that extensive use of third- or fourth-generation cephalosporins can lead to rapid emergence of drug-resistant bacteria in nurseries. Also of concern, recent studies have identified a principal risk factor for development of invasive infection with *Candida* and other fungi in preterm neonates to be extended therapy with third-generation cephalosporins.

Empirical use of cefotaxime in neonates should be restricted to those with evidence of meningitis or with gram-negative sepsis. Continued cefotaxime therapy should be limited to those infants with gram-negative meningitis caused by susceptible organisms or those with ampicillin-resistant enteric infections.

**CURRENT PRACTICE**

The combination of ampicillin and an aminoglycoside, usually gentamicin or tobramycin, is suitable for initial treatment of presumed early-onset neonatal sepsis. If there is a concern for endemic or epidemic staphylococcal infection, typically occurring beyond 6 days of age, the initial treatment of late-onset neonatal sepsis should include vancomycin.

The increasing use of antibiotics, particularly in NICUs, can result in alterations in antimicrobial susceptibility patterns of bacteria and can necessitate changes in initial empirical therapy. This alteration of the microbial flora in nurseries where the use of broad-spectrum antimicrobial agents is routine supports recommendations from the CDC for the judicious use of antibiotics. The hospital laboratory must regularly monitor isolates of pathogenic bacteria to assist the physician in choosing the most appropriate therapy. The clinical pharmacology and dosage schedules of the various antimicrobial agents considered for neonatal sepsis are provided in Chapter 37.

**CONTINUATION OF THERAPY WHEN RESULTS OF CULTURES ARE AVAILABLE**

The choice of antimicrobial therapy should be reevaluated when results of cultures and susceptibility tests become available. The duration of therapy depends on the initial response to the appropriate antibiotics but should be 10 days, with sepsis documented by positive culture of blood and minimal or absent focal infection. The usual duration of therapy for infants with meningitis caused by gram-negative enteric bacilli is 21 days. However, in complicated cases of meningitis caused by gram-negative enteric bacilli, GBS, or other pathogens, the duration of therapy is variable and is best determined in consultation with an infectious diseases specialist.

The third-generation cephalosporins cefotaxime, ceftriaxone, and ceftazidime have important theoretical advantages for treatment of sepsis or meningitis compared with therapeutic regimens that include an aminoglycoside. Unlike the aminoglycosides, third-generation cephalosporins are not associated with ototoxicity and nephrotoxicity. However, little toxicity from aminoglycosides occurs when use is brief or when continued for the duration of therapy, if serum trough levels are maintained at less than 2 μg/mL. Because cephalosporins have no dose-related toxicity, measurements of serum concentrations, obligatory with the use of aminoglycosides beyond 72 hours or in infants with renal insufficiency, are unnecessary. However, routine use of the cephalosporins for presumptive sepsis therapy in neonates often leads to problems with drug-resistant enteric organisms. Extensive use of the third-generation cephalosporins in the nursery could result in the emergence of resistance caused by derepression of chromosomally mediated β-lactamases. Cefotaxime is preferred to...
other third-generation cephalosporins for use in neonates because it has been used more extensively\textsuperscript{626-628} and because it does not affect the binding of bilirubin.\textsuperscript{635,636} Cefazidime or meropenem in combination with an aminoglycoside should be used in therapy for \textit{P. aeruginosa} meningitis because of their excellent in vitro activity and its good penetration into the CSF. Use of ceftriaxone in the neonate should be determined on a case-by-case basis because of its ability to displace bilirubin from serum albumin and result in biliary sludging.

**MANAGEMENT OF THE INFANT WHOSE MOTHER RECEIVED INTRAPARTUM ANTIMICROBIAL AGENTS**

Antimicrobial agents commonly are administered to women in labor who have risk factors associated with sepsis in the fetus, including premature delivery, prolonged rupture of membranes, fever, or other signs of chorioamnionitis or GBS colonization. Antimicrobial agents cross the placenta and achieve concentrations in fetal tissues that are parallel to concentrations achieved in other well-vascularized organs. Placental transport of antibiotics is discussed in more detail in Chapter 37.

Protocols for prevention of GBS infection in the newborn by administration of a penicillin to the mother were published in 1992 by ACOG\textsuperscript{637} and the AAP.\textsuperscript{638} These guidelines were revised in 1996 by the CDC,\textsuperscript{639} in 1997 by the AAP,\textsuperscript{640} and in 2002 by the CDC, AAP, and ACOG.\textsuperscript{642} Recent data suggest that nearly 50\% of women receive intrapartum chemoprophylaxis because of the presence of one or more risk factors for neonatal sepsis or because of a positive antenatal screening culture for GBS.\textsuperscript{643}

When ampicillin or penicillin is administered to the mother, drug concentrations in the fetus are achieved that are more than 30\% of the concentrations in the blood of the mother.\textsuperscript{644} Concentrations of penicillin, ampicillin, and cefazolin that are bactericidal for GBS are achieved in the amniotic fluid approximately 3 hours after completion of a maternal intravenous dose. Parenteral antibiotic therapy administered to a mother with signs of chorioamnionitis in labor essentially is treating the fetus early in the course of the intrapartum infection.\textsuperscript{645,646} However, for some infected fetuses, the treatment administered in utero is insufficient to prevent signs of early-onset GBS disease. Although maternal intrapartum prophylaxis has been associated with a 75\% decrease in the incidence of early-onset GBS disease since 1993,\textsuperscript{647-648} the regimen has had no impact on the incidence of late-onset disease.\textsuperscript{649}

The various algorithms prepared to guide empirical management of the neonate born to a mother with risk factors for GBS disease who received intrapartum antimicrobial prophylaxis for prevention of early-onset GBS disease focus on three clinical scenarios:\textsuperscript{647-650}

1. Infants who have signs of sepsis should receive a full diagnostic evaluation and should be treated, typically with ampicillin and gentamicin, until laboratory studies are available.
2. Infants born at 35 or more weeks of gestation who appear healthy and whose mothers received intrapartum prophylaxis with penicillin, ampicillin, or cefazolin for 4 or more days before delivery do not have to be evaluated or treated but should be observed in the hospital for 48 hours.
3. Infants who are less than 35 weeks of gestation, who appear healthy, and whose mothers received penicillin, ampicillin, or cefazolin for less than 4 hours before delivery should receive a limited evaluation, including a blood culture and a complete blood cell count with a differential count, and be observed for 48 hours in the hospital. The same management probably is necessary for infants of any gestation whose mothers received vancomycin for prophylaxis because nothing is known about the amniotic fluid penetration of this drug or its efficacy in preventing early-onset GBS disease.

The first two clinical scenarios are readily identified, but the third category often leads to controversy regarding optimal management. Recent recommendations for prevention and treatment of early-onset GBS infection are discussed in detail in Chapter 12.

Management of the infant born to a mother who received an antimicrobial agent within hours of delivery must include consideration of the effect of the drug on cultures obtained from the infant after birth. Intrapartum therapy provides some treatment of the infant in utero, and variable concentrations of drug will be present in the infant’s body fluids. If the infant is infected and the bacterial pathogen is susceptible to the drug administered to the mother, cultures of the infant can be sterile despite a clinical course suggesting sepsis.

**TREATMENT OF THE INFANT WHOSE BACTERIAL CULTURE RESULTS ARE NEGATIVE**

Whether or not the mother received antibiotics before delivery, the physician must decide on the subsequent course of therapy for the infant who was treated for presumed sepsis and whose bacterial culture results are negative. If the neonate appears to be well and there is reason to believe that infection was unlikely, treatment can be discontinued at 48 hours. If the clinical condition of the infant remains uncertain and suspicion of an infectious process remains, therapy should be continued as outlined for documented bacterial sepsis unless another diagnosis becomes apparent. Significant bacterial infection can occur without bacteremia. Squire and colleagues\textsuperscript{651} found that results of premortem blood cultures were negative in 7 (18\%) of 39 infants with unequivocal infection at autopsy. Some infants with significant systemic bacterial infection may not be identified by the usual single blood-culture technique. The physician must consider this limitation when determining length of empirical therapy. However, if treatment for infection is deemed necessary, parenteral administration for 10 days is recommended.

**MANAGEMENT OF THE INFANT WITH CATHETER-ASSOCIATED INFECTION**

Investigators in Connecticut found that multiple catheters, LBW, low gestational age at birth, and low Apgar scores were significant risk factors for LOS.\textsuperscript{509} Benjamin and colleagues\textsuperscript{510} reported a retrospective study at Duke University conducted from 1995 to 1999 of all neonates who had central venous access. The goal of the Duke study was to evaluate the relationship between central venous
catheter removal and outcome in bacteremic neonates. Infants bacteremic with *S. aureus* or a gram-negative rod who had their catheter retained beyond 24 hours had a 10-fold higher rate of infection-related complications than those in whom the central catheter was removed promptly. Compared with neonates who had three or fewer positive intravascular catheter blood cultures for coagulase-negative staphylococci, neonates who had four consecutive positive blood cultures were at significantly increased risk for end-organ damage and death. In neonates with central venous catheter–associated infection, prompt removal of the device is advised unless there is rapid clinical improvement and sterilization of blood cultures after initiation of therapy.

**TREATMENT OF NEONATAL MENINGITIS**

Because the pathogens responsible for neonatal meningitis are largely the same as those that cause neonatal sepsis, initial therapy and subsequent therapy are similar. Meningitis caused by gram-negative enteric bacilli can pose special management problems. Eradication of the pathogen often is delayed, and serious complications can occur. The persistence of gram-negative bacilli in CSF despite bacterialidal levels of the antimicrobial agent led to the evaluation of lumbar intrathecal and intraventricular gentamicin. Mortality and morbidity were not significantly different in infants who received parenteral drug alone or parenteral plus intrathecal therapy. The study of the intraventricular gentamicin was stopped early because of the high mortality in the parenteral plus intrathecal therapy group.

Feigin and colleagues provide a review of the management of meningitis in children, including neonates. Ampicillin or penicillin G, initially with an aminoglycoside, are appropriate antimicrobial agents for treating infection caused by GBS. Cefotaxime has superior in vitro and in vivo bactericidal activity against many microorganisms. Treatment of enteric gram-negative bacillary meningitis should include cefotaxime and an aminoglycoside until results of susceptibility testing are known.

If meningitis develops in a LBW infant who has been in the nursery for a prolonged period or in a neonate who has received previous courses of antimicrobial therapy for presumed sepsis, alternative empirical antibiotic regimens should be considered. Enterococci and antibiotic-resistant, gram-negative enteric bacilli are potential pathogens in these settings. A combination of vancomycin, an aminoglycoside, and cefotaxime may be appropriate. Cefazidime or meropenem in addition to an aminoglycoside should be considered for *P. aeruginosa* meningitis.

Other antibiotics may be necessary for the treatment of highly resistant organisms. Meropenem, ciprofloxacin, or trimethoprim-sulfamethoxazole can be the only antimicrobial agents active in vitro against bacteria that are highly resistant to broad-spectrum β-lactam antibiotics or aminoglycosides. Some of these drugs require careful monitoring because of toxicity to the newborn (see Chapter 37), and ciprofloxacin has not been approved for use in the United States in infants younger than 3 months. Definitive treatment of meningitis caused by gram-negative enteric bacilli should be determined by in vitro susceptibility tests, and assistance from an infectious diseases specialist can be helpful.

Use of dexamethasone as adjunctive treatment in childhood bacterial meningitis has been recommended based on reduction of neurologic sequelae in infants and children, in particular hearing loss, and especially in cases of *H. influenzae* type b meningitis. Only one randomized controlled study exists for neonates, conducted in 52 full-term neonates, and the mortality (22% dexamethasone vs. 28% controls) and morbidity at 24 months (30% vs. 39%) did not significantly differ between groups.

If cultures of blood and CSF for bacterial pathogens by usual laboratory techniques are negative in the neonate with meningitis, the differential diagnosis of aseptic meningitis must be reviewed, particularly in view of diagnosing treatable infections (Table 6-14).

**MANAGEMENT OF THE INFANT WITH A BRAIN ABSCESS**

If purulent foci or abscesses are present, they should be drained. However, some brain abscesses resolve with medical therapy alone. Brain abscesses can be polymicrobial or result from organisms that uncommonly cause meningitis, such as *Citrobacter*, *Enterobacter*, *Proteus*, and *Salmonella* spp. Aspiration of the abscess provides identification of the pathogens to guide rational antimicrobial therapy.

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**Table 6-14 Infectious and Noninfectious Causes of Aseptic Meningitis* in the Neonate**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFECTIOUS AGENT</strong></td>
<td></td>
</tr>
<tr>
<td>Bacteria</td>
<td>Partially treated meningitis</td>
</tr>
<tr>
<td></td>
<td>Parameningeal focus (brain or epidural abscess)</td>
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<tr>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Viruses</td>
<td>Herpes simplex meningoencephalitis</td>
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<tr>
<td></td>
<td>Cytomegalovirus</td>
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<tr>
<td></td>
<td>Enteroviruses</td>
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<tr>
<td></td>
<td>Rubella</td>
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<tr>
<td></td>
<td>Acquired immunodeficiency syndrome</td>
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<tr>
<td></td>
<td>Lymphohytic choriomeningitis</td>
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<tr>
<td></td>
<td>Varicella</td>
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<tr>
<td>Spirochetes</td>
<td>Syphilis</td>
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<tr>
<td></td>
<td>Lyme disease</td>
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<tr>
<td>Parasites</td>
<td>Toxoplasmosis</td>
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<tr>
<td></td>
<td>Chagas disease</td>
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<tr>
<td>Mycoplasma</td>
<td>Mycoplasma hominis infection</td>
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<tr>
<td></td>
<td>Ureaplasma urealyticum infection</td>
</tr>
<tr>
<td>Fungi</td>
<td>Candidiasis</td>
</tr>
<tr>
<td></td>
<td>Coccioidiomycosis</td>
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<tr>
<td></td>
<td>Cryptococcosis</td>
</tr>
<tr>
<td><strong>NONINFECTIOUS CAUSES</strong></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Traumatic lumbar puncture</td>
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<tr>
<td>Malignancy</td>
<td>Teratoma</td>
</tr>
<tr>
<td></td>
<td>Medullloblastoma</td>
</tr>
<tr>
<td></td>
<td>Choroid plexus papilloma and carcinoma</td>
</tr>
</tbody>
</table>

*Aseptic meningitis is defined as meningitis in the absence of evidence of bacterial pathogen detectable in cerebrospinal fluid by usual laboratory techniques.*
TREATMENT OF THE INFANT WITH MENINGITIS WHOSE BACTERIAL CULTURE RESULTS ARE NEGATIVE

In the absence of a detectable bacterial pathogen, an aggressive diagnostic approach is necessary for the infant with meningitis, defined by CSF pleocytosis and variable changes in the concentration of CSF protein and glucose. The most frequent cause of aseptic or nontuberculous bacterial meningitis in the neonate is prior antimicrobial therapy resulting in negative blood and CSF cultures. Congenital infections need to be excluded. Treatable diseases, such as partially treated bacterial disease, meningoencephalitis caused by herpes simplex virus, syphilis, cytomegalovirus, toxoplasmosis, Lyme disease in regions where *Borrelia* is prevalent, tuberculous, and malignancy, need to be considered in the differential diagnosis. The history of illness and contacts in the mother and family and epidemiologic features, such as animal exposures and recent travel, should be explored. Reexamination of the infant for focal signs of disease, including special techniques such as ophthalmologic examination, and consideration of appropriate diagnostic imaging studies of the long bones, skull, and brain can provide further information in determining the source of infection. Treatment of possible bacterial or nonbacterial causes of aseptic meningitis may be necessary before the results of culture, PCR, or serology tests are available to indicate the diagnosis.

TREATMENT OF ANAEROBIC INFECTIONS

The importance of anaerobic bacteria as a cause of serious neonatal infection is uncertain. *Clostridium*, *Peptococcus*, and *Peptostreptococcus* are highly sensitive to penicillin G, but *B. fragilis* spp. usually are resistant. If anaerobic organisms are known or suspected to be responsible for infection (as in peritonitis), initiating therapy with a clinically appropriate agent, such as clindamycin, metronidazole, meropenem, ticarcillin, or piperacillin/tazobactam, is warranted.

ADJUNCTIVE THERAPIES FOR TREATMENT OF NEONATAL SEPSIS

Despite appropriate antimicrobial and optimal supportive therapy, mortality rates resulting from neonatal sepsis remain high, especially for the VLBW infant. With the hope of improving survival and decreasing the severity of sequelae in survivors, investigators have considered adjunctive modes of treatment, including granulocyte transfusion, exchange transfusion, and the use of standard intravenous immune globulin (IVIG) or pathogen-specific polyclonal or monoclonal antibody reagents for deficits in neonatal host defenses. These therapies are discussed in further detail in Chapter 4. Pentoxifylline has been documented to reduce plasma TNF-α concentrations in premature infants with sepsis and to improve survival, but the number of infants treated (five of five survived) and number of controls (one of four survived) was too small to provide more than a suggestion of efficacy. 661 In neutropenic infants with sepsis, the administration of G-CSF and human granulocyte-macrophage colony-stimulating factor (GM-CSF) have had variable effects on outcome. 664-667 Although the results of selected studies indicate that some of these techniques improved survival, the potential adverse effects (e.g., graft-versus-host reaction, pulmonary leukocyte sequestration) are sufficiently concerning to warrant further study in experimental protocols.

IVIG preparations have been assessed for adjunctive therapy for neonatal sepsis based on the hypothesis that infected infants lack circulating antibodies against bacterial pathogens and that IVIG can provide some antibody for protection. Ohlsson and Lacy668 performed a meta-analysis of eight randomized studies evaluating 3871 infants of IVIG for treatment of suspected or proven bacterial/fungal infection compared with placebo or no invention. No differences in mortality during hospital stay, length of hospital stay, or death or major disability at 2 years were identified, leading the authors to conclude that routine administration of IVIG to prevent mortality in infants with suspected or proven infection is not recommended. A critical and definitive study in this analysis was the. placebo-controlled multicenter trial in LBW or ventilated neonates (INIS [International Neonatal Immunotherapy Study]) comparing the adjunctive use of 10 mg/kg IVIG versus placebo at the time of suspected infection and 48 hours later; no difference in the primary outcome variables of mortality or major disability at 2 years were identified, nor were differences seen in secondary outcomes including the incidence of subsequent sepsis.669

Prognosis

Before the advent of antibiotics, almost all infants with neonatal sepsis died. 5 Dunham2 reported that physicians used various treatments, including “erysipelas serum” and transfusions, without altering the course of the disease. The introduction of sulfonamides and penicillin and later introduction of broad-spectrum antibiotics, such as chloramphenicol and streptomycin, decreased the mortality rate to about 60%. 5,5 During this period, some infants undoubtedly died because of treatment with high dosages of chloramphenicol, which can cause cardiovascular collapse (i.e., gray baby syndrome).

The introduction of the aminoglycosides, first with kanamycin in the early 1960s and gentamicin late in that decade, vastly improved therapy for bacteremia caused by gram-negative organisms, the leading cause of sepsis at that time. 6 These therapies, together with an improved understanding of neonatal physiology and advances in life-support systems, combined to result in a steady decrease in neonatal mortality in the United States 6 and in Europe 6,10,261,286,670 during the period 1960 to 1985. Mortality rates for sepsis, including infants of all weights and gestational ages, decreased from 40% to 50% in the 1960s 6,261,286,670 to 10% to 20% in the 1970s and 1980s 6,10,261,452,670 Population-based surveillance of selected counties in the United States conducted by the CDC from 1993 to 1998 reported 2196 cases of neonatal sepsis caused by GBS, of which 92 (4%) were fatal. 649

The postnatal age at which infection occurs, once thought to be of prognostic significance, has become less important within the past 2 decades. Fulminant sepsis, with signs of illness present at birth or during the first day of life, has a high mortality rate, varying from 14% to 20%,6,12,261,288 to as high as 70%. 671 However, when
infections occurring during the first 24 hours of life, most of which are caused by GBS; are excluded from the analysis, the percentage of deaths caused by early-onset sepsis does not differ significantly from that associated with late-onset infection. 12,24,27,677 Mortality from sepsis is higher for preterm than for term infants in virtually all published studies 8 but is approximately the same for all major bacterial pathogens 10,260 (see Tables 6-4 and 6-5).

In recent surveys, the mortality rate for neonatal meningitis has declined from 25%,10,25,672,673 to 10% to 15%,12,24,27,674,675 § This decrease represents a significant improvement from prior years, when studies reported a case-fatality rate of more than 30%.22,436,654,655,676 Mortality is greater among preterm than term infants.12,24,27,677

Significant sequelae develop in 17% to 60% of infants who survive neonatal meningitis caused by gram-negative enteric bacilli or GBS. 24,672,673 These sequelae include mental and motor disabilities, convulsions, hydrocephalus, hearing loss, and abnormal speech patterns. The most extensive experience with the long-term observation of infants who had GBS meningitis as neonates was reported by Edwards and colleagues.677,678 Sixty-one patients were treated between 1974 and 1979, and 21% died. Of the 38 survivors who were available for evaluation at 3 years of age or older, 29% had severe neurologic sequelae, 21% had minor deficits, and 50% were functioning normally. Presenting factors that were associated with death or severe disability included comatose or semicomatose state, decreased perfusion, total peripheral white blood cell count less than 5000/mm³, absolute neutrophil count less than 1000/mm³, and CSF protein level greater than 300 mg/dL. A comparable study evaluating 35 newborns over a period of 3 to 18 years demonstrated more favorable outcomes, with 60% of survivors considered normal at the time of follow-up compared with sibling controls, 15% with mild to moderate neurologic residua, and 25% with major sequelae.679 Franco and coworkers675 reported the results of frequent and extensive neurologic, developmental, and psychometric assessments on a cohort of 10 GBS meningitis survivors followed for 1 to 14 years and found that 1 child had severe CNS damage; 5 children, including 1 with hydrocephalus, had mild academic or behavioral problems; and 4 children were normal.

The neurodevelopmental outcomes described for infants with gram-negative bacillary meningitis are similar to those reported for GBS meningitis. Unhanand and colleagues 14 reported findings from their 21-year experience with gram-negative meningitis at two hospitals in Dallas, Texas. Among 72 patients less than 28 days of age at the onset of symptoms, there were 60 survivors, 43 of whom were followed and evaluated for a period of at least 6 months. Neurologic sequelae, occurring alone or in combination, were described in 56% and included hydrocephalus (≈30%), seizure disorder (≈30%), developmental delay (≈30%), cerebral palsy (25%), and hearing loss (15%). Forty-four percent of the survivors were developmentally normal at follow-up. Among infants with gram-negative bacillary meningitis, thrombocytopenia, CSF white blood cell count greater than 2000/mm³, CSF protein greater than 200 mg/dL, CSF glucose-to-blood glucose ratio of less than 0.5, prolonged (>48 hours) positive CSF cultures, and elevated endotoxin and IL-1 concentrations in CSF were indicators of a poor outcome.24,438,546,678 Investigators in England and Wales679 found that independent predictors of adverse outcome 12 hours after admission were the presence of seizures, coma, ventilatory support, and leukopenia.

Computed tomography reveals a high incidence of CNS residua among newborns with meningitis. McCracken and colleagues679 report that, among 44 infants with gram-negative bacillary meningitis, only 30% of computed tomographic scans were considered normal. Hydrocephalus was found in 20% of cases; areas of infarct, cerebritis, diffuse encephalomalacia, or cortical atrophy in 30%; brain abscess in about 20%; and subdural effusions in 7%. Two or more abnormalities were detected in about one third of infants.

The prognosis of brain abscess in the neonate is guarded because about one half of these children die, and sequelae such as hydrocephalus are common among survivors. Of 17 children who had brain abscess during the neonatal period and were followed for at least 2 years, only 4 had normal intellect and were free of seizures.352 In neonates with brain abscess, the poor outcome probably is caused by destruction of brain parenchyma as a result of hemorrhagic infarcts and necrosis.

### Prevention

#### OBSTETRIC FACTORS

Improvement in the health of pregnant women with increased use of prenatal care facilities has led to lower rates of prematurity. Increased use of antenatal steroids in pregnant women with preterm labor and of surfactant in their infants has resulted in significantly fewer cases of respiratory distress syndrome. More appropriate management of prolonged interval after rupture of maternal membranes, maternal peripartum infections, and fetal distress has improved infant outcome. Because these factors are associated with sepsis in the newborn, improved care of the mother should decrease the incidence of neonatal infection. The development of neonatal intensive care expertise and units with appropriate equipment has resulted in the survival of VLBW infants. Increasingly, obstetric problems are anticipated, and mothers are transferred to medical centers with NICUs before delivery.

#### CHEMOPROPHYLAXIS

The use of antibiotics to prevent infection can be valuable when they are directed against specific microorganisms for a limited time. In the neonate, the use of silver nitrate eye drops or intramuscular ceftriaxone to prevent gonococcal ophthalmia, vaccination with bacillus Calmette-Guérin (BCG) or prophylactic use of isoniazid to reduce morbidity from tuberculosis in infants who must return to endemic areas, and use of hexachlorophene baths to prevent staphylococcal disease have been recognized as effective modes of chemoprophylaxis. The value of using antimicrobial agents against unknown pathogens in infants believed to be at high risk of infection or undergoing invasive procedures is
 uncertain. Studies of penicillin administered to the mother during labor for prevention of neonatal disease caused by GBS are reviewed earlier and in Chapter 12.

Prophylaxis using low-dose vancomycin as a strategy to prevent LOS in high-risk neonates has been the subject of several recent clinical investigations. A meta-analysis incorporating these studies found that low-dose prophylactic vancomycin reduced the incidence of total neonatal nosocomial sepsis, and specifically CoNS sepsis in the preterm infants, but that mortality and length of NICU stay did not differ between the treatment and placebo groups. A potential confounding factor in these studies is that low-dose vancomycin in the intravenous infusion may itself have prevented recovery of pathogens from blood cultures drawn from the central lines. Because clear clinical benefits have not been demonstrated, the rationale for routine prophylaxis with intravenous vancomycin cannot presently outweigh the theoretical concern of selection for antibiotic-resistant pathogens (e.g., vancomycin-resistant enterococci). An intriguing alternative approach was studied in a randomized prospective trial by Garland and colleagues—the use of a vancomycin-heparin lock solution in peripherally inserted central catheters in VLBW and other critically ill neonates. The study found the antibiotic lock solution to be associated with a marked reduction in the incidence of catheter-associated bloodstream infections (5% vs. 30% in controls), providing proof-of-principle for wider investigation of this method that reduces systemic antibiotic exposure.

**MATERNAL FACTORS**

The antiviral and antibacterial activity of human milk has been recognized for many years and is discussed extensively in Chapter 5. Evidence that breastfeeding defends against neonatal sepsis and gram-negative meningitis was first reported more than 30 years ago from Sweden. Studies carried out in Pakistan have shown that even partial breastfeeding appears to be protective among neonates in a resource-limited nation with a high neonatal mortality rate from clinical sepsis. In a study from Georgetown University, human milk–fed VLBW infants had a significant reduction in sepsis or meningitis compared with exclusively formula-fed VLBW infants (OR, 0.47; 95% CI, 0.23 to 0.95). Breastfed infants have a lower incidence of gastrointestinal illness, respiratory illness, and otitis media than those who are formula fed. A protective effect of breastfeeding against infections of the urinary tract also has been suggested. Breastfeeding is also associated with general immune stimulatory effects, as evidenced by larger thymus size and improved antibody responses to immunization.

Lactoferrin is the major whey protein in human milk and has immunomodulatory activities. A study of bovine lactoferrin supplementation in VLBW neonates identified efficacy in decreasing the incidence of LOS. The decrease occurred for gram-positive bacteremia and fungemia.

**IMMUNOPROPHYLAXIS**

The immaturity of the neonatal immune system is characterized by decreased levels of antibody against common pathogens; decreased complement activity, especially alternative pathway components; diminished polymorphonuclear leukocyte production, mobilization, and function; diminished T-lymphocyte cytokine production to many antigens; and reduced levels of lactoferrin and transferrin. Recognition of these factors has resulted in attempts at therapeutic intervention aimed specifically at each component of the deficient immune response.

Infants are protected from infection by passively transferred maternal IgG. To enhance the infant’s ability to ward off severe infections, immunization of pregnant women and women in the childbearing years has been selectively adopted. Programs to immunize pregnant women in resource-limited countries with tetanus toxoid have markedly decreased the incidence of neonatal tetanus. Investigational programs for immunization of pregnant women with polysaccharide pneumococcal, H. influenzae type b and GBS vaccines aim to provide infants with protection in the first months of life. Studies of safety and immunogenicity of polysaccharide conjugate vaccines for GBS show promise of a reduction in incidence of late- and early-onset disease in newborns. Use of vaccines in pregnant women is discussed in Chapter 38.

Several clinical trials have explored the use of IVIG to correct the antibody deficiency of neonates, particularly very preterm newborns, and thereby reduce the incidence of sepsis. In 1994, the NICHD Neonatal Research Network reported a randomized clinical trial of 2416 subjects to determine the effects of prophylactic IVIG on the risk of sepsis in premature neonates. No reduction in mortality, morbidity, nor incidence of nosocomial infections was achieved by IVIG administration. The use of hyperimmune IVIG preparations and human monoclonal antibodies to prevent specific infections (e.g., CoNS, S. aureus) in high-risk neonates is also an area of active exploration; however, although these products appear safe and well tolerated, no reduction in staphylococcal infection was documented in two recent large, randomized multicenter studies. A systematic meta-analysis of 19 studies published through 2013, including approximately 5000 infants, calculated IVIG prophylaxis and provided a 3% to 4% reduction in nosocomial infections but did not reduce mortality nor other important clinical outcomes (e.g., NEC, length of hospital stay). The cost of IVIG and the value assigned to these clinical outcomes will dictate use; the authors suggest there is no need for further randomized clinical trials, and that basic scientists and clinicians will need to explore new avenues for prophylaxis against bacterial infection in this special patient population.

An interesting older study by Sidiropoulos and coworkers explored the potential benefit of low-dose (12 g in 12 hours) or high-dose (24g daily for 5 days) IVIG given to pregnant women at risk for preterm delivery because of choioamnionitis. Cord blood IgG levels were doubled in infants older than 32 weeks of gestational age whose mothers received the higher dosage schedule but were unaffected in infants born earlier, suggesting little or no placental transfer of IVIG before the 32nd week of gestation. Among the infants delivered after 32 weeks, 6 (37%) of 16 born to untreated mothers developed clinical, laboratory, or radiologic evidence of infection and required antimicrobial therapy, whereas none of 7 infants born to treated mothers became infected. Although this study suggests that intraterine fetal prophylaxis can be beneficial in selected
cases, widespread use of IVIG for all women having premature onset of labor is not feasible because of uncertain timing before delivery, widespread shortages of IVIG, and cost. The decreased number of circulating polymorphonuclear leukocytes and reduced myeloid reserves in the bone marrow of newborns have been ascribed to impaired production of cytokines, IL-3, G-CSF, GM-CSF, TNF-α, and interferon-γ.\textsuperscript{706,707} Considerable experience with in vitro myeloid cell cultures and animal models suggested that cytokine or growth factor therapy to stimulate myelopoiesis could be an effective aid in preventing sepsis among newborns with hereditary or acquired congenital neutropenia. Individual studies of prophylactic GM-CSF in neonates were inconsistent in demonstrating that absolute neutrophil counts are increased or that the incidence of sepsis is reduced.\textsuperscript{566,667,710} Very recently, a single-blind, multicenter, double-blind controlled trial of GM-CSF in 280 infants at or less than 31 weeks of gestation demonstrated that although neutrophil counts rose more rapidly in the treatment group in the first 11 days after study initiation, there was no difference in the incidence of sepsis nor improved survival associated with these changes.\textsuperscript{711} It is important to note that although G-CSF therapy of severe congenital neutropenia reverses neutropenia, demonstrable functional deficiency of the neutrophils persists, and this probably explains why these neonates remain at significantly elevated risk of infection.\textsuperscript{712}

The amino acid glutamine has been recognized as important for gut and immune function in critically ill adults, and recent attention has focused on its potential benefit to the neonate, especially because it is not included in standard intravenous amino acid solutions. A large, multicenter, double-blind clinical trial of glutamine supplementation was found not to decrease the incidence of sepsis nor the mortality in ELBW infants,\textsuperscript{713} and this failure to provide a statistically significant benefit was borne out in a recent meta-analysis of seven randomized trials, including more than 2300 infants in total.\textsuperscript{714}

A few recent studies have examined the effect of probiotic administration of \textit{Lactobacillus} or \textit{Bifidobacterium} spp., generally intended as prophylaxis against NEC in neonates, on the secondary outcome of systemic bacterial infection, yielding conflicting results.\textsuperscript{715-717} A recent meta-analysis of nine trials randomizing 1425 infants suggests that enteral supplementation of probiotic bacteria reduced the risk of severe NEC, but there was no evidence of a comparable beneficial effect on the incidence of nosocomial sepsis.\textsuperscript{718}

The iron-binding glycoprotein lactoferrin is a component of the innate immune system produced at mucosal sites and activated in response to infection or inflammation. By restricting microbial iron access and through the direct cell wall lytic activity of its component peptides, lactoferrin exhibits broad-spectrum antimicrobial activity.\textsuperscript{719} Bovine lactoferrin, sharing 77% homology with the human protein, has been granted “generally recognized as safe” (GRAS) status by the FDA. A recent randomized study of bovine lactoferrin supplementation in VLBW neonates demonstrated a reduced rate of a first episode of LOS in the treatment group (RR, 0.34; 95% CI, 0.17 to 0.70).\textsuperscript{716} Certainly, this simple and promising intervention deserves further exploration as a tool to reduce the incidence of nosocomial infection in this extremely high-risk population.

**DECONTAMINATION OF FOMITES**

Because contamination of equipment poses a significant infectious challenge for the newborn, disinfection of all materials that are involved in the care of the newborn is an important responsibility of nursery personnel. The basic mechanisms of large pieces of equipment must be cleaned appropriately or replaced because they have been implicated in nursery epidemics. The use of disposable equipment and materials packaged in individual units, such as containers of sterile water for a nebulization apparatus, are important advances in the prevention of infection. The frequency of catheter-associated CoNS sepsis has led to attempts to prevent bacterial colonization of intravascular catheters through use of attachment-resistant polymeric materials, antibiotic impregnation, and immunotherapy directed against adherence factors.\textsuperscript{720} These procedures are reviewed in Chapter 35.

**EPIDEMIOLOGIC SURVEILLANCE**

**Endemic Infection**

Nursery-acquired infections can become apparent days to several months after discharge of the infant. A surveillance system that provides information about infections within the nursery and involves follow-up of infants after discharge should be established. Various techniques can be used for surveillance and are reviewed in Chapter 35.

**Epidemic Infection**

The medical and nursing staff must be aware of the possibility of outbreaks or epidemics in the nursery. Prevention of disease is based on the level of awareness of personnel. Infection in previously well infants who lack high-risk factors associated with sepsis must be viewed with suspicion. Several cases of infection occurring within a brief period, caused by the same or an unusual pathogen, and occurring in close physical proximity should raise concern about the possibility of a nursery outbreak. Techniques for management of infection outbreaks in nurseries are discussed in Chapter 35.

**Sepsis in the Newborn Recently Discharged From the Hospital**

When fever or other signs of systemic infection occur in the first weeks after the newborn is discharged from the nursery, appropriate management requires consideration of the possible sources of infection. Infection acquired at birth or from a household contact is the most likely cause. Congenital infection can be present with signs of disease that are detected after discharge. Late-onset infection from microorganisms acquired in the nursery can occur weeks or occasionally months after birth. Infection can occur after discharge because of underlying anatomic, physiologic, or metabolic abnormalities.

The newborn is susceptible to infectious agents that colonize or cause disease in other household members. If an infant whose gestation and delivery were uneventful is discharged from the nursery and develops signs of an
infectious disease in the first weeks of life, the infection was probably acquired from someone in the infant’s environment. Respiratory and gastrointestinal infections are common and can be accompanied by focal disease such as otitis media. A careful history of illnesses in household members can suggest the source of the infant’s infection.

CONGENITAL INFECTION

Signs of congenital infection can appear or be identified after discharge from the nursery. Hearing impairment caused by congenital rubella or cytomegalovirus infection can be noticed by a parent at home. Hydrocephalus with gradually increasing head circumference caused by congenital toxoplasmosis can be apparent only after serial physical examinations. Chorioretinitis, jaundice, or pneumonia can occur as late manifestations of congenital infection. A LP may be performed in the course of a sepsis evaluation. CSF pleocytosis and increased protein concentration can be caused by congenital infection and warrant appropriate follow-up diagnostic studies.

LATE-ONSET DISEASE

Late-onset disease can present after the first week to months after birth as sepsis and meningitis or other focal infections. GBS (see Chapter 12) is the most frequent cause of LOS in the neonate, followed by E. coli. Organisms acquired in the nursery also can cause late-onset disease. Skin and soft tissue lesions or other focal infections, including osteomyelitis and pneumonia from S. aureus, can occur weeks after birth. The pathogenesis of LOS is obscure in many cases. The reason why an organism becomes invasive and causes sepsis or meningitis after colonizing the mucous membranes, skin, or upper respiratory, gastrointestinal, or genitourinary tracts remains obscure. Nosocomially acquired or health care–associated organisms are discussed in further detail in Chapter 35.

INFECTIONS IN THE HOUSEHOLD

Infection can be associated with an underlying anatomic defect, physiologic abnormality, or metabolic disease. The infant who fails to thrive or presents with fever can have a urinary tract infection as the first indication of an anatomic abnormality. Infants with lacrimal duct stenosis or choanal atresia can develop focal infection. Sepsis caused by gram-negative enteric bacilli occurs frequently in infants with galactosemia (see “Pathogenesis”). The infected infant can be an important source of infection to family members. In one study in New York, 12.6% of household contacts developed suppurative lesions during the 10-month period after introduction into the home of an infant with a staphylococcal lesion. The incidence of suppurative infections in household contacts of infants without lesions was less than 2%. Damato and coworkers demonstrated colonization of neonates with enteric organisms possessing R factor–mediated resistance to kanamycin and persistence of these strains for more than 12 months after birth. During the period of observation, one third of the household contacts of the infants became colonized with the same strain.

Infections in infants have been associated with bites or licks from household pets. Pasteurella multocida is part of the oral flora of dogs, cats, and rodents. A recent review of 25 cases of P. multocida infection in the neonatal period found animal exposure to cats and/or dogs in 52% of cases, the majority of which did not involve bites or trauma; the balance were felt to represent vertical transmission from an infected mother. In one case report, a 5-week-old infant with P. multocida meningitis frequently was licked by the family dog, and the organism was identified in cultures of the dog’s mouth but not of the parents’ throats. P. multocida sepsis and meningitis was reported in 2-month-old twin infants after household exposure to a slaughtered sheep. A neonatal case of Campylobacter jejuni sepsis was proven genetically to result from transmission from the family dog. The epidemiologic link between cats and dogs in young infants suggests that parents should limit contact between pets and infants.

FEVER IN THE FIRST MONTH OF LIFE

Reviews of fever in the first weeks of life indicate that elevation of temperature (>38.8° C [101.8° F]) is relatively uncommon. However, when fever occurs in the young infant, the incidence of severe disease, including bacterial sepsis, meningitis, and pneumonia, is sufficiently high to warrant careful evaluation and conservative management. Approximately 12% of all febrile (>38.0° C [100.4° F]) neonates presenting to emergency departments are found to have a serious bacterial infection. Important pathogens in the age group include GBS and E. coli, and occult bacteremia and urinary tract infections are the most common foci of disease.

A careful history of the pregnancy, delivery, nursery experience, interval since discharge from the nursery, and infections in the household should be obtained. Physical examination should establish the presence or absence of signs associated with congenital infection and late-onset diseases. Culture of blood and urine should be performed if no other focus is apparent, and culture of the CSF and a chest radiograph should be considered if the infant is believed to have systemic infection. Risk stratification algorithms have been evaluated to incorporate ancillary clinical testing in hopes of supplementing the often incomplete picture that emerges from history and physical examination. For example, the “Rochester criteria” for analysis of febrile infants, originally proposed by Dagan and colleagues, used criteria such as normal peripheral leukocyte count (5000–15,000/mm3), normal absolute band neutrophil count (<1500/mm3) and absence of pyuria to identify low-risk patients. However, when Ferrera and coworkers retrospectively applied these criteria to the subset of patients in their first 4 weeks of life, 6% of the neonates fulfilling low-risk criteria actually had serious bacterial infections. Similarly, when groups of febrile newborns were retrospectively stratified as low risk by the “Philadelphia criteria” or “Boston criteria,” developed for older infants, it became apparent that 3.5% to 4.6% of the neonates with a serious bacterial infection would have been missed.

Consequently, because of the inability to accurately predict serious bacterial infections in this age group, a complete sepsis evaluation should be performed and include a culture of blood, urine, and CSF; a complete blood cell and...
differential count; examination of CSF for cells, glucose, and protein; and a urinalysis. Although a peripheral blood cell count is routinely ordered, it is not sufficiently discriminatory to preclude the mandatory collection of blood for culture.\textsuperscript{73,74} Unlike older infants,\textsuperscript{75} the presence of signs consistent with a viral upper respiratory tract infection in the neonate does not obviate the need for a full diagnostic evaluation. Indeed, neonates infected with respiratory syncytial virus had equivalent rates of serious bacterial infection as those testing negative for the virus.\textsuperscript{74} However, recent data suggests that febrile infants younger than 60 days and positive for influenza virus infection may indeed have lower rates of bacteremia and urinary tract infection than similar infants without influenza infection.\textsuperscript{74}

Because of the high rates of serious bacterial infections, guidelines prepared by Baraff and colleagues\textsuperscript{72} for the management of infants and children with fever without source state that all febrile infants younger than 28 days should be hospitalized for parenteral antibiotic therapy, regardless of the results of laboratory studies.

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146. 6 • Bacterial Sepsis and Meningitis


Bacterial Sepsis and Meningitis


