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 sequel 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 species, and Mycobacterium tuberculosis are described in detail in 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 manifests as a fulminant, systemic
illness during the first 24 hours of life (median age of onset approximately 6 hours), with most other cases manifesting on the second day of life. Infants with early-onset disease may 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. 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 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., group B streptococcus) of life. Very late onset infection secondary to group B streptococcus (disease in infants >3 months old) is discussed in Chapter 13. 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 and meningitis include organisms acquired from the maternal genital tract and organisms acquired after birth from human contacts or infrequently from contaminated hospital equipment or materials when prolonged intensive care is needed for a neonate. The mortality rate usually is lower than for early-onset sepsis but can range from 2% to 40%, with the latter figure typically for infants with very low birth weight infants with gram-negative sepsis.

Because different microorganisms are responsible for disease by 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-onset and late-onset infections, whereas others, such as *S. aureus*, CoNS, and *Pseudomonas aeruginosa*, rarely cause early-onset disease and typically are associated with late-onset disease. The survival of very low birth weight infants with prolonged stays in the neonatal intensive care unit (NICU) has been accompanied by increased risk for nosocomial or hospital-associated infections and for very late onset disease (see Chapter 35).[1]

**BACTERIOLOGY**

The changing pattern of organisms responsible for neonatal sepsis is reflected in a series of reports by pediatricians at the Yale–New Haven Hospital covering the period 1928-2003 (Table 6–2) [2-8]. 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 antibiotics, gram-negative enteric bacilli, particularly *E. coli*, became the predominant cause of serious infection in the newborn. Reports for the periods 1966-1978 and 1979-1988 document the increase in importance of GBS and *E. coli* as agents of neonatal sepsis. In a more recent analysis from 1989-2003, CoNS species, predominantly *Staphylococcus epidermidis*, emerged as the most commonly identified agent of neonatal sepsis, with GBS, *E. coli*, *Enterococcus faecalis*, *S. aureus*, and *Klebsiella* species also occurring with substantial frequency. Later reports also document the problem of sepsis in very premature and low birth weight infants who have survived with the aid of sophisticated life-support equipment and advances in neonatal intensive care—CoNS are particularly threatening in these infants. Emerging data from the same center indicate that although intrapartum antibiotic prophylaxis protocols have reduced the overall incidence of early-onset sepsis, they 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 (Table 6–3). 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 [10] and East Africa [11] and a more recently significant pathogen in Connecticut [7] and southern Israel [12]. *S. epidermidis* was responsible for 53% of cases in Liverpool [13], and CoNS account for 35% to 48% of all late-onset sepsis in very low birth weight infants across the United States [14,15] and in Israel [16]. *Klebsiella* and *Enterobacter* species were the most common bacterial pathogens in Tel Aviv [17]. Sepsis and focal infections in neonates in developing countries are discussed further in Chapter 2.

A survey of five university hospitals in Finland [10] provides data about the association of the etiologic agent and mortality based on age at onset of sepsis (Table 6–4) and birth weight (Table 6–5). Infants with sepsis onset during the first 24 hours of life and weighing less than 1500 g at birth had the highest mortality rate. The mortality rates for neonatal sepsis over time are documented in the Yale Medical Center reports. In the preantibiotic era, neonatal sepsis usually was fatal. Even with the introduction of penicillins and aminoglycosides in the reports from 1944-1965, 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 1989-2003, mortality from neonatal sepsis in this academic medical center was rare, 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-onset 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 critically ill infants.

The Yale data also provide information about the microorganisms responsible for early-onset and late-onset bacterial sepsis (Table 6–6). GBS were responsible for most early-onset disease. CoNS, S. aureus, E. coli, Enterococcus species, and Klebsiella species 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 infants after age 30 days.

The incidence of neonatal sepsis showed a strong inverse correlation to birth weight in the latest Yale cohort: birth weight 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 very low birth weight 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 very low birth weight infants in a study of the efficacy of intravenous immunoglobulin in preventing nosocomial infections [18]. Of the very low birth weight infants, 16% developed septicemia at a median age of 17 days, with an overall mortality rate of 21% and 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 [19] reported patterns of pathogens causing early-onset sepsis in very low birth weight infants (400 to 1500 g) in the centers participating in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. Compared with earlier cohorts, a marked reduction in group B streptococcal infections (from 5.9 to 1.7 per 1000 live births) and an increase in E. coli infections (3.2 to 6.8 per 1000 live births) were noted, although the overall incidence of neonatal sepsis in this population did not change.

Organisms responsible for bacterial meningitis in newborns are listed in Table 6–7, which summarizes data collected from 1932-1997 at neonatal centers in the United States [20-23], The Netherlands [24], Great Britain [25,26], and Israel [12]. Gram-negative enteric bacilli and GBS currently are responsible for most early-onset disease. S. pneumoniae, Neisseria meningitidis, and type b and nontypable Haemophilus influenzae—are relatively infrequent causes of meningitis in the neonate [27]. A nationwide survey of causative agents of neonatal meningitis in Sweden in 1976-1983 indicated a shift from bacterial to viral or unidentified microorganisms, with lower attributable mortality rates [28].
GROUP B STREPTOCOCCI

Group B ß-hemolytic streptococci were implicated in human disease shortly after the precipitin-grouping technique was described [29]. For the past 3 decades, GBS have been the most common organisms causing invasive disease in neonates throughout the United States and western Europe (see Chapter 13).

\textit{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 ß-hemolysis on sheep blood agar media. GBS can be differentiated immunochemically on the basis of their type-specific polysaccharides. Ten capsular types—Ia, Ib, II, III, IV, V, VI, VII, and VIII—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 more 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 women and men and in the lower gastrointestinal and upper respiratory tracts of newborns. Patterns of early-onset, late-onset, and very late onset disease have been associated with GBS (see Table 6–1). Early-onset disease manifests as a multisystem illness with rapid onset typically during the first 1 or 2 days 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 currently estimated at 8%, but was 50% in the 1970s [30].

Clinical manifestations of late-onset neonatal sepsis are more insidious than the manifestations of early-onset disease, and meningitis is frequently a part of the clinical picture. Some infants with meningitis have a fulminant onset, however, with rapid progression to centrally mediated apnea. Many infants are products of a normal pregnancy and delivery and have no problems in the nursery. It is uncertain whether group B streptococcal 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

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Organism} & \textbf{No. Died/Total} & \textbf{\%} \\
\hline
Group B streptococci & 28/93 & 30 \\
Escherichia coli & 8/26 & 31 \\
\textit{Staphylococcus aureus} & 3/14 & 21 \\
Other & 15/47 & 32 \\
Total & 54/180 & 30 \\
\hline
\end{tabular}
\caption{Mortality for Onset of Signs at <24 hr, 24 hr–7 day, and 8–20 day}
\end{table}

from other infants or personnel in the nursery. In late-onset infection, most strains belong to serotype III. The mortality rate, estimated at 3%, is lower than the mortality for early-onset disease. With increasing survival of extremely low birth weight (<1000 g) infants, very late onset disease (>89 days) has been described [16].

In addition to sepsis and meningitis, other manifestations of neonatal disease caused by GBS include pneumonia, empyema, facial cellulitis, ethmoiditis, orbital cellulitis, conjunctivitis, necrotizing fasciitis, osteomyelitis, suppurative arthritis, and impetigo. Bacteremia without systemic or focal signs of sepsis can occur. Group B streptococcal infection in pregnant women can result in peripartum infections, including septic abortion, chorioamnionitis, peripartum bacteremia, septic pelvic thrombophlebitis, meningitis, and toxic shock syndrome [31].

**GROUP A STREPTOCOCCI**

Streptococcal puerperal sepsis has been recognized as a cause of morbidity and mortality among parturient women since the 16th century [32–36]. Neonatal group...
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<tbody>
<tr>
<td>β-hemolytic streptococci (group not stated)</td>
<td>9</td>
<td>12</td>
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<tr>
<td>β-hemolytic streptococci Group A</td>
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<td>—</td>
<td>1</td>
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<td>Group B</td>
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<td>41</td>
<td>68</td>
<td>113</td>
<td>134</td>
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<td>2</td>
<td>4</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>1</td>
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<tr>
<td>Staphylococcus epidermidis or coagulase-negative staphylococci</td>
<td>12</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>4</td>
<td>—</td>
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<td>Staphylococcus aureus</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>21</td>
<td>18</td>
<td>—</td>
<td>8</td>
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<tr>
<td>Streptococcus pneumoniae</td>
<td>—</td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>12</td>
<td>21</td>
<td>—</td>
<td>—</td>
<td>7</td>
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<td>Listeria monocytogenes</td>
<td>25</td>
<td>44</td>
<td>16</td>
<td>50</td>
<td>132</td>
<td>2</td>
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<td>4</td>
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<td>—</td>
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<td>Klebsiella and Enterobacter species</td>
<td>3</td>
<td>13</td>
<td>2</td>
<td>3</td>
<td>19</td>
<td>8</td>
<td>10</td>
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<td>5</td>
<td>8</td>
<td>3</td>
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<td>Haemophilus species</td>
<td>—</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>12</td>
<td>—</td>
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<td>1</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
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<td>—</td>
<td>—</td>
<td>1</td>
<td>3</td>
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<td>—</td>
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<td>6</td>
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<tr>
<td>Salmonella species</td>
<td>2</td>
<td>4</td>
<td>—</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>—</td>
<td>1</td>
</tr>
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<td>28</td>
<td>1</td>
<td>7</td>
<td>15</td>
<td>32</td>
<td>46</td>
<td>—</td>
<td>23</td>
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</table>

*Survey of 16 newborn nurseries participating in neonatal meningitis study of intrathecal gentamicin under the direction of Dr. George McCracken, Jr.

1Authors report an additional nine cases of gram-positive and six cases of gram-negative meningitis with organisms not otherwise specified.

2Authors report 18 cases related to enteric bacteria, including E. coli, Proteus species, and Klebsiella-Enterobacter group.
A streptococcal infection now is reported infrequently [37–43], but it can occur rarely in epidemic form in nurseries [37,44–47]. The reemergence of virulent group A streptococcal infections during the last 3 decades, including invasive disease and toxic shock syndrome, has been reflected in more case reports of severe disease in pregnant women and newborns.

Group A streptococcal disease in the mother can affect the fetus or newborn in two clinical patterns. Maternal streptococcal bacteremia during pregnancy can lead to intrauterine infection resulting in fetal loss or stillbirth; alternatively, acquisition of group A streptococci from the maternal genital tract can cause early-onset neonatal sepsis similar to early-onset group B streptococcal 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 [48–50].

The features of 38 cases of neonatal invasive group A streptococcal infection from the literature were catalogued more recently [51]. Overall mortality rate in neonatal invasive group A streptococcal infection was significantly high (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 group A streptococcal infection was documented in three quarters of cases—42% of neonates had pneumonia, sometimes complicated by empyema, and 17% had a toxic shock syndrome-like presentation. Among the cases of early-onset group A streptococcal infection, puerperal sepsis or toxic shock syndrome–like sepsis in the mother during the peripartum period was an associated factor in 62% of cases. In late-onset cases of neonatal group A streptococcal infection reviewed in this series, soft tissue infections, meningitis, and pneumonia were among the reported clinical manifestations. An earlier review by Greenberg and colleagues [52] on 15 cases of group A streptococcal 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, omphalitis, Ludwig angina [53], pneumonia, and osteomyelitis, have been reported. Because all group A streptococci 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 group A streptococci.

**STREPTOCOCCUS PNEUMONIAE**

Although pneumococcal infections in the neonate are unusual occurrences, they are associated with substantial morbidity and mortality [54–61]. Bortolussi and colleagues [54] reported five infants with pneumococcal sepsis who had respiratory distress and clinical signs of infection on the first day of life. Three infants died, two within 12 hours of onset. *S. pneumoniae* was isolated from the vaginas of three of the mothers. Radiographic features were consistent with hyaline membrane disease or pneumonia or both. The clinical features were strikingly similar to features of early-onset group B streptococcal infection, including the association of prolonged interval after rupture of membranes, early-onset respiratory distress, abnormal chest radiographs, hypotension, leukopenia, and rapid deterioration. Fatal pneumococcal bacteremia in a mother 4 weeks postpartum 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 the mother and the infant [55].

Hoffman and colleagues from the United States Multicenter Pneumococcal Surveillance Group [59] 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 1993-2001. 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. 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 group B streptococcal disease in neonates may result in an increase in neonatal infections caused by β-lactam–resistant organisms [60].

**OTHER STREPTOCOCCI**

Human isolates of group C and G streptococci form large β-hemolytic colonies that closely resemble those of group A streptococci and share many virulence genes, including genes 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 [62–65]. Likewise, group G streptococci are an infrequent cause of neonatal sepsis and pneumonia [66–70]. Maternal intrapartum transmission was the likely source for most cases [68], and concurrent endometritis and bacteremia in the mother and sepsis in the neonate have been reported [69]. Dyson and Read [68] found very high rates of colonization in neonates born at New York Hospital in a 1-year survey of discharge cultures in 1979; the monthly incidence of cultures of group G streptococci from the nose and umbilicus ranged from 41% to 70%. During this period, group B streptococcal colonization was only 1% to 11% [68].

Viridans streptococci are a heterogeneous group of β-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 schemata for these streptococci, and they may bear different designations in the literature. *Streptococcus faecalis* is capable of causing neonatal sepsis and meningitis that is clinically similar to sepsis caused by GBS [71–73]. Rare cases of neonatal sepsis caused by *Streptococcus mitis* have been reported [74,75].

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 [76]. In this series, most infants had early-onset infection with clinical features similar to 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 [10], Liverpool [13], Indianapolis [77], and Montreal [78]. Among ventilated neonates in a NICU in Ankara, Turkey, the most prominent bacteria in bronchoalveolar lavage cultures were multidrug-resistant viridans streptococci; but these were also one of the most common bloodstream isolates (29%) in the same population [79]. 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 (\textit{E. faecalis} and \textit{Enterococcus 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 [80]. 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 \textit{E. faecalis}, with a smaller number caused by \textit{E. faecium} [71,72,81-84]. In 4 years beginning in 1974, 30 neonates with enterococcal sepsis occurred among 30,059 deliveries at Parkland Memorial Hospital in Dallas [81]. During this period, enterococci were second only to GBS (99 cases) and were more common than \textit{E. coli} (27 cases) as a cause of neonatal sepsis. The clinical presentation in most cases was similar to early-onset sepsis of any cause [83]. Among infants with respiratory distress as a prominent sign of infection, chest radiographs were similar to radiographs showing the hyaline membrane–appearing pattern of group B streptococcal infection. Enterococcal bacteremia during 10 years beginning in January 1977 was reported in 56 neonates from Jefferson Davis Hospital in Houston, Texas [85]. Patients 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; many cases were nosocomial [85]. 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 [82]. The presence of a central venous catheter (77%) and a diagnosis of necrotizing enterocolitis (33%) were common characteristics.

\textit{Enterococcus} species generally are resistant to cephalosporins and are only moderately susceptible to penicillin \textit{G} and ampicillin; they require the synergistic activity of penicillin \textit{G} at high dosage and an aminoglycoside for maximal bactericidal action. Nontenterococcal strains are susceptible to penicillin \textit{G}, ampicillin, and most cephalosporins. Vancomycin-resistant \textit{Enterococcus} has been reported from NICUs, causing illnesses clinically indistinguishable from vancomycin-sensitive strains [82]; these resistant strains raise concerns about the efficacy of antimicrobial agents currently approved for use in neonates [86]. Use of high doses of ampicillin is one option, but other drugs, including the newer streptogramin combination of quinupristin and dalfopristin and the oxazolidinone linezolid, may be suggested by the susceptibility pattern (see Chapter 37).

\textbf{STAPHYLOCOCCUS AUREUS AND COAGULASE-NEGATIVE STAPHYLOCOCCI}

\textit{S. aureus} and CoNS, especially \textit{S. epidermidis}, colonize skin and mucosa. Isolation of \textit{S. aureus} from tissue, blood, or other body fluid usually is clearly associated with disease. Most episodes of sepsis caused by \textit{S. aureus} are hospital acquired, and mortality can be high (23% among 216 Swedish neonates with \textit{S. aureus} bacteremia during the years 1967-1984), with low birth weight as the most important risk factor [87]. More recently, reports of pneumonia and other severe nosocomial infection in neonates caused by community-acquired methicillin-resistant \textit{S. aureus} strains, including the epidemic USA300 clone, have been documented [88,89]. Molecular epidemiologic techniques have established direct transmission of community-acquired methicillin-resistant \textit{S. aureus} between postpartum women [90] and among NICU patients [91].

CoNS include more than 30 different species. \textit{S. epidermidis} is the dominant species of CoNS responsible for neonatal sepsis, but other species, including \textit{Staphylococcus capitis}, \textit{Staphylococcus hemolyticus}, and, \textit{Staphylococcus hominis}, have been identified as causes of sepsis in newborns [92]. A well-documented increased incidence of CoNS sepsis [8,14-16,18] has accompanied the increased survival of very low birth weight and extremely low birth weight infants with developmentally immature immune systems and prolonged stay in NICUs. 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 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]. 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 an infant with suspected late-onset sepsis [94], and adoption of a standard practice of two blood cultures can reduce the number of neonates diagnosed with CoNS and exposed to intravenous antibiotic therapy [95]. 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. \textit{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 glycolys) that stimulates adherence of microcolonies to various surfaces in the environment and on epithelial surfaces, ultimately leading to establishment of a biofilm [96,97]. In addition to this adhesin function, the slime may protect staphylococci against antibiotics and host defense mechanisms such as macrophage phagocytosis [98]. Parenteral nutrition with a lipid emulsion administered through a venous catheter with 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 [99]. Disease in newborn infants caused by S. aureus and CoNS is discussed in detail in Chapter 17.

**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 [100]. *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 [101]. Although most people exposed to *L. monocytogenes* do not develop illness, pregnant women can suffer fetal loss, and neonates can develop early-onset or late-onset sepsis and meningitis. Neonatal disease resulting from *Listeria* is discussed in detail in Chapter 14.

**EScherichia COLI**

*E. coli* is second only to GBS as the most common cause of early-onset and late-onset neonatal sepsis and meningitis [9,102–104]. Coliform organisms are prevalent in the maternal birth canal, and most infants are colonized in the 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 [105]. One of these, the O18:K1:H7 clone, is distributed globally, whereas others such as O83:K1 and O45:K1 are restricted to a smaller subset of countries [106]. 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 [107].

The K1 capsular antigen present in certain strains of *E. coli* is uniquely associated with neonatal meningitis [108–110]. K1 antigen is polysialic acid that is immunochemically identical to the capsular antigen of group B *N. meningitidis*. McCracken and coworkers [109] found K1 strains in the blood or CSF of 65 of 77 neonates with meningitis related to *E. coli*. These strains also were cultured from the blood of some infants (14 of 36) and adults (43 of 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 [24]. Infants with meningitis caused by K1 strains had significantly higher mortality and morbidity rates than infants with meningitis caused by non-K1 *E. coli* strains [110]. The severity of disease was directly related to the presence, amount, and persistence of K1 antigen in CSF. Strains of *E. coli* with K1 antigen were isolated from cultures of stool of 7% to 38% (varying with time and location of the study) of healthy newborns and from approximately 50% of nurses and mothers of the infants [110,111]. 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 [111,112]. High rates of carriage of K1 strains by nursery personnel indicate, however, that postnatal acquisition of the K1 strains in the nursery also may occur [110,111].

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 shown in tissue culture [113]. Next the organisms can establish high-grade bacteremia in the immunosusceptible neonate through the complement resistance properties of its O-lipopolysaccharide and K1 capsule–mediated impairment of opsonophagocytic killing [114]. Finally, the pathogen possesses a series of surface protein determinants (e.g., O45, K1, CNF1) that mediate binding to and invade brain endothelial cells, as shown in human tissue culture experiments and the neonatal rat model of meningitis [115].

**KLEBSIELLA SPECIES**

*Klebsiella* is a genus of Enterobacteriaceae that has emerged as a significant nosocomial pathogen in neonates [116,117]. 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 [118–120]. Previously thought to be a nonpathogenic organism inhabiting soil and water, *K. planticola* has been implicated as a cause of neonatal sepsis [121,122].

In a 4-year retrospective study from Israel [123], *Klebsiella* species caused 31% of late-onset neonatal sepsis. *Klebsiella* was also the most common single agent in a review of sepsis in Jamaican neonates [124]. Greenberg and colleagues [12] performed an 8-year prospective study of neonatal sepsis and meningitis at Soroka University Medical Center during 1986-1994; 49 (20%) of 250 cases were caused by *K. pneumoniae*, with a mortality rate of 29%. Risk factors for infection included prematurity, very low birth weight, prolonged rupture of membranes (>24 hours), and cesarean section or instrument delivery. *Klebsiella* species seem to be common causes of liver abscess complicating bacteremia in neonates [125].
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 [126–128]. Enhanced infection control measures and changes in use of routine broad-spectrum antibiotics can reduce the frequency of these serious infections.

**ENTEROBACTER SPECIES**

Among the Enterobacter aerogenes (i.e., Aerobacter aerogenes) species, Enterobacter cloacae, Enterobacter sakazakii, and Enterobacter hormaechei have caused sepsis and a severe form of necrotizing meningitis in neonates [129–134]. In 2008, the taxonomy of E. sakazakii was revised, resulting in identification of five species belonging to a new genus, Cronobacter [135]. For purposes of this chapter, the discussion of earlier articles retains the designation of E. sakazakii.

Enterobacter septicemia was the most common nosocomial infection in neonates at the Ondokuz Mayis University Hospital in Samsun, Turkey, from 1988-1992 [136]. Willis and Robinson [130] 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 [131] reviewed 30 cases of E. cloacae bacteremia in children, including 10 infants younger than 2 months. The high frequency of multidrug resistance among isolates from patients in the NICUs was attributed to routine extended-spectrum cephalosporin usage [137]. An outbreak of E. sakazakii in a French NICU in 1994 involved 17 cases including 7 neonates with necrotizing enterocolitis, 1 case of sepsis, and 1 case of meningitis; 8 infants were colonized, but asymptomatic; there were 3 deaths. Four separable pulse types of E. sakazakii were identified, but the deaths were attributable to only one [138]. In a 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 [139].

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 [140–143], contaminated total parenteral nutrition fluid [144,145], bladder catheterization devices [144], and contaminated saline [146]. Effective infection control measures require reinforcement of procedures including proper hand hygiene, aseptic technique, isolation protocols, and disinfection of environmental surfaces.

**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. In 1990, Citrobacter koseri replaced Citrobacter diversus [147]. For the purposes of this chapter, C. koseri replaces C. diversus, even though the original article may refer to the latter name.

Citrobacter species are responsible for sporadic and epidemic clusters of neonatal sepsis and meningitis, and C. koseri is uniquely associated with brain abscesses [147–155]. Neonatal disease can occur as early-onset or late-onset presentations. Brain abscesses caused by C. koseri have been reported in a pair of twins [156]. Doran [147] reviewed outbreaks of C. koseri in NICUs resulting in sepsis and meningitis, septic arthritis, and skin and soft tissue infections. Other focal infections in neonates caused by Citrobacter species include bone, pulmonary, and urinary tract infections [147].

During the period 1960-1980, 74 cases of meningitis caused by Citrobacter species were reported to the Centers for Disease Control and Prevention (CDC) of the U.S. Public Health Service [148]. In 1999, Doran [147] reviewed an additional 36 cases of neonatal meningitis caused by Citrobacter species. 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 [153]. 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 [157]. Such persistence of C. koseri in the CNS is well illustrated by a case report of recovery of the organism from CSF during a surgical procedure 4 years after treatment of neonatal meningitis [152]. The mortality rate for meningitis resulting from Citrobacter species was about 30%; most of the infants who survived had some degree of mental retardation. A review of 110 survivors of meningitis caused by Citrobacter revealed only 20 infants who were believed to have structurally intact brains and age-appropriate development [147].

Citrobacter species usually are resistant to ampicillin and variably susceptible to aminoglycosides. Historically, most infants were treated with a combination of penicillin or cephalosporin plus an aminoglycoside. Surgical drainage has been used in some cases with variable success. Choosing antimicrobial agents with the most advantageous susceptibility pattern and selected surgical drainage seems to be the most promising approach to therapy, but no one regimen has been found to be more successful than another. 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 [154] used these markers to investigate an outbreak of six cases of neonatal meningitis caused by C. koseri in three Baltimore hospitals from 1983-1985. 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 [155].
Serratia marcescens

P. aeruginosa is frequently associated with hospital-acquired infections in infants in the NICU [158–160]. Late-onset sepsis has occurred in infants infected from healthcare equipment [160–163], the hands of healthcare workers [164], milk bottles [159], aqueous solutions such as theophylline [159], hand hygiene washes [160], and lipid parenteral feeds [162]. The gastrointestinal tracts of hospitalized infants provide a reservoir for transmission and infection [161]. Investigation of an outbreak of multidrug-resistant S. marcescens in the NICU identified exposure to inhalational therapy as an independent risk factor for acquisition [165].

In a review by Campbell and colleagues [166] of neonatal bacteremia and meningitis caused by S. marcescens, 11 (29%) of 38 infants had meningitis as a complication of bacteremia. Mean gestational age was 28 weeks, and mean birth weight was 1099 g. 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 arteriosus treated medically or surgically, and 20% had necrotizing enterocolitis with perforation. All patients were treated for a minimum of 21 days with combination antimicrobial therapy that included a third-generation cephalosporin or a ureidopenicillin and an aminoglycoside, typically gentamicin. Three of 10 patients died. Four of the seven 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 abscess resulting in multicystic encephalomalacia and severe developmental retardation [167].

Pseudomonas aeruginosa

P. aeruginosa usually is a cause of late-onset disease in infants who are presumably infected from their endogenous flora or from equipment, aqueous solutions, or occasionally the hands of healthcare workers. An outbreak of P. aeruginosa sepsis in a French NICU was associated with contamination of a milk bank pasteurizer [168]. Stevens and colleagues [169] 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 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 [170].

A retrospective review of sepsis in infants admitted over the 10-year period 1988–1997 to the NICU at Children’s Hospital of the King’s Daughters in Norfolk, Virginia, identified 825 cases of late-onset sepsis [14]. Infants with Pseudomonas sepsis had the highest frequency of clinically fulminant onset (56%), and 20 of the 36 (56%) infants with Pseudomonas sepsis died within 48 hours of collection of blood culture.

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 [171] reviewed the course of 18 infants at Yale-New Haven Hospital NICU who had P. aeruginosa isolated from cultures of the conjunctiva during 10 years beginning in 1986. Five infants developed bacteremia, including three with meningitis, and two infants died. More recently, 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 healthcare worker experiencing intermittent otitis externa [172].

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 1968–1979 were from patients younger than 3 months, and more than half were from infants younger than 1 year [173]. A 21-year review of gram-negative enteric meningitis in Dallas beginning in 1969 identified Salmonella as the cause in 4 of 72 cases [23]. Investigators from Turkey reported seven cases of neonatal meningitis caused by Salmonella during the years 1995–2001 [174]. Two of the five survivors developed communicating hydrocephalus, and one had a subdural empyema. In a case of neonatal meningitis caused by Salmonella enterica serotype Ancona, the pathogen was isolated simultaneously from the newborn’s CSF, parental fecal samples, and the mother’s breast milk [175].

Reed and Klugman [176] 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 four had late-onset infection with acquisition from a carrier or an environmental source. Two neonates developed meningitis, and three died.

Neisseria meningitidis

Although N. meningitidis is a leading cause of bacterial sepsis and meningitis among children and adolescents, it rarely is associated with invasive infection in neonates [12, 26, 177]. N. meningitidis may colonize the female genital tract [178–180] and has been associated with pelvic inflammatory disease [181]. The infant can be infected at delivery by organisms present in the maternal genital tract, or intratérine infection can result during maternal meningococccemia [182]. Meningococcal sepsis is rare in neonates, but more than 50 cases (including 13 from the preantibiotic era) have been described [183–185]. Early-onset and late-onset forms [178, 179, 185] of meningococcal sepsis in neonates have been reported. Purpura similar to meningococcemia in older children has been observed in a 15-day-old infant [186] and a 25-day-old infant [187].

Shepard and colleagues [185] 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 (versus 973.8 per 100,000 for GBS). Sixteen patients had meningitis, and 6 of these also had...
meningococcemia. Six patients had early-onset disease. The overall mortality rate was 14%. Ten isolates were serogroup B, four were serogroup C, three were serogroup Y, one was nongroupable, and four were unavailable. A case of meningococcal meningitis in a 2-week-old infant was successfully treated with no evidence of neurologic sequelae [188].

**HAEMOPHILUS INFLUENZAE**

Because of the introduction of *H. influenzae* type b conjugate vaccines in 1988, there has been a substantial decrease in the incidence of *H. influenzae* type b disease in infants and children in the United States and many other countries [189–191]. Given the estimated proportion of individuals who 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 [192–194].

Despite increased reporting of invasive infections caused by nontypable *H. influenzae* in adults and older children [195–197], such infections in neonates remain uncommon [198–201]. Five clinical syndromes have been associated with neonatal disease caused by *H. influenzae*: (1) sepsis or respiratory distress syndrome, (2) pneumonia, (3) meningitis, (4) soft tissue or joint infection, and (5) otitis media or mastoiditis. The overall mortality rate was 5.5% for 45 cases reviewed by Friessen and Cho [202]; the mortality rate was 90% for 20 infants with a gestation lasting less than 30 weeks. Clinical and epidemiologic characteristics were similar to neonatal disease caused by GBS, including early-onset (<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 nontypable *H. influenzae* and signs of respiratory distress syndrome revealed hyaline membranes with gram-negative coccobacilli within the membranes, similar to findings of hyaline membranes secondary to GBS [203].

Examination of placentas from mothers of infants with sepsis caused by nontypable *H. influenzae* revealed acute chorioamnionitis and acute villitis in some [199]. *H. influenzae* also has been responsible for maternal disease, including bacteremia, chorioamnionitis [204], acute or chronic salpingitis, and tubo-ovarian abscess [200]. A cluster of eight cases of early-onset infections over 53 months caused by β-lactamase-negative, nontypable *H. influenzae* was reported from an NICU in Israel [205]. In this series, a presentation resembling pneumonia rather than classic respiratory distress syndrome characterized the infants’ respiratory problems. Neonatal sepsis caused by *Haemophilus parasuis* [206–208] and *Haemophilus aphrophilus* [209] has 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 [210]. With the exception of *Clostridium tetani* and *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 [211–213]. Newborns are colonized with these organisms during or just before delivery. A review of the literature on neonatal bacteremia caused by anaerobic bacteria by Brook [214] in 1990 included 179 cases, with a mortality rate of 26%. *Bacteroides* and *Clostridium* species were the most common isolates. Predisposing factors for infection included premature rupture of membranes, preterm delivery, and necrotizing enterocolitis.

Anaerobic bacteria have been isolated from the blood of newborns with sepsis [212,215,216], from various organs at autopsy [217], from an infant with an adrenal abscess [218], from an infant with an infected cephalhematoma [219], and from infants with necrotizing fasciitis of the scalp associated with placement of a scalp electrode [220]. Feder [221] reviewed meningitis caused by *Bacteroides fragilis*; seven of nine reported cases occurred in neonates.

The incidence of neonatal sepsis caused by anaerobic bacteria is uncertain, but more recent data available from surveys suggest the incidence is low (<5%) [12,14,214]. Noel and colleagues [215] identified 29 episodes of anaerobic bacteremia in neonates in the intensive care unit at New York Hospital during 18 years. Chow and coworkers [217] analyzed 59 cases of neonatal sepsis associated with anaerobic pathogens and classified them into four groups: (1) transient bacteremia after premature rupture of membranes and maternal amnionitis, (2) sepsis after postoperative complications, (3) fulminant septicemia (in the case of clostridial infections), and (4) intrauterine death associated with septic abortion. The mortality rate associated with neonatal anaerobic sepsis reported in the literature ranges from 4% to 38% [217,222,223].

Serious infections of the bloodstream or CNS of neonates caused by *Bacillus cereus* have been reported [224,225] and in certain cases have proven intractable and refractory to antibiotic therapy [226,227]. One outbreak of *B. cereus* infections in an NICU was traced to contamination of balloons used in mechanical ventilation [228]. *B. fragilis* has been identified as a cause of pneumonia, sepsis, or meningitis in the immediate newborn period [229–231].

Infections caused by *Clostridium* species can be localized, as in the case of omphalitis [232], cellulitis, and necrotizing fasciitis [233], or can manifest as sepsis or meningitis [234]. Disease in neonates has been related to *Clostridium perfringens*, *Clostridium septicum*, *Clostridium sordellii*, *Clostridium butyricum*, *Clostridium tertium*, and *Clostridium paraputrificum* [235]. The presenting signs usually are similar to signs of other forms of bacterial sepsis. Chaney [234] reported a case of bacteremia caused by *C. perfringens* in a mother and neonate in which the neonate had classic features of adult clostridial sepsis, including active hemolysis, hyperbilirubinemia, and hemoglobinuria. Motz and colleagues [236] reviewed five...
cases of clostridial meningitis resulting from \textit{C. butyricum} and \textit{C. perfringens}. Clostridial sepsis has a high mortality rate [234].

**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 neonatal mortality in developing countries, resulting in an estimated 180,000 deaths annually [237]. In the United States, tetanus in the newborn is exceedingly rare [238]. Since 1984, only three cases of neonatal tetanus have been reported [238–240]. 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 [241].

In many developing countries, the incidence and mortality of neonatal tetanus remain startlingly high [242–245]. Mustafa and colleagues [246] 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 per 1000 live births, more than double that reported from the stable rural community (3.2 per 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 [247]. Among 62 cases of neonatal tetanus in Ethiopia, 90% were born at home, and 70% lacked antenatal care [245]. Three quarters of infants in this series died in the hospital, and risk factors for fatal outcome included an incubation period of less than 1 week, onset of symptoms less than 48 hours, tachycardia, and fever [245]. The mortality rate for neonates with tetanus in Lima, Peru, was 45% and was not improved with use of intrathecal tetanus antitoxin [248]. A meta-analysis of intrathecal therapy in tetanus suggested benefit in adults, but not in neonates [249].

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 wound as the most important risk factor [250]. Although commercial ghee is available in Pakistan, the ghee used in rural areas is made at home from unpasteurized milk. Oudesluys-Murphy [251] 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 [251–254].

**MIXED INFECTIONS**

Multiple organisms frequently are present in brain, liver, or lung abscesses; aspirates in the lung after pneumonia; or pleural empyema. Such mixed infections infrequently are found in cultures of the blood or CSF, however. When several species are found, the significance of each is uncertain because it is possible that none 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 necrotizing enterocolitis in a very low birth weight infant. Neonatal meningitis caused by \textit{S. pneumoniae} and \textit{Acinetobacter calcoaceticus} [255] and sepsis caused by \textit{P. aeruginosa} and \textit{Yersinia enterocolitica} [256] 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 Tassin and coworkers [257] in 5% of 231 Swedish neonates, by Vesikari and associates [258] in 4% of 377 Finnish infants, and by Bruun and Paerregaard [259] in 7% of 81 Danish neonates. Faix and Kovarik [260] reviewed the records of 385 specimens of blood or CSF submitted to the microbiology laboratories at the University of Michigan Medical Center for the period of 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 rate was high (60%).

Factors predisposing to mixed infection included prolonged rupture of membranes (>24 hours); total parental nutrition; necrotizing enterocolitis; presence of an intravascular catheter or ventriculostomy; and entities associated with multiple pathogens, including peritonitis, pseudomembranous colitis, and hepatic necrosis. Chow and colleagues [217] reported polymicrobial bacteremia in eight newborns with anaerobic coisolates or aerobic and anaerobic organisms in combination. Jarvis and associates [261] reported an outbreak of polymicrobial bacteremia caused by \textit{K. pneumoniae} and \textit{E. cloacae} associated with use of a contaminated lipid emulsion.

Mixed infections also can include bacteria and viruses or bacteria and fungi, typically \textit{Candida}, in the situation of intravascular central catheter or peritoneal infections associated with bowel perforation. Sferra and Pacini [262] reported mixed viral-bacterial meningitis in five patients, including neonates with CSF isolates of enterovirus and GBS in a 10-day-old infant and enterovirus and \textit{Salmonella} in a 12-day-old infant.

**UNCOMMON BACTERIAL PATHOGENS**

Numerous additional bacterial pathogens have been identified as rare or uncommon causes of neonatal sepsis and meningitis. These are listed in Table 6–8 with their references and were reviewed by Giacoia [263].
The reported incidence of neonatal sepsis varies from less than 1 to 8.1 cases per 1000 live births [12,116,123,257,264–269]. A 2-year study of 64,858 infants from the Atlanta metropolitan area beginning in January 1982 (Table 6–9) reported an incidence of early-onset group B streptococcal disease of 1.09 per 1000 live births and an incidence of 0.57 per 1000 live births for late-onset disease [267]. The increased usage of intrapartum antibiotic prophylaxis for women with group B streptococcal colonization with or without other risk factors associated with neonatal group B streptococcal disease has been associated with a 70% reduction in the incidence of early-onset group B streptococcal sepsis to 0.44 per 1000 live births in 1999, a rate comparable to that of late-onset sepsis (see Chapter 13 [7]).

The incidence of meningitis usually is a fraction of the number of neonates with early-onset sepsis. During the 8-year period 1986-1994 at the Soroka University Medical Center in southern Israel, Greenberg and colleagues [12] found incidences of neonatal bacterial sepsis of 3.2 cases per 1000 live births and of meningitis of 0.5 case per 1000 live births. 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 (see Table 6–6).

### 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 low birth weight, 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.

### TABLE 6–8 Unusual Pathogens Responsible for Neonatal Sepsis and Meningitis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Achromobacter species</td>
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<td>Acinetobacter species</td>
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<td>Bacillus anthracis</td>
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<tr>
<td>Bacillus cereus</td>
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<td>Borrelia (relapsing fever)</td>
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<td>Brucella species</td>
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<td>Burkholderia cepacia</td>
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<td>Burkholderia pseudomallei</td>
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<td>Campylobacter species</td>
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<td>Capnocytophaga species</td>
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<td>Corynebacterium species</td>
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<td>Edwardsiella tarda</td>
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<td>Escherichia bermanii</td>
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<td>Chryseobacterium (Flavobacterium) species</td>
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<td>Gardnerella vaginalis</td>
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<td>Ochrobacterium anthopri</td>
<td>789</td>
</tr>
<tr>
<td>Pantoea agglomerans</td>
<td>790</td>
</tr>
<tr>
<td>Pasteurella species</td>
<td>715, 791, 792</td>
</tr>
<tr>
<td>Pleasomonas species</td>
<td>793-795</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>796-798</td>
</tr>
<tr>
<td>Pseudomonas pseudomallei</td>
<td>799</td>
</tr>
<tr>
<td>Psychrobacter immululo</td>
<td>800</td>
</tr>
<tr>
<td>Ralstonia pickettii</td>
<td>801</td>
</tr>
<tr>
<td>Rothia dentocariosa</td>
<td>802</td>
</tr>
<tr>
<td>Shigella sonnei</td>
<td>803-805</td>
</tr>
<tr>
<td>Staphylococcus capitis</td>
<td>806</td>
</tr>
<tr>
<td>Stomatococcus mucilaginosus</td>
<td>807</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>808, 809</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>810, 811</td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td>812</td>
</tr>
</tbody>
</table>

### TABLE 6–9 Incidence and Mortality of Group B Streptococcal Disease by Birth Weight, Atlanta 1982-1983

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>Total Births</th>
<th>Early Onset</th>
<th>Late Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases/Deaths</td>
<td>Cases/1000</td>
<td>Cases/Deaths</td>
</tr>
<tr>
<td>&lt;1500 g</td>
<td>835</td>
<td>5 (1)</td>
<td>5.99</td>
</tr>
<tr>
<td>1500-2499 g</td>
<td>4380</td>
<td>11 (2)</td>
<td>2.51</td>
</tr>
<tr>
<td>&gt;2500 g</td>
<td>59,303</td>
<td>53 (5)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

### Birth Weight

The factor associated most significantly with enhanced risk for bacterial sepsis and meningitis in neonates is low birth weight (see Tables 6–5 and 6–9) [12,18,270–272]. Infection is the most common cause of death in infants with very low birth weight [271,272]. 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 study in England and Wales, neonates weighing less than 2000 g at birth acquired meningitis six times more frequently than infants weighing more than 2000 g [26]. The lower the infant’s birth weight, the higher is the incidence of sepsis (see Table 6–5). An Israeli study of 5555 very low birth weight infants documented the increased risk of late-onset sepsis with decreasing birth weight; late-onset sepsis 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 neonates weighing 750 to 999 g, and 53% of neonates weighing less than 750 g at birth [16]. In a study of infants in Atlanta (see Table 6–9), the importance of birth weight was identified as a predisposing factor for development of early-onset and late-onset sepsis. If very low birth weight infants survived the first days of life, rates of sepsis decreased, but remained elevated [267]; 16% of 2416 infants with birth weights of 501 to 1500 g who were enrolled in a study sponsored by NICHD developed sepsis at a median of 17 days of age [18].

### Risk Factors of Infant and Mother

The relative importance of other factors associated with systemic infection in the newborn is more difficult to define. In their prospective study of 229 infants with sepsis and meningitis, Greenberg and coworkers [12] found that certain conditions were common: 130 (57%) were premature (<37 weeks’ 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 [273] found that maternal urinary tract infection, 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 group B streptococcal sepsis in a study from Chicago [274] were affected by birth weight, duration of rupture of membranes, and occurrence of maternal peripartum fever. Infants with one or more of these perinatal risk factors had an attack rate of 8 per 1000 live births and a mortality rate of 33% compared with infants without such risk factors, who had an attack rate of 0.6 per 1000 live births and a mortality rate of 6% (Table 6–10). Maternal fever during labor or after delivery suggests a concurrent infectious event in the 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 more than 38 °C (>100.4 °F) occurred an average of 6 hours after initiation of epidural anesthesia in 14.5% of women receiving an epidural anesthetic compared with 1% 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% in women with 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%) [275]. Fetal 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 Table 6–11. 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%). More recent published data concur with the data observed 30 years ago. The National Center for Health Statistics reported continued...
disparities between blacks and whites in maternal and infant health indicators [277]. In 1996, significant differences were found between blacks and the general population in terms of neonatal mortality (9.6 deaths versus 4.8 deaths per 1000 live births), low birth weight (13% versus 7.4%), and severe complications of pregnancy (23 complications versus 14 complications per 100 deliveries). A review of the literature from 1966-1994 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 group B streptococcal disease in infants from the Atlanta metropolitan area [267], 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 than in white infants. After controlling for other significant risk factors, such as low birth weight and maternal age younger than 20 years, 30% of early-onset disease and 92% of late-onset disease could be attributed to black race. The increased incidence of group B streptococcal 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 13.5 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 group B streptococcal 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 (Table 6-12) [280,281]. This difference may partially reflect the fact that female infants had lower rates of respiratory distress syndrome (i.e., hyaline membrane disease) than 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 of 28 to 40 weeks’ gestation. Female infants had higher indices of pulmonary maturity than 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 [12,283-285].

**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, including unique cultural features and sexual practices, local obstetric and nursery practices, and patterns of antimicrobial agent usage. The bacteriology of neonatal sepsis among male infants [12,283-285].
In tropical areas, a different pattern can be observed [289–291]. In Riyadh, Saudi Arabia, from 1980–1984, *E. coli*, *Klebsiella* species, and *Serratia* species were the dominant causes of neonatal sepsis; GBS was an infrequent cause [291]. Later data from this geographic location revealed *E. coli* and CoNS were the most common pathogens, however, causing early-onset and late-onset sepsis [292].

Every year, 4 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, India, and Pakistan. 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].

GBS is the most frequent cause of early-onset 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 [298–300]. 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% with a vertical transmission rate of 22.5% [299]. Middle-class women followed in the private setting were more frequently colonized with GBS than women 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 [300] 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 employing 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 employed 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, seems to be important in determining infants at risk for infection. The most significant factors enhancing risk for neonatal sepsis are low birth weight 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 [301] evaluating the awareness of perinatal group B streptococcal 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 infants with very low birth weight have one or more procedures that place them at risk for infection. Any disruption of the protective capability 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 [302].

**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 35). 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 35). Epidemics or outbreaks associated with contamination of nursery equipment and solutions caused by *Proteus* species, *Klebsiella* species, *S. marcescens*, *Pseudomonas* species, and *Flavobacterium* also have been reported. An unusual and unexplained outbreak of early-onset group B streptococcal sepsis with an attack rate of 14 per 1000 live births occurred in Kansas City during January through August of 1990 [303].

Molecular techniques to distinguish among bacterial strains are 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 [154,304]. 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–based methods are widely used tools to assign strain identity or relatedness [305–307].

Antimicrobial agents play a major role in the ecology of the microbial flora in the nursery. Extensive
prolonged use of these drugs eliminates susceptible strains and allows for 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 [45] in their use of benzathine penicillin G to control an outbreak of group A streptococcal 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 Zwet and colleagues [308] 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 eight 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 [309].

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 [126] performed a prospective investigation of extended-spectrum β-lactamase-producing *K. pneumoniae* colonization and infection during the 2-year period 1997–1999 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 [137] concluded that indiscriminate use of third-generation cephalosporins was responsible for the selection of extended-spectrum β-lactamase–producing, multiresistant strains in their NICU, where extended-spectrum β-lactamase production was detected in 86.6% of *Klebsiella* species, 73.4% of *Enterobacter* species, and 63.6% of *E. coli* strains. Nosocomial infections in the nursery and their epidemiology and management are discussed further in Chapter 35.

**PATHOGENESIS**

The developing fetus is relatively protected from the microbial flora of the mother. Procedures disturbing the integrity of the uterine contents, such as amniocentesis [310], cervical cerclage [311,312], transcervical chorionic villus sampling [313], or percutaneous umbilical blood sampling [310,314], can permit entry of skin or vaginal organisms into the amniotic sac, however, causing amnionitis and secondary fetal infection.

Initial colonization of the neonate usually occurs after rupture of the maternal membranes [280,315]. In most cases, the infant is colonized with the microflora of the birth canal during delivery. 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 [316]. Fetal infection can result from aspiration of infected amniotic fluid [317], leading to stillbirth, premature delivery, or neonatal sepsis [310,316,318,319]. The organisms most commonly isolated from infected amniotic fluid are GBS, *E. coli* and other enteric bacilli, anaerobic bacteria, and genital mycoplasmas [310,318].

Studies have reported that amniotic fluid inhibits the growth of *E. coli* and other bacteria because of the presence of lysozyme, transferrin, immunoglobulins (IgA and IgG, but not IgM), zinc and phosphate, and lipid-rich substances [319–325]. The addition of meconium to amniotic fluid in vitro has resulted in increased growth of *E. coli* and GBS in some studies [326,327]. In other in vitro studies of the bacteriostatic activity of amniotic fluid, the growth of GBS was not inhibited [328–330]. Bacterial inhibition by amniotic fluid is discussed further 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 hema
togenous infection during or shortly after 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 the mother and neonate are cases caused by *H. influenzae* type b [331], *H. parainfluenzae* [208], *S. pneumoniae* [58,332], group A streptococcus [42], *N. meningitidis* [182], Citrobacter species [333], and *Morganella morganii* [334]; concurrent cases of meningitis have been reported as caused by *S. pneumoniae* [335], *N. meningitidis* [182], and GBS [336]. Many neonates are bacteremic at the time of delivery, which indicates that invasive infection occurred antepartum [337]. Infants with signs of sepsis during the first 24 hours of life also have the highest mortality rate [10]. These data suggest the importance of initiating chemoprophylaxis for women with group B streptococcal colonization or other risk factors for invasive disease in the neonate at the time of onset of labor (see Chapter 13) [338].

Microorganisms acquired by the newborn 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* [339]. In most cases, the microorganisms proliferate at the initial site of attachment without resulting in illness. Occasionally, 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 abscesses can occur in infants who have electrodes placed
during labor for monitoring of heart rate [85,340,341]. The incidence of this type of infection in the hands of experienced clinicians is generally quite low (0.1% to 5.2%), however [342]. A 10-year survey of neonatal enterococcal bacteremia detected 6 of 44 infants with scalp abscesses as the probable source of their bacteremia [85]. The investigators were unable to deduce from the data available 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 the skin, such as inoculum size [351] and infection) are at increased risk for sepsis. Microbial factors traumatic delivery, fetal hypoxia, maternal peripartum birth weight, premature rupture of membranes, septic or Infants with one or more predisposing factors (e.g., low NEONATAL BACTERIAL SEPSIS

such as an infected circumcision site or infection with hemorrhage or infarction. Certain organisms are in tissue that is devitalized because of anoxia or vasculitis of microorganisms (i.e., septic emboli) and proliferation with necrosis [23]. 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 apparent, 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 [344] 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 [345,346]. 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 [315], but in most circumstances, bacteria gain access to the brain through the bloodstream to the choroid plexus during the course of sepsis [344]. Infants with developmental defects, such as a midline dermal sinus or myelomeningocele, are particularly susceptible to invasion of underlying nervous tissue [23].

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 infection. Certain organisms are more likely than others to invade nervous tissue and cause local or widespread necrosis [23]. Most cases of meningitis related to C. koseri (formerly C. diversus) and E. sakazako-kii are associated with formation of cysts and abscesses. Other gram-negative bacilli with potential to cause brain abscesses include Proteus, Citrobacter, Pseudomonas, S. marcescens, and occasionally GBS [155,166,347–349]. Volpe [350] commented 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., low birth weight, premature rupture of membranes, septic or traumatic delivery, fetal hypoxia, maternal peripartum infection) are at increased risk for sepsis. Microbial factors such as inoculum size [351] and virulence properties of the organism [310] undoubtedly are significant. Immature 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 have impairment of various immune functions, including neutrophil bactericidal activity, antibody response, lymphocyte proliferation, and complement functions (see Chapter 4). Indirect hyperbilirubinemia that commonly occurs with breast-feeding jaundice rarely is associated with neonatal sepsis [352]. 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 agent [353]. Evidence of diffuse hepatocellular damage and bile stasis has been described in such infected and jaundiced infants [354,355].

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 [356–359]. 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. The exact cause of increased morbidity in infants presenting with hypothermia is poorly understood, however. In many infants, it is unclear whether hypothermia predisposes to or results from bacterial infection. In a large outbreak of S. marcescens neonatal infections affecting 159 cases in Gaza City, Palestine, hypothermia was the most common presenting symptom, recorded in 38% of cases [360].

Infants with galactosemia have increased susceptibility to sepsis caused by gram-negative enteric bacilli, in particular E. coli [361–363]. Among eight infants identified with galactosemia by routine newborn screening in Massachusetts, four had systemic infection caused by E. coli [362]. Three of these four 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 none of the infants. Galactosemic neonates seem to 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 [364,365]. The gold standard for diagnosis of classic galactosemia is measurement of galactose-1-phosphate uridylytransferase activity in erythrocytes, and the sole therapy is galactose restriction in the diet [366]. Shurin [364] observed that infants became ill when serum galactose levels were high 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 in infants with hereditary fructose intolerance [367]. 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 [368,369].

Iron may have an important role in the susceptibility of neonates to infection. Iron added to serum in vitro enhances the growth of many organisms, including *E. coli*, *Klebsiella* species, *Pseudomonas* species, *Salmonella* species, *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 [370]. The iron-binding proteins lactoferrin and transferrin are present in serum, saliva, and breast milk. The newborn has low levels of these proteins, however [371]. The iron-sequestering capacity of oral bovine lactoferrin supplementation may be one contributing factor to its reported efficacy in prophylaxis of bacterial sepsis in very low birth weight infants [372].

Barry and Reeve [373] showed 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 case 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 three cases of sepsis in the infants who did not receive iron. Results of this study were similar to the experience reported by Farmer [374] 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 seem to be safe and do not contribute to a higher rate of sepsis in preterm infants [375].

Studies have suggested a higher risk for contracting ascending intrauterine infection in the first than the second born of twins [376,377]. Comparing delivery methods, no difference was observed in the incidence of neonatal sepsis in twins delivered in the vertex/vertex position compared with cases requiring uterine manipulation (vertex/breech extraction) [378]. Vaginal delivery of twin A followed by cesarean delivery of twin B may be associated with a higher rate of endometritis and neonatal sepsis, however, compared with cases in which both twins are delivered by cesarean section [379].

Pass and colleagues [380] showed that low birth weight twins were at higher risk for group B streptococcal infection than low birth weight singletons; infection developed in 3 of 56 twin births, or 53.5 cases per 1000 live births, compared with infections in 7 of 603 singleton births, or 11.6 cases per 1000 live births. Edwards and associates [381] studied group B streptococcal 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 twins in two pairs and in one twin in four other pairs. Cases of late-onset group B streptococcal disease in twin pairs occurred closely in time to one another: 19 and 20 days of age in one set and 28 and 32 days of age in the other set. In another case report of late-onset group B streptococcal infection in identical twins, twin A had fulminant fatal meningitis, whereas twin B recovered completely. 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 [382].

In twins, the presence of virulent organisms in the environment, especially the maternal genital tract; the 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 monochorial, 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.

The incidence of infection in preterm twins cobedding in the nursery did not differ, however, from twins cared for in separate beds [383].

Infections in twins, including disease related to *Treponema pallidum*, echoviruses 18 and 19, and *Toxoplasma gondii*, are discussed in Chapters 18, 24, and 31. Neonatal infections in twins have been caused by group A streptococci (case report of streptococcal sepsis in a mother and infant twins) [384], *Salmonella* species [385], *C. koseri* (brain abscesses in twins) [156], malaria [386,387], coccidioidomycosis [388], cytomegalovirus infection [389–391], and rubella [392].

**UMBILICAL CORD AS A FOCUS OF INFECTION**

Historically, the umbilical cord was a particularly common portal of entry for systemic infection in newborns, 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 [393]. 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 [394]. In 1930, Cruickshank [395] wrote, “in Prague, before antiseptic and aseptic dressing of the cord was introduced, sepsis neonatorum was as common as puerperal sepsis . . . after the introduction of cord dressing in the hospital the
number of newborn children developing fever sank from 45% to 11.3%, [396]

Closure of the umbilical vessels and the subsequent aseptic necrosis of the cord begins 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* species, and shortly thereafter with fecal organisms [396,397]. 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 (Fig. 6–1) [396,398,399]. Although umbilical discharge or an “oozing” cord is the most common manifestation of omphalitis, periumbilical cellulitis and fascitis are the conditions most often associated with hospitalization [398]. Infants presenting with fasciitis have a high incidence of bacteremia, intra-vascular coagulopathy, shock, and death [398]. 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 fasciitis [393]. Septic embolization arising from the infected umbilical vessels is uncommon, but can produce metastatic spread to various organs, including the lungs, pancreas, kidneys, and skin [394]. Such emboli can arise from the umbilical arteries and from 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 30 of life [400].

Omphalitis is now a rare infection in developed countries because of modern umbilical cord care. Complications of omphalitis include various infections, such as septic umbilical arteritis [394,401], suppurrative thrombophlebitis of the umbilical or portal veins or the ductus venosus [401–403], peritonitis [399,401,402,404], intestinal gangrene [399], pyourachus (infection of the urachal remnant) [405], liver abscess, endocarditis, pyelophlebitis [399,406], and subacute necrotizing funisitis [407]. Some of these infections can occur in the absence of signs of omphalitis [394,401].

### 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.

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, compared with placebo [408]; however, the impacts of this practice on the risk of neonatal infection differed among early studies [408,409]. Roberts and Dalziel [410] more recently performed a large meta-analysis of 21 randomized controlled studies from the Cochrane Pregnancy and Childbirth Group Trials register, comprising 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 (relative risk 0.69), intensive care admissions (relative risk 0.80) and systemic infections in the first 48 hours of life (relative risk 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-addicted [411–413] and heroin-addicted [414,415] 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 [415,416]. Drug abuse is a multifactorial problem; it is virtually impossible to separate the consequences of direct pharmacologic effects on the fetus from the consequences secondary to...
inadequate nutrition, lack of prenatal care, and infectious medical complications encountered in addicted pregnant women [415,416].

ADMINISTRATION OF DRUGS OTHER THAN ANTIBIOTICS TO THE NEONATE

Administration of indomethacin to neonates for the closure of a patent ductus arteriosus has been associated with a higher incidence of sepsis and necrotizing enterocolitis in the indomethacin-treated groups compared with infants for whom surgery or other medications [417–419]. The mechanism by which indomethacin predisposes low birth weight infants to sepsis is unknown [420]. A meta-analysis of studies comparing ibuprofen with indomethacin for patent ductus arteriosus closure did not identify differences in the incidence of sepsis, mortality, or duration of hospitalization [421].

O’Shea and colleagues [420] described the outcomes of very low birth weight (500 to 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 compared with a control population. Further trials of dexamethasone administration for prophylaxis of chronic lung disease in very low birth weight infants confirmed a lack of increased risk for sepsis [422].

A strong association between intravenous lipid administration to newborns and bacteremia caused by CoNS has been established [99,423]. 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 [423] identified exposure to intravenous lipids at anytime during hospitalization as the most important risk factor (odds ratio 9.4) for development of CoNS bacteremia in very low birth weight infants, calculating that 85% 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 every 72 hours may reduce bloodstream infection rates and mortality by approximately 50% [424].

More recently, a surprisingly strong association between ranitidine therapy in neonates admitted to one NICU and the risk of late-onset bacterial sepsis was reported [425]. The mechanism for such an association is unclear, but warrants further analysis.

PATHOLOGY

Infants with severe and rapidly fatal sepsis generally have minimal or no histologic indication of an infectious process [315,426]. Findings typical of bacteremia, such as multiple disseminated abscesses of similar size, purulent vasculitis, and intravascular identification of bacteria, are evident in a few infants [426]. 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 [344,426]. The pathology of infections of the respiratory, genitourinary, and gastrointestinal tracts and focal suppurrative diseases is discussed in subsequent chapters.

The pathology of neonatal meningitis [344,427,428] and brain abscess [429,430] is similar to that in older children and adults. The major features are ventriculitis (including encephalitis 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 [431]. 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 collections can collect around the base of the brain without a significant increase in intracranial pressure. Hydrocephalus may result from ductal or aqueductal obstruction, or from closure of the fourth ventricle by purulent exudate or by means of inflammatory impairment of CSF resorption through the arachnoid channels [344,432]. Ventriculitis has been described in 20% to 90% of cases [23,344,432] and often is the reason for persistence of bacteria in CSF when obstruction ensues and for a slow clinical recovery [433]. 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 large size of the lesions and poor capsule formation. They occur most frequently in association with meningitis caused by C. koseri, E. sakazakii, S. marcescens, and Proteus mirabilis and usually are located in the cerebrum, involving several lobes [153,166,347,429]. 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 [347,350].

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 as a sign of infection by Schiano and colleagues [434]. 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 to 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 [435,436].

A low Apgar score, suggesting distress at or before delivery, also has been correlated with sepsis and
associated adverse outcomes in the newborn period [435,437]. 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 [438]. Among infants born after rupture of the amniotic membranes for 24 hours or more, St. Geme and colleagues [316] found a significant increase in the risk for perinatal bacterial infection in infants 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 higher attack rates for sepsis. Because low Apgar scores (<3 at 1 minute, <6 at 5 minutes) were significantly associated with low birth weight and shorter gestation, the use of the score is less valuable as an indicator of sepsis in premature than in term infants [439].

The earliest signs of sepsis often are subtle and nonspecific. Poor feeding, diminished activity, or “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 [440]. The nonspecific and subtle nature of the signs of sepsis in newborns is even more problematic in identifying sepsis in infants with very low birth weight. In a study by Fanaroff and colleagues [18], the clinical signs of late-onset sepsis 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 skin manifestations, including petechiae, abscesses, and sclerema [440]. The most common laboratory indicators of the metabolic derangement accompanying sepsis.

Bonadio and coworkers [441] attempted to determine the most reliable clinical signs of sepsis in more than 200 febrile infants from birth to 8 weeks old. They found that changes in affect, peripheral perfusion, and respiratory status best identified 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. More recently, Kudawla and associates [442] developed a scoring system for late-onset neonatal sepsis in infants weighing 1000 to 2500 g. Clinical parameters included lethargy, tachycardia, grunting, abdominal distention, increased prefeed residual gastric aspirates, fever, and chest retractions. These data needed to be combined with laboratory parameters such as elevated C-reactive protein or absolute neutrophil or band count to achieve high sensitivity and specificity.

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 [441], even among infants with maternal risk factors for infection [443]. Occasionally, bacteremia occurs without clinical signs [444–446]. Albers and associates [444] described case histories of three 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 during the first 10 days of life. The same pathogen was isolated repeatedly (i.e., three, three, and two times) from the blood of the three infants even though they remained well. The infants subsequently were treated with appropriate antimicrobial agents.

Bacteremia caused by GBS can occur with minimal or no systemic or focal signs [446–448], and it may be sustained over several days [449]. Most healthy-appearing infants with group B streptococcal bacteremia were born at term and had early-onset (<7 days old) infection. Similarly, among 44 neonates with enterococcal bacteremia, 3 (76%) of 18 with early-onset infection but none with late-onset infection appeared well [85]. The true incidence of bacteremia without clinical signs is uncertain because few cultures of blood are performed for infants who show no signs of sepsis.

Table 6–13 lists the common clinical signs of neonatal bacteremia. Clinical signs of neonatal bacterial meningitis are presented in Table 6–14. Noninfectious conditions with clinical manifestations similar to those of sepsis are listed in Table 6–15.

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>Percent of Infants with Sign</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>33</td>
</tr>
<tr>
<td>Lethargy</td>
<td>25</td>
</tr>
<tr>
<td>Irritability</td>
<td>16</td>
</tr>
<tr>
<td>Anorexia</td>
<td>28</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>17</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
</tr>
</tbody>
</table>

Data from references 3, 4, 737, and 738.

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>Percent of Infants with Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthermia 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>

Data from references 20, 26, 450, and 450.
**TABLE 6–15** Differential Diagnosis: Clinical Signs Associated with Neonatal Sepsis and Some Noninfectious Conditions

<table>
<thead>
<tr>
<th><strong>Respiratory Distress (Apnea, Cyanosis, Costal and Sternal Retraction, Rales, Grunting, Diminished Breath Sounds, Tachypnea)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient tachypnea of the newborn</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>Atelectasis</td>
</tr>
<tr>
<td>Aspiration pneumonia, including meconium aspiration</td>
</tr>
<tr>
<td>Pneumonothorax</td>
</tr>
<tr>
<td>Pneumomediastinum</td>
</tr>
<tr>
<td>CNS disease: hypoxia, hemorrhage</td>
</tr>
<tr>
<td>Congenital abnormalities, including tracheoesophageal fistula, choanal atresia, diaphragmatic hernia, hypoplastic lungs</td>
</tr>
<tr>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td>Hypothermia (neonatal cold injury)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Neonatal drug withdrawal syndrome</td>
</tr>
<tr>
<td>Medication error with inhaled epinephrine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Temperature Abnormality (Hyperthermia or Hypothermia)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered environmental temperature</td>
</tr>
<tr>
<td>Disturbance of CNS thermoregulatory mechanism, including anoxia, hemorrhage, kernicterus</td>
</tr>
<tr>
<td>Hyperthyroidism or hypothyroidism</td>
</tr>
<tr>
<td>Neonatal drug withdrawal syndrome</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Vaccine reaction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Jaundice</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast milk jaundice</td>
</tr>
<tr>
<td>Blood group incompatibility</td>
</tr>
<tr>
<td>Red blood cell hemolysis, including blood group incompatibility, G6PD deficiency</td>
</tr>
<tr>
<td>Resorption of blood from closed space hemorrhage</td>
</tr>
<tr>
<td>Gastrointestinal obstruction, including pyloric stenosis</td>
</tr>
<tr>
<td>Extrahepatic or intrahepatic biliary tract obstruction</td>
</tr>
<tr>
<td>Inborn errors of metabolism, including galactosemia, glycogen storage disease type IV, tyrosinemia, disorders of lipid metabolism, peroxisomal disorders, defective bile acid synthesis (trihydroxycoprostanic acidemia)</td>
</tr>
<tr>
<td>Hereditary diseases, including cystic fibrosis, $\alpha_1$-antitrypsin deficiency, bile excretory defects (Dubin-Johnson syndrome, Rotor syndrome, Byler disease, Aagenaes syndrome)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Prolonged parenteral hyperalimentation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Hepatomegaly</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell hemolysis, including blood group incompatibility, G6PD deficiency</td>
</tr>
<tr>
<td>Infant of a diabetic mother</td>
</tr>
<tr>
<td>Inborn errors of metabolism, including galactosemia, glycogen storage disease, organic acidemias, urea cycle disorders, hereditary fructose intolerance, peroxisomal disorders</td>
</tr>
<tr>
<td>Biliary atresia</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Benign liver tumors, including hemangioma, hamartoma</td>
</tr>
<tr>
<td>Malignant liver tumors, including hepatoblastoma, metastatic neuroblastoma, congenital leukemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Gastrointestinal Abnormalities (Anorexia, Regurgitation, Vomiting, Diarrhea, Abdominal Distention)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal allergy</td>
</tr>
<tr>
<td>Overfeeding, aerophagia</td>
</tr>
<tr>
<td>Intestinal obstruction (intraluminal or extrinsic)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Hypercalcemia or hypocalcemia</td>
</tr>
</tbody>
</table>

*Continued*
The temperature of an infant with sepsis may be elevated, depressed, or normal [447–453]. In a multicenter survey of nearly 250 infants with early-onset group B streptococcal 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 [447]. Comparing temperatures by gestational age, it was observed that term infants were more likely to have fever than preterm infants (12% versus 1%), whereas preterm infants more frequently had hypothermia (13% versus 3%). Phagocytes of an infant born after an uncomplicated labor can produce adult concentrations of interleukin-1, a potent pyrogen. The phagocytes of infants born after cesarean section have a markedly suppressed ability to produce this pyrogen [454]. In the studies reviewed in Table 6–13, approximately 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 °C (100.4 °F) measured rectally generally is accepted...
SECTION II Bacterial Infections

as the lower limit of the definition of fever. Although some clinical studies indicate that axillary [455], skin-mattress [456], and infrared tympanic membrane thermometry [457] are accurate and less dangerous than rectal measurements for obtaining core temperature, the reliability of these methods, particularly in febrile infants, has been questioned [458–460]. A 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 [461]. 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 [453].

There is no study of temperatures in neonates that is prospective, assesses all infants (febrile and afebrile), includes rectal and axillary temperatures, includes premature and term infants, and requires positive cultures of blood or other body fluids to define invasive bacterial infection. Voora and colleagues [462] observed 100 term infants in Chicago with an axillary or rectal temperature of equal to or greater than 37.8°C (≥100.1°F) during the first 4 days of life, and Osborn and Bolus [463] 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 equal to or greater than 37.8°C (≥100.1°F) per axilla [462]. 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 seven infants with sustained fever in the study by Osborn and Bolus [463], five had proven bacterial or viral infections. Of 65 infants reported by Voora and colleagues [462], 10 had documented systemic bacterial disease. Temperature elevation without other signs of infection was infrequent. Only one infant (with cytomegalovirus infection) of the five Los Angeles infants had fever without other signs. Only 2 infants (with bacteremia caused by E. coli or GBS) 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 to have 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 [353,464–468]. 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 regardless of the type of bacterial pathogen.

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 colleagues [469] evaluated liver size in healthy term infants examined within 24 hours of birth and again at 72 to 96 hours. Measurements ranged from 1.6 to 4 cm below the costal margin, and there was no significant difference between early and late examinations. Reiff and Osborn [470] 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 newborn 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 [125]. Splenomegaly is less common than hepatomegaly and infrequently is mentioned in reports of bacterial sepsis of the newborn [471].

Lymph nodes infrequently are palpable in newborns unless they are infected with viruses, spirochetes, or protozoa. Bamji and coworkers [472] examined 214 healthy neonates in New York and identified palpable nodes at one or more sites in one third of the infants. Embree and Muriithi [473] 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 group B streptococcal infection in infants,
is a condition in which local inflammation can be the only initial sign of sepsis that can include concurrent meningitis [474–476].

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

Various skin lesions can accompany bacteremia, including cellulitis, abscess, petechiae, purpuric lesions, sclerema, erythema multiforme, and ecthyma. These lesions are described in Chapter 10.

NEUROLOGIC SIGNS

The onset of meningitis in the neonate is accompanied by neural 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 6–14, but Volpe [350] identified seizures, in many cases subtle, in 75% of infants with bacterial meningitis. Approximately 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 [350]. 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 [448,477]. 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 18% of term infants and 17% of preterm infants [23]. Nuchal rigidity, an important sign in older children and adults, is uncommon in neonates [23]. 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 [432,438]. Occasionally, the onset of meningitis has been followed by a transient or persistent diabetes insipidus [477].

Early clinical signs of brain abscess in the newborn are subtle and frequently unnoticed by the physician or parent. Presenting signs include signs of increased intracranial pressure (e.g., emesis, bulging fontanelle, enlarging head size, separated sutures), focal cranial signs (e.g., hemiparesis, focal seizures), and acute signs of meningitis. Of six infants with brain abscesses described by Hoffman and colleagues [429], 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 [478], pseudomonal endophthalmitis in a premature neonate with late-onset sepsis [479], and epidural abscess caused by S. aureus in 3-week-old [480], 4-week-old [481], and 7-week-old infants [482].

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 a term infant who develops late-onset sepsis. 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 presented in Table 6–15. Laboratory tests to assist in the diagnosis of sepsis are discussed in Chapter 36.

MATERNAL HISTORY

Many infants, particularly infants 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, intrapartum scalp electrodes, and traumatic delivery. The following features are identified by the American College of Obstetrics and Gynecology (ACOG) as the basis for identification of women who should receive intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal disease:

1. Antenatal colonization with GBS
2. Unknown group B streptococcal colonization status and
   a. Preterm labor (<37 weeks’ gestation)
   b. Fever during labor (defined by temperature of ≥38°C [≥100.4°F])
   c. Rupture of membranes for 18 or more hours
3. Urine culture that grows GBS during the current pregnancy
4. Prior delivery of a neonate with invasive group B streptococcal infection

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 the NICU was documented using a database of 24,584 cultures from 3710 infants by Evans and colleagues [483]. 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 establish definitively 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 [486-488]. Before the widespread use of automated blood-culturing systems, lysis direct plating was the most often employed 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. Geme and colleagues [489] used this technique to investigate the distinction of sepsis from contamination in cultures of blood growing CoNS.

Time to Detection of a Positive Blood Culture

Bacterial growth is evident in most cultures of blood from neonates within 48 hours [490-492]. With use of conventional culture techniques and subculture at 4 and 14 hours, only 4 of 105 cultures that had positive results (one GBS and three S. aureus) required more than 48 hours of incubation [491]. By use of a radiometric technique (BACTEC 460), 40 of 41 cultures that grew GBS and 13 of 16 cultures with E. coli were identified within 24 hours [492]. 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 [493].

Optimal Number of Cultures

The optimal number of cultures to obtain for the diagnosis of bacteremia in the newborn is 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 [494] 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 Strutters and colleagues [95], 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 [495] 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 [496] 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 per milliliter of blood. These data of Dietzman and coworkers [496] 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 [497,498]. Several more recent studies have found, however, 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 [499-502]. If one blood culture is to be collected before antimicrobial therapy is initiated, a volume of 1 mL or more seems to 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 NICU and are preferred blood culture sampling sites [503-505]. Results of cultures of blood obtained from indwelling umbilical or central venous catheters can present ambiguities in interpretation (e.g., contamination versus catheter colonization versus systemic infection). Obtaining blood cultures from a peripheral vessel and catheters in an ill-appearing neonate is useful in the interpretation of results. A 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 [506].

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 bacteremia 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, or core temperature greater than 38° C or less than 36.5° 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, as follows:

1. Time to growth in conventional media: The longer the time needed to detect growth (>2 to 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 [507], comparisons of results of cultures of blood and cultures of skin at the venipuncture site [508], and quantitative blood cultures [491]. 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 [509] 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. At present, management of a sick premature infant, especially a very low birth weight infant, 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 [510–516]. 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 [511–513,515]. Positive results were found for gram-positive and gram-negative organisms. In contrast to findings reported for adult populations [517], 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 50 colonies per milliliter of *S. aureus* in the peripheral blood; approximately 50% of neonates with *E. coli* bacteremia have higher concentrations [496]. *Candida* and *S. epidermidis* septicemia in young infants also have been diagnosed by this method [518–521]. Reported that bacteria were identified in peripheral blood smears in 17 of 19 infants with septicemia. Rodwell and associates [522] were able to identify bacteria in direct blood smears, however, 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. Buffy-coat examination of blood smears has been 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 [523] found positive cultures of urine in only 1.6% of infants with early-onset sepsis compared with 7.4% of infants with late-onset sepsis. DiGeronimo [524] performed a chart review of 146 clinically septic infants who had cultures of blood and urine. Of 11 infants with positive blood cultures, only one 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, urine should be collected for culture from infants with suspected late-onset sepsis before initiation of antimicrobial therapy. The presence of elevated leukocyte counts (>10 per high-power field) in urine of infants less than 90 days of age is an accurate predictor of urinary tract infections complicated by bacteremia [525].

Because of the difficulty in collecting satisfactory clean-voided specimens of urine from newborns, 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 [526–528]. 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 very low birth weight neonates. Application of a clinical pain scoring system employing a blinded observer and video recording found suprapubic aspiration to provide more discomfort than transurethral catheterization in female and circumcised male infants younger than 2 months of age [529].

**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 andHey [530] found that among ventilated infants who became septic, the same organism usually was present in cultures of tracheal aspirate and blood. Growth of a bacterial pathogen from a tracheal aspirate culture does not predict which infants will develop sepsis, however. Similarly, cultures of the pharynx or trachea do not predict the causative organism in the blood of a neonate with clinical sepsis [531]. A review of the literature by Srinivasan and Vidyasagar [532] suggests endotracheal aspirates are of poor sensitivity (approximately 50%), modest specificity (approximately 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 [533]. 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 [534] 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 [535,536].

**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 *Lamins* (horsehoe crab) amebocytes and bacterial endotoxin was investigated for diagnosis of neonatal meningitis with equivocal results [537–541]. Counterimmunoelectrophoresis also was used successfully for detecting the capsular polysaccharide antigens of various pathogenic bacteria, including *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, and GBS (see Chapter 13) in CSF, serum, and urine. Less complex and more rapid detection methods have replaced these two assays.

Latex agglutination detection now is preferred because of its speed, simplicity, and greater sensitivity for selected organisms. Kits designed to detect cell wall or capsular or cell wall antigen released into body fluids are commercially available. Latex agglutination assays have been shown to be of potential benefit in early detection of bacterial antigens in 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. *N. meningitidis* group B shares a common capsular antigen, however, with the neonatal meningitis pathogen *E. coli* serotype K1, which should allow cross-identification of the latter using a meningococcal latex reagent [542]. The sensitivity of latex agglutination methods for identifying infants with group B streptococcal meningitis ranges from 73% to 100% for CSF and 75% to 84% for urine [543]. Possible cross-reactions have occurred when concentrated urine was tested. GBS cell wall antigen can occasionally cross-react with antigens from *S. pneumoniae*, CoNS, enterococci, and gram-negative enteric bacteria, including *P. 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 [544]. 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 employed 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 should be considered for examination of CSF in any neonate before initiation of therapy. Of infants with sepsis, 15% have accompanying meningitis. The overall incidence of bacterial meningitis is less than 1 case per 1000 infants, but the incidence for low birth weight (<2500 g) infants or premature infants is severalfold higher than the incidence for term infants. Data from NICHD Neonatal Research Network surveyed 9641 very low birth weight infants who survived 3 days or more: 30% had one or more lumbar punctures, and 5% of infants who had lumbar puncture had late-onset meningitis [545]. For the diagnosis of some noninfectious CNS diseases in neonates (e.g., intracranial hemorrhage), cranial ultrasonography and, occasionally, computed tomography (CT) or magnetic resonance imaging (MRI) are the techniques of choice. Among infants with hypoxic-ischemic encephalopathy,
lumbar puncture should be considered only for infants in whom meningitis is a possible diagnosis. Some investigators suggest that too many healthy term infants have a diagnostic evaluation for sepsis, including lumbar puncture, based solely on maternal risk factors and that lumbar puncture rarely provides clinically useful information. Other investigators have questioned the role of lumbar puncture on admission in the premature infant with respiratory distress and found that the yield of the procedure is very low [546–548]. Of more than 1700 infants with respiratory distress syndrome evaluated for meningitis, these high-risk neonates were identified in CSF of only 4. Three of the four infants with meningitis were bacteremic with the same pathogen [548].

A large, retrospective study assessed the value of lumbar puncture 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 one infant was believed to have bacterial meningitis [549]. Fielkow and colleagues [550] found no cases of meningitis among 284 healthy-appearing infants who had lumbar puncture performed because of maternal risk factors, whereas 2.5% of 799 neonates with clinical signs of sepsis had meningitis regardless of maternal risk factors. The value of lumbar puncture has been established for infants with clinical signs of sepsis, but lumbar puncture performed because of maternal risk features in a healthy-appearing neonate is less likely to be useful.

The considerations are quite different for very low birth weight neonates (400 to 1500 g), as documented in a study by Stoll and colleagues [545] performed through NICHD Neonatal Research Network. One third (45 of 134) of these high-risk neonates with meningitis has negative blood cultures. Lower gestational age and prior sepsis were important risk factors for development of meningitis, which carried a significant risk of mortality compared with uninfected infants (23% versus 2%). These results indicate the critical importance of lumbar puncture and suggest that meningitis may be significantly underdiagnosed in very low birth weight infants [545].

### Method of Lumbar Puncture

Lumbar puncture is more difficult to perform in neonates than in older children or adults; traumatic lumbar punctures resulting in blood in CSF are more frequent, and care must be taken in the infant who is in respiratory distress. Gleason and colleagues [551] suggested 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 [552] evaluated the role of locally administered lidocaine before lumbar puncture and found that the local anesthesia decreased the degree of struggling of the infant. Other investigators concluded, however, that local anesthesia failed to influence physiologic changes in the neonate undergoing lumbar puncture [553]. Fiser and colleagues [554] suggested that the administration of oxygen before lumbar puncture prevents most hypoxemia resulting from this procedure in infants.

The physician can choose to withhold or delay lumbar puncture in some infants who would be placed at risk for cardiac or respiratory compromise by the procedure. Weisman and colleagues [555] observed that transient hypoxemia occurred during lumbar puncture 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 lumbar puncture in older children, such as signs of increased intracranial pressure, signs of a bleeding disorder, and infection in the area that the needle would traverse to obtain CSF, are less likely to be concerns in the neonate.

### 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 [556] showed that the blood culture was sterile when CSF yielded a pathogen in 6 (15%) of 39 infants with bacterial meningitis. Franco and colleagues [557] reported that in 26 neonates with bacterial meningitis, only 13 had a positive blood culture. In surveys from two large databases—NICUs managed by the Pediatric Medical Group [558] and 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 very low birth weight neonates with meningitis had negative blood cultures. A significant number of infants with meningitis do not have this diagnosis established unless lumbar puncture is performed.

Ideally, lumbar puncture 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 lumbar puncture 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, lumbar puncture 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 CSF of healthy newborn infants differ from those of older infants, children, and adults (Table 6–16). 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 [559–568]. The cell content in CSF of a neonate is higher than in older infants. Polymorphonuclear leukocytes often are present in CSF of normal newborns,
whereas more than a single polymorphonuclear neutrophil in CSF of older infants or children should be considered abnormal. Similarly, protein concentration is higher in preterm than in term infants and highest in very low birth weight infants (Table 6–17) [568].

In term infants, total protein concentration decreases with age, reaching values of healthy older infants (<40 mg/dL) before the third month of life. In low birth weight infants or preterm infants, CSF leukocyte and protein concentrations decline with postnatal age, but may remain elevated months after birth [569]. CSF glucose levels are lower in neonates than in older infants and can be related to lower concentrations of glucose observed in blood. Healthy term infants may have glucose blood levels of 30 mg/dL, and preterm infants may have levels of 20 mg/dL [568]. The physiologic basis for the higher concentration of protein and the increased numbers of white blood cells in CSF of healthy, uninfected preterm and term infants is unknown. Explanations that have been offered include possible mechanical irritation of the meninges during delivery and increased permeability of the blood-brain barrier.

In nearly all of the studies of CSF in newborns, “normal” or “healthy” refers to the absence of clinical manifestations at the time of examination of CSF. Only the study by Ahmed and colleagues [562] included in the definition of normal the absence of viral infection, defined by lack of evidence of cytopathic effect in five cell lines and negative polymerase chain reaction for enteroviruses. None of the studies included information about the health of the infant after the newborn period. It now is recognized that infants with congenital infections, such as rubella, cytomegalovirus infection, toxoplasmosis, acquired immunodeficiency syndrome (AIDS), and syphilis, can have no signs of illness during the newborn period. Observations of these infants over the course of months or years can reveal abnormalities that are inapparent at birth. Until more data are available, it seems prudent to observe carefully infants with white blood cells greater than 20 per mm$^3$ or protein level greater than 100 mg/dL in 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 [HIV], and T. pallidum).

In newborns with bacterial meningitis, there can be thousands of white blood cells in CSF, and polymorphonuclear leukocytes predominate early in the course of the disease [20,560]. The number of white blood cells in CSF can vary greatly in infants with gram-negative and gram-positive meningitis. The median number of cells per cubic millimeter in CSF of 98 infants with gram-negative

### TABLE 6–16 Hematologic and Chemical Characteristics of Cerebrospinal Fluid in Healthy Newborns: Results of Selected Studies

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>No. Patients</th>
<th>Age (Days)</th>
<th>White Blood Cells (mm$^3$)*</th>
<th>Neutrophils (mm$^3$)*</th>
<th>Glucose (mg/dL)*</th>
<th>Protein (mg/dL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naidoo$^{568}$ (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>Sarff$^{560}$ (1976)</td>
<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>
</tr>
<tr>
<td>Bonadio$^{561}$ (1992)</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>Ahmed$^{562}$ (1996)</td>
<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</td>
<td>59 ± 25.3</td>
</tr>
<tr>
<td>Ahmed$^{562}$ (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 6–17 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. 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>355 (60-1780)</td>
<td>3 (1-8)</td>
<td>11 (0-50)</td>
<td>70 (41-89)</td>
<td>162 (115-222)</td>
</tr>
<tr>
<td></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></td>
<td>29-84</td>
<td>15</td>
<td>808 (0-6810)</td>
<td>4 (0-11)</td>
<td>2 (0-36)</td>
<td>49 (29-90)</td>
<td>137 (76-260)</td>
</tr>
<tr>
<td>1000-1500</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></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 (34-227)</td>
</tr>
<tr>
<td></td>
<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>
</tr>
</tbody>
</table>

meningitis was more than 2000 (range 6 to 40,000), whereas the median number of cells per cubic millimeter in 21 infants with group B streptococcal meningitis was less than 100 (range 8 to >10,000) [560]. 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. Appropriate media should be inoculated with the CSF specimen. Sarff and colleagues [560] detected organisms in Gram stain smears of CSF in 83% of infants with group B streptococcal meningitis and in 78% of infants with gram-negative meningitis. After initiation of appropriate antimicrobial therapy, gram-positive bacteria usually clear from CSF within 36 hours, whereas in some patients with meningitis caused by gram-negative enteric bacilli, cultures can remain positive for many days [567].

Microorganisms can be isolated from CSF that has normal white blood cell and chemistry test values. Visser and Hall [556] 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 CSF identified an increase in the number of cells and in the protein level. Presumably, the initial lumbar puncture was performed early in the course of meningitis before an inflammatory response occurred. Other investigators reported isolation of enterovirus [570] and *S. pneumoniae* [571] 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 [572] 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 lumbar puncture 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 lumbar puncture before sterilization of the blood by appropriate antimicrobial therapy occurs. This dissemination is especially likely to occur in neonates with intense bacteremia where sterilization by lysis more rapidly than red blood cells, or the number of white blood cells is decreased for other reasons [583–586]. Several formulas have been used in an attempt to interpret cytologic findings in CSF contaminated by blood [587–589]. None of the corrections applied to bloody CSF can be used with confidence, however, for excluding meningitis in the neonate [590–592]. In a cohort study of lumbar punctures performed at 150 neonatal units from 1997–2004, 39.5% (2519 of 6374) were traumatic, and 50 of these infants were found to have meningitis by culture. The authors found of the leukocyte count to account for blood contamination resulted in loss of sensitivity and only marginal gain in specificity, and would not aid in the diagnosis of bacterial (or fungal) meningitis [593].

Protein in CSF usually is elevated after a traumatic lumbar puncture because of the presence of red blood cells. It has been estimated in older children and adults...
that an increase of 1 mg/dL in CSF protein occurs for every 1000 red blood cells/µL. The concentration of glucose does not seem to be altered by blood from a traumatic lumbar puncture; a low CSF glucose concentration should be considered an important finding even when associated with a traumatic lumbar puncture.

Because a “bloody tap” is difficult to interpret, it can be valuable to repeat the lumbar puncture 24 to 48 hours later. If the results of the second lumbar puncture 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 CSF.

Brain Abscesses

Brain abscess is a rare entity in the neonate, usually complicating meningitis caused by certain gram-negative bacilli. CSF in an infant with a brain abscess can show 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 CSF if meningitis is not present. Sudden clinical deterioration and the appearance of many cells (>1000/mm³), with most polymorphonuclear cells, suggest rupture of the abscess into 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 chemistry, 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 CD 11b [594], granulocyte colony-stimulating factor [595], interleukin receptor antagonist [596], interleukin-6 [597–599], procalcitonin [600–602], serum amyloid A [603], and prohepcidin [604], 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. Proinflammatory cytokines, such as white blood cell count, absolute neutrophil count, and acute-phase reactants. Proinflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor-α, have been identified in serum and CSF in infants after perinatal asphyxia, raising doubts about the specificity of some of these markers [581,582,605,606]. Mehr and Doyle [607] reviewed the more recent literature on cytokines as aids in the diagnosis of neonatal bacterial sepsis. These assays and procedures are discussed in detail in Chapter 36.

Attention has focused more recently on the use of real-time polymerase chain reaction 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 PCR technologies and their consequent clinical utility has ranged from equivocal [608,609] to highly promising [610,611]. 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 and 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 compared with mortality for older infants with serious bacterial infection, 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 and 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, and 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 very low birth weight infants), and occasionally P. aeruginosa, and for maternally acquired etiologic agents.

GBS continue to exhibit significant in vitro susceptibility to penicillins and cephalosporins. Of 3813 case isolates in active population-based surveillance by the CDC from 1996-2003, all were sensitive to penicillin, ampicillin, cefazolin, and vancomycin [612]. New reports in the United States and Japan have identified GBS strains with reduced β-lactam susceptibility, however, and first-step mutations in the PBPs2 protein reminiscent of the emergence of β-lactam resistance in pneumococci decades ago [613,614]. In the CDC surveillance, GBS resistance to clindamycin (15%) and erythromycin (30%) also was noted to be increasing [612].

In vitro studies [615–617] and experimental animal models of bacteremia [618,619] indicate that the bactericidal 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 when 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 (see Chapter 13). 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 penicillinase-resistant penicillins, such as naftilin, 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 17). Vancomycin-resistant and glycopeptide-resistant S. aureus has been reported from Japan and the United States, but none of these strains has been isolated from neonates.

**Proteus 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 14.

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 nursery. 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. Aminoglycosides, including gentamicin, tobramycin, netilmicin, and amikacin, are highly active in vitro against virtually all isolates of *E. coli*, *P. aeruginosa*, *Enterobacter* species, *Klebsiella* species, and *Proteus* species.

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

The third-generation cephalosporins, cefotaxime, ceftiraxone, and ceftazidime, possess attractive features for therapy for bacterial sepsis and meningitis in newborns, including 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. The third-generation 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) [620–623]. 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 *P. aeruginosa* and excellent CSF penetration that appears safe and efficacious in the neonate for treatment of most nosocomial gram-negative pathogens [624].

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-generation or fourth-generation cephalosporins can lead to rapid emergence of drug-resistant bacteria in nurseries [625]. Also of concern, 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 [626,627]. Empirical use of cefotaxime in neonates should be restricted to infants with evidence of meningitis or with gram-negative sepsis. Continued cefotaxime therapy should be limited to infants with gram-negative meningitis caused by susceptible organisms or infants with ampicillin-resistant enteric infections [628].

**CURRENT PRACTICE**

The combination of ampicillin and an aminoglycoside, usually gentamicin or tobramycin, is suitable for initial treatment of presumed early-onset neonatal sepsis [629]. 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 microflora 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. 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 cephaplorins, cefotaxime, ceftriaxone, and ceftazidine, have important theoretical advantages for treatment of sepsis or meningitis compared with therapeutic regimens that include an aminoglycoside. In contrast to the aminoglycosides, third-generation cephalosporins are not associated with ototoxicity and nephrotoxicity. Little toxicity from aminoglycosides occurs when use is brief, however, 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, which are required with the use of aminoglycosides beyond 72 hours or in infants with renal insufficiency, are unnecessary. Routine use of cephalosporins for presumptive sepsis therapy in neonates often leads to problems with drug-resistant enteric organisms, however. Extensive use of third-generation cephalosporins in the nursery could result in the emergence of resistance caused by de-repression of chromosomally mediated β-lactamases [630].

Cefotaxime is preferred to other third-generation cephalosporins for use in neonates because it has been used more extensively [621–623] and because it does not affect the binding of bilirubin [630,631]. Ceftazidime or meropenem in combination with an aminoglycoside should be used in therapy for P. aeruginosa meningitis because of excellent in vitro activity and good penetration into 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 AN 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 group B streptococcal 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 infection with GBS in the newborn by administration of a penicillin to the mother were published in 1992 by ACOG [632] and the American Academy of Pediatrics (AAP) [633]. These guidelines were revised in 1996 by the CDC [634]; in 1997 by the AAP [635]; and in 2002 by the CDC [636], AAP, and ACOG [684]. More 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 [637].

When ampicillin or penicillin is administered to the mother, drug concentrations in the fetus are more than 30% of the concentrations in the blood of the mother [638]. 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 [639,640]. For some infected fetuses, the treatment administered in utero is insufficient, however, to prevent signs of early-onset group B streptococcal disease. Although maternal intrapartum prophylaxis has been associated with a 73% decrease in the incidence of early-onset group B streptococcal disease since 1993 [641,642], the regimen has had no impact on the incidence of late-onset disease [643].

The various algorithms prepared to guide empirical management of the neonate born to a mother with risk factors for group B streptococcal disease who received intrapartum antimicrobial prophylaxis for prevention of early-onset group B streptococcal disease focus on three clinical scenarios: [641–644]

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’ gestation who appear healthy and whose mothers received intrapartum prophylaxis with penicillin, ampicillin, or cefazolin for 4 or more hours 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’ 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 group B streptococcal disease.

The first two clinical scenarios are readily identified, but the third category often leads to controversy regarding optimal management. Recommendations for prevention and treatment of early-onset group B streptococcal infection are discussed in detail in Chapter 13.

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 are 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 AN 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 seem 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 [645] 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. If treatment for infection is deemed necessary, parental administration for 10 days is recommended.

MANAGEMENT OF AN INFANT WITH CATHETER-ASSOCIATED INFECTION

Investigators in Connecticut found that multiple catheters, low birth weight, low gestational age at birth, and low Apgar scores were significant risk factors for late-onset sepsis [504]. Benjamin and colleagues [505] reported a retrospective study at Duke University from 1995–1999 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 infants in whom the central catheter was removed promptly. Compared with neonates who had three or fewer positive intravascular catheter blood cultures for CoNS, neonates who had four consecutive positive blood cultures were at significantly increased risk for end-organ damage and death. In neonates with infection associated with a central venous catheter, 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 the pathogens 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 [23,119,348,632]. The persistence of gram-negative bacilli in CSF despite bactericidal levels of the antimicrobial agent led to the evaluation of lumbar intrathecal [646] and intraventricular [647] gentamicin. Mortality and morbidity were not significantly different in infants who received parenteral drug alone or parenteral plus intrathecal therapy [646]. The study of intraventricular gentamicin was stopped early because of the high mortality in the parenteral plus intraventricular therapy group [647].

Feigin and colleagues [629] reviewed the management of meningitis in children, including neonates. Ampicillin and penicillin G, initially with an aminoglycoside, are appropriate antimicrobial agents for treating infection caused by GBS. Ceftazidime has superior in vitro and in vivo bactericidal activity against many microorganisms [621]. 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 low birth weight 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. Ceftazidime or meropenem in addition to an aminoglycoside should be considered for P. aeruginosa meningitis.

Other antibiotics may be necessary to treat highly resistant organisms. Meropenem [648], ciprofloxacin [649–651], or trimethoprim-sulfamethoxazole [652,653] 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; consultation with 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; in 52 full-term neonates, mortality (22% dexamethasone versus 28% controls) and morbidity at 24 months (30% versus 39%) were not significantly different between groups [654]. 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 6–18).

MANAGEMENT OF AN INFANT WITH A BRAIN ABSCESS

If purulent foci or abscesses are present, they should be drained. Some brain abscesses resolve with medical therapy alone, however [348,653]. Brain abscesses can be
diagnosis. The history of illness and contacts in the mother and family members 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 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, polymerase chain reaction, 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* usually is 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, mepenomycin, 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 infants with very low birth weight. 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 immunoglobulin (IVIG) or pathogen-specific polyclonal or monoclonal antibody reagents for deficits in neonatal host defenses. These therapies are discussed in further detail in Chapters 4 and 13. Pentoxifylline has been documented to reduce plasma tumor necrosis factor-α concentrations in premature infants with sepsis and to improve survival, but the number of controls (one of four survived) were too small to provide more than a suggestion of efficacy [656]. In neutropenic infants with sepsis, the administration of granulocyte colony-stimulating factor and human granulocyte-macrophage colony-stimulating factor has had variable effects on outcome [657–660]. 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 Lacy [661] performed a meta-analysis of 553 neonates with suspected infection who had been enrolled in randomized clinical trials in seven countries through 2003 to evaluate the effect of

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**TABLE 6–18 Infectious and Noninfectious Causes of Aseptic Meningitis* in Neonates**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Disease</th>
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<tbody>
<tr>
<td><strong>Infectious Agent</strong></td>
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<tr>
<td>Bacteria</td>
<td>Partially treated meningitis</td>
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<tr>
<td></td>
<td>Parameningeal focus (brain or epidural abscess)</td>
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<tr>
<td></td>
<td>Tuberculosis</td>
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<tr>
<td>Viruses</td>
<td>Herpes simplex meningoencephalitis</td>
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<td></td>
<td>Cytomegalovirus</td>
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<td></td>
<td>Enteroviruses</td>
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<td></td>
<td>Rubella</td>
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<td></td>
<td>Acquired immunodeficiency syndrome</td>
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<td>Lymphocytic choriomeningitis</td>
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<td></td>
<td>Varicella</td>
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<td>Spirochetes</td>
<td>Syphilis</td>
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<td></td>
<td>Lyme disease</td>
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<tr>
<td>Parasites</td>
<td>Toxoplasmosial</td>
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<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>Fungi</td>
<td>Candidiasis</td>
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<tr>
<td></td>
<td>Coccioidiomycosis</td>
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<td></td>
<td>Cryptococcosis</td>
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<tr>
<td><strong>Noninfectious Causes</strong></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Traumatic lumbar puncture</td>
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<tr>
<td></td>
<td>Teratoma</td>
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<tr>
<td></td>
<td>Medulloblastoma</td>
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<tr>
<td></td>
<td>Choroid plexus papilloma and carcinoma</td>
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</tbody>
</table>

* Aseptic meningitis is defined as meningitis in the absence of evidence of a bacterial pathogen detectable in cerebrospinal fluid by usual laboratory techniques.
**CHAPTER 6 Bacterial Sepsis and Meningitis**

IVIG on subsequent outcomes. The results revealed a borderline significant reduction in mortality (relative risk 0.63, 95% confidence interval 0.40 to 1.00). In the studies in which analysis was restricted to neonates with subsequently proven systemic bacterial infection, a statistically significant reduction of mortality was identified (relative risk 0.55, 95% confidence interval 0.31 to 0.98). Based on these preliminary encouraging data from diverse studies, an ongoing, placebo-controlled multicenter trial in low birth weight or ventilated neonates (INIS [International Neonatal Immunotherapy Study]) is comparing the additive use of 10 mg/kg of IVIG versus placebo at the time of suspected infection and 48 hours later; mortality and major disability at 2 years are the major outcome variables [662].

**PROGNOSIS**

**p1665** Before the advent of antibiotics, almost all infants with neonatal sepsis died [5]. Dunham [2] 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% [3,5]. 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 [257,258,286,663] during the period 1960-1985. Mortality rates for sepsis, including infants of all weights and gestational ages, decreased from 40% to 50% in the 1960s [8,6,258,663] to 10% to 20% in the 1970s and 1980s [6,10,258,447,663]. Population-based surveillance of selected counties in the United States conducted by the CDC from 1993-1998 reported 2196 cases of neonatal sepsis caused by GBS, of which 92 (4%) were fatal [643].

**p1666** The postnatal age at which infection occurs, previously 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, ranging from 14% to 20% [6,12,258,288] to 70% [664]. When infections occurring during the first 24 hours of life, most of which are caused by GBS, are excluded from the analysis, however, the percentage of deaths resulting from early-onset sepsis does not differ significantly from late-onset infection. Mortality from sepsis is higher for preterm than for term infants in virtually all published studies, but is approximately the same for all major bacterial pathogens (see Tables 6–4 and 6–5) [10,257].

In more recent surveys, the mortality rate for neonatal meningitis has declined from 25% [10,24,665,666] to 10% to 15% [12,23,26,667,668]. This decrease represents a significant improvement from prior years, when studies reported a case-fatality rate of more than 30% [21,431,648,649,669]. Mortality is greater among preterm than term infants [12,23,26,670].

Significant sequelae develop in 17% to 60% of infants who survive neonatal meningitis caused by gram-negative enteric bacilli or GBS [23,665-668]. These sequelae include mental and motor disabilities, convulsive disorders, hydrocephalus, hearing loss, and abnormal speech patterns. The most extensive experience with the long-term observation of infants who had group B streptococcal meningitis as neonates was reported by Edwards and colleagues [670]. During the period 1974-1979, 61 patients were treated, 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/mm^3^, absolute neutrophil count less than 1000/mm^3^, and CSF protein level greater than 300 mg/dL.

A comparable study evaluating 35 newborns over 3 to 18 years showed 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 [669]. Franco and coworkers [668] reported the results of frequent and extensive neurologic, developmental, and psychometric assessments on a cohort of 10 survivors of group B streptococcal meningitis followed for 1 to 14 years. The investigators found that one child had severe CNS damage; five children, including one with hydrocephalus, had mild academic or behavioral problems; and four children were normal.

The neurodevelopmental outcomes described for infants with gram-negative bacillary meningitis are similar to the outcomes reported for group B streptococcal meningitis. Unhanand and colleagues [23] reported findings from their 21-year experience with gram-negative meningitis at two hospitals in Dallas, Texas. Of 72 patients less than 28 days old at the onset of symptoms, there were 60 survivors, 43 of whom were followed and evaluated for at least 6 months. Neurologic sequelae, occurring alone or in combination, were described in 56% and included hydrocephalus (approximately 30%), seizure disorder (approximately 30%), developmental delay (approximately 30%), cerebral palsy (25%), and hearing loss (15%). At follow-up, 44% 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/mm^3^, 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 interleukin-1 concentrations in CSF were indicators of a poor outcome.
**SECTION II Bacterial Infections**

[23, 433, 541, 671]. Investigators in England and Wales [668] found that independent predictors of adverse outcome 12 hours after admission were the presence of seizures, coma, ventilatory support, and leukopenia.

CT reveals a high incidence of CNS residua among newborns with meningitis. McCracken and colleagues [672] reported that of CT scans performed in 44 infants with gram-negative bacillary meningitis, only 30% of the scans were considered normal. Hydrocephalus was found in 20% of cases; areas of infarct, cerebritis, diffuse encephalomalacia, or cortical atrophy were found in 30%; brain abscess was found in about 20%; and subdural effusions were found 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 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 [348]. 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 outcomes. 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 very low birth weight 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 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 13.

Prophylaxis using low-dose vancomycin as a strategy to prevent late-onset sepsis in high-risk neonates has been the subject of several more recent clinical investigations [673–676]. 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 preterm infants, but that mortality and length of NICU stay did not differ between the treatment and placebo groups [677]. 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 shown, 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 [678]—the use of a vancomycin-heparin lock solution in peripherally inserted central catheters in neonates with very low birth weight 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% versus 30% in controls), providing proof-of-principle for wider investigation of this method that reduces systemic antibiotic exposure [678].

**MATERNAL FACTORS**

The antiviral and antibacterial activity of human milk has been recognized for many years [679–682] and is discussed extensively in Chapter 3. Evidence that breast-feeding defends against neonatal sepsis and gram-negative meningitis was first reported more than 30 years ago from Sweden [683]. Studies done in Pakistan have shown that even partial breast-feeding seems to be protective among neonates in a resource-limited nation with a high neonatal mortality rate from clinical sepsis [684]. In a study from Georgetown University, very low birth weight infants fed human milk had a significant reduction in sepsis or meningitis compared with very low birth weight infants exclusively fed formula (odds ratio 0.47, 95% confidence interval 0.23 to 0.95) [685]. Breast-fed infants have a lower incidence of gastroenteritis, respiratory illness, and otitis media than formula-fed infants. A protective effect of breast-feeding against infections of the urinary tract also has been suggested [686]. Breast-feeding is also associated with general immunostimulatory effects as evidenced by larger thymus size [687] and improved antibody responses to immunization [688, 689]. Lactoferrin is the major whey protein in human milk and has immunomodulatory activities. A study of bovine lactoferrin supplementation in very low birth weight neonates identified efficacy in decreasing the incidence of late-onset sepsis. The decrease occurred for gram-positive bacteremia and fungemia [372].

**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 leucocyte production, mobilization, and function; diminished T-lymphocyte cytokine production to many antigens; and reduced levels of lactoferrin and transferrin [686]. Recognition of these factors has resulted in attempts at therapeutic intervention aimed specifically at each component of the deficient immune response [690].

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 their childbearing years has been selectively adopted [688,691–693]. Programs in countries with limited resources to immunize pregnant women 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 group B streptococcal 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-onset and early-onset disease in newborns [693]. Use of vaccines in pregnant women is discussed in Chapter 1.

Several clinical trials have explored the use of IVIG to correct the antibody deficiency of neonates, particularly very preterm newborns, and 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 [694]. No reduction in mortality, morbidity, or 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 seem to be safe and well tolerated, no reduction in staphylococcal infection was documented in two more recent large, randomized multicenter studies [695,696]. A systematic meta-analysis of 19 published studies through 2003 including approximately 5000 infants calculated that IVIG prophylaxis provided a 3% to 4% reduction in nosocomial infections, but did not reduce mortality or other important clinical outcomes (e.g., necrotizing enterocolitis, length of hospital stay) [697]. The costs of IVIG and the value assigned to these clinical outcomes are expected to dictate use; basic scientists and clinicians need to explore new avenues for prophylaxis against bacterial infection in this special patient population [697].

An older study by Sidiropoulos and coworkers [698] explored the potential benefit of low-dose (12 g in 12 hours) or high-dose (24 g 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’ 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 leucocytes and reduced myeloid reserves in the bone marrow of newborns have been ascribed to impaired production of cytokines, interleukin-3, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor-α, and interferon-γ [699,700]. Considerable experience with vitro and in vivo cell cultures and animal models [701,702] 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 granulocyte-macrophage colony-stimulating factor in newborns were inconsistent in showing that absolute neutrophil counts are increased or that the incidence of sepsis is reduced [659,660,703]. A single-blind, multicenter randomized controlled trial of granulocyte-macrophage colony-stimulating factor in 280 infants at 31 weeks’ gestation or less showed that although neutrophil counts increased more rapidly in the treatment group in the first 11 days after study initiation, there were no differences in the incidence of sepsis or improved survival associated with these changes [704]. Although therapy of severe congenital neutropenia with granulocyte colony-stimulating factor reverses neutropenia, demonstrable functional deficiency of the neutrophils persists, and this probably explains why these neonates remain at significantly elevated risk of infection [705].

The amino acid glutamine has been recognized as important for gut and immune function in critically ill adults, and more recent attention has focused on its potential benefit to neonates, 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 or the mortality in extremely low birth weight infants [706], and this failure to provide a statistically significant benefit was borne out in a meta-analysis of seven randomized trials including more than 2300 infants [707].

A few studies have examined the effect of probiotic administration of Lactobacillus or Bifidobacterium species, generally intended as prophylaxis against necrotizing enterocolitis in neonates, on the secondary outcome of systemic bacterial infection, yielding conflicting results [708–710]. A meta-analysis of nine randomized trials comprising 1425 infants suggested that enteral supplementation of probiotic bacteria reduced the risk of severe necrotizing enterocolitis, but there was no evidence of a comparable beneficial effect on the incidence of nosocomial sepsis [711].

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
DECONTOAMINATION 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. These procedures are reviewed in Chapter 35.

EPIEMIOLOGIC SURVEILLANCE

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.

Newborns are 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 is apparent only after serial physical examinations. Chorioretinitis, jaundice, or pneumonia can occur as late manifestations of congenital infection. A lumbar puncture 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 manifest after the first week to months after birth as sepsis and meningitis or other focal infections. GBS (see Chapter 13) is the most frequent cause of late-onset sepsis 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 late-onset sepsis is obscure in many cases. The reason why an organism becomes invasive and causes sepsis or meningitis is unclear. Infections on the mucous membranes; skin; or upper respiratory, genitourinary, or gastrointestinal tracts remain 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. An 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 [714], 12.6% of household contacts developed suppurrative lesions during the 10-month period after introduction into the home of an infant with a staphylococcal lesion. The incidence of suppurrative infections in household contacts of infants without lesions was less than 2%. Damato and coworkers [713] showed 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 review of 25 cases of *P. multocida* infection in the neonatal period found animal exposure to cats or dogs or both in 52% of cases, most of which did not involve bites or trauma; the balance were believed to represent vertical transmission from an infected mother [715]. 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 [716]. *P. multocida* sepsis and meningitis was reported in 2-month-old twins after household exposure to a slaughtered sheep [717]. A neonatal case of *Campylobacter jejuni* sepsis was proven genetically to result from transmission from the family dog [718]. The epidemiologic link between cats and dogs and infection in young infants suggests that parents should limit contact between pets and infants.

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**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]) [719–724] is relatively uncommon. 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 [719,723]. Approximately 12% of all febrile (>38° C [>100.4° F]) neonates presenting to emergency departments are found to have a serious bacterial infection [726,727]. Important pathogens in neonatal age group include *GBS* and *E. coli*, and occult bacteremia and urinary tract infections are the most common foci of disease [726,727].

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 done if no other focus is apparent, and culture of 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 [725].

The “Rochester criteria” for analysis of febrile infants, originally proposed by Dagan and colleagues [722], used criteria such as normal peripheral leukocyte count (5000 to 15,000/mm³), normal absolute band neutrophil count (<1500/mm³) and absence of pyuria to identify low-risk patients. When Ferrera and coworkers [721] retrospectively applied these criteria to the subset of patients in their first 4 weeks of life, 6% of the neonates fulfilling low-risk criteria had serious bacterial infections. Similarly, when groups of febrile newborns were retrospectively stratified as low risk by the “Philadelphia criteria” [728] or “Boston criteria” [729] 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 [726,727].

Consequently, because of the inability to predict serious bacterial infections accurately in this age group, a complete sepsis evaluation should be performed and includes a culture of blood, urine, and *GBS*; 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 [730,731]. In contrast to older infants [732], 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. Neonates infected with respiratory syncytial virus had equivalent rates of serious bacterial infection as neonates testing negative for the virus [733]. More recent data suggest, however, that febrile infants less than 60 days of age positive for influenza virus infection may have lower rates of bacteremia and urinary tract infection than similar infants without influenza infection [734]. Because of the high rates of serious bacterial infections, guidelines prepared by Baraff and colleagues [719] 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.

**Acknowledgments**

Drs. S. Michael Marcy, Carol Baker, and Debra L. Palazzi contributed to this chapter in earlier editions. The authors are indebted to these scholars for their roles in the preparation of this chapter.

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