CHAPTER 6

Bacterial Sepsis and Meningitis

Victor Nizet ✪ **Jerome O. Klein**

CHAPTER OUTLINE

Bacterial sepsis in the neonate is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteremia in the first month of life. Meningitis in the neonate usually is a sequela of bacteremia and is discussed in this chapter because meningitis and sepsis typically share a common cause and pathogenesis. Infections of the bones, joints, and soft tissues and of the respiratory, genitourinary, and gastrointestinal tracts can be accompanied by bacteremia, but the cause, clinical features, diagnosis, and management of these infections are sufficiently different to warrant separate discussions. Bloodstream and central nervous system (CNS) infections caused by group B streptococci (GBS), *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS), *Neisseria gonorrhoeae*, *Listeria monocytogenes*, *Salmonella* 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

DOI: 10.1016/B978-1-4160-6400-8.00006-7

TABLE 6–1 Characteristics of Early-Onset and Late-Onset Neonatal Sepsis

Characteristic	Early-Onset*	Late-Onset†
Time of onset (days)	0-6	7-90
Complications of pregnancy or delivery	+	±
Source of organism	Mother's genital tract	Mother's genital tract; postnatal environment
Usual clinical presentation	Fulminant	Slowly progressive or fulminant
	Multisystem	Focal
	Pneumonia frequent	Meningitis frequent
Mortality rate (%)	3-50‡	2-40‡

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

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 antimicrobial agents, 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

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

Organism	No. Cases						
	1928-1932*	1933-1943†	1944-1957†	1958-1965‡	1966-1978§	1979-1988¶	1999-2003¶
β-hemolytic streptococci	15	18	11	8	86	83	155
Group A	—	16	5	0	0	0	0
Group B	—	2	4	1	76	64	86
Group D (*Enterococcus*)	—	0	1	7	9	19	65
Viridans streptococci	—	—	—	—	—	11	10
Staphylococcus aureus	11	4	8	2	12	14	70
Staphylococcus epidermidis	—	—	—	—	—	36	248
Streptococcus pneumoniae	2	5	3	2	2	2	0
Haemophilus species	—	—	—	1	9	9	5
Escherichia coli	10	11	23	33	76	46	106
Pseudomonas aeruginosa	1	0	13	11	5	6	33
Klebsiella and *Enterobacter* species	0	0	0	8	28	25	97
Others	0	6	4	9	21	38	54
Total no. cases	*39*	*44*	*62*	*73*	*239*	*270*	*784*
Mortality rate for years	87%	90%	67%	45%	26%	16%	3%

*Data from Dunham.[2]
†Data from Nyhan and Fousek.[3]
‡Data from Gluck et al.[4]
§Data from Freedman et al.[5]
¶Data from Gladstone et al.[6]
¶Data from Bizzarro et al.[8]

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 cases. Organisms that cause acute bacterial meningitis in older children and adults—*Streptococcus 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].

TABLE 6–3 Surveys of Neonatal Bacteremia

Country or Region	Site	Year of Publication	Reference
United States	New Haven	1933	2
		1958	3
		1966	4
		1981	5
		1990	6
		2001	7
		2005	8
	New York	1949	735
	Minneapolis	1956	736
	Nashville	1961	737
	Baltimore	1965	738
	Los Angeles	1981	264
	Indianapolis	1982	77
	Philadelphia	1985	169
	Kansas City	1987	96
	Multicenter	1998	18
	Eastern Virginia	2000	14
	Multicenter	2002	15
Canada	Montreal	1985	78
Europe	Finland	1985	10
		1989	258
	Liverpool	1985	13
	Göttingen	1985	286
	Göteborg	1990	257
	London	1981	287
		1991	25
	Mallorca	1993	265
	Denmark	1991	259
	Norway	1998	739
Middle East	Tel Aviv	1983	17
	Beer-Sheva	1997	12
	Israel	2002	16
Africa	Nigeria	1984	11
	Ethiopia	1997	740
	South Africa	1998	741
Asia	Hyderabad	1985	742
Australia	South Brisbane	1997	743

GROUP B STREPTOCOCCI

Group B β-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).

Streptococcus agalactiae, the species designation of GBS, has a characteristic colonial morphology on suitable solid media. The organism produces a mucoid colony with a narrow zone of β-hemolysis on sheep blood agar media. GBS can be differentiated immunochemically on the basis of their type-specific polysaccharides. Ten capsular types—Ia, Ib, II, III, IV, V, IV, 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

TABLE 6–4 Bacteremia in Finnish Neonates Related to Times of Onset of Signs and Mortality

	Mortality for Onset of Signs at					
	<24 hr		24 hr–7 day		8-20 day	
Organism	No. Died/Total	%	No. Died/Total	%	No. Died/Total	%
Group B streptococci	28/93	30	0/26	0	1/11	0
Escherichia coli	8/26	31	14/45	31	3/10	30
Staphylococcus aureus	3/14	21	7/64	11	1/12	8
Other	15/47	32	9/55	16	4/7	57
Total	*54/180*	*30*	*30/190*	*16*	*9/40*	*23*

Data from Vesikari R, et al. Neonatal septicemia. Arch Dis Child 60:542-546, 1985.

TABLE 6–5 Bacteremia in Finnish Neonates Related to Birth Weight and Mortality

	Mortality for Onset of Signs at					
	<1500 g		1500-2500 g		>2500 g	
Organism	**No. Died/Total**	**%**	**No. Died/Total**	**%**	**No. Died/Total**	**%**
Group B streptococci	11/15	73	10/36	20	8/79	10
Escherichia coli	11/15	73	8/19	42	6/47	13
Staphylococcus aureus	4/9	44	4/26	15	3/55	5
Other	12/18	67	7/21	33	9/70	13
Total	*38/57*	*67*	*29/102*	*28*	*26/251*	*10*

Data from Vesikari R, et al. Neonatal septicemia. Arch Dis Child 60:542-546, 1985.

TABLE 6–6 Microbiology of Neonatal Sepsis at Yale–New Haven Hospital, 1989-2003

	No. Isolates				
	Age When Cultured (days)				
Microorganism	**0-4**	**5-30**	**>30**	**Transported Infants**	**Total**
Staphylococcus aureus	8	18	20	24	70
Coagulase-negative staphylococci	6	119	42	81	248
Group B streptococci	53	12	7	14	86
Enterococcus species	5	21	23	33	82
Viridans streptococci	0	3	3	4	10
Stomatococcus species	0	0	0	1	1
Bacillus species	1	0	1	0	2
Listeria monocytogenes	1	0	0	0	1
Escherichia coli	25	27	12	41	106
Klebsiella pneumoniae	0	20	9	18	47
Klebsiella oxytoca	0	7	8	4	19
Enterobacter aerogenes	0	1	3	4	8
Enterobacter agglomerans	0	3	1	0	4
Enterobacter cloacae	0	7	5	7	19
Serratia marcescens	0	6	10	7	23
Pseudomonas aeruginosa	2	14	4	13	33
Acinetobacter species	1	0	2	1	4
Proteus mirabilis	0	1	1	1	3
Citrobacter freundii	1	0	0	1	2
Haemophilus influenzae	5	0	0	0	5
Bacteroides species	0	0	1	2	3
Yersinia enterocolitica	0	1	0	2	3
Other gram-negative rods	0	3	0	1	4
Candida and other fungi/yeast	3	41	16	18	78
Total	*112*	*304*	*169*	*277*	*862*

Data from Bizzaro MJ, et al. Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics 116:595, 2005.

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

t0040 **TABLE 6–7** Bacteria Associated with Neonatal Meningitis in Selected Studies

Organism	No. Cases of Association								
	Boston, 1932-1957, 77 Cases[20]	Los Angeles, 1963-1968, 125 Cases[21]	Houston, 1967-1972, 51 Cases[22]	Multihospital Survey,* 1971-1973, 131 Cases[744]	The Netherlands, 1976-1982, 280 Cases[24]	Great Britain, 1985-1987, 329 Cases[25]	Dallas, 1969-1989, 257 Cases[45]	Israel, 1986-1994, 32 Cases[31†]	Great Britain, 1996-1997, 144 Cases[45]
β-hemolytic streptococci (group not stated)	9	12	—	—	—	—	—	—	—
β-hemolytic streptococci									
Group A	—	—	1	2	—	—	—	—	—
Group B	—	—	18	41	68	113	134	6	69
Group D	—	—	—	2	4	—	—	—	1
Staphylococcus epidermidis or coagulase-negative staphylococci	—	5	—	3	—	9	—	2	2
Staphylococcus aureus	12	1	3	1	7	4	—	—	—
Streptococcus pneumoniae	7	4	3	2	6	21	18	—	8
Listeria monocytogenes	—	6	5	7	12	21	—	—	7
Escherichia coli	25	44	16‡	50	132	2	42	4	26
Pseudomonas aeruginosa	4	1	2	2	4	3	—	1	—
Klebsiella and *Enterobacter* species	3	13	‡	3	19	8	10	4	—
Proteus species	2	5	‡	4	5	8	3	2	—
Haemophilus species	—	2	2	3	2	12	—	—	1
Neisseria meningitidis	1	—	—	1	3	14	—	—	6
Salmonella species	2	4	—	3	3	2	4	—	1
Miscellaneous	12	28	1	7	15	32	46	—	23

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

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

‡*Authors report 16 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 in utero 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 streptococcus 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 α-hemolytic and nonhemolytic streptococci that are constituents of the normal flora of the respiratory and gastrointestinal tracts of infants, children, and adults. There are several classification schemata for these streptococci, and they may bear different designations in the literature. *Streptococcus bovis* is capable of causing neonatal sepsis and meningitis that is clinically similar to sepsis caused by GBS [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 bronchioalveolar lavage cultures were multidrug-resistant viridans streptococci (66%), and these were also one of the most common bloodstream isolates (29%) in the same population [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* (*E. faecalis* and *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 *E. faecalis*, with a smaller number caused by *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 *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 McNeeley and colleagues [82]. The presence of a central venous catheter (77%) and a diagnosis of necrotizing enterocolitis (33%) were common characteristics.

Enterococcus species generally are resistant to cephalosporins and are only moderately susceptible to penicillin G and ampicillin; they require the synergistic activity of penicillin at high dosage and an aminoglycoside for maximal bactericidal action. Nonenterococcal strains are susceptible to penicillin G, ampicillin, and most cephalosporins. Vancomycin-resistant *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).

STAPHYLOCOCCUS AUREUS AND COAGULASE-NEGATIVE STAPHYLOCOCCI

S. aureus and CoNS, especially *S. epidermidis*, colonize skin and mucosa. Isolation of *S. aureus* from tissue, blood, or other body fluid usually is clearly associated with disease. Most episodes of sepsis caused by *S. aureus* are hospital acquired, and mortality can be high (23% among 216 Swedish neonates with *S. aureus* bacteremia during 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 *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 *S. aureus* between postpartum women [90] and among NICU patients [91].

CoNS include more than 30 different species. *S. epidermidis* is the dominant species of CoNS responsible for neonatal sepsis, but other species, including *Staphylococcus capitis*, *Staphylococcus hemolyticus*, and, *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. *S. epidermidis* and other CoNS species can adhere to and grow on surfaces of synthetic polymers used in the manufacture of catheters. Strains obtained from infected ventricular shunts or

intravenous catheters produce a mucoid substance (i.e., slime or glycocalyx) that stimulates adherence of microcolonies to various surfaces in the environment and on epithelial surfaces, ultimately leading to establishment of a biofilm [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 aquisition 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., OmpA, IbeA-C, 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 56 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

Similar to other members of Enterobacteriaceae, *Serratia marcescens* increasingly is associated with hospital-acquired infections in infants in the NICU [158–160]. Late-onset sepsis has occurred in infants infected from health care equipment [160–163], the hands of heath care 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 multi-drug-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 health care 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 health care 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 intrauterine infection can result during maternal meningococcemia [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 in *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 Friesen 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 ($\leq$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 parainfluenzae* [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 *C. butyricum* and *C. perfringens*. Clostridial sepsis has a high mortality rate [234].

NEONATAL TETANUS

Neonatal tetanus is caused by the gram-positive anaerobic spore-forming bacillus *C. tetani*. The organism is present in soil and can be present in human and animal feces. Infection usually occurs after contamination of the umbilical stump. Maternal and neonatal tetanus are important causes of mortality in developing countries, 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 *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 cases 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 one or more of the organisms in a mixed culture is a contaminant.

Bacteremia with more than one organism occurs in patients with immunodeficiency, major congenital abnormalities, or contamination of a body fluid with multiple organisms, as is present in peritonitis typically as a sequela of severe necrotizing enterocolitis in a very low birth weight infant. Neonatal meningitis caused by *S. pneumoniae* and *Acinetobacter calcoaceticus* [255] and sepsis caused by *P. aeruginosa* and *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 Tessin 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 parenteral 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 *K. pneumoniae* and *E. cloacae* associated with use of a contaminated lipid emulsion.

Mixed infections also can include bacteria and viruses or bacteria and fungi, typically *Candida*, in the situation of intravascular central catheter or peritoneal infections associated with bowel perforation. 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 *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].

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

Organism	Reference
Achromobacter species	745-747
Acinetobacter species	748-752
Bacillus anthracis	753
Bacillus cereus	225, 226, 228, 754
Borrelia (relapsing fever)	755, 756
Brucella species	757, 758
Burkholderia cepacia	759-761
Burkholderia pseudomallei	762
Campylobacter species	718, 763
Capnocytophaga species	764-766
Corynebacterium species	767, 768
Edwardsiella tarda	769-771
Escherichia hermanii	772, 773
Chryseobacterium (*Flavobacterium*) species	774, 775
Gardnerella vaginalis	776, 777
Helicobacter cinaedi	778
Lactobacillus species	779, 780
Leptospira species	781, 782
Leuconostoc species	783, 784
Morganella morganii	785-787
Mycoplasma hominis	788
Ochrobactrum anthropi	789
Pantoea agglomerans	790
Pasteurella species	715, 791, 792
Plesiomonas species	793-795
Proteus mirabilis	796-798
Pseudomonas pseudomallei	799
Psychrobacter immobilis	800
Ralstonia pickettii	801
Rothia dentocariosa	802
Shigella sonnei	803-805
Staphylococcus capitis	806
Stomatococcus mucilaginosus	807
Vibrio cholerae	808, 809
Yersinia enterocolitica	810, 811
Yersinia pestis	812

EPIDEMIOLOGY

INCIDENCE OF SEPSIS AND MENINGITIS

The reported incidence of neonatal sepsis varies from less than 1 to 8.1 cases per 1000 live births [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 6–9 Incidence and Mortality of Group B Streptococcal Disease by Birth Weight, Atlanta 1982-1983

		Early Onset		Late Onset	
Birth Weight	Total Births	Cases/(Deaths)	Cases/1000	Cases/(Deaths)	Cases/1000
<1500 g	835	5 (1)	5.99	0	0
1500-2499 g	4380	11 (2)	2.51	6 (0)	1.37
>2500 g	59,303	53 (5)	0.89	23 (0)	0.39

Data from Schuchat A, et al. Population-based risk factors for neonatal group B streptococcal disease: results of a cohort study in metropolitan Atlanta. J Infect Dis 162:672, 1990.

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].

TABLE 6–10 Relationship of Attack Rates and Fatalities of Neonatal Group B Streptococcal Early-Onset Disease to Perinatal Characteristics

Characteristic	Attack Rate per 1000 Live Births	Mortality Rate (%)
Birth weight (g)		
<1000	26	90
1001-1500	8	25
1501-2000	9	29
2001-2500	4	33
>2500	1	3
Rupture of membranes (hr)		
<18	1	20
19-24	6	27
25-48	9	18
>48	11	33
Peak intrapartum temperature (° C)		
<37.5	2	29
>37.5	7	17
Perinatal risk factors		
Present	7.6	33
Absent	0.6	6
Total no. infants = 32.384	2	26

Data from Boyer KM, et al. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease, I: epidemiologic rationale. J Infect Dis 148:795-801, 1983.

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

TABLE 6–11 Selected Characteristics of Women,* Their Pregnancies, and Newborns

Characteristic	Percent with Characteristics	
	White Women	Black Women
Premature rupture of membranes: time from rupture to onset of labor (hr)		
<8	70.9	56.7
8-23	18.3	21.9
24-48	5.4	11.7
≥49	5.4	9.7
Puerperal infection	3.6	4.1
Type of delivery		
Vaginal vertex	91.7	92.4
Vaginal breech	3.3	2.6
Cesarean section	4.9	5
Birth weight <2500 g	7.1	13.4
Neutrophilic infiltration of		
Amnion	9	7.9
Chorion	13.1	15.6
Umbilical vein	14.6	7.5

**Approximately 18,700 white women and 19,800 black women were evaluated. Data from Niswander KR, Gordon M. The women and their pregnancies. The Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. U.S. Department of Health, Education and Welfare Publication No. (NIH) 73-379. Washington, DC, U.S. Government Printing Office, 1972.*

TABLE 6–12 Incidence of Fetal and Neonatal Infections by Sex

Infection	No. Infants		Ratio of Male to Female
	Male	Female	
Intrauterine infections			
Syphilis	118	134	0.89
Tuberculosis	15	14	1.07
Toxoplasmosis	118	103	1.14
Listeriosis	26	37	0.70
Perinatal sepsis			
Gram-negative organisms	82	34	2.41
Gram-positive organisms	58	31	1.87
Perinatal meningitis			
Gram-negative organisms	126	44	2.87
Gram-positive organisms	45	39	1.15

Data based on a review of the literature and study of Johns Hopkins Hospital case records, 1930-1963. From Washburn TC, Medearis DN Jr, Childs B. Sex differences in susceptibility to infections. Pediatrics 35:57, 1965.

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 and meningitis in western Europe* and Jamaica [288] is generally similar to that in the United States.

*References [10, 13, 25, 257–259, 265, 286, 287].

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 and sub-Saharan Africa. The global perspective of neonatal sepsis is discussed in Chapter 2. The most common isolates responsible for neonatal sepsis vary by country, but include a wide spectrum of gram-negative and gram-positive species, the most common of which are *E. coli*, *S. aureus*, *Pseudomonas*, and *Klebsiella* [295]. Multidrug-resistant strains are an increasing threat to intervention programs [296,297].

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 [298] 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 and

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 hematogenous 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 morgagnii* [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 mucosal membranes such as endotracheal suctioning [343]. Invasion of the bloodstream also can follow multiplication of organisms in the upper respiratory tract or other foci. Although the source of bacteremia frequently is inapparent, careful inspection can reveal a focus, such as an infected circumcision site or infection of the umbilical stump, in some neonates. Metastatic foci of infection can follow bacteremia and can involve the lungs, kidney, spleen, bones, or CNS.

Most cases of neonatal meningitis result from bacteremia. Fetal meningitis followed by stillbirth [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 infarction. 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. sakazakii* 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 nine 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 uridyltransferase 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, but this is controversial. 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].

INFECTION IN TWINS

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 monochorionic, should have high rates of simultaneous early-onset infection, but it is particularly intriguing that some cases of late-onset disease occur in twins almost simultaneously. 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 fasciitis are the conditions most often associated with hospitalization [398]. Infants presenting with fasciitis have a high incidence of bacteremia, intravascular 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], suppurative 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].

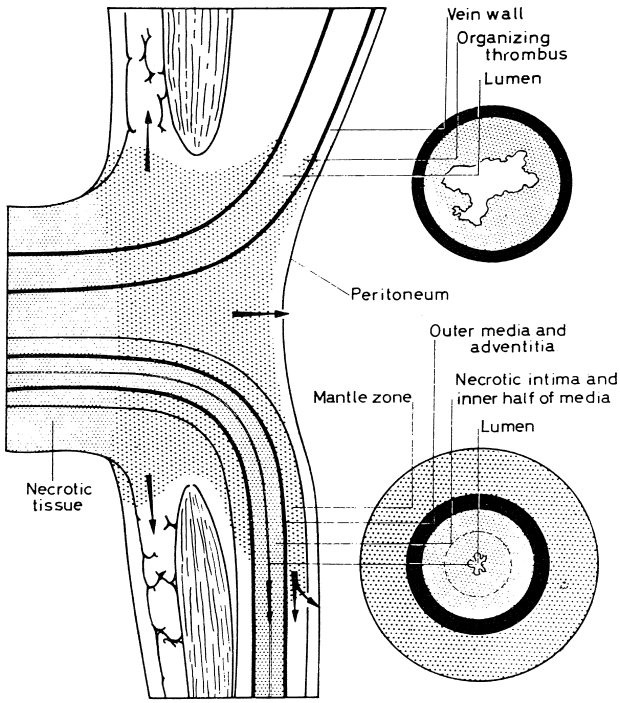

FIGURE 6–1 After birth, the necrotic tissue of the umbilical stump separates. This provokes some inflammation, which is limited by a fibroblastic reaction extending to the inner margin of the *coarsely stippled area*. The inner half of the media and the intima of the umbilical arteries become necrotic, but this does not stimulate an inflammatory reaction. *Arrows* indicate routes by which infection may spread beyond the granulation tissue barriers. Organisms invading the thrombus in the vein may disseminate by emboli. *(From Morison JE. Foetal and Neonatal Pathology, 3rd ed. Washington, DC, Butterworth, 1970.)*

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 treated with 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 infections 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 suppurative 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 inflammation of the choroid plexus), vasculitis, cerebral edema, infarction, cortical neuronal necrosis, and periventricular leukomalacia; chronic pathologic features include hydrocephalus, multicystic encephalomalacia and porencephaly, and cerebral cortical and white matter atrophy [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 material can collect around the base of the brain without a significant increase in intracranial pressure. Hydrocephalus may result from closure of the aqueduct or the foramina of the fourth ventricle by purulent exudate or by means of inflammatory impairment of CSF resorption through the arachnoid channels [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 [155,166,347,429]. 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 temperature instability (10%). Unexplained metabolic acidosis (11%) and hypoglycemia (10%) were 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 bacterial sepsis. 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 6–13 Clinical Signs of Bacterial Sepsis

Clinical Sign	Percent of Infants with Sign
Hyperthermia	51
Hypothermia	15
Respiratory distress	33
Apnea	22
Cyanosis	24
Jaundice	35
Hepatomegaly	33
Lethargy	25
Irritability	16
Anorexia	28
Vomiting	25
Abdominal distention	17
Diarrhea	11

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

TABLE 6–14 Clinical Signs of Bacterial Meningitis

Clinical Sign	Percent of Infants with Sign
Hypothermia or fever	62
Lethargy or irritability	52
Anorexia or vomiting	48
Respiratory distress	41
Bulging or full fontanelle	35
Seizures	31
Jaundice	28
Nuchal rigidity	16
Diarrhea	14

Data from references 20, 26, 430, and 450.

TABLE 6–15 Differential Diagnosis: Clinical Signs Associated with Neonatal Sepsis and Some Noninfectious Conditions

Respiratory Distress (Apnea, Cyanosis, Costal and Sternal Retraction, Rales, Grunting, Diminished Breath Sounds, Tachypnea)
Transient tachypnea of the newborn
Respiratory distress syndrome
Atelectasis
Aspiration pneumonia, including meconium aspiration
Pneumothorax
Pneumomediastinum
CNS disease: hypoxia, hemorrhage
Congenital abnormalities, including tracheoesophageal fistula, choanal atresia, diaphragmatic hernia, hypoplastic lungs
Congenital heart disease
Cardiac arrhythmia
Hypothermia (neonatal cold injury)
Hypoglycemia
Neonatal drug withdrawal syndrome
Medication error with inhaled epinephrine
Temperature Abnormality (Hyperthermia or Hypothermia)
Altered environmental temperature
Disturbance of CNS thermoregulatory mechanism, including anoxia, hemorrhage, kernicterus
Hyperthyroidism or hypothyroidism
Neonatal drug withdrawal syndrome
Dehydration
Congenital adrenal hyperplasia
Vaccine reaction
Jaundice
Breast milk jaundice
Blood group incompatibility
Red blood cell hemolysis, including blood group incompatibility, G6PD deficiency
Resorption of blood from closed space hemorrhage
Gastrointestinal obstruction, including pyloric stenosis
Extrahepatic or intrahepatic biliary tract obstruction
Inborn errors of metabolism, including galactosemia, glycogen storage disease type IV, tyrosinemia, disorders of lipid metabolism, peroxisomal disorders, defective bile acid synthesis (trihydroxycoprostanic acidemia)
Hereditary diseases, including cystic fibrosis, α_1-antitrypsin deficiency, bile excretory defects (Dubin-Johnson syndrome, Rotor syndrome, Byler disease, Aagenaes syndrome)
Hypothyroidism
Prolonged parenteral hyperalimentation
Hepatomegaly
Red blood cell hemolysis, including blood group incompatibility, G6PD deficiency
Infant of a diabetic mother
Inborn errors of metabolism, including galactosemia, glycogen storage disease, organic acidemias, urea cycle disorders, hereditary fructose intolerance, peroxisomal disorders
Biliary atresia
Congestive heart failure
Benign liver tumors, including hemangioma, hamartoma
Malignant liver tumors, including hepatoblastoma, metastatic neuroblastoma, congenital leukemia
Gastrointestinal Abnormalities (Anorexia, Regurgitation, Vomiting, Diarrhea, Abdominal Distention)
Gastrointestinal allergy
Overfeeding, aerophagia
Intestinal obstruction (intraluminal or extrinsic)
Necrotizing enterocolitis
Hypokalemia
Hypercalcemia or hypocalcemia

Continued

TABLE 6–15 Differential Diagnosis: Clinical Signs Associated with Neonatal Sepsis and Some Noninfectious Conditions—cont'd

Hypoglycemia
Inborn errors of metabolism, including galactosemia, urea cycle disorders, organic acidemias
Ileus secondary to pneumonia
Congenital adrenal hyperplasia
Gastric perforation
Neonatal drug withdrawal syndrome
Lethargy
CNS disease, including hemorrhage, hypoxia, or subdural effusion
Congenital heart disease
Neonatal drug withdrawal syndrome
Hypoglycemia
Hypercalcemia
Familial dysautonomia
Seizure Activity (Tremors, Hyperactivity, Muscular Twitching)
Hypoxia
Intracranial hemorrhage or kernicterus
Congenital CNS malformations
Neonatal drug withdrawal syndrome
Hypoglycemia
Hypocalcemia
Hyponatremia, hypernatremia
Hypomagnesemia
Inborn errors of metabolism, including urea cycle disorders, organic acidemias, galactosemia, glycogen storage disease, peroxisomal disorders
Pyridoxine deficiency
Petechiae, Purpura, and Vesiculopustular Lesions
Birth trauma
Blood group incompatibility
Neonatal isoimmune thrombocytopenia
Maternal idiopathic thrombocytopenic purpura
Maternal lupus erythematosus
Drugs administered to mother
Giant hemangioma (Kasabach-Merritt syndrome)
Thrombocytopenia with absent radii syndrome
Disseminated intravascular coagulopathy
Coagulation factor deficiencies
Congenital leukemia
Child abuse
Cutaneous histiocytosis

CNS, central nervous system; G6PD, glucose-6-phosphate dehydrogenase.

FEVER AND HYPOTHERMIA

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

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 preterm 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 in utero infections and of some noninfectious conditions, such as cardiac failure and metabolic diseases, including galactosemia and glycogen storage disease. Tender hepatomegaly can be a sign of bacterial liver abscess in neonates, a potential complication of misplaced central umbilical catheters [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 identical signs of illness as observed in infants with sepsis. Meningitis can be heralded by increasing irritability, alteration in consciousness, poor tone, tremors, lip smacking, or twitching of facial muscles or an extremity. Seizures were present in 31% of the infants reviewed in Table 6–14, 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 cerebral 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, intrauterine 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:[483,484]

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 $\geq 38^\circ$ C [$\geq 100.4^\circ$ 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 3371 infants by Evans and colleagues [485]. 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 15 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 Struthers 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 ($\geq$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 produce 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 and Hey [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 *Limulus* (horseshoe 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 features 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, bacterial pathogens 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.

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

If a Lumbar Puncture Is Not Performed

Is it sufficient to culture only blood and urine for the diagnosis of neonatal bacterial meningitis? Visser and Hall [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 Pediatrix 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,

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

Study (Year)	No. Patients	Age (Days)	White Blood Cells (mm^3)*	Neutrophils (mm^3)*	Glucose (mg/dL)*	Protein (mg/dL)*
Naidoo[559] (1968)	135	1	12 (0-42)	7 (0-26)	48 (38-64)	73 (40-148)
	20	7	3 (0-9)	2 (0-5)	55 (48-62)	47 (27-65)
Sarff[560] (1976)	87	Most <7	8.2 ± 7.1, median 5 (0-32)	61	52 (34-119)	90 (20-170)
Bonadio[561] (1992)	35	0-4 wk	11 ± 10.4, median 8.5	0.4 ± 1.4, median 0.15	46 ± 10.3	84 ± 45.1
	40	4-8 wk	7.1 ± 9.2, median 4.5	0.2 ± 0.4, median 0	46 ± 10	59 ± 25.3
Ahmed[562] (1996)	108	0-30	7.3 ± 13.9, median 4	0.8 ± 6.2, median 0	51.2 ± 12.9	64.2 ± 24.2

**Expressed as mean with range (number in parentheses) or ± standard deviation unless otherwise specified.*
Data from Ahmed A, et al. Cerebrospinal fluid values in the term neonate. Pediatr Infect Dis J 15:298, 1996.

TABLE 6–17 Hematologic and Chemical Characteristics of Cerebrospinal Fluid in Healthy Very Low Birth Weight Infants

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

Data from Rodriguez AF, Kaplan SL, Mason EO. Cerebrospinal fluid values in the very low birth weight infant. J Pediatr 116:971, 1990.

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 not decline to normal values for older infants for several 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 blood glucose 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

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, and 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 β-lactam agents (i.e., third-generation cephalosporins) depends on the inoculum.

Smith and colleagues [573] performed a large cohort study of CSF parameters in preterm neonates with meningitis. Analysis of first lumbar puncture of 4632 neonates less than 34 weeks' gestation found significant differences in culture-proven meningitis cases versus controls in CSF leukocyte count (110 cells/mm^3 versus 6 cells/mm^3), total protein (217 mg/dL versus 130 mg/dL), and glucose (43 mg/dL versus 49 mg/dL). The sensitivity for predicting meningitis was only 71%, however, for CSF leukocyte count greater than 25 cells/mm^3, 61% for CSF protein greater than 170 mg/dL, and 32% for CSF glucose less than 24 mg/dL. The positive predictive value for each of these parameters was low (4% to 10%), emphasizing the critical need for CSF culture to establish the diagnosis of meningitis. In terms of excluding meningitis, a normal CSF protein was the most useful parameter because 96% of premature neonates with meningitis had CSF protein greater than 90 mg/dL [573].

Investigators have sought a sensitive and specific CSF metabolic determinant of bacterial meningitis with little success. Among products that have been evaluated and found to be inadequate to distinguish bacterial meningitis from other neurologic disease (including cerebroventricular hemorrhage and asphyxia) are γ-aminobutyric acid [574], lactate dehydrogenase [575], and creatine kinase brain isoenzyme [576]. Cyclic-3′,5′-adenosine monophosphate was elevated in CSF of neonates with bacterial meningitis compared with CSF of infants who had nonbacterial meningitis or a control group [577]. Elevated CSF concentrations of C-reactive protein have been reported for infants older than 4 weeks with bacterial meningitis [578]; however, the test was found to be of no value in neonates [579,580]. Current investigations of the proinflammatory cytokines interleukin-6 and interleukin-8 indicate that there is a cytokine response in CSF after birth asphyxia and that these assays are not useful in detecting infants with meningitis [581,582].

Traumatic Lumbar Puncture

A traumatic lumbar puncture can result in blood in CSF and can complicate the interpretation of the results for CSF white blood cell count and chemistries. Schwersenski and colleagues [549] found that 13.8% of 712 CSF specimens obtained during the first week of life were bloody and that an additional 14.5% were considered inadequate for testing.

If the total number of white blood cells compared with the number of red blood cells exceeds the value for whole blood, the presence of CSF pleocytosis is suggested. Some investigators have found that the observed white blood cell counts in bloody CSF were lower than would be predicted based on the ratio of white blood cells to red blood cells in peripheral blood; the white blood cells lyse more rapidly than red blood cells, or the number of white blood cells is decreased for other reasons [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 Abscess

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/mm^3), 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 chemistries, histopathology of the placenta and umbilical cord, smears of gastric or tracheal aspirates, and diagnostic imaging studies. New assays for diagnosis of early-onset sepsis, including serum concentrations of neutrophil 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, 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 PBPx2 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 nafcillin, and to first-generation cephalosporins. Methicillin-resistant staphylococci that are resistant to other penicillinase-resistant penicillins and cephalosporins have been encountered in many nurseries in the United States. Antimicrobial susceptibility patterns must be monitored by surveillance of staphylococcal strains causing infection and disease in each NICU. Bacterial resistance must be considered whenever staphylococcal disease is suspected or confirmed in a patient, and empirical vancomycin therapy should be initiated until the susceptibility pattern of the organism is known. Virtually all staphylococcal strains isolated from neonates have been susceptible to vancomycin. Synergistic activity is provided by the combination of an aminoglycoside (see Chapter 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.

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

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

L. monocytogenes is susceptible to penicillin and ampicillin and resistant to cephalosporins. Ampicillin is the preferred agent for treating *L. monocytogenes*, although an aminoglycoside can be continued in combination with ampicillin if the patient has meningitis. Specific management of *L. monocytogenes* infection is discussed in Chapter 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 neonate. These patterns vary by hospital or community and by time within the same institution or community. Although isolates from neonates should be monitored to determine the emergence of new strains with unique antimicrobial susceptibility patterns, the general pattern of antibiotic susceptibility in the hospital is a good guide to initial therapy for neonates. 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, ceftriaxone, 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 microbial flora in nurseries where the use of broad-spectrum antimicrobial agents is routine supports recommendations from the CDC for the judicious use of antibiotics. The hospital laboratory must regularly monitor isolates of pathogenic bacteria to assist the physician in choosing the most appropriate therapy. The clinical pharmacology and dosage schedules of the various antimicrobial agents considered for neonatal sepsis are provided in Chapter 37.

CONTINUATION OF THERAPY WHEN RESULTS OF CULTURES ARE AVAILABLE

The choice of antimicrobial therapy should be reevaluated when results of cultures and susceptibility tests become available. The duration of therapy depends on

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

The third-generation cephalosporins, cefotaxime, ceftriaxone, and ceftazidime, have important theoretical advantages for treatment of sepsis or meningitis compared with therapeutic regimens that include an aminoglycoside. 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 [484]. 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 75% 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, parenteral 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. Cefotaxime 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 [348,655]. Brain abscesses can be

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

Cause	Disease
Infectious Agent	
Bacteria	Partially treated meningitis
	Parameningeal focus (brain or epidural abscess)
	Tuberculosis
Viruses	Herpes simplex meningoencephalitis
	Cytomegalovirus
	Enteroviruses
	Rubella
	Acquired immunodeficiency syndrome
	Lymphocytic choriomeningitis
	Varicella
Spirochetes	Syphilis
	Lyme disease
Parasites	Toxoplasmosis
	Chagas disease
Mycoplasma	*Mycoplasma hominis* infection
	Ureaplasma urealyticum infection
Fungi	Candidiasis
	Coccidioidomycosis
	Cryptococcosis
Noninfectious Causes	
Trauma	Subarachnoid hemorrhage
	Traumatic lumbar puncture
Malignancy	Teratoma
	Medulloblastoma
	Choroid plexus papilloma and carcinoma

**Aseptic meningitis is defined as meningitis in the absence of evidence of a bacterial pathogen detectable in cerebrospinal fluid by usual laboratory techniques.*

polymicrobial or result from organisms that uncommonly cause meningitis, such as *Citrobacter* [148,150], *Enterobacter* [130], *Proteus* [348], and *Salmonella* species [651]. Aspiration of the abscess provides identification of the pathogens to guide rational antimicrobial therapy.

TREATMENT OF AN INFANT WITH MENINGITIS WHOSE BACTERIAL CULTURE RESULTS ARE NEGATIVE

In the absence of a detectable bacterial pathogen, an aggressive diagnostic approach is necessary for the infant with meningitis, defined by CSF pleocytosis and variable changes in the concentration of CSF protein and glucose. The most frequent cause of aseptic or nontuberculous bacterial meningitis in the neonate is prior antimicrobial therapy resulting in negative blood and CSF cultures. Congenital infections need to be excluded. Treatable diseases, such as partially treated bacterial disease and meningoencephalitis caused by herpes simplex virus, syphilis, cytomegalovirus, toxoplasmosis, Lyme disease in regions where *Borrelia* is prevalent, tuberculosis, and malignancy, need to be considered in the differential 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, meropenem, ticarcillin, or piperacillin/tazobactam, is warranted.

ADJUNCTIVE THERAPIES FOR TREATMENT OF NEONATAL SEPSIS

Despite appropriate antimicrobial and optimal supportive therapy, mortality rates resulting from neonatal sepsis remain high, especially for 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 infants treated (five of five survived) and 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

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 adjunctive 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

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 [4,6,286,663] 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].

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

*References [6, 10, 85, 257, 258, 286, 447].

†References [7, 10, 12, 18, 257, 258, 446, 447].

[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 5. 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 leukocyte 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 chorioamnionitis. 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 intrauterine fetal prophylaxis can be beneficial in selected cases, widespread use of IVIG for all women having premature onset of labor is not feasible because of uncertain timing before delivery, widespread shortages of IVIG, and cost.

The decreased number of circulating polymorphonuclear leukocytes and reduced myeloid reserves in the bone marrow of newborns have been ascribed to impaired production of cytokines, interleukin-3, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor-α, and interferon-γ [699,700]. Considerable experience with in vitro myeloid 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 neonates 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 randomly 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

[712]. Bovine lactoferrin, sharing 77% homology with the human protein, has been granted "generally recognized as safe" (GRAS) status by the FDA. A randomized study of bovine lactoferrin supplementation in very low birth weight neonates showed a reduced rate of a first episode of late-onset sepsis in the treatment group (risk ratio 0.34, 95% confidence interval 0.17 to 0.70) [372]. This simple, promising intervention warrants further exploration as a tool to reduce the incidence of nosocomial infection in this extremely high-risk population.

DECONTAMINATION OF FOMITES

Because contamination of equipment poses a significant infectious challenge for the newborn, disinfection of all materials that are involved in the care of the newborn is an important responsibility of nursery personnel. The basic mechanisms of large pieces of equipment must be cleaned appropriately or replaced because they have been implicated in nursery epidemics. The use of disposable equipment and materials packaged in individual units, such as containers of sterile water for a nebulization apparatus, are important advances in the prevention of infection. The frequency of catheter-associated CoNS sepsis has led to attempts to prevent bacterial colonization of intravascular catheters through use of attachment-resistant polymeric materials, antibiotic impregnation, and immunotherapy directed against adherence factors [713]. These procedures are reviewed in Chapter 35.

EPIDEMIOLOGIC SURVEILLANCE

Endemic Infection

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

Epidemic Infection

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

SEPSIS IN THE NEWBORN RECENTLY DISCHARGED FROM THE HOSPITAL

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

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 after colonizing the mucous membranes; skin; or upper respiratory, genitourinary, or gastrointestinal tracts remains obscure. Nosocomially acquired or health care–associated organisms are discussed in further detail in Chapter 35.

INFECTIONS IN THE HOUSEHOLD

Infection can be associated with an underlying anatomic defect, physiologic abnormality, or metabolic disease. 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 suppurative lesions during the 10-month period after introduction into the home of an infant with a staphylococcal lesion. The incidence of suppurative infections in household contacts of infants without lesions was less than 2%. Damato and coworkers [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 twin infants 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.

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 [719,725]. 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/mm^3), normal absolute band neutrophil count (<1500/mm^3) 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 CSF; a complete blood cell and differential count; examination of CSF for cells, glucose, and protein; and a urinalysis. Although a peripheral blood cell count is routinely ordered, it is not sufficiently discriminatory to preclude the mandatory collection of blood for culture [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.

REFERENCES

[1] R.P. Gaynes, et al., Nosocomial infections among neonates in high-risk nurseries in the United States, Pediatrics 93 (1996) 357.
[2] E.C. Dunham, Septicemia in the newborn, Am. J. Dis. Child. 45 (1933) 229.
[3] W.L. Nyhan, M.D. Fousek, Septicemia of the newborn, Pediatrics 22 (1958) 268.
[4] L. Gluck, H.F. Wood, M.D. Fousek, Septicemia of the newborn, Pediatr. Clin. North. Am. 13 (1966) 1131.
[5] R.M. Freedman, et al., A half century of neonatal sepsis at Yale, Am. J. Dis. Child. 35 (1981) 140.
[6] I.M. Gladstone, et al., A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience, Pediatr. Infect. Dis. J. 9 (1990) 819.
[7] R.S. Baltimore, et al., Early-onset neonatal sepsis in the era of group B streptococcal prevention, Pediatrics 108 (2001) 1094.
[8] M.J. Bizzarro, et al., Seventy-five years of neonatal sepsis at Yale: 1928–2003, Pediatrics 116 (2005) 595–602.
[9] M.J. Bizzarro, et al., Changing patterns in neonatal *Escherichia coli* sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis, Pediatrics 121 (2008) 689–696.

[10] R. Vesikari, et al., Neonatal septicemia, Arch. Dis. Child. 60 (1985) 542.
[11] I. Winfred, The incidence of neonatal infections in the nursery unit at the Ahmadu Bello University Teaching Hospital, Zaria, Nigeria, East Afr. Med. J. 61 (1984) 197.
[12] D. Greenberg, et al., A prospective study of neonatal sepsis and meningitis in Southern Israel, Pediatr. Infect. Dis. J. 16 (1997) 768.
[13] O.J. Hensey, C.A. Hart, R.W.I. Cooke, Serious infection in a neonatal intensive care unit: a two-year survey, J. Hyg. (Camb) 95 (1985) 289.
[14] M.G. Karlowicz, E.S. Buescher, A.E. Surka, Fulminant late-onset sepsis in a neonatal intensive care unit, 1988–1997, and the impact of avoiding empiric vancomycin therapy, Pediatrics 106 (2000) 1387.
[15] B.J. Stoll, et al., Late-onset sepsis in very low birth weight neonates: the experience of the NICHD neonatal research network, Pediatrics 110 (2002) 285.
[16] I.R. Makhoul, et al., Epidemiology, clinical, and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: a national survey, Pediatrics 109 (2002) 34.
[17] J. Karpuch, M. Goldberg, D. Kohelet, Neonatal bacteremia: a 4-year prospective study, Isr. J. Med. Sci. 19 (1983) 963.
[18] A.A. Fanaroff, et al., Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants, Pediatr. Infect. Dis. 17 (1998) 593.
[19] B.J. Stoll, et al., Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants, N. Engl. J. Med. 347 (2002) 240–247.
[20] M. Ziai, R.J. Haggerty, Neonatal meningitis, N. Engl. J. Med. 259 (1958) 314.
[21] A.W. Mathies Jr., P.F. Wehrle, Management of Bacterial Meningitis, WB Saunders, Philadelphia, 1974.
[22] M.D. Yow, et al., Initial antibiotic management of bacterial meningitis, Medicine (Baltimore) 52 (1973) 305.
[23] M. Unhanand, et al., Gram-negative enteric bacillary meningitis: a twenty-one-year experience, J. Pediatr. 122 (1993) 15.
[24] C.J.J. Mulder, L. van Alphen, H.C. Zanen, Neonatal meningitis caused by *Escherichia coli* in the Netherlands, J. Infect. Dis. 150 (1984) 935.
[25] J. de Louvois, et al., Infantile meningitis in England and Wales: a two year study, Arch. Dis. Child. 66 (1991) 603.
[26] D.E. Holt, et al., Neonatal meningitis in England and Wales: 10 years on, BMJ 84 (2001) F85.
[27] M.T. Moreno, et al., Neonatal sepsis and meningitis in a developing Latin American country, Pediatr. Infect. Dis. J. 13 (1994) 516.
[28] R. Bennhagen, N.W. Svenningsen, A.N. Bekassy, Changing pattern of neonatal meningitis in Sweden: a comparative study 1976 vs. 1983, Scand. J. Infect. Dis. 19 (1987) 587.
[29] R.C. Lancefield, Serologic differentiation of human and other groups of hemolytic streptococci, J. Exp. Med. 57 (1933) 571.
[30] C.J. Baker, et al., Suppurative meningitis due to streptococci of Lancefield group B: a study of 33 infants, J. Pediatr. 82 (1973) 724.
[31] P.M. Schlievert, J.E. Gocke, J.R. Deringer, Group B streptococcal toxic shock-like syndrome: report of a case and purification of an associated pyrogenic toxin, Clin. Infect. Dis. 17 (1993) 26.
[32] D. Charles, B. Larsen, Streptococcal puerperal sepsis and obstetric infections: a historical perspective, Rev. Infect. Dis. 8 (1986) 411.
[33] I. Loudon, Puerperal fever, the streptococcus, and the sulphonamides, 1911–1945, BMJ 295 (1987) 485.
[34] B.P. Watson, An outbreak of puerperal sepsis in New York City, Am. J. Obstet. Gynecol. 16 (1928) 159.
[35] J.F. Jewett, et al., Childbed fever: a continuing entity, JAMA 206 (1968) 344.
[36] W.R. McCabe, A.A. Abrams, An outbreak of streptococcal puerperal sepsis, N. Engl. J. Med. 272 (1965) 615.
[37] J.R. Campbell, et al., An outbreak of M serotype 1 group A streptococcus in neonatal intensive care unit, J. Pediatr. 129 (1996) 396.
[38] V.K. Wong, H.T. Wright Jr., Group A β-hemolytic streptococci as a cause of bacteremia in children, Am. J. Dis. Child. 142 (1988) 831.
[39] D.J. Murphy Jr., Group A streptococcal meningitis, Pediatrics 71 (1983) 1.
[40] M.H. Rathore, L.L. Barton, E.L. Kaplan, Suppurative group A β-hemolytic streptococcal infections in children, Pediatrics 89 (1992) 743.
[41] M. Wilschanski, et al., Neonatal septicemia caused by group A beta-hemolytic streptococcus, Pediatr. Infect. Dis. J. 8 (1989) 536.
[42] N.R. Panaro, L.I. Lutwick, E.K. Chapnick, Intrapartum transmission of group A streptococcus, Clin. Infect. Dis. 17 (1993) 79.
[43] L.M. Mahieu, et al., Congenital streptococcal toxic shock syndrome with absence of antibodies against streptococcal pyrogenic exotoxins, J. Pediatr. 127 (1995) 987.
[44] C.C. Geil, W.K. Castle, E.A. Mortimer, Group A streptococcal infections in newborn nurseries, Pediatrics 46 (1970) 849.
[45] H.M. Gezon, M.J. Schaberg, J.O. Klein, Concurrent epidemics of *Staphylococcus aureus* and group A streptococcus disease in a newborn nursery-control with penicillin G and hexachlorophene bathing, Pediatrics 51 (1973) 383.
[46] G. Peter, J. Hazard, Neonatal group A streptococcal disease, J. Pediatr. 87 (1975) 454.
[47] J.D. Nelson, H.C. Dillon Jr., J.B. Howard, A prolonged nursery epidemic associated with a newly recognized type of group A streptococcus, J. Pediatr. 89 (1976) 792.
[48] U. Acharya, C.A.R. Lamont, K. Cooper, Group A beta-hemolytic streptococcus causing disseminated intravascular coagulation and maternal death, Lancet 1 (1988) 595.
[49] J. Kavi, R. Wise, Group A beta-hemolytic streptococcus causing disseminated intravascular coagulation and maternal death, Lancet 1 (1988) 993.
[50] G.R. Swingler, et al., Disseminated intravascular coagulation associated with group A streptococcal infection in pregnancy, Lancet 1 (1988) 1456.
[51] I. Miyairi, et al., Neonatal invasive group A streptococcal disease: case report and review of the literature, Pediatr. Infect. Dis. J. 23 (2004) 161–165.
[52] D. Greenberg, et al., Neonatal sepsis caused by *Streptococcus pyogenes*—resurgence of an old etiology? Pediatr. Infect. Dis. J. 18 (1999) 479.
[53] P. Patamasucon, J.D. Siegel, G.H. McCracken Jr., Streptococcal submandibular cellulitis in young infants, Pediatrics 67 (1981) 378.
[54] R. Bortolussi, T.R. Thompson, P. Ferrieri, Early-onset pneumococcal sepsis in newborn infants, Pediatrics 60 (1977) 352.
[55] P.J. Shaw, D.L. Robinson, J.G. Watson, Pneumococcal infection in a mother and infant, Lancet 2 (1984) 47.
[56] H. Westh, L. Skibsted, B. Korner, *Streptococcus pneumoniae* infections of the female genital tract and in the newborn child, Rev. Infect. Dis. 12 (1990) 416.
[57] E.N. Robinson Jr., Pneumococcal endometritis and neonatal sepsis, Rev. Infect. Dis. 12 (1990) 799.
[58] B.R. Hughes, J.L. Mercer, L.B. Gosbel, Neonatal pneumococcal sepsis in association with fatal maternal pneumococcal sepsis, Aust. N Z J Obstet. Gynaecol. 41 (2001) 457.
[59] J.A. Hoffman, et al., Streptococcus pneumoniae infections in the neonate, Pediatrics 112 (2003) 1095.
[60] L.C. McDonald, K. Bryant, J. Snyder, Peripartum transmission of penicillin-resistant *Streptococcus pneumoniae*, J. Clin. Microbiol. 41 (2003) 2258–2260.
[61] R.A. Primhak, M.S. Tanner, R.C. Spencer, Pneumococcal infection in the newborn, Arch. Dis. Child. 69 (1993) 317–318.
[62] P. Stewardson-Krieger, S.P. Gotoff, Neonatal meningitis due to group C beta hemolytic streptococcus, J. Pediatr. 90 (1977) 103.
[63] R.J. Quinn, et al., Meningitis caused by *Streptococcus dysgalactiae* in a preterm infant, Am. J. Clin. Pathol. 70 (1978) 948–950.
[64] J.A. Hervas, et al., Neonatal sepsis and meningitis due to *Streptococcus equisimilis*, Pediatr. Infect. Dis. J. 4 (1985) 694.
[65] M. Arditi, et al., Group C β-hemolytic streptococcal infections in children: nine pediatric cases and review, Rev. Infect. Dis. 11 (1989) 34.
[66] C.J. Baker, Unusual occurrence of neonatal septicemia due to group G streptococcus, Pediatrics 53 (1974) 568.
[67] P.C. Appelbaum, et al., Neonatal sepsis due to group G streptococci, Acta Paediatr. Scand. 69 (1980) 599.
[68] A.E. Dyson, S.E. Read, Group G streptococcal colonization and sepsis in neonates, J. Pediatr. 99 (1981) 944.
[69] H. Carstensen, C. Pers, O. Pryds, Group G streptococcal neonatal septicemia: two case reports and a brief review of the literature, Scand. J. Infect. Dis. 20 (1988) 407.
[70] R. Auckenthaler, P.E. Hermans, J.A. Washington II., Group G streptococcal bacteremia: clinical study and review of the literature, Rev. Infect. Dis. 5 (1983) 196.
[71] C.R. Fikar, J. Levy, *Streptococcus bovis* meningitis in a neonate, Am. J. Dis. Child. 133 (1979) 1149.
[72] D.L. Headings, et al., Fulminant neonatal septicemia caused by *Streptococcus bovis*, J. Pediatr. 92 (1978) 282.
[73] P.J. Gavin, et al., Neonatal sepsis caused by *Streptococcus bovis* variant (biotype II/2): report of a case and review, J. Clin. Microbiol. 41 (2003) 3433–3435.
[74] G.E. Bignardi, D. Isaacs, Neonatal meningitis due to *Streptococcus mitis*, Rev. Infect. Dis. 11 (1989) 86.
[75] H.H. Hellwege, et al., Neonatal meningitis caused by *Streptococcus mitis*, Lancet 1 (1984) 743.
[76] R.A. Broughton, R. Krafka, C.J. Baker, Non-group D alpha-hemolytic streptococci: new neonatal pathogens, J. Pediatr. 99 (1981) 450.
[77] S.P. Kumar, M. Delivoria-Papadopoulos, Infections in newborn infants in a special care unit, Ann. Clin. Lab. Sci. 15 (1985) 351.
[78] L. Spigelblatt, et al., Changing pattern of neonatal streptococcal septicemia, Pediatr. Infect. Dis. J. 4 (1985) 56.
[79] A. Gunlemez, et al., Multi-resistant viridans streptococcal pneumonia and sepsis in the ventilated newborn, Ann. Trop. Paediatr. 24 (2004) 253–258.
[80] W. Ludwig, et al., The phylogenetic position of *Streptococcus* and *Enterococcus*, J. Gen. Microbiol. 131 (1985) 543–551.
[81] J.D. Siegel, G.H. McCracken Jr., Group D streptococcal infections, J. Pediatr. 93 (1978) 542.
[82] D.F. McNeeley, F. Saint-Louis, G.J. Noel, Neonatal enterococcal bacteremia: an increasingly frequent event with potentially untreatable pathogens, Pediatr. Infect. Dis. J. 15 (1996) 800.
[83] J.B. Alexander, G.P. Giacoia, Early onset nonenterococcal group D streptococcal infection in the newborn infant, J. Pediatr. 93 (1978) 489.
[84] K. Bavikatte, et al., Group D streptococcal septicemia in the neonate, Am. J. Dis. Child. 133 (1979) 493.
[85] S.R.M. Dobson, C.J. Baker, Enterococcal sepsis in neonates: features by age at onset and occurrence of focal infection, Pediatrics 85 (1990) 165.
[86] D.F. McNeeley, et al., An investigation of vancomycin-resistant *Enterococcus faecium* within the pediatric service of a large urban medical center, Pediatr. Infect. Dis. J. 17 (1998) 184.
[87] F. Espersen, et al., *Staphylococcus aureus* bacteremia in children below the age of one year, Acta Paediatr. Scand. 78 (1989) 56.

[88] C. Eckhardt, et al., Transmission of methicillin-resistant *Staphylococcus aureus* in the neonatal intensive care unit from a patient with community-acquired disease, Infect. Control Hosp. Epidemiol. 24 (2003) 460–461.
[89] S. Yee-Guardino, et al., Recognition and treatment of neonatal community-associated MRSA pneumonia and bacteremia, Pediatr. Pulmonol. 43 (2008) 203–205.
[90] L. Saiman, et al., Hospital transmission of community-acquired methicillin-resistant *Staphylococcus aureus* among postpartum women, Clin. Infect. Dis. 37 (2003) 1313–1319.
[91] M.D. David, et al., Community-associated methicillin-resistant *Staphylococcus aureus*: nosocomial transmission in a neonatal unit, J. Hosp. Infect. 64 (2006) 244–250.
[92] S.M. Wang, et al., *Staphylococcus capitis* bacteremia of very low birth weight premature infants at neonatal intensive care units: clinical significance and antimicrobial susceptibility, J. Microbiol. Immunol. Infect. 32 (1999) 26–32.
[93] T. Strunk, et al., Neonatal immune responses to coagulase-negative staphylococci, Curr. Opin. Infect. Dis. 20 (2007) 370–375.
[94] S. Baumgart, et al., Sepsis with coagulase-negative staphylococci in critically ill newborns, Am. J. Dis. Child. 137 (1983) 461.
[95] S. Struthers, et al., A comparison of two versus one blood culture in the diagnosis and treatment of coagulase-negative staphylococcus in the neonatal intensive care unit, J. Perinatol. 22 (2002) 547–549.
[96] R.T. Hall, et al., Characteristics of coagulase negative staphylococci from infants with bacteremia, Pediatr. Infect. Dis. J. 6 (1987) 377.
[97] M. Otto, Virulence factors of the coagulase-negative staphylococci, Front. Biosci. 9 (2004) 841–863.
[98] A.L. Shiau, C.L. Wu, The inhibitory effect of *Staphylococcus epidermidis* slime on the phagocytosis of murine peritoneal macrophages is interferon-independent, Microbiol. Immunol. 42 (1998) 33–40.
[99] J. Freeman, et al., Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units, N. Engl. J. Med. 323 (1990) 301.
[100] Centers for Disease Control and Prevention, Public health dispatch: outbreak of listeriosis—Northeastern United States 2002, MMWR Morb. Mortal. Wkly. Rep. 51 (2002) 950.
[101] K.M. Posfay-Barbe, E.R. Wald, Listeriosis, Semin. Fetal. Neonatal. Med. 14 (2009) 228–233.
[102] S.J. Schrag, et al., Risk factors for invasive, early-onset *Escherichia coli* infections in the era of widespread intrapartum antibiotic use, Pediatrics 118 (2006) 570–576.
[103] J. Raymond, et al., Evidence for transmission of *Escherichia coli* from mother to child in late-onset neonatal infection, Pediatr. Infect. Dis. J. 27 (2008) 186–188.
[104] S.M. Soto, et al., Comparative study of virulence traits of *Escherichia coli* clinical isolates causing early and late neonatal sepsis, J. Clin. Microbiol. 46 (2008) 1123–1125.
[105] E. Bingen, et al., Phylogenetic analysis of *Escherichia coli* strains causing neonatal meningitis suggests horizontal gene transfer from a predominant pool of highly virulent B2 group strains, J. Infect. Dis. 177 (1998) 642.
[106] S. Bonacorsi, E. Bingen, Molecular epidemiology of *Escherichia coli* causing neonatal meningitis, Int. J. Med. Microbiol. 295 (2005) 373–381.
[107] C. Peigne, et al., The plasmid of *Escherichia coli* strain S88 (O45:K1:H7) that causes neonatal meningitis is closely related to avian pathogenic *E. coli* plasmids and is associated with high-level bacteremia in a neonatal rat meningitis model, Infect. Immun. 77 (2009) 2272–2284.
[108] J.B. Robbins, et al., *Escherichia coli* K1 capsular polysaccharide associated with neonatal meningitis, N. Engl. J. Med. 290 (1974) 1216.
[109] G.H. McCracken Jr., et al., Relation between *Escherichia coli* K1 capsular polysaccharide antigen and clinical outcome in neonatal meningitis, Lancet 2 (1974) 246.
[110] G.H. McCracken Jr., L.D. Sarff, Current status and therapy of neonatal *E. coli* meningitis, Hosp. Pract. 9 (1974) 57.
[111] L.D. Sarff, et al., Epidemiology of *Escherichia coli* K1 in healthy and diseased newborns, Lancet 1 (1975) 1099.
[112] G. Peter, J.S. Nelson, Factors affecting neonatal *E. coli* K1 rectal colonization, J. Pediatr. 93 (1978) 866.
[113] J.L. Burns, et al., Transcytosis of gastrointestinal epithelial cells by *Escherichia coli* K1, Pediatr. Res. 49 (2001) 30–37.
[114] Y. Xie, K.J. Kim, K.S. Kim, Current concepts on *Escherichia coli* K1 translocation of the blood-brain barrier, FEMS Immunol. Med. Microbiol. 42 (2004) 271–279.
[115] S.H. Huang, M.F. Stins, K.S. Kim, Bacterial penetration across the blood-brain barrier during the development of neonatal meningitis, Microbes. Infect. 2 (2000) 1237–1244.
[116] J.A. Hervás, et al., Increase of *Enterobacter* in neonatal sepsis: a twenty-two-year study, Pediatr. Infect. Dis. J. 20 (2001) 1134.
[117] A. Gupta, Hospital-acquired infections in the neonatal intensive care unit—*Klebsiella pneumoniae*, Semin. Perinatol. 26 (2002) 340.
[118] S.K. Sood, D. Mulvihill, R.S. Daum, Intrarenal abscess caused by *Klebsiella pneumoniae* in a neonate: modern management and diagnosis, Am. J. Perinatol. 6 (1989) 367.
[119] S. Basu, et al., An unusual case of neonatal brain abscess following *Klebsiella pneumoniae* septicemia, Infection 29 (2001) 283.
[120] H. Ozkan, et al., Perianal necrotizing fasciitis in a neonate, Indian J. Pediatr. 64 (1997) 116.
[121] R. Podschun, H. Acktun, J. Okpara, Isolation of *Klebsiella planticola* from newborns in a neonatal ward, J. Clin. Microbiol. 36 (1998) 2331.
[122] G.L. Westbrook, et al., Incidence and identification of *Klebsiella planticola* in clinical isolates with emphasis on newborns, J. Clin. Microbiol. 38 (2000) 1495.
[123] E. Leibovitz, et al., Sepsis at a neonatal intensive care unit: a four-year retrospective study (1989–1992), Isr. J. Med. Sci. 33 (1997) 734.
[124] Y. Bell, et al., Neonatal sepsis in Jamaican neonates, Ann. Trop. Paediatr. 25 (2005) 293–296.
[125] E. Simeunovic, et al., Liver abscess in neonates, Pediatr. Surg. Int. 25 (2009) 153–156.
[126] C.L. Pessoa-Silva, et al., Extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* in a neonatal intensive care unit: risk factors for infection and colonization, J. Hosp. Infect. 53 (2003) 198.
[127] E. Roilides, et al., Septicemia due to multiresistant *Klebsiella pneumoniae* in a neonatal unit: a case-control study, Am. J. Perinatol. 17 (2000) 35.
[128] P.W. Stone, et al., Attributable costs and length of stay of an extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* outbreak in a neonatal intensive care unit, Infect. Control Hosp. Epidemiol. 24 (2003) 601.
[129] M.B. Kleiman, et al., Meningoencephalitis and compartmentalization of the cerebral ventricles caused by *Enterobacter sakazakii*, J. Clin. Microbiol. 14 (1981) 352.
[130] J. Willis, J.E. Robinson, *Enterobacter sakazakii* meningitis in neonates, Pediatr. Infect. Dis. J. 7 (1988) 196.
[131] W.A. Bonadio, D. Margolis, M. Tovar, *Enterobacter cloacae* bacteremia in children: a review of 30 cases in 12 years, Clin. Pediatr. 30 (1991) 310.
[132] S. Harbarth, et al., Outbreak of *Enterobacter cloacae* related to understaffing, overcrowding, and poor hygiene practices, Infect. Control Hosp. Epidemiol. 20 (1999) 598.
[133] P.J. Wenger, et al., An outbreak of *Enterobacter hormaechei* infection and colonization in an intensive care nursery, Clin. Infect. Dis. 24 (1997) 1243.
[134] C.L. da Silva, et al., *Enterobacter hormaechei* bloodstream infection at three neonatal intensive care units in Brazil, Pediatr. Infect. Dis. J. 21 (2002) 175.
[135] C. Iversen, et al., *Cronobacter* gen. nov., a new genus to accommodate the biogroups of *Enterobacter sakazakii*, and proposal of *Cronobacter sakazakii* gen. nov., comb. nov., *Cronobacter malonaticus* sp. nov., *Cronobacter turicensis* sp. nov., *Cronobacter muytjensii* sp. nov., *Cronobacter dublinensis* sp. nov., *Cronobacter genomospecies* 1, and of three subspecies, *Cronobacter dublinensis* subsp. *dublinensis* subsp. nov., *Cronobacter dublinensis* subsp. *lausannensis* subsp. nov. and *Cronobacter dublinensis* subsp. *lactaridi* subsp. nov, Int. J. Syst. Evol. Microbiol. 58 (2008) 1442–1447.
[136] N. Gurses, *Enterobacter* septicemia in neonates, Pediatr. Infect. Dis. J. 14 (1995) 638.
[137] A. Jain, et al., Prevalence of extended-spectrum beta-lactamase-producing gram-negative bacteria in septicaemic neonates in a tertiary care hospital, J. Med. Microbiol. 52 (2003) 421.
[138] S. Townsend, E. Hurrell, S. Forsythe, Virulence studies of *Enterobacter sakazakii* isolates associated with a neonatal intensive care unit outbreak, BMC Microbiol. 8 (2008) 64.
[139] H.N. Chen, et al., Late-onset *Enterobacter cloacae* sepsis in very-low-birth-weight neonates: experience in a medical center, Pediatr Neonatol 50 (2009) 3–7.
[140] H.L. Muytjens, L.A.A. Kollee, *Enterobacter sakazakii* meningitis in neonates: causative role of formula? Pediatr. Infect. Dis. J. 9 (1990) 372.
[141] F.R. Noriega, et al., Nosocomial bacteremia caused by *Enterobacter sakazakii* and *Leuconostoc mesenteroides* resulting from extrinsic contamination of infant formula, Pediatr. Infect. Dis. J. 9 (1990) 447.
[142] D. Drudy, et al., *Enterobacter sakazakii*: an emerging pathogen in powdered infant formula, Clin. Infect. Dis. 42 (2006) 996–1002.
[143] *Cronobacter* species isolation in two infants—New Mexico, 2008, MMWR Morb. Mortal. Wkly. Rep. 58 (2009) 1179–1183.
[144] T.F. Fok, et al., Risk factors for *Enterobacter* septicemia in a neonatal unit: case-control study, Clin. Infect. Dis. 27 (1998) 1204.
[145] A.T. Tresoldi, et al., Enterobacter cloacae sepsis outbreak in a newborn unit caused by contaminated total parenteral nutrition solution, Am. J. Infect. Control. 28 (2000) 258.
[146] H.S. Cheng, et al., Outbreak investigation of nosocomial *Enterobacter cloacae* bacteraemia in a neonatal intensive care unit, Scand. J. Infect. Dis. 32 (2000) 293.
[147] T.I. Doran, The role of *Citrobacter* in clinical disease of children: review, Clin. Infect. Dis. 28 (1999) 384.
[148] D.R. Graham, J.D. Band, *Citrobacter diversus* brain abscess and meningitis in neonates, JAMA 245 (1981) 1923.
[149] D.R. Graham, et al., Epidemic nosocomial meningitis due to *Citrobacter diversus* in neonates, J. Infect. Dis. 144 (1981) 203.
[150] A.M. Kaplan, et al., Cerebral abscesses complicating neonatal *Citrobacter freundii* meningitis, West. J. Med. 127 (1977) 418.
[151] F.Y.C. Lin, et al., Outbreak of neonatal *Citrobacter diversus* meningitis in a suburban hospital, Pediatr. Infect. Dis. J. 6 (1987) 50.
[152] S.C. Eppes, et al., Recurring ventriculitis due to *Citrobacter diversus*: clinical and bacteriologic analysis, Clin. Infect. Dis. 17 (1993) 437.
[153] S.D. Foreman, et al., Neonatal *Citrobacter* meningitis; pathogenesis of cerebral abscess formation, Ann. Neurol. 16 (1984) 655.
[154] J.G. Morris, et al., Molecular epidemiology of neonatal meningitis due to *Citrobacter diversus*: a study of isolates from hospitals in Maryland, J. Infect. Dis. 154 (1986) 409.

[155] M.W. Kline, E.O. Mason Jr., S.L. Kaplan, Characterization of *Citrobacter diversus* strains causing neonatal meningitis, J. Infect. Dis. 157 (1988) 101.
[156] O. Etuwewe, et al., Brain abscesses due to *Citrobacter koseri* in a pair of twins, Pediatr. Infect. Dis. J. 28 (2009) 1035.
[157] S.M. Townsend, et al., *Citrobacter koseri* brain abscess in the neonatal rat: survival and replication within human and rat macrophages, Infect. Immun. 71 (2003) 5871–5880.
[158] O. Assadian, et al., Nosocomial outbreak of *Serratia marcescens* in a neonatal intensive care unit, Infect. Control Hosp. Epidemiol. 23 (2002) 457.
[159] F. Fleisch, et al., Three consecutive outbreaks of *Serratia marcescens* in a neonatal intensive care unit, Clin. Infect. Dis. 34 (2002) 767.
[160] T.N. Jang, et al., Use of pulsed-field gel electrophoresis to investigate an outbreak of *Serratia marcescens* infection in a neonatal intensive care unit, J. Hosp. Infect. 48 (2001) 13.
[161] M.T. Newport, et al., Endemic *Serratia marcescens* infection in a neonatal intensive care nursery associated with gastrointestinal colonization, Pediatr. Infect. Dis. 4 (1985) 160.
[162] P. Berthelot, et al., Investigation of a nosocomial outbreak due to *Serratia marcescens* in a maternity hospital, Infect. Control Hosp. Epidemiol. 20 (1999) 233.
[163] M.M. Cullen, et al., *Serratia marcescens* outbreak in a neonatal intensive care unit prompting review of decontamination of laryngoscopes, J. Hosp. Infect. 59 (2005) 68–70.
[164] M. Zaidi, et al., Epidemic of *Serratia marcescens* bacteremia and meningitis in a neonatal unit in Mexico City, Infect. Control Hosp. Epidemiol. 10 (1989) 14.
[165] L.L. Maragakis, et al., Outbreak of multidrug-resistant *Serratia marcescens* infection in a neonatal intensive care unit, Infect. Control Hosp. Epidemiol. 29 (2008) 418–423.
[166] J.R. Campbell, T. Diacovo, C.J. Baker, *Serratia marcescens* meningitis in neonates, Pediatr. Infect. Dis. J. 11 (1992) 881.
[167] M. Ries, et al., Brain abscesses in neonates—report of three cases, Eur. J. Pediatr. 152 (1993) 745.
[168] C. Gras-Le Guen, et al., Contamination of a milk bank pasteuriser causing a *Pseudomonas aeruginosa* outbreak in a neonatal intensive care unit, Arch. Dis. Child. Fetal Neonatal Ed. 88 (2003) F434–F435.
[169] D.C. Stevens, M.B. Kleiman, R.L. Schreiner, Early-onset *Pseudomonas* sepsis of the neonate, Perinatol Neonatol 6 (1982) 75.
[170] S.P. Ghosal, P.C. SenGupta, A.K. Mukherjee, Noma neonatorum: its aetiopathogenesis, Lancet 2 (1978) 289.
[171] S.S. Shah, P.G. Gallagher, Complications of conjunctivitis caused by *Pseudomonas aeruginosa* in a newborn intensive care unit, Pediatr. Infect. Dis. J. 17 (1998) 97.
[172] A. Zawacki, et al., An outbreak of *Pseudomonas aeruginosa* pneumonia and bloodstream infection associated with intermittent otitis externa in a healthcare worker, Infect. Control Hosp. Epidemiol. 25 (2004) 1083–1089.
[173] Centers for Disease Control, Reported isolates of *Salmonella* from CSF in the United States, 1968–1979, J. Infect. Dis. 143 (1981) 504.
[174] M. Totan, et al., Meningitis due to *Salmonella* in preterm neonates, Turk. J. Pediatr. 44 (2002) 45.
[175] F.J. Cooke, et al., Report of neonatal meningitis due to *Salmonella enterica* serotype *Agona* and review of breast milk-associated neonatal *Salmonella* infections, J. Clin. Microbiol. 47 (2009) 3045–3049.
[176] R.P. Reed, K.P. Klugman, Neonatal typhoid fever, Pediatr. Infect. Dis. J. 13 (1994) 774.
[177] A. Schuchat, et al., Bacterial meningitis in the United States in 1995, N. Engl. J. Med. 337 (1997) 970.
[178] W.A. Sunderland, et al., Meningococcemia in a newborn infant whose mother had meningococcal vaginitis, J. Pediatr. 81 (1972) 856.
[179] R.N. Jones, J. Stepack, A. Eades, Fatal neonatal meningococcal meningitis: association with maternal cervical-vaginal colonization, JAMA 236 (1976) 2652.
[180] S.M. Fiorito, et al., An unusual transmission of *Neisseria meningitidis*: neonatal conjunctivitis acquired at delivery from the mother's endocervical infection, Sex. Transm. Dis. 28 (2001) 29.
[181] D.J. Cher, et al., A case of pelvic inflammatory disease associated with *Neisseria meningitidis* bacteremia, Clin. Infect. Dis. 17 (1993) 134.
[182] Z.A. Bhutta, I.A. Khan, Z. Agha, Fatal intrauterine meningococcal infection, Pediatr. Infect. Dis. J. 10 (1991) 868.
[183] K. Chugh, C.K. Bhalla, K.K. Joshi, Meningococcal abscess and meningitis in a neonate, Pediatr. Infect. Dis. J. 7 (1988) 136.
[184] C.A. Arango, M.H. Rathore, Neonatal meningococcal meningitis: case reports and review of literature, Pediatr. Infect. Dis. J. 15 (1996) 1134.
[185] C.W. Shepard, N.E. Rosenstein, M. Fischer, Active Bacterial Core Surveillance Team. Neonatal meningococcal disease in the United States, 1990 to 1999, Pediatr. Infect. Dis. J. 22 (2003) 418.
[186] F.P. Manginello, et al., Neonatal meningococcal meningitis and meningococcemia, Am. J. Dis. Child. 133 (1979) 651.
[187] H.W. Clegg, et al., Fulminant neonatal meningococcemia, Am. J. Dis. Child. 134 (1980) 354.
[188] M.C. Falcao, et al., Neonatal sepsis and meningitis caused by *Neisseria meningitidis*: a case report, Rev. Inst. Med. Trop. Sao. Paulo. 49 (2007) 191–194.
[189] W.G. Adams, et al., Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era, JAMA 269 (1993) 221.
[190] H. Peltola, T. Kilpi, M. Anttila, Rapid disappearance of *Haemophilus influenzae* type b meningitis after routine childhood immunization with conjugate vaccines, Lancet 340 (1992) 592.
[191] K.M. Bisgard, et al., *Haemophilus influenzae* invasive disease in the United States, 1994–1995: near disappearance of a vaccine-preventable childhood disease, Emerg. Infect. Dis. 4 (1998) 229.
[192] A.K. Takala, et al., Reduction of oropharyngeal carriage of *Haemophilus influenzae* type b (Hib) in children immunized with Hib conjugate vaccine, J. Infect. Dis. 164 (1991) 982.
[193] T.V. Murphy, et al., Decreased *Haemophilus* colonization in children vaccinated with *Haemophilus influenzae* type b conjugate vaccine, J. Pediatr. 122 (1993) 517.
[194] J.C. Mohle-Boetani, et al., Carriage of *Haemophilus influenzae* type b in children after widespread vaccination with *Haemophilus influenzae* type b vaccines, Pediatr. Infect. Dis. J. 12 (1993) 589.
[195] G. Urwin, et al., Invasive disease due to *Haemophilus influenzae* serotype f: clinical and epidemiologic characteristics in the *H. influenzae* serotype b vaccine era, Clin. Infect. Dis. 22 (1996) 1069.
[196] P.T. Heath, et al., Non-type b *Haemophilus influenzae* disease: clinical and epidemiologic characteristics in the *Haemophilus influenzae* type b vaccine era, Pediatr. Infect. Dis. J. 20 (2001) 300.
[197] D.G. Perdue, L.R. Bulkow, G.B. Gellin, Invasive *Haemophilus influenzae* disease in Alaskan residents aged 10 years and older before and after infant vaccination programs, JAMA 283 (2000) 3089.
[198] L.L. Barton, R.D. Cruz, C. Walentik, Neonatal *Haemophilus influenzae* type C sepsis, Am. J. Dis. Child. 136 (1982) 463.
[199] P. Campognone, D.B. Singer, Neonatal sepsis due to nontypeable *Haemophilus influenzae*, Am. J. Dis. Child. 140 (1986) 117.
[200] R.J. Wallace Jr., et al., Nontypable *Haemophilus influenzae* (biotype 4) as a neonatal, maternal and genital pathogen, Rev. Infect. Dis. 5 (1983) 123.
[201] T.J. Falia, et al., Population-based study of non-typeable *Haemophilus influenzae* invasive disease in children and neonates, Lancet 341 (1993) 851.
[202] C.A. Friesen, C.T. Cho, Characteristic features of neonatal sepsis due to *Haemophilus influenzae*, Rev. Infect. Dis. 8 (1986) 777.
[203] L.D. Lilien, et al., Early-onset *Haemophilus* sepsis in newborn infants: clinical, roentgenographic, and pathologic features, Pediatrics 62 (1978) 299.
[204] K. Silverberg, F.H. Boehm, *Haemophilus influenzae* amnionitis with intact membranes: a case report, Am. J. Perinatol. 7 (1990) 270.
[205] S. Hershckowitz, et al., A cluster of early neonatal sepsis and pneumonia caused by nontypable *Haemophilus influenzae*, Pediatr. Infect. Dis. J. 23 (2004) 1061–1062.
[206] J.S. Bradley, *Haemophilus parainfluenzae* sepsis in a very low birth weight premature infant: a case report and review of the literature, J. Perinatol. 19 (1999) 315.
[207] R.N. Holt, et al., Three cases of *Hemophilus parainfluenzae* meningitis, Clin. Pediatr. (Phila) 13 (1974) 666.
[208] S.H. Zinner, et al., Puerperal bacteremia and neonatal sepsis due to *Hemophilus parainfluenzae*: report of a case with antibody titers, Pediatrics 49 (1972) 612.
[209] A. Miano, et al., Neonatal *Haemophilus aphrophilus* meningitis, Helv. Paediatr. Acta 31 (1977) 499.
[210] S.L. Gorbach, J.G. Bartlett, Anaerobic infections, N. Engl. J. Med. 290 (1974) 1177.
[211] S.L. Gorbach, et al., Anaerobic microflora of the cervix in healthy women, Am. J. Obstet. Gynecol. 117 (1973) 1053.
[212] A.W. Chow, L.B. Guze, Bacteroidaceae bacteremia: clinical experience with 112 patients, Medicine (Baltimore) 53 (1974) 93.
[213] S.M. Finegold, Anaerobic infections, Surg. Clin. North. Am. 60 (1980) 49.
[214] I. Brook, Bacteremia due to anaerobic bacteria in newborns, J. Perinatol. 10 (1990) 351.
[215] G.J. Noel, D.A. Laufer, P.J. Edelson, Anaerobic bacteremia in a neonatal intensive care unit: an eighteen year experience, Pediatr. Infect. Dis. J. 7 (1988) 858.
[216] S. Mitra, D. Panigrahi, A. Narang, Anaerobes in neonatal septicaemia: a cause for concern, J. Trop. Pediatr. 43 (1997) 153.
[217] A.W. Chow, et al., The significance of anaerobes in neonatal bacteremia: analysis of 23 cases and review of the literature, Pediatrics 54 (1974) 736.
[218] S. Ohta, et al., Neonatal adrenal abscess due to *Bacteroides*, J. Pediatr. 93 (1978) 1063.
[219] Y.H. Lee, R.B. Berg, Cephalhematoma infected with *Bacteroides*, Am. J. Dis. Child. 121 (1971) 72.
[220] S.F. Siddiqi, P.M. Taylor, Necrotizing fasciitis of the scalp: a complication of fetal monitoring, Am. J. Dis. Child. 136 (1982) 226.
[221] H.M. Feder Jr., *Bacteroides fragilis* meningitis, Rev. Infect. Dis. 9 (1987) 783.
[222] J.R. Harrod, D.A. Stevens, Anaerobic infections in the newborn infant, J. Pediatr. 85 (1974) 399.
[223] L.M. Dunkle, T.J. Brotherton, R.D. Feigin, Anaerobic infections in children: a prospective survey, Pediatrics 57 (1976) 311.
[224] H.M. Feder Jr., et al., *Bacillus* species isolates from cerebrospinal fluid in patients without shunts, Pediatrics 82 (1988) 909–913.
[225] N.J. Hilliard, R.L. Schelonka, K.B. Waites, *Bacillus cereus* bacteremia in a preterm neonate, J. Clin. Microbiol. 41 (2003) 3441–3444.
[226] A.B. John, et al., Intractable *Bacillus cereus* bacteremia in a preterm neonate, J. Trop. Pediatr. 53 (2007) 131–132.
[227] R. Tuladhar, et al., Refractory *Bacillus cereus* infection in a neonate, Int. J. Clin. Pract. 54 (2000) 345–347.

B978-1-4160-6400-8.00006-7, 00006

[228] W.C. Van Der Zwet, et al., Outbreak of *Bacillus cereus* infections in a neonatal intensive care unit traced to balloons used in manual ventilation, J. Clin. Microbiol. 38 (2000) 4131–4136.
[229] M.D. Yohannan, et al., Congenital pneumonia and early neonatal septicemia due to *Bacteroides fragilis*, Eur. J. Clin. Microbiol. Infect. Dis. 11 (1992) 472–473.
[230] G.L. Keffer, G.R. Monif, Perinatal septicemia due to the Bacteroidaceae, Obstet. Gynecol. 71 (1988) 463–465.
[231] H.M. Feder Jr., *Bacteroides fragilis* meningitis, Rev. Infect. Dis. 9 (1987) 783–786.
[232] A.I. Airede, Pathogens in neonatal omphalitis, J. Trop. Pediatr. 38 (1992) 129.
[233] A. Kosloske, et al., Cellulitis and necrotizing fasciitis of the abdominal wall in pediatric patients, J. Pediatr. Surg. 16 (1981) 246.
[234] N.E. Chaney, *Clostridium* infection in mother and infant, Am. J. Dis. Child. 134 (1980) 1175.
[235] R.P. Spark, D.A. Wike, Nontetanus clostridial neonatal fatality after home delivery, Ariz. Med. 40 (1983) 697.
[236] R.A. Motz, A.G. James, B. Dove, *Clostridium perfringens* meningitis in a newborn infant, Pediatr. Infect. Dis. J. 15 (1996) 708.
[237] M.H. Roper, J.H. Vandelaer, F.L. Gasse, Maternal and neonatal tetanus, Lancet 370 (2007) 1947–1959.
[238] F.B. Pascual, et al., Tetanus surveillance—United States, 1998–2000, MMWR. Surveill. Summ. 52 (2003) 1.
[239] A.S. Craig, et al., Neonatal tetanus in the United States: a sentinel event in the foreign-born, Pediatr. Infect. Dis. J. 16 (1997) 955.
[240] S. Kumar, L.M. Malecki, A case of neonatal tetanus, South. Med. J. 84 (1991) 396.
[241] Centers for Disease Control, Neonatal tetanus—Montana, 1998, MMWR. Morb. Mortal. Wkly. Rep. 47 (1998) 928.
[242] J. Vandelaer, et al., Tetanus in developing countries: an update on the Maternal and Neonatal Tetanus Elimination Initiative, Vaccine 21 (2003) 3442.
[243] A. Quddus, et al., Neonatal tetanus: mortality rate and risk factors in Loralai District, Pakistan Int J Epidemiol 31 (2002) 648.
[244] C.D. Idema, et al., Neonatal tetanus elimination in Mpumalanga Province, South Africa, Trop. Med. Int. Health 7 (2002) 622.
[245] S. Amsalu, S. Lulseged, Tetanus in a children's hospital in Addis Ababa: review of 113 cases, Ethiop. Med. J. 43 (2005) 233–240.
[246] B.E. Mustafa, et al., Neonatal tetanus in rural and displaced communities in the East Nile Province, J. Trop. Pediatr. 42 (1996) 110.
[247] R.B. Arnold, T.I. Soewarso, A. Karyadi, Mortality from neonatal tetanus in Indonesia: results of two surveys, Bull. World Health Organ. 64 (1986) 259.
[248] J.I.H. Herrero, R.R. Beltran, A.M.M. Sanchanz, Failure of intrathecal tetanus antitoxin in the treatment of tetanus neonatorum, J. Infect. Dis. 164 (1991) 619.
[249] E. Abrutyn, J.A. Berlin, Intrathecal therapy in tetanus, JAMA 266 (1991) 2262.
[250] H.P. Traverso, et al., Ghee application to the umbilical cord: a risk factor for neonatal tetanus, Lancet 1 (1989) 486.
[251] A.M. Oudesluys-Murphy, Umbilical cord care and neonatal tetanus, Lancet 1 (1989) 843.
[252] Centers for Disease Control and Prevention. Progress toward the global elimination of neonatal tetanus, 1989–1993, JAMA 273 (1995) 196.
[253] R.E. Black, D.H. Huber, G.T. Curlin, Reduction of neonatal tetanus by mass immunization of nonpregnant women: duration of protection provided by one or two doses of aluminum-adsorbed tetanus toxoid, Bull. World Health Organ. 58 (1980) 927.
[254] F. Schofield, Selective primary health care: strategies for control of disease in the developing world. XXII. Tetanus: a preventable problem, Rev. Infect. Dis. 8 (1986) 144.
[255] D.S. Gromisch, et al., Simultaneous mixed bacterial meningitis in an infant, Am. J. Dis. Child. 119 (1970) 284.
[256] L. Pacifico, et al., Early-onset *Pseudomonas aeruginosa* sepsis and *Yersinia enterocolitica* neonatal infection: a unique combination in a preterm infant, Eur. J. Pediatr. 146 (1987) 192.
[257] I. Tessin, B. Trollfors, K. Thiringer, Incidence and etiology of neonatal septicaemia and meningitis in western Sweden 1975–1986, Acta Paediatr. Scand. 79 (1990) 1023.
[258] T. Vesikari, et al., Neonatal septicaemia in Finland 1981–85, Acta Paediatr. Scand. 78 (1989) 44.
[259] B. Bruun, A. Paerregaard, Septicemia in a Danish neonatal intensive care unit, 1984 to 1988, Pediatr. Infect. Dis. J. 10 (1991) 159.
[260] R.G. Faix, S.M. Kovarik, Polymicrobial sepsis among intensive care nursery infants, J. Perinatol. 9 (1989) 131.
[261] W.R. Jarvis, et al., Polymicrobial bacteremia associated with lipid emulsion in a neonatal intensive care unit, Pediatr. Infect. Dis. J. 2 (1983) 203.
[262] T.J. Sferra, D.L. Pacini, Simultaneous recovery of bacterial and viral pathogens from CSF, Pediatr. Infect. Dis. J. 7 (1988) 552.
[263] G.P. Giacoia, Uncommon pathogens in newborn infants, J. Perinatol. 14 (1994) 134.
[264] J.E. Hodgman, Sepsis in the neonate, Perinatol Neonatol 5 (1981) 45.
[265] J.A. Hervás, et al., Neonatal sepsis and meningitis in Mallorca, Spain, 1977–1991, Clin. Infect. Dis. 16 (1993) 719.
[266] Public Health Laboratory Service Report. Neonatal meningitis: a review of routine national data 1975–83, BMJ 290 (1985) 778.
[267] A. Schuchat, et al., Population-based risk factors for neonatal group B streptococcal disease: results of a cohort study in metropolitan Atlanta, J. Infect. Dis. 162 (1990) 672.
[268] L. Cordero, M. Sananes, L.W. Ayers, Bloodstream infections in a neonatal intensive-care unit: 12 years' experience with an antibiotic control program, Infect. Control Hosp. Epidemiol. 20 (1999) 242.
[269] E. Persson, et al., Septicaemia and meningitis in neonates and during early infancy in the Goteborg area of Sweden, Acta. Paediatr. 91 (2002) 1087.
[270] C. Simon, et al., Neonatal sepsis in an intensive care unit and results of treatment, Infection 19 (1991) 146.
[271] B.J. Stoll, N. Hansen, Infections in VLBW infants: studies from the NICHD Neonatal Research Network, Semin. Perinatol. 27 (2003) 293.
[272] L. Barton, J.E. Hodgman, Z. Pavlova, Causes of death in the extremely low birth weight infant, Pediatrics 103 (1999) 446.
[273] Z.A. Bhutta, K. Yusuf, Early-onset neonatal sepsis in Pakistan: a case control study of risk factors in a birth cohort, Am. J. Perinatol. 14 (1997) 577.
[274] K.M. Boyer, et al., Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease, I: epidemiologic rationale, J. Infect. Dis. 148 (1983) 795.
[275] E. Lieberman, et al., Epidural analgesia, intrapartum fever, and neonatal sepsis evaluation, Pediatrics 99 (1997) 415.
[276] K.R. Niswander, M. Gordon, The women and their pregnancies, The Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. U.S. Department of Health, Education and Welfare Publication No. (NIH) 73-379. U.S. Government Printing Office, Washington, DC, 1972.
[277] National Center for Health Statistics. Healthy People 2000. Maternal and Infant Health Progress Review, (1999) Live broadcast from Washington, DC, May 5, 1999.
[278] K. Fiscella, Race, perinatal outcome, and amniotic infection, Obstet. Gynecol. Surv. 51 (1996) 60.
[279] Centers for Disease Control and Prevention. Group B streptococcal disease in the United States, 1990: report from a multistate active surveillance system, In CDC Surveillance Summaries, November 20, 1992. MMWR. Morb. Mortal. Wkly. Rep. 41 (1992) 25.
[280] K. Benirschke, S. Driscoll, The Pathology of the Human Placenta, Springer-Verlag, New York, 1967.
[281] T.C. Washburn, D.N. Medearis Jr., B. Childs, Sex differences in susceptibility to infections, Pediatrics 35 (1965) 57.
[282] J.S. Torday, et al., Sex differences in fetal lung maturation, Am. Rev. Respir. Dis. 123 (1981) 205.
[283] A. Sinha, D. Yokoe, R. Platt, Epidemiology of neonatal infections: experience during and after hospitalization, Pediatr. Infect. Dis. J. 22 (2003) 244.
[284] A. Schuchat, et al., Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study, Pediatrics 105 (2000) 21.
[285] A.H. Sohn, et al., Prevalence of nosocomial infections in neonatal intensive care unit patients: results from the first national point-prevalence study, J. Pediatr. 139 (2001) 821.
[286] C. Speer, et al., Neonatal septicemia and meningitis in Gottingen, West Germany, Pediatr. Infect. Dis. J. 4 (1985) 36.
[287] O. Battisi, R. Mitchison, P.A. Davies, Changing blood culture isolates in a referral neonatal intensive care unit, Arch. Dis. Child. 56 (1981) 775.
[288] D.E. MacFarlane, Neonatal group B streptococcal septicaemia in a developing country, Acta Paediatr. Scand. 76 (1987) 470.
[289] A.K. Ako-Nai, et al., The bacteriology of neonatal septicaemiae in Ile-Ife, Nigeria, J. Trop. Pediatr. 45 (1999) 146.
[290] K.A. Kuruvilla, et al., Bacterial profile of sepsis in a neonatal unit in South India, Indian Pediatr. 35 (1998) 851.
[291] A. Ohlsson, T. Bailey, F. Takieddine, Changing etiology and outcome of neonatal septicemia in Riyadh, Saudi Arabia, Acta Paediatr. Scand. 75 (1986) 540.
[292] R.A. Kilani, M. Basamad, Pattern of proven bacterial sepsis in a neonatal intensive care unit in Riyadh-Saudi Arabia: a 2-year analysis, J. Med. Liban. 48 (2000) 77.
[293] R. Knippenberg, et al., Systematic scaling up of neonatal care in countries, Lancet 365 (2005) 1087–1098.
[294] J.E. Lawn, S. Cousens, J. Zupan, 4 million neonatal deaths. When? Where? Why? Lancet 365 (2005) 891–900.
[295] S. Vergnano, et al., Neonatal sepsis: an international perspective, Arch. Dis. Child. Fetal Neonatal Ed. 90 (2005) F220–F224.
[296] S. Rahman, et al., Multidrug resistant neonatal sepsis in Peshawar, Pakistan, Arch. Dis. Child. Fetal Neonatal Ed. 87 (2002) F52–F54.
[297] B. Blomberg, et al., High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania, J. Clin. Microbiol. 43 (2005) 745–749.
[298] A. Amin, Y.M. Abdulrazzaq, S. Uduman, Group B streptococcal serotype distribution of isolates from colonized pregnant women at the time of delivery in United Arab Emirates, J. Infect. 45 (2002) 42.
[299] M. Tsolia, et al., Group B streptococcus colonization of Greek pregnant women and neonates: prevalence, risk factors and serotypes, Clin. Microbiol. Infect. 9 (2003) 832.
[300] B.J. Stoll, A. Schuchat, Maternal carriage of group B streptococci in developing countries, Pediatr. Infect. Dis. J. 17 (1998) 499.
[301] K. Cogwill, et al., Report from the CDC. Awareness of perinatal group B streptococcal infection among women of childbearing age in the United States, 1999 and 2002, J. Womens Health 12 (2003) 527.

[302] C.M. Beck-Sague, et al., Blood stream infections in neonatal intensive care unit patients: results of a multicenter study, Pediatr. Infect. Dis. J. 13 (1994) 1110.
[303] W.G. Adams, et al., Outbreak of early onset group B streptococcal sepsis, Pediatr. Infect. Dis. J. 12 (1993) 565.
[304] T. Cheasty, et al., The use of serodiagnosis in the retrospective investigation of a nursery outbreak associated with *Escherichia coli* O157:H7, J. Clin. Pathol. 51 (1998) 498.
[305] C. Hoyen, et al., Use of real time pulsed field gel electrophoresis to guide interventions during a nursery outbreak of *Serratia marcescens* infection, Pediatr. Infect. Dis. J. 18 (1999) 357.
[306] D.M. Olive, P. Bean, Principles and applications of methods for DNA-based typing of microbial organisms, J. Clin. Microbiol. 37 (1999) 1661.
[307] A. Dent, P. Toltzis, Descriptive and molecular epidemiology of gram-negative bacilli infections in the neonatal intensive care unit, Curr. Opin. Infect. Dis. 16 (2003) 279.
[308] W.C. van der Zwet, et al., Nosocomial outbreak of gentamicin-resistant *Klebsiella pneumoniae* in a neonatal intensive care unit controlled by a change in antibiotic policy, J. Hosp. Infect. 42 (1999) 295.
[309] R. Raz, et al., The elimination of gentamicin-resistant gram-negative bacteria in newborn intensive care unit, Infection 15 (1987) 32.
[310] R.S. Gibbs, P. Duff, Progress in pathogenesis and management of clinical intraamniotic infection, Am. J. Obstet. Gynecol. 164 (1991) 1317.
[311] D. Charles, W.R. Edwards, Infectious complications of cervical cerclage, Am. J. Obstet. Gynecol. 141 (1981) 1065.
[312] J.M. Aarts, J.T. Brons, H.W. Bruinse, Emergency cerclage: a review, Obstet. Gynecol. Surv. 50 (1995) 459.
[313] M. Fejgin, et al., Fulminant sepsis due to group B beta-hemolytic streptococci following transcervical chorionic villi sampling, Clin. Infect. Dis. 17 (1993) 142.
[314] I. Wilkins, et al., Amnionitis and life-threatening respiratory distress after percutaneous umbilical blood sampling, Am. J. Obstet. Gynecol. 160 (1989) 427.
[315] J.E. Morison, Foetal and Neonatal Pathology, third ed., Butterworth, Washington, DC, 1970.
[316] J.W. St. Geme Jr., et al., Perinatal bacterial infection after prolonged rupture of amniotic membranes: an analysis of risk and management, J. Pediatr. 104 (1984) 608.
[317] W.A. Blanc, Pathways of fetal and early neonatal infection: viral placentitis, bacterial and fungal chorioamnionitis, J. Pediatr. 59 (1961) 473.
[318] S.L. Hillier, et al., Microbiologic causes and neonatal outcomes associated with chorioamnion infection, Am. J. Obstet. Gynecol. 165 (1991) 955.
[319] P.R. Yoder, et al., A prospective, controlled study of maternal and perinatal outcome after intra-amniotic infection at term, Am. J. Obstet. Gynecol. 145 (1983) 695.
[320] B. Larsen, I.S. Snyder, R.P. Galask, Bacterial growth inhibition by amniotic fluid, I: in vitro evidence for bacterial growth-inhibiting activity, Am. J. Obstet. Gynecol. 119 (1974) 492.
[321] J.L. Kitzmiller, S. Highby, W.E. Lucas, Retarded growth of *E. coli* in amniotic fluid, Obstet. Gynecol. 41 (1973) 38.
[322] P. Axemo, et al., Amniotic fluid antibacterial activity and nutritional parameters in term Mozambican and Swedish pregnant women, Gynecol. Obstet. Invest. 42 (1996) 24.
[323] T.M. Scane, D.F. Hawkins, Antibacterial activity in human amniotic fluid: relationship to zinc and phosphate, Br. J. Obstet. Gynaecol. 91 (1984) 342.
[324] M.A. Nazir, et al., Antibacterial activity of amniotic fluid in the early third trimester: its association with preterm labor and delivery, Am. J. Perinatol. 4 (1987) 59.
[325] S.M. Baker, N.N. Balo, F.T. Abdel Aziz, Is vernix a protective material to the newborn? A biochemical approach, Indian J. Pediatr. 62 (1995) 237.
[326] A.L. Florman, D. Teubner, Enhancement of bacterial growth in amniotic fluid by meconium, J. Pediatr. 74 (1969) 111.
[327] I.A. Hoskins, et al., Effects of alterations of zinc-to-phosphate ratios and meconium content on group B streptococcus growth in human amniotic fluid in vitro, Am. J. Obstet. Gynecol. 157 (1988) 770.
[328] C. Altieri, et al., In vitro survival of *Listeria monocytogenes* in human amniotic fluid, Zentralbl. Hyg. Umweltmed. 202 (1999) 377.
[329] G. Evaldson, C.E. Nord, Amniotic fluid activity against *Bacteroides fragilis* and group B streptococci, Med. Microbiol. Immunol. 170 (1981) 11.
[330] A.I. Eidelman, et al., The effect of meconium staining of amniotic fluid on the growth of *Escherichia coli* and group B streptococcus, J. Perinatol. 22 (2002) 467.
[331] G. Marston, E.R. Wald, *Hemophilus influenzae* type b sepsis in infant and mother, Pediatrics 58 (1976) 863.
[332] M.M. Tarpay, D.V. Turbeville, H.F. Krous, Fatal *Streptococcus pneumoniae* type III sepsis in mother and infant, Am. J. Obstet. Gynecol. 136 (1980) 257.
[333] J.M. Mastrobattista, V.M. Parisi, Vertical transmission of a *Citrobacter* infection, Am. J. Perinatol. 14 (1997) 465.
[334] T. Boussemart, et al., *Morganella morganii* and early-onset neonatal infection, Arch. Pediatr. 11 (2004) 37.
[335] B. Tempest, Pneumococcal meningitis in mother and neonate, Pediatrics 53 (1974) 759.
[336] J. Grossman, R.L. Tompkins, Group B beta-hemolytic streptococcal meningitis in mother and infant, N. Engl. J. Med. 290 (1974) 387.
[337] S.P. Pyati, et al., Penicillin in infants weighing two kilograms or less with early-onset group B streptococcal disease, N. Engl. J. Med. 308 (1983) 1383.
[338] M.C. Maberry, L.C. Gilstrap, Intrapartum antibiotic therapy for suspected intraamniotic infection: impact on the fetus and neonate, Clin. Obstet. Gynecol. 34 (1991) 345.
[339] L.M. Sacks, J.C. McKitrick, R.R. MacGregor, Surface cultures and isolation procedures in infants born under unsterile conditions, Am. J. Dis. Child. 137 (1983) 351.
[340] I. Brook, E.H. Frazier, Microbiology of scalp abscess in newborn, Pediatr. Infect. Dis. J. 11 (1992) 766.
[341] R.M. Freedman, R. Baltimore, Fatal *Streptococcus viridans* septicemia and meningitis: a relationship to fetal scalp electrode monitoring, J. Perinatol. 10 (1990) 272.
[342] L. Cordero, C.W. Anderson, F.P. Zuspan, Scalp abscess: a benign and infrequent complication of fetal monitoring, Am. J. Obstet. Gynecol. 146 (1983) 126.
[343] W. Storm, Transient bacteremia following endotracheal suctioning in ventilated newborns, Pediatrics 65 (1980) 487.
[344] D.B. Singer, Infections of Fetuses and Neonates, Blackwell Scientific Publications, Boston, 1991.
[345] Y. Sorokin, et al., Cerebrospinal fluid leak in the neonate—complication of fetal scalp electrode monitoring: case report and review of the literature, Isr. J. Med. Sci. 26 (1990) 633.
[346] P. Nieburg, S.J. Gross, Cerebrospinal fluid leak in a neonate with fetal scalp electrode monitoring, Am. J. Obstet. Gynecol. 147 (1983) 839.
[347] R.C. Nagle, et al., Brain abscess aspiration in nursery with ultrasound guidance, J. Neurosurg. 65 (1986) 557.
[348] D. Renier, et al., Brain abscesses in neonates: a study of 30 cases, J. Neurosurg. 69 (1988) 877.
[349] T. Jadavji, R.P. Humphreys, C.G. Prober, Brain abscesses in infants and children, Pediatr. Infect. Dis. 4 (1985) 394.
[350] J.J. Volpe, Neurology of the Newborn, second ed., WB Saunders, Philadelphia, 1987.
[351] H.C. Dillon, S. Khare, B.M. Gray, Group B streptococcal carriage and disease: a 6-year prospective study, J. Pediatr. 110 (1987) 31.
[352] M.J. Maisels, E. Kring, Risk of sepsis in newborns with severe hyperbilirubinemia, Pediatrics 90 (1992) 741.
[353] F. Tiker, et al., Early onset conjugated hyperbilirubinemia in newborn infants, Indian J. Pediatr. 73 (2006) 409–412.
[354] B.A. Haber, A.M. Lake, Cholestatic jaundice in the newborn, Clin. Perinatol. 17 (1990) 483.
[355] J.C. Rooney, D.J. Hills, D.M. Danks, Jaundice associated with bacterial infection in the newborn, Am. J. Dis. Child. 122 (1971) 39.
[356] R. Dagan, R. Gorodischer, Infections in hypothermic infants younger than 3 months old, Am. J. Dis. Child. 138 (1984) 483.
[357] R.B. Johanson, et al., Effect of post-delivery care on neonatal body temperature, Acta Paediatr. 81 (1992) 859.
[358] M. Michael, D.J. Barrett, P. Mehta, Infants with meningitis without CSF pleocytosis, Am. J. Dis. Child. 140 (1986) 851.
[359] A.S. El-Radhy, et al., Sepsis and hypothermia in the newborn infant: value of gastric aspirate examination, J. Pediatr. 104 (1983) 300.
[360] A.M. Al Jarousha, et al., An outbreak of *Serratia marcescens* septicaemia in neonatal intensive care unit in Gaza City, Palestine, J. Hosp. Infect. 70 (2008) 119–126.
[361] P.H. Barr, Association of *Escherichia coli* sepsis and galactosemia in neonates, J. Am. Board. Fam. Pract. 5 (1992) 89.
[362] H.L. Levy, et al., Sepsis due to *Escherichia coli* in neonates with galactosemia, N. Engl. J. Med. 297 (1977) 823.
[363] S. Kelly, Septicemia in galactosemia, JAMA 216 (1971) 330.
[364] S.B. Shurin, *Escherichia coli* septicemia in neonates with galactosemia, Letter to the editorN. Engl. J. Med. 297 (1977) 1403.
[365] R.H. Kobayashi, B.V. Kettelhut, A. Kobayashi, Galactose inhibition of neonatal neutrophil function, Pediatr. Infect. Dis. J. 2 (1983) 442.
[366] A.M. Bosch, Classical galactosaemia revisited, J. Inherit. Metab. Dis. 29 (2006) 516–525.
[367] M. Odievre, et al., Hereditary fructose intolerance: Diagnosis, management and course in 55 patients, Am. J. Dis. Child. 132 (1978) 605.
[368] J. Guerra-Moreno, N. Barrios, P.J. Santiago-Borrero, Severe neutropenia in an infant with methylmalonic acidemia, Bol. Asoc. Med. P. R. 95 (2003) 17.
[369] R.J. Hutchinson, K. Bunnell, J.G. Thoene, Suppression of granulopoietic progenitor cell proliferation by metabolites of the branched-chain amino acids, J. Pediatr. 106 (1985) 62.
[370] V.L. Negre, et al., The siderophore receptor IroN, but not the high-pathogenicity island or the hemin receptor ChuA, contributes to the bacteremic step of *Escherichia coli* neonatal meningitis, Infect. Immun. 72 (2004) 1216–1220.
[371] E.D. Weinberg, Iron and susceptibility to infectious disease, Science 184 (1974) 952.
[372] P. Manzoni, et al., Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial, JAMA 302 (2009) 1421–1428.
[373] D.M.J. Barry, A.W. Reeve, Increased incidence of gram-negative neonatal sepsis with intramuscular iron administration, Pediatrics 60 (1977) 908.
[374] K. Farmer, The disadvantages of routine administration of intramuscular iron to neonates, N. Z. Med. J. 84 (1976) 286.

[375] C.L. Berseth, et al., Growth, efficacy, and safety of feeding an iron-fortified human milk fortifier, Pediatrics 114 (2004) e699–e706.
[376] I.M. Usta, et al., Comparison of the perinatal morbidity and mortality of the presenting twin and its co-twin, J. Perinatol. 22 (2002) 391.
[377] K. Benirschke, Routes and types of infection in the fetus and newborn, Am. J. Dis. Child. 99 (1960) 714.
[378] J.M. Alexander, et al., The relationship of infection to method of delivery in twin pregnancy, Am. J. Obstet. Gynecol. 177 (1997) 1063–1066.
[379] J.M. Alexander, et al., Cesarean delivery for the second twin, Obstet. Gynecol. 112 (2008) 748–752.
[380] M.A. Pass, S. Khare, H.C. Dillon Jr., Twin pregnancies: incidence of group B streptococcal colonization and disease, J Pediatr 97 (1980) 635.
[381] M.S. Edwards, C.V. Jackson, C.J. Baker, Increased risk of group B streptococcal disease in twins, JAMA 245 (1981) 2044.
[382] K.S. Doran, et al., Late-onset group B streptococcal infection in identical twins: insight to disease pathogenesis, J. Perinatol. 22 (2002) 326–330.
[383] K. LaMar, D.A. Dowling, Incidence of infection for preterm twins cared for in cobedding in the neonatal intensive-care unit, J. Obstet. Gynecol. Neonatal. Nurs. 35 (2006) 193–198.
[384] P.I. Nieburg, M.L. William, Group A beta-hemolytic streptococcal sepsis in a mother and infant twins, J. Pediatr. 87 (1975) 453.
[385] J.G. Larsen, et al., Multiple antibiotic resistant *Salmonella agora* infection in malnourished neonatal twins, Mt. Sinai. J. Med. 46 (1979) 542.
[386] H.R. Devlin, R.M. Bannatyne, Neonatal malaria, Can. Med. Assoc. J. 116 (1977) 20.
[387] S. Romand, et al., Congenital malaria: a case observed in twins born to an asymptomatic mother, Presse. Med. 23 (1994) 797.
[388] T. Shafai, Neonatal coccidioidomycosis in premature twins, Am. J. Dis. Child. 132 (1978) 634.
[389] S. Saigal, W.A. Eisele, M.A. Chernesky, Congenital cytomegalovirus infection in a pair of dizygotic twins, Am. J. Dis. Child. 136 (1982) 1094.
[390] J.J. Duvekot, et al., Congenital cytomegalovirus infection in a twin pregnancy: a case report, Eur. J. Pediatr. 149 (1990) 261.
[391] T. Lazzarotto, et al., Congenital cytomegalovirus infection in twin pregnancies: viral load in the amniotic fluid and pregnancy outcome, Pediatrics 112 (2003) e153.
[392] R.C. Montgomery, K. Stockdell, Congenital rubella in twins, J. Pediatr. 76 (1970) 772.
[393] N. Fraser, B.W. Davies, J. Cusack, Neonatal omphalitis: a review of its serious complications, Acta Paediatr. 95 (2006) 519–522.
[394] I. Forshall, Septic umbilical arteritis, Arch. Dis. Child. 32 (1957) 25.
[395] J.N. Cruickshank, Child Life Investigations: The Causes of Neo-natal Death, His Majesty's Stationery Office, London, 1930 Medical Research Council Special Report Series No. 145.
[396] A.H. Cushing, Omphalitis: a review, Pediatr. Infect. Dis. J. 4 (1985) 282.
[397] V.O. Rotimi, B.I. Duerden, The development of the bacterial flora in normal neonates, J. Med. Microbiol. 14 (1981) 51.
[398] W.H. Mason, et al., Omphalitis in the newborn infant, Pediatr. Infect. Dis. J. 8 (1989) 521.
[399] E.A. Ameh, P.T. Nmadu, Major complications of omphalitis in neonates and infants, Pediatr. Surg. Int. 18 (2002) 413.
[400] W.W. Meyer, J. Lind, The ductus venosus and the mechanism of its closure, Arch. Dis. Child. 41 (1966) 597.
[401] J.E. Morison, Umbilical sepsis and acute interstitial hepatitis, J. Pathol. Bacteriol. 56 (1944) 531.
[402] R.I.K. Elliott, The ductus venosus in neonatal infection, Proc. R. Soc. Med. 62 (1969) 321.
[403] K. Bedtke, H. Richarz, Nabelsepsis mit Pylephlebitis, multiplen Leberabscessen, Lungenabscessen und Osteomyelitis. Ausgang in Heilung, Monatsschr. Kinderheilkd. 105 (1957) 70.
[404] E.N. Thompson, S. Sherlock, The aetiology of portal vein thrombosis with particular reference to the role of infection and exchange transfusion, QJM 33 (1964) 465.
[405] R.W. MacMillan, J.N. Schullinger, T.V. Santulli, Pyourachus: an unusual surgical problem, J. Pediatr. Surg. 8 (1973) 387–389.
[406] C. Navarro, W.A. Blanc, Subacute necrotizing funisitis: a variant of cord inflammation with a high rate of perinatal infection, J. Pediatr. 85 (1974) 689.
[407] A. Ohlsson, Treatment of preterm premature rupture of the membranes: a meta-analysis, Am. J. Obstet. Gynecol. 160 (1989) 890.
[408] P. Crowley, I. Chalmers, M.J. Keirse, The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials, Br. J. Obstet. Gynaecol. 97 (1990) 11.
[409] S.T. Vermillion, et al., Effectiveness of antenatal corticosteroid administration after preterm premature rupture of the membranes, Am. J. Obstet. Gynecol. 183 (2000) 925.
[410] D. Roberts, S. Dalziel, Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth, Cochrane Database Syst. Rev. (3) CD004454, (2006).
[411] Z. Gottesfeld, S.E. Ullrich, Prenatal alcohol exposure selectively suppresses cell-mediated but not humoral immune responsiveness, Int. J. Immunopharmacol. 17 (1995) 247.
[412] S. Johnson, et al., Immune deficiency in fetal alcohol syndrome, Pediatr. Res. 15 (1981) 908.
[413] K.W. Culver, et al., Lymphocyte abnormalities in infants born to drug-abusing mothers, J. Pediatr. 111 (1987) 230.
[414] Chemical dependency and pregnancy, Clin. Perinatol. 18 (1991) 1.
[415] Drug abuse in pregnancy, Clin. Obstet. Gynecol. 36 (1993) 221.
[416] Drug Use in Pregnancy: Mother and Child, MTP Press, Boston, 1986.
[417] R. Ojala, S. Ikonen, O. Tammela, Perinatal indomethacin treatment and neonatal complications in preterm infants, Eur. J. Pediatr. 159 (2000) 153.
[418] C.A. Major, et al., Tocolysis with indomethacin increases the incidence of necrotizing enterocolitis in the low-birth-weight neonate, Am. J. Obstet. Gynecol. 170 (1994) 102.
[419] V.C. Herson, et al., Indomethacin-associated sepsis in very-low-birth-weight infants, Am. J. Dis. Child. 142 (1988) 555.
[420] T.M. O'Shea, et al., Follow-up of preterm infants treated with dexamethasone for chronic lung disease, Am. J. Dis. Child. 147 (1993) 658.
[421] A. Ohlsson, R. Walia, S. Shah, Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants, Cochrane Database Syst. Rev. CD003481, (2008).
[422] J.L. Tapia, et al., The effect of early dexamethasone administration on bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome, J. Pediatr. 132 (1998) 48–52.
[423] C. Avila-Figueroa, et al., Intravenous lipid emulsions are the major determinant of coagulase-negative staphylococcal bacteremia in very low birth weight newborns, Pediatr. Infect. Dis. J. 17 (1998) 10–17.
[424] A.G. Matlow, et al., A randomized trial of 72- versus 24-hour intravenous tubing set changes in newborns receiving lipid therapy, Infect. Control Hosp. Epidemiol. 20 (1999) 487–493.
[425] S. Bianconi, et al., Ranitidine and late-onset sepsis in the neonatal intensive care unit, J. Perinat. Med. 35 (2007) 147–150.
[426] A.J. Barson, A Postmortem Study of Infection in the Newborn from 1976 to 1988, John Wiley & Sons, New York, 1990.
[427] P.H. Berman, B.Q. Banker, Neonatal meningitis: a clinical and pathological study of 29 cases, Pediatrics 38 (1966) 6.
[428] J.T. Stocker, L.P. Dehner, Pediatric Pathology, JB Lippincott, Philadelphia, 1992.
[429] H.J. Hoffman, E.B. Hendrick, J.L. Hiscox, Cerebral abscesses in early infancy, J. Neurosurg. 33 (1970) 172.
[430] D.G. Watson, Purulent neonatal meningitis: a study of forty-five cases, J. Pediatr. 50 (1957) 352.
[431] J.J. Volpe, Neurology of the Newborn, third ed., WB Saunders, Philadelphia, 1995.
[432] J.M. Perlman, N. Rollins, P.J. Sanchez, Late-onset meningitis in sick, very-low-birth-weight infants: clinical and sonographic observations, Am. J. Dis. Child. 146 (1992) 1297.
[433] F.H. Gilles, J.L. Jammes, W. Berenberg, Neonatal meningitis: the ventricle as a bacterial reservoir, Arch. Neurol. 34 (1977) 560.
[434] M.A. Schiano, J.C. Hauth, L.C. Gilstrap, Second-stage fetal tachycardia and neonatal infection, Am. J. Obstet. Gynecol. 148 (1984) 779.
[435] G.S. Shah, et al., Risk factors in early neonatal sepsis, Kathmandu. Univ. Med. J. (KUMJ) 4 (2006) 187–191.
[436] F. Mwanyumba, et al., Placental inflammation and perinatal outcome, Eur. J. Obstet. Gynecol. Reprod. Biol. 108 (2003) 164–170.
[437] E. Kermorvant-Duchemin, et al., Outcome and prognostic factors in neonates with septic shock, Pediatr. Crit. Care. Med. 9 (2008) 186–191.
[438] M. Soman, B. Green, J. Daling, Risk factors for early neonatal sepsis, Am. J. Epidemiol. 121 (1985) 712.
[439] T. Hegyi, et al., The Apgar score and its components in the preterm infant, Pediatrics 101 (1998) 77.
[440] K.R. Powell, Evaluation and management of febrile infants younger than 60 days of age, Pediatr. Infect. Dis. J. 9 (1990) 153.
[441] W.A. Bonadio, et al., Reliability of observation variables in distinguishing infectious outcome of febrile young infants, Pediatr. Infect. Dis. J. 12 (1993) 111.
[442] M. Kudawla, S. Dutta, A. Narang, Validation of a clinical score for the diagnosis of late onset neonatal septicemia in babies weighing 1000–2500 g, J. Trop. Pediatr. 54 (2008) 66–69.
[443] S. Fielkow, S. Reuter, S.P. Gotoff, Cerebrospinal fluid examination in symptom-free infants with risk factors for infection, J. Pediatr. 119 (1991) 971.
[444] W.H. Albers, C.W. Tyler, B. Boxerbaum, Asymptomatic bacteremia in the newborn infant, J. Pediatr. 69 (1966) 193.
[445] M. Petanovic, Z. Zagar, The significance of asymptomatic bacteremia for the newborn, Acta Obstet. Gynecol. Scand. 80 (2001) 813.
[446] J.B. Howard, G.H. McCracken, The spectrum of group B streptococcal infections in infancy, Am. J. Dis. Child. 128 (1974) 815.
[447] L.E. Weisman, et al., Early-onset group B streptococcal sepsis: a current assessment, J. Pediatr. 121 (1992) 428.
[448] P. Yagupsky, M.A. Menegus, K.R. Powell, The changing spectrum of group B streptococcal disease in infants: an eleven-year experience in a tertiary care hospital, Pediatr. Infect. Dis. J. 10 (1991) 801.
[449] P.G. Ramsey, R. Zwerdling, Asymptomatic neonatal bacteremia, Letter to the editorN. Engl. J. Med. 295 (1976) 225.
[450] J.S. Yu, A. Grauang, Purulent meningitis in the neonatal period, Arch. Dis. Child. 38 (1963) 391.
[451] S.L. Solomon, E.M. Wallace, E.L. Ford-Jones, et al., Medication errors with inhalant epinephrine mimicking an epidemic of neonatal sepsis, N. Engl. J. Med. 310 (1984) 166.
[452] W.A. Bonadio, M. Hegenbarth, M. Zachariason, Correlating reported fever in young infants with subsequent temperature patterns and rate of serious bacterial infections, Pediatr. Infect. Dis. J. 9 (1990) 158.

[453] J. Messaritakis, et al., Rectal-skin temperature difference in septicaemic newborn infants, Arch. Dis. Child. 65 (1990) 380.
[454] C.A. Dinarello, et al., Production of leukocytic pyrogen from phagocytes of neonates, J. Infect. Dis. 144 (1981) 337.
[455] S.R. Mayfield, et al., Temperature measurement in term and preterm neonates, J. Pediatr. 104 (1984) 271.
[456] K.J. Johnson, P. Bhatia, E.F. Bell, Infrared thermometry of newborn infants, Pediatrics 87 (1991) 34.
[457] A.J. Schuman, The accuracy of infrared auditory canal thermometry in infants and children, Clin. Pediatr. 32 (1993) 347.
[458] D. Anagnostakis, et al., Rectal-axillary difference in febrile and afebrile infants and children, Clin. Pediatr. 32 (1993) 268.
[459] M.E. Weisse, et al., Axillary vs. rectal temperatures in ambulatory and hospitalized children, Pediatr. Infect. Dis. J. 10 (1991) 541.
[460] G.L. Freed, J.K. Fraley, Lack of agreement of tympanic membrane temperature assessments with conventional methods in a private practice setting, Pediatrics 89 (1992) 384.
[461] S. Hutton, et al., Accuracy of different temperature devices in the postpartum population, J. Obstet. Gynecol. Neonatal. Nurs. 38 (2009) 42–49.
[462] S. Voora, et al., Fever in full-term newborns in the first four days of life, Pediatrics 69 (1982) 40.
[463] L.M. Osborn, R. Bolus, Temperature and fever in the full-term newborn, J. Fam. Pract. 20 (1985) 261.
[464] F.J. Garcia, A. Nager, Jaundice as an early diagnostic sign of urinary tract infection in infancy, Pediatrics 109 (2002) 846.
[465] S. Zamora-Castorena, M.T. Murguia-de-Sierra, Five year experience with neonatal sepsis in a pediatric center, Rev. Invest. Clin. 50 (1998) 463.
[466] A.I. Airede, Urinary-tract infections in African neonates, J. Infect. 25 (1992) 55.
[467] R.A. Seeler, Urosepsis with jaundice due to hemolytic *Escherichia coli*, Am. J. Dis. Child. 126 (1973) 414.
[468] H. Bilgen, et al., Urinary tract infection and hyperbilirubinemia, Turk. J. Pediatr. 48 (2006) 51–55.
[469] S. Ashkenazi, et al., Size of liver edge in full-term, healthy infants, Am. J. Dis. Child. 138 (1984) 377.
[470] M.I. Reiff, L.M. Osborn, Clinical estimation of liver size in newborn infants, Pediatrics 71 (1983) 46.
[471] J. Sfeir, et al., Early onset neonatal septicemia caused by *Listeria monocytogenes*, Rev. Chil. Pediatr. 61 (1990) 330.
[472] M. Bamji, et al., Palpable lymph nodes in healthy newborns and infants, Pediatrics 78 (1986) 573.
[473] J. Embree, J. Muriithi, Palpable lymph nodes. Letter to the editor, Pediatrics 81 (1988) 598.
[474] R. Monfort Gil, et al., Group B streptococcus late-onset disease presenting as cellulitis-adenitis syndrome, Ann. Pediatr. 60 (2004) 75.
[475] S. Artigas Rodriguez, et al., Group B streptococcus cellulitis-adenitis syndrome in neonates. Is it a marker of bacteremia, An. Esp. Pediatr. 56 (2002) 251.
[476] E.A. Albanyan, C.J. Baker, Is lumbar puncture necessary to exclude meningitis in neonates and young infants: lessons from the group B streptococcus cellulitis-adenitis syndrome, Pediatrics 102 (1998) 985.
[477] A.H. Bell, et al., Meningitis in the newborn: a 14 year review, Arch. Dis. Child. 64 (1989) 873.
[478] M.I. Weintraub, R.N. Otto, Pneumococcal meningitis and endophthalmitis in a newborn, JAMA 219 (1972) 1763.
[479] K. Matasova, J. Hudecova, M. Zibolen, Bilateral endogenous endophthalmitis as a complication of late-onset sepsis in a premature infant, Eur. J. Pediatr. 162 (2003) 346.
[480] F. Nejat, et al., Spinal epidural abscess in a neonate, Pediatr. Infect. Dis. J. 21 (2002) 797.
[481] R.S. Walter, et al., Spinal epidural abscess in infancy: successful percutaneous drainage in a nine-month-old and review of the literature, Pediatr. Infect. Dis. J. 19 (1991) 860.
[482] K. Tang, C. Xenos, S. Sgouros, Spontaneous spinal epidural abscess in a neonate: with a review of the literature, Childs Nerv. Syst. 17 (2001) 629.
[483] R.W. Steele, A revised strategy for the prevention of group B streptococcal infection in pregnant women and their newborns, Medscape Womens Health 1 (1996) 2.
[484] American College of Obstetricians and Gynecologists, ACOG Committee Opinion: no. 279, December 2002. Prevention of early-onset group B streptococcal disease in newborns, Obstet. Gynecol. 100 (2002) 1405.
[485] M.E. Evans, et al., Sensitivity, specificity, and predictive value of body surface cultures in a neonatal intensive care unit, JAMA 259 (1988) 248.
[486] D. Hertz, et al., Comparison of DNA probe technology and automated continuous-monitoring blood culture systems in the detection of neonatal bacteremia, J. Perinatol. 19 (1999) 290.
[487] J.D. Anderson, C. Trombley, N. Cimolai, Assessment of the BACTEC NR660 blood culture system for the detection of bacteremia in young children, J. Clin. Microbiol. 27 (1989) 721.
[488] J.M. Campos, J.R. Spainhour, Rapid detection of bacteremia in children with modified lysis direct plating method, J. Clin. Microbiol. 22 (1985) 674.
[489] J.W. St. Geme III, et al., Distinguishing sepsis from blood culture contamination in young infants with blood cultures growing coagulase-negative staphylococci, Pediatrics 86 (1990) 157.
[490] I. Kurlat, B.J. Stoll, J.E. McGowan Jr., Time to positivity for detection of bacteremia in neonates, J. Clin. Microbiol. 27 (1989) 1068.
[491] M.D. Pichichero, J.K. Todd, Detection of neonatal bacteremia, J. Pediatr. 94 (1979) 958.
[492] A.H. Rowley, E.R. Wald, Incubation period necessary to detect bacteremia in neonates, Pediatr. Infect. Dis. J. 5 (1986) 590.
[493] L.A. Jardine, et al., Neonatal blood cultures: effect of delayed entry into the blood culture machine and bacterial concentration on the time to positive growth in a simulated model, J. Paediatr. Child. Health 45 (2009) 210–214.
[494] K. Sprunt, Commentary, Year Book Medical Publishers, Chicago, 1973.
[495] P.R. Neal, et al., Volume of blood submitted for culture from neonates, J. Clin. Microbiol. 24 (1986) 353.
[496] D.E. Dietzman, G.W. Fischer, F.D. Schoenknecht, Neonatal *Escherichia coli* septicemia—bacterial counts in blood, J. Pediatr. 85 (1974) 128.
[497] J.K. Kennaugh, et al., The effect of dilution during culture on detection of low concentrations of bacteria in blood, Pediatr. Infect. Dis. J. 3 (1984) 317.
[498] G. Jawaheer, T.J. Neal, N.J. Shaw, Blood culture volume and detection of coagulase negative staphylococcal septicaemia in neonates, Arch. Dis. Child. (1997) 76:57F.
[499] J.A. Kellogg, J.P. Manzella, D.A. Bankert, Frequency of low-level bacteremia in children from birth to fifteen years of age, J. Clin. Microbiol. 28 (2000) 2181.
[500] J.A. Kellogg, et al., Frequency of low-level bacteremia in infants from birth to two months of age, Pediatr. Infect. Dis. J. 16 (1997) 381.
[501] R.L. Schelonka, et al., Volume of blood required to detect common neonatal pathogens, J. Pediatr. 129 (1996) 275.
[502] T.G. Connell, et al., How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital, Pediatrics 119 (2007) 891–896.
[503] M. Pourcyrous, et al., Indwelling umbilical arterial catheter: a preferred sampling site for blood cultures, Pediatrics 81 (1988) 621.
[504] V. Bhandari, et al., Nosocomial sepsis in neonates with single lumen vascular catheters, Indian. J. Pediatr. 64 (1997) 529.
[505] D.K. Benjamin Jr., et al., Bacteremia, central catheters, and neonates: when to pull the line, Pediatrics 107 (2001) 1272–1276.
[506] C. Marconi, et al., Usefulness of catheter tip culture in the diagnosis of neonatal infections, J. Pediatr. (Rio J) 85 (2009) 80–83.
[507] T.E. Wiswell, W.E. Hachey, Multiple site blood cultures in the initial evaluation for neonatal sepsis during the first week of life, Pediatr. Infect. Dis. J. 10 (1991) 365.
[508] O. Hammerberg, et al., Comparison of blood cultures with corresponding venipuncture site cultures of specimens from hospitalized premature neonates, J. Pediatr. 120 (1992) 120.
[509] C.M. Healy, et al., Distinctive features of neonatal invasive staphylococcal disease, Pediatrics 114 (2004) 953.
[510] A.A. Humphrey, Use of the buffy layer in the rapid diagnosis of septicemia, Am. J. Clin. Pathol. 14 (1944) 358.
[511] R.J. Boyle, et al., Early identification of sepsis in infants with respiratory distress, Pediatrics 62 (1978) 744.
[512] H.S. Faden, Early diagnosis of neonatal bacteremia by buffy-coat examination, J. Pediatr. 88 (1976) 1032.
[513] W. Storm, Early detection of bacteremia by peripheral smears in critically ill newborns, Acta Paediatr. Scand. 70 (1981) 415.
[514] M.B. Kleiman, et al., Rapid diagnosis of neonatal bacteremia with acridine orange-stained buffy coat smears, J. Pediatr. 105 (1984) 419.
[515] P. Kite, et al., Comparison of five tests used in diagnosis of neonatal bacteremia, Arch. Dis. Child. 63 (1988) 639.
[516] S.K. Tak, P.C. Bhandari, B. Bhandari, Value of buffy coat examination in early diagnosis of neonatal septicemia, Indian Pediatr. 17 (1980) 339.
[517] D.L. Powers, G.L. Mandell, Intraleukocytic bacteria in endocarditis patients, JAMA 227 (1974) 312.
[518] H.E.J. Cattermole, R.P.A. Rivers, Neonatal *Candida* septicaemia: diagnosis on buffy smear, Arch. Dis. Child. 62 (1987) 302.
[519] R.J. Ascuitto, et al., Buffy coat smears of blood drawn through central venous catheters as an aid to rapid diagnosis of systemic fungal infections, J. Pediatr. 106 (1985) 445.
[520] D.M. Selby, et al., Overwhelming neonatal septicemia diagnosed upon examination of peripheral blood smears, Clin. Pediatr. 29 (1990) 706.
[521] W. Strom, Early detection of bacteremia by peripheral blood smears in critically ill newborns, Acta Paediatr. Scand. 70 (1981) 415.
[522] R.L. Rodwell, A.L. Leslie, D.I. Tudehope, Evaluation of direct and buffy coat films of peripheral blood for the early detection of bacteraemia, Aust. Paediatr. J. 25 (1989) 83.
[523] V.E. Visser, R.T. Hall, Urine culture in the evaluation of suspected neonatal sepsis, J. Pediatr. 94 (1979) 635.
[524] R.J. DiGeronimo, Lack of efficacy of the urine culture as part of the initial workup of suspected neonatal sepsis, Pediatr. Infect. Dis. J. 9 (1992) 764.
[525] B.K. Bonsu, M.B. Harper, Leukocyte counts in urine reflect the risk of concomitant sepsis in bacteriuric infants: a retrospective cohort study, BMC. Pediatr. 7 (2007) 24.
[526] R. Tobiansky, N. Evans, A randomized controlled trial of two methods for collection of sterile urine in neonates, J. Paediatr. Child. Health 34 (1998) 460.
[527] M.T. Garcia Munoz, et al., Suprapubic bladder aspiration: utility and complication, An. Esp. Pediatr. 45 (1996) 377.
[528] J.D. Nelson, P.C. Peters, Suprapubic aspiration of urine in premature and term infants, Pediatrics 36 (1965) 132.

[529] E. Kozer, et al., Pain in infants who are younger than 2 months during suprapubic aspiration and transurethral bladder catheterization: a randomized, controlled study, Pediatrics 118 (2006) e51–e56.
[530] Y.L. Lau, E. Hey, Sensitivity and specificity of daily tracheal aspirate cultures in predicting organisms causing bacteremia in ventilated neonates, Pediatr. Infect. Dis. J. 10 (1991) 290.
[531] L. Finelli, J.R. Livengood, L. Saiman, Surveillance of pharyngeal colonization: detection and control of serious bacterial illness in low birth weight infants, Pediatr. Infect. Dis. J. 13 (1994) 854.
[532] H.B. Srinivasan, D. Vidyasagar, Endotracheal aspirate cultures in predicting sepsis in ventilated neonates, Indian J. Pediatr. 65 (1998) 79–84.
[533] J.O. Klein, S.S. Gellis, Diagnostic needle aspiration in pediatric practice: with special reference to lungs, middle ear, urinary bladder, and amniotic cavity, Pediatr. Clin. North. Am. 18 (1971) 219.
[534] L. Eisenfeld, et al., Systemic bacterial infections in neonatal deaths, Am. J. Dis. Child. 137 (1983) 645.
[535] T.M. Minckler, et al., Microbiology experience in human tissue collection, Am. J. Clin. Pathol. 45 (1966) 85.
[536] J.R. Pierce, G.B. Merenstein, J.T. Stocker, Immediate postmortem cultures in an intensive care nursery, Pediatr. Infect. Dis. J. 3 (1984) 510.
[537] J. Levin, et al., Detection of endotoxin in the blood of patients with sepsis due to gram-negative bacteria, N. Engl. J. Med. 283 (1970) 1313.
[538] I. Levin, T.E. Poore, N.S. Young, Gram-negative sepsis: detection of endotoxemia with the limulus test, Ann. Intern. Med. 76 (1972) 1.
[539] R.I. Stumacher, M.J. Kovnat, W.R. McCabe, Limitations of the usefulness of the limulus assay for endotoxin, N. Engl. J. Med. 288 (1973) 1261.
[540] R.J. Elin, et al., Lack of clinical usefulness of the limulus test in the diagnosis of endotoxemia, N. Engl. J. Med. 293 (1975) 521.
[541] G.H. McCracken Jr., L.D. Sarff, Endotoxin in CSF detection in neonates with bacterial meningitis, JAMA 235 (1976) 617.
[542] M.A. Sobanski, et al., Meningitis antigen detection: interpretation of agglutination by ultrasound-enhanced latex immunoassay, Br. J. Biomed. Sci. 56 (1999) 239–246.
[543] K.L. McGowan, Diagnostic value of latex agglutination tests for bacterial infections, Rep Pediatr Infect Dis 8 (1992) 31.
[544] P.J. Sanchez, et al., Significance of a positive urine group B streptococcal latex agglutination test in neonates, J. Pediatr. 116 (1990) 601.
[545] B.J. Stoll, et al., To tap or not to tap: high likelihood of meningitis without sepsis among very low birth weight infants, Pediatrics 113 (2004) 1181–1186.
[546] M.G. Weiss, S.P. Ionides, C.L. Anderson, Meningitis in premature infants with respiratory distress: role of admission lumbar puncture, J. Pediatr. 119 (1991) 973.
[547] K.D. Hendricks-Munoz, D.L. Shapiro, The role of the lumbar puncture in the admission sepsis evaluation of the premature infant, J. Perinatol. 10 (1990) 60.
[548] M. Eldadah, et al., Evaluation of routine lumbar punctures in newborn infants with respiratory distress syndrome, Pediatr. Infect. Dis. J. 6 (1987) 243.
[549] J. Schwersenski, L. McIntyre, C.R. Bauer, Lumbar puncture frequency and CSF analysis in the neonate, Am. J. Dis. Child. 145 (1991) 54.
[550] S. Fielkow, S. Reuter, S.P. Gotoff, Clinical and laboratory observations: cerebrospinal fluid examination in symptom-free infants with risk factors for infection, J. Pediatr. 119 (1991) 971.
[551] C.A. Gleason, et al., Optimal position for a spinal tap in preterm infants, Pediatrics 71 (1983) 31.
[552] J.M.B. Pinheiro, S. Furdon, L.F. Ochoa, Role of local anesthesia during lumbar puncture in neonates, Pediatrics 91 (1993) 379.
[553] F.L. Porter, et al., A controlled clinical trial of local anesthesia for lumbar punctures in newborns, Pediatrics 88 (1991) 663.
[554] D.H. Fiser, et al., Prevention of hypoxemia during lumbar puncture in infancy with preoxygenation, Pediatr. Emerg. Care 9 (1993) 81.
[555] L.E. Weisman, G.B. Merenstein, J.R. Steenbarger, The effect of lumbar puncture position in sick neonates, Am. J. Dis. Child. 137 (1983) 1077.
[556] V.E. Visser, R.T. Hall, Lumbar puncture in the evaluation of suspected neonatal sepsis, J. Pediatr. 96 (1980) 1063.
[557] S.M. Franco, V.E. Cornelius, B.F. Andrews, Should we perform lumbar punctures on the first day of life? Am. J. Dis. Child. 147 (1993) 133.
[558] H.P. Garges, et al., Neonatal meningitis. What is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters, Pediatrics 117 (2006) 1094.
[559] B.T. Naidoo, The CSF in the healthy newborn infant, S. Afr. Med. J. 42 (1968) 933.
[560] L.D. Sarff, L.H. Platt, G.H. McCracken Jr., Cerebrospinal fluid evaluation in neonates: comparison of high-risk infants with and without meningitis, J. Pediatr. 88 (1976) 473.
[561] W.A. Bonadio, et al., Reference values of normal CSF composition in infants ages 0 to 8 weeks, Pediatr. Infect. Dis. J. 11 (1992) 589.
[562] A. Ahmed, et al., Cerebrospinal fluid values in the term neonate, Pediatr. Infect. Dis. J. 15 (1996) 298.
[563] H. Wolf, L. Hoepffner, The CSF in the newborn and premature infant, World Neurol. 2 (1961) 871.
[564] E. Otila, Studies on the CSF in premature infants, Acta Paediatr. Scand. 35 (1948) 9.
[565] A. Gyllensward, S. Malmstrom, The CSF in immature infants, Acta Paediatr. Scand. 135 (1962) 54.
[566] S. Widell, On the CSF in normal children and in patients with acute abacterial meningoencephalitis, Acta Pediatr. 47 (1958) 711.
[567] G.H. McCracken Jr., The rate of bacteriologic response to antimicrobial therapy in neonatal meningitis, Am. J. Dis. Child. 123 (1972) 547.
[568] A.F. Rodriguez, S.L. Kaplan, E.O. Mason Jr., Cerebrospinal fluid values in the very low birth weight infant, J. Pediatr. 116 (1990) 971.
[569] M.J. Mhanna, et al., Cerebrospinal fluid values in very low birth weight infants with suspected sepsis at different ages, Pediatr. Crit. Care Med. 9 (2008) 294–298.
[570] A.S. Yeager, F.W. Bruhn, J. Clark, Cerebrospinal fluid: presence of virus unaccompanied by pleocytosis, J. Pediatr. 85 (1974) 578.
[571] C.M. Moore, M. Ross, Acute bacterial meningitis with absent or minimal CSF abnormalities: a report of three cases, Clin. Pediatr. (Phila) 12 (1973) 117.
[572] G. Sarman, A.A. Moise, M.S. Edwards, Meningeal inflammation in neonatal gram-negative bacteremia, Pediatr. Infect. Dis. J. 14 (1995) 701.
[573] P.B. Smith, et al., Meningitis in preterm neonates: importance of cerebrospinal fluid parameters, Am. J. Perinatol. 25 (2008) 421–426.
[574] T. Hedner, K. Iversen, P. Lundborg, Aminobutyric acid concentrations in the CSF of newborn infants, Early. Hum. Dev. 7 (1982) 53.
[575] S. Engelke, et al., Cerebrospinal fluid lactate dehydrogenase in neonatal intracranial hemorrhage, Am. J. Med. Sci. 29 (1986) 391.
[576] G. Worley, et al., Creatine kinase brain isoenzyme: relationship of CSF concentration to the neurologic condition of newborns and cellular localization in the human brain, Pediatrics 76 (1985) 15.
[577] C.Y. Lin, M. Ishida, Elevation of cAMP levels in CSF of patients with neonatal meningitis, Pediatrics 71 (1983) 932.
[578] C.J. Corrall, et al., C-reactive protein in spinal fluid of children with meningitis, J. Pediatr. 99 (1981) 365.
[579] E. BenGershom, G.J. Briggeman-Mol, F. de Zegher, Cerebrospinal fluid C-reactive protein in meningitis: diagnostic value and pathophysiology, Eur. J. Pediatr. 145 (1986) 246.
[580] A.G. Philip, C.J. Baker, Cerebrospinal fluid C-reactive protein in neonatal meningitis, J. Pediatr. 102 (1983) 715.
[581] A. Martin-Ancel, et al., Interleukin-6 in the cerebrospinal fluid after perinatal asphyxia is related to early and late neurological manifestations, Pediatrics 100 (1997) 789.
[582] K. Sayman, et al., Cytokine response in cerebrospinal fluid after birth asphyxia, Pediatr. Res. 43 (1998) 746.
[583] G. Chow, J.W. Schmidley, Lysis of erythrocytes and leukocytes in traumatic lumbar punctures, Arch. Neurol. 41 (1984) 1084.
[584] R.W. Steele, et al., Leukocyte survival in CSF, J. Clin. Microbiol. 23 (1986) 965.
[585] J.P. Osborne, B. Pizer, Effect on the white cell count of contaminating CSF with blood, Arch. Dis. Child. 56 (1981) 400.
[586] R.W. Novak, Lack of validity of standard corrections for white blood cell counts of blood-contaminated CSF in infants, Am. J. Clin. Pathol. 82 (1984) 95.
[587] J.H. Mayefsky, K.J. Roghmann, Determination of leukocytosis in traumatic spinal tap specimens, Am. J. Med. 82 (1987) 1175.
[588] A. Mehl, Interpretation of traumatic lumbar puncture: a prospective experimental model, Clin. Pediatr. 25 (1986) 523.
[589] A. Mehl, Interpretation of traumatic lumbar puncture: predictive value in the presence of meningitis, Clin. Pediatr. 25 (1986) 575.
[590] W.A. Bonadio, et al., Distinguishing CSF abnormalities in children with bacterial meningitis and traumatic lumbar puncture, J. Infect. Dis. 162 (1990) 251.
[591] S.H. Naqvi, et al., Significance of neutrophils in CSF samples processed by cytocentrifugation, Clin. Pediatr. 22 (1983) 608.
[592] W.A. Bonadio, Bacterial meningitis in children whose CSF contains polymorphonuclear leukocytes without pleocytosis, Clin. Pediatr. 27 (1988) 198.
[593] R.G. Greenberg, et al., Traumatic lumbar punctures in neonates: test performance of the cerebrospinal fluid white blood cell count, Pediatr. Infect. Dis. J. 27 (2008) 1047–1051.
[594] E. Weirich, et al., Neutrophil CD11b expression as a diagnostic marker for early-onset neonatal infection, J. Pediatr. 132 (1998) 445.
[595] C. Kennon, et al., Granulocyte colony-stimulating factor as a marker for bacterial infection in neonates, J. Pediatr. 128 (1996) 765.
[596] H. Kuster, et al., Interleukin-1 receptor antagonist and interleukin-6 for early diagnosis of neonatal sepsis 2 days before clinical manifestation, Lancet 352 (1998) 1271.
[597] H. Doellner, et al., Interleukin-6 concentrations in neonates evaluated for sepsis, J. Pediatr. 132 (1998) 295.
[598] A. Panero, et al., Interleukin 6 in neonates with early and late onset infection, Pediatr. Infect. Dis. J. 16 (1997) 370.
[599] D. Harding, et al., Is interleukin-6-174 genotype associated with the development of septicemia in preterm infants? Pediatrics 112 (2003) 800.
[600] B. Resch, W. Gusenleitner, W.D. Muller, Procalcitonin and interleukin-6 in the diagnosis of early-onset sepsis of the neonate, Acta Paediatr. 92 (2003) 243.
[601] A. Kordek, et al., Umbilical cord blood serum procalcitonin concentration in the diagnosis of early neonatal infection, J. Perinatol. 23 (2003) 148.
[602] C. Chiesa, et al., Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates, Clin. Infect. Dis. 26 (1998) 664.

[603] M. Cetinkaya, et al., Comparison of serum amyloid A concentrations with those of C-reactive protein and procalcitonin in diagnosis and follow-up of neonatal sepsis in premature infants, J. Perinatol. 29 (2009) 225–231.
[604] E. Yapakci, et al., Serum pro-hepcidin levels in term and preterm newborns with sepsis, Pediatr. Int. 51 (2009) 289–292.
[605] B.H. Yoon, et al., Interleukin-6 concentrations in umbilical cord plasma are elevated in neonates with white matter lesions associated with periventricular leukomalacia, Am. J. Obstet. Gynecol. 174 (1996) 1433.
[606] O. Dammann, A. Leviton, Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn, Pediatr. Res. 42 (1997) 1.
[607] S. Mehr, L.W. Doyle, Cytokines as markers of bacterial sepsis in newborn infants: a review, Pediatr. Infect. Dis. J. 19 (2000) 879.
[608] T. Reier-Nilsen, et al., Comparison of broad range 16S rDNA PCR and conventional blood culture for diagnosis of sepsis in the newborn: a case control study, BMC. Pediatr. 9 (2009) 5.
[609] A. Ohlin, et al., Real-time PCR of the 16S-rRNA gene in the diagnosis of neonatal bacteraemia, Acta Paediatr. 97 (2008) 1376–1380.
[610] K.Y. Chan, et al., Rapid identification and differentiation of gram-negative and gram-positive bacterial bloodstream infections by quantitative polymerase chain reaction in preterm infants, Crit. Care Med. 37 (2009) 2441–2447.
[611] L.H. Chen, et al., Rapid diagnosis of sepsis and bacterial meningitis in children with real-time fluorescent quantitative polymerase chain reaction amplification in the bacterial 16S rRNA gene, Clin. Pediatr. (Phila) 48 (2009) 641–647.
[612] M.L. Castor, et al., Antibiotic resistance patterns in invasive group B streptococcal isolates, Infect. Dis. Obstet. Gynecol. (2008).
[613] S. Dahesh, et al., Point mutation in the group B streptococcal pbp2x gene conferring decreased susceptibility to beta-lactam antibiotics, Antimicrob. Agents Chemother. 52 (2008) 2915–2918.
[614] K. Kimura, et al., First molecular characterization of group B streptococci with reduced penicillin susceptibility, Antimicrob. Agents Chemother. 52 (2008) 2890–2897.
[615] H.M. Swingle, R.L. Bucciarelli, E.M. Ayoub, Synergy between penicillins and low concentrations of gentamicin in the killing of group B streptococci, J. Infect. Dis. 152 (1985) 515.
[616] C.N. Baker, C. Thornsberry, R.R. Facklam, Synergism, killing kinetics, and antimicrobial susceptibility of group A and B streptococci, Antimicrob. Agents Chemother. 19 (1981) 716.
[617] V. Schauf, et al., Antibiotic-killing kinetics of group B streptococci, J. Pediatr. 89 (1976) 194.
[618] A. Deveikis, et al., Antimicrobial therapy of experimental group B streptococcal infection in mice, Antimicrob. Agents Chemother. 11 (1977) 817.
[619] R.J. Backes, et al., Activity of penicillin combined with an aminoglycoside against group B streptococci in vitro and in experimental endocarditis, J. Antimicrob. Chemother. 18 (1986) 491.
[620] C.M. Odio, et al., Comparative efficacy of ceftazidime vs. carbenicillin and amikacin for treatment of neonatal septicemia, Pediatr. Infect. Dis. J. 6 (1987) 371.
[621] P. Begue, et al., Pharmacokinetics and clinical evaluation of cefotaxime in children suffering from purulent meningitis, J. Antimicrob. Chemother. 14 (1984) 161.
[622] C.M. Odio, et al., Cefotaxime vs. conventional therapy for treatment of bacterial meningitis of infants and children, Pediatr. Infect. Dis. J. 5 (1986) 402.
[623] C.M. Odio, Cefotaxime for treatment of neonatal sepsis and meningitis, Diagn. Microbiol. Infect. Dis. 22 (1995) 111.
[624] J.S. Bradley, et al., Meropenem pharmacokinetics, pharmacodynamics, and Monte Carlo simulation in the neonate, Pediatr. Infect. Dis. J. 27 (2008) 794–799.
[625] C.S. Bryan, et al., Gentamicin vs. cefotaxime for therapy of neonatal sepsis, Am. J. Dis. Child. 139 (1985) 1086.
[626] P. Manzoni, et al., Risk factors for progression to invasive fungal infection in preterm neonates with fungal colonization, Pediatrics 118 (2006) 2359–2364.
[627] D.K. Benjamin Jr., et al., Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months, Pediatrics 117 (2006) 84–92.
[628] P. Man, et al., An antibiotic policy to prevent emergence of resistant bacilli, Lancet 355 (2000) 973.
[629] R.D. Feigin, G.H. McCracken, J.O. Klein, Diagnosis and management of meningitis, Pediatr. Infect. Dis. J. 11 (1992) 785.
[630] J.S. Bradley, et al., Once-daily ceftriaxone to complete therapy of uncomplicated group B streptococcal infection in neonates: a preliminary report, Clin. Pediatr. 31 (1992) 274.
[631] S.L. Kaplan, C.C. Patrick, Cefotaxime and aminoglycoside treatment of meningitis caused by gram-negative enteric organisms, Pediatr. Infect. Dis. J. 9 (1990) 810.
[632] Group B Streptococcal Infections in Pregnancy, American College of Gynecology, Washington, DC, 1996.
[633] American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn, Guidelines for prevention of group B streptococcal (GBS) infection by chemoprophylaxis, Pediatrics 90 (1992) 775.
[634] Centers for Disease Control and Prevention, Prevention of perinatal group B streptococcal: a public health perspective, MMWR. Morb. Mortal. Wkly. Rep. 45 (1996) 1.
[635] American Academy of Pediatrics, Committee on Infectious Diseases/Committee on Fetus and Newborn. Revised guidelines for prevention of early-onset group B streptococcal infection, Pediatrics 99 (1997) 489.
[636] S. Schrag, et al., Prevention of perinatal group B streptococcal disease: revised guidelines from CDC, MMWR. Morb. Mortal. Wkly. Rep. 51 (2002) 1.
[637] I.P. Uy, et al., Changes in early-onset group B beta hemolytic streptococcus disease with changing recommendations for prophylaxis, J. Perinatol. 22 (2002) 516.
[638] M.A. MacAulay, M. Abou-Sabe, D. Charles, Placental transfer of ampicillin, Am. J. Obstet. Gynecol. 96 (1966) 943.
[639] H. Nau, Clinical pharmacokinetics in pregnancy and perinatology, II: penicillins, Dev. Pharmacol. Ther. 10 (1987) 174.
[640] D.H. Adamkin, E. Marshall, L.B. Weiner, The placental transfer of ampicillin, Am. J. Perinatol. 1 (1984) 310.
[641] B.S. Brozanski, et al., Effect of a screening-based prevention policy on prevalence of early-onset group B streptococcal sepsis, Obstet. Gynecol. 95 (2000) 496.
[642] M.R. Moore, S.J. Schrag, A. Schuchat, Effects of intrapartum antimicrobial prophylaxis for prevention of group-B-streptococcal disease on the incidence and ecology of early-onset neonatal sepsis, Lancet Infect. Dis. 3 (2003) 201.
[643] S.J. Schrag, et al., Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis, N. Engl. J. Med. 342 (2000) 15.
[644] S.P. Gotoff, K.M. Boyer, Prevention of early-onset neonatal group B streptococcal disease, Pediatrics 99 (1997) 866.
[645] E. Squire, B. Favara, J. Todd, Diagnosis of neonatal bacterial infection: hematologic and pathologic findings in fatal and nonfatal cases, Pediatrics 64 (1979) 60.
[646] G.H. McCracken Jr., S.G. Mize, A controlled study of intrathecal antibiotic therapy in gram-negative enteric meningitis of infancy. Report of the Neonatal Meningitis Cooperative Study Group, J. Pediatr. 89 (1976) 66.
[647] G.H. McCracken Jr., S.G. Mize, N. Threlkeld, Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy, Lancet 1 (1980) 787.
[648] N. Koksal, et al., Meropenem in neonatal severe infections due to multiresistant gram-negative bacteria, Indian J. Pediatr. 68 (2001) 15.
[649] M. Khaneja, et al., Successful treatment of late-onset infection due to resistant *Klebsiella pneumoniae* in an extremely low birth weight infant using ciprofloxacin, J. Perinatol. 19 (1999) 311.
[650] H.L. van den Oever, et al., Ciprofloxacin in preterm neonates: case report and review of the literature, Eur. J. Pediatr. 157 (1998) 843.
[651] R. Wessalowski, et al., Multiple brain abscesses caused by *Salmonella enteritidis* in a neonate: successful treatment with ciprofloxacin, Pediatr. Infect. Dis. J. 12 (1993) 683.
[652] R.E. Levitz, R. Quintiliani, Trimethoprim-sulfamethoxazole for bacterial meningitis, Ann. Intern. Med. 100 (1984) 881.
[653] Z. Spirer, et al., Complete recovery from an apparent brain abscess treated without neurosurgery: the importance of early CT scanning, Clin. Pediatr. (Phila) 21 (1982) 106.
[654] A.S. Daoud, et al., Lack of effectiveness of dexamethasone in neonatal bacterial meningitis, Eur. J. Pediatr. 158 (1999) 230–233.
[655] M.S. Tekerekoglu, et al., Analysis of an outbreak due to *Chryseobacterium meningosepticum* in a neonatal intensive care unit, New Microbiol. 26 (2003) 57.
[656] R. Lauterbach, M. Zembala, Pentoxifylline reduces plasma tumour necrosis factor-alpha concentration in premature infants with sepsis, Eur. J. Pediatr. 155 (1996) 404.
[657] K.R. Schibler, et al., A randomized, placebo-controlled trial of granulocyte colony-stimulating factor administration to newborn infants with neutropenia and clinical signs of early-onset sepsis, Pediatrics 102 (1998) 6.
[658] P. Kocherlakota, E.F. LaGamma, Preliminary report: rhG-CSF may reduce the incidence of neonatal sepsis in prolonged preeclampsia-associated neutropenia, Pediatrics 102 (1998) 1107.
[659] K. Bilgin, et al., A randomized trial of granulocyte-macrophage colony-stimulating factor in neonates with sepsis and neutropenia, Pediatrics 107 (2001) 36.
[660] A. Ahmad, et al., Comparison of recombinant granulocyte colony-stimulating factor, recombinant human granulocyte-macrophage colony-stimulating factor and placebo for treatment of septic preterm infants, Pediatr. Infect. Dis. J. 21 (2002) 1061.
[661] A. Ohlsson, J.B. Lacy, Intravenous immunoglobulin for suspected or subsequently proven infection in neonates, Cochrane Database Syst. Rev. CD001239, (2004).
[662] INIS Study, International Neonatal Immunotherapy Study: non-specific intravenous immunoglobulin therapy for suspected or proven neonatal sepsis: an international, placebo controlled, multicentre randomised trial, BMC Pregnancy Childbirth 8 (2008) 52.
[663] R. Bennet, et al., The outcome of neonatal septicemia during fifteen years, Acta Paediatr. Scand. 78 (1989) 40.
[664] M.M. Placzek, A. Whitelaw, Early and late neonatal septicaemia, Arch. Dis. Child. 58 (1983) 728.
[665] J. de Louvois, Septicaemia and Meningitis in the Newborn, John Wiley & Sons, New York, 1990.
[666] G. Klinger, et al., Predicting the outcome of neonatal bacterial meningitis, Pediatrics 106 (2000) 477.

[667] E. Wald, et al., Long-term outcome of group B streptococcal meningitis, Pediatrics 77 (1986) 217.
[668] S.M. Franco, V.E. Cornelius, B.F. Andrews, Long-term outcome of neonatal meningitis, Am. J. Dis. Child. 146 (1992) 567.
[669] K.A. Horn, et al., Neurological sequelae of group B streptococcal neonatal infection, Pediatrics 53 (1974) 501.
[670] M.S. Edwards, et al., Long-term sequelae of group B streptococcal meningitis in infants, J. Pediatr. 106 (1985) 717.
[671] G.H. McCracken Jr., et al., Cerebrospinal fluid interleukin-1B and tumor necrosis factor concentrations and outcome from neonatal gram-negative enteric bacillary meningitis, Pediatr. Infect. Dis. J. 8 (1989) 155.
[672] G.H. McCracken Jr., et al., Moxalactam therapy for neonatal meningitis due to gram-negative enteric bacilli: a prospective controlled evaluation, JAMA 252 (1984) 1427.
[673] J. Baier, J.A. Bocchini Jr., E.G. Brown, Selective use of vancomycin to prevent coagulase-negative staphylococcal nosocomial bacteremia in high risk very low birth weight infants, Pediatr. Infect. Dis. J. 17 (1998) 179.
[674] R.W. Cooke, et al., Low-dose vancomycin prophylaxis reduces coagulase-negative staphylococcal bacteraemia in very low birthweight infants, J. Hosp. Infect. 37 (1997) 297–303.
[675] M.A. Kacica, et al., Prevention of gram-positive sepsis in neonates weighing less than 1500 grams, J. Pediatr. 125 (1994) 253–258.
[676] P.S. Spafford, et al., Prevention of central venous catheter-related coagulase-negative staphylococcal sepsis in neonates, J. Pediatr. 125 (1994) 259–263.
[677] A.P. Craft, N.N. Finer, K.J. Barrington, Vancomycin for prophylaxis against sepsis in preterm neonates, Cochrane Database Syst. Rev. CD001971, (2000).
[678] J.S. Garland, et al., A vancomycin-heparin lock solution for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters: a prospective, randomized trial, Pediatrics 116 (2005) e198–e205.
[679] P. Van de Perre, Transfer of antibody via mother's milk, Vaccine 21 (2003) 3374.
[680] L.A. Hanson, et al., Antiviral and Antibacterial Factors in Human Milk, Raven Press, New York, 1988.
[681] N.B. Mathus, et al., Anti-infective factors in preterm human colostrum, Acta Paediatr. Scand. 79 (1990) 1039.
[682] C.F. Isaacs, et al., Antiviral and antibacterial lipids in human milk and infant formula feeds, Arch. Dis. Child. 65 (1990) 861.
[683] J. Winberg, G. Wessner, Does breast milk protect against septicaemia in the newborn? Lancet 1 (1971) 1091.
[684] R.N. Ashraf, et al., Breast feeding and protection against neonatal sepsis in a high risk population, Arch. Dis. Child. 66 (1991) 488.
[685] M.A. Hylander, D.M. Strobino, R. Dhanireddy, Human milk feedings and infection among very low birth weight infants, Pediatrics 102 (1998) E38.
[686] G.V. Coppa, et al., Preliminary study of breastfeeding and bacterial adhesion to uroepithelial cells, Lancet 1 (1990) 569.
[687] H. Hasselbalch, et al., Decreased thymus size in formula-fed infants compared with breastfed infants, Acta Paediatr. 85 (1996) 1029–1032.
[688] H.F. Pabst, et al., Effect of breast-feeding on immune response to BCG vaccination, Lancet 1 (1989) 295.
[689] S.A. Silfverdal, et al., Long term enhancement of the IgG2 antibody response to *Haemophilus influenzae* type b by breast-feeding, Pediatr. Infect. Dis. J. 21 (2002) 816–821.
[690] M. Cohen-Wolkowiez, D.K. Benjamin Jr., E. Capparelli, Immunotherapy in neonatal sepsis: advances in treatment and prophylaxis, Curr. Opin. Pediatr. 21 (2009) 177–181.
[691] J.A. Englund, W.P. Glezen, Maternal immunization for the prevention of infection in early infancy, Semin. Pediatr. Infect. Dis. 2 (1991) 225.
[692] M. Vicari, B. Dodet, J. Englund, Protection of newborns through maternal immunization, Vaccine 21 (2003) 3351.
[693] C.J. Baker, M.A. Rench, P. McInnes, Immunization of pregnant women with group B streptococcal type III capsular polysaccharide-tetanus toxoid conjugate vaccine, Vaccine 21 (2003) 3468.
[694] A.A. Fanaroff, et al., A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network, N. Engl. J. Med. 330 (1994) 1107–1113.
[695] M. DeJonge, et al., Clinical trial of safety and efficacy of INH-A21 for the prevention of nosocomial staphylococcal bloodstream infection in premature infants, J. Pediatr. 151 (2007) 260.
[696] D.K. Benjamin, et al., A blinded, randomized, multicenter study of an intravenous *Staphylococcus aureus* immune globulin, J. Perinatol. 26 (2006) 290–295.
[697] A. Ohlsson, J.B. Lacy, Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants, Cochrane Database Syst. Rev. CD000361, (2004).
[698] D. Sidiropoulos, et al., Transplacental passage of intravenous immunoglobulin in the last trimester of pregnancy, J. Pediatr. 109 (1986) 505.
[699] E. Roilides, P.A. Pizzo, Modulation of host defenses by cytokines: evolving adjuncts in prevention and treatment of serious infections in immunocompromised patients, Clin. Infect. Dis. 15 (1992) 508.
[700] R.L. Roberts, et al., Neutropenia in an extremely premature infant treated with recombinant human granulocyte colony-stimulating factor, Am. J. Dis. Child. 145 (1991) 808.
[701] M.S. Cairo, et al., A randomized, double-blind, placebo-controlled trial of prophylactic recombinant human granulocyte-macrophage colony-stimulating factor to reduce nosocomial infections in very low birth weight neonates, J. Pediatr. 134 (1999) 64.
[702] K.D. Yang, F.J. Bohnsack, H.R. Hill, Fibronectin in host defense: implications in the diagnosis, prophylaxis and therapy of infectious diseases, Pediatr. Infect. Dis. J. 12 (1993) 234.
[703] M.C. Yoder, Therapeutic administration of fibronectin: current uses and potential applications, Clin. Perinatol. 18 (1991) 325.
[704] R. Carr, et al., Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMS trial): a single-blind, multicentre, randomised controlled trial, Lancet 373 (2009) 226–233.
[705] M. Donini, et al., G-CSF treatment of severe congenital neutropenia reverses neutropenia but does not correct the underlying functional deficiency of the neutrophil in defending against microorganisms, Blood 109 (2007) 4716–4723.
[706] B.B. Poindexter, et al., Parenteral glutamine supplementation does not reduce the risk of mortality or late-onset sepsis in extremely low birth weight infants, Pediatrics 113 (2004) 1209–1215.
[707] T.R. Tubman, S.W. Thompson, W. McGuire, Glutamine supplementation to prevent morbidity and mortality in preterm infants, Cochrane Database Syst. Rev. CD001457, (2008).
[708] H.C. Lin, B.H. Su, W. Oh, Oral probiotics prevent necrotizing enterocolitis, J. Pediatr. 148 (2006) 849.
[709] H.C. Lin, et al., Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants, Pediatrics 115 (2005) 1–4.
[710] P. Manzoni, et al., Oral supplementation with *Lactobacillus casei* subspecies *rhamnosus* prevents enteric colonization by *Candida* species in preterm neonates: a randomized study, Clin. Infect. Dis. 42 (2006) 1735–1742.
[711] K. Alfaleh, J. Anabrees, D. Bassler, Probiotics reduce the risk of necrotizing enterocolitis in preterm infants: a meta-analysis, Neonatology 97 (2009) 93–99.
[712] N. Orsi, The antimicrobial activity of lactoferrin: current status and perspectives, Biometals 17 (2004) 189–196.
[713] J.J. Damato, D.V. Eitzman, H. Baer, Persistence and dissemination in the community of R-factors of nosocomial origin, J. Infect. Dis. 129 (1974) 205.
[714] J.O. Klein, Family spread of staphylococcal disease following a nursery outbreak, N. Y. State. J. Med. 60 (1960) 861.
[715] N. Nakwan, T. Atta, K. Chokephaibulkit, Neonatal pasteurellosis: a review of reported cases, Arch. Dis. Child. Fetal Neonatal Ed. 94 (2009) F373–F376.
[716] S.A. Bhave, L.M. Guy, *Pasteurella multocida* meningitis in an infant with recovery, BMJ 2 (1977) 741.
[717] C. Guillet, et al., *Pasteurella multocida* sepsis and meningitis in 2-month-old twin infants after household exposure to a slaughtered sheep, Clin. Infect. Dis. 45 (2007) e80–e81.
[718] T.F. Wolfs, et al., Neonatal sepsis by *Campylobacter jejuni*: genetically proven transmission from a household puppy, Clin. Infect. Dis. 32 (2001) E97–E99.
[719] L.J. Baraff, et al., Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Agency for Health Care Policy and Research, Ann. Emerg. Med. 22 (1993) 1198.
[720] M.D. Baker, Evaluation and management of infants with fever, Pediatr. Clin. North. Am. 46 (1999) 1061.
[721] P.C. Ferrera, J.M. Bartfield, H.S. Snyder, Neonatal fever: utility of the Rochester criteria in determining low risk for serious bacterial infections, Am. J. Emerg. Med. 15 (1997) 299.
[722] R. Dagan, et al., Ambulatory care of febrile infants younger than 2 months of age classified as being at low risk for having serious bacterial infections, J. Pediatr. 112 (1988) 355.
[723] J.C. King Jr., E.D. Berman, P.F. Wright, Evaluation of fever in infants less than 8 weeks old, South. Med. J. 80 (1987) 948.
[724] J.O. Klein, P.C. Schlessinger, R.B. Karasic, Management of the febrile infant under three months of age, Pediatr. Infect. Dis. J. 3 (1984) 75.
[725] P. Ishimine, Fever without source in children 0 to 36 months of age, Pediatr. Clin. North. Am. 53 (2006) 167–194.
[726] M.D. Baker, L.M. Bell, Unpredictability of serious bacterial illness in febrile infants from birth to 1 month of age, Arch. Pediatr. Adolesc. Med. 153 (1999) 508–511.
[727] H.A. Kadish, et al., Applying outpatient protocols in febrile infants 1-28 days of age: can the threshold be lowered? Clin. Pediatr. (Phila) 39 (2000) 81–88.
[728] M.D. Baker, L.M. Bell, J.R. Avner, Outpatient management without antibiotics of fever in selected infants, N. Engl. J. Med. 329 (1993) 1437–1441.
[729] M.N. Baskin, E.J. O'Rourke, G.R. Fleisher, Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone, J. Pediatr. 120 (1992) 22–27.
[730] B.K. Bonsu, M. Chb, M.B. Harper, Identifying febrile young infants with bacteremia: is the peripheral white blood cell count an accurate screen? Ann. Emerg. Med. 42 (2003) 216–225.
[731] L. Brown, T. Shaw, W.A. Wittlake, Does leucocytosis identify bacterial infections in febrile neonates presenting to the emergency department? Emerg. Med. J. 22 (2005) 256–259.
[732] D.S. Greenes, M.B. Harper, Low risk of bacteremia in febrile children with recognizable viral syndromes, Pediatr. Infect. Dis. J. 18 (1999) 258–261.
[733] D.A. Levine, et al., Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections, Pediatrics 113 (2004) 1728–1734.
[734] W.I. Krief, et al., Influenza virus infection and the risk of serious bacterial infections in young febrile infants, Pediatrics 124 (2009) 30–39.

[735] W.A. Silverman, W.E. Homan, Sepsis of obscure origin in the newborn, Pediatrics 3 (1949) 157.
[736] R.T. Smith, E.S. Platou, R.A. Good, Septicemia of the newborn: current status of the problem, Pediatrics 17 (1956) 549.
[737] R.S. Moorman, S.H. Sell, Neonatal septicemia, South. Med. J. 54 (1962) 137.
[738] K.C. Buetow, S.W. Klein, R.B. Lane, Septicemia in premature infants, Am. J. Dis. Child. 110 (1965) 29.
[739] A. Ronnestad, et al., Blood culture isolates during 6 years in a tertiary neonatal intensive care unit, Scand. J. Infect. Dis. 30 (1998) 245.
[740] B. Ghiorghis, Neonatal sepsis in Addis Ababa, Ethiopia: a review of 151 bacteremic neonates, Ethiop. Med. J. 35 (1997) 169.
[741] H. Saloojee, et al., Changing antibiotic resistance patterns in a neonatal unit and its implications for antibiotic usage, (1998).
[742] S. Karan, Purulent meningitis in the newborn, Childs Nerv. Syst. 2 (1986) 26.
[743] K.P. Sanghvi, D.I. Tudehope, Neonatal bacterial sepsis in a neonatal intensive care unit: a 5-year analysis, J Pediatr Child Health 32 (1996) 333.
[744] G.H. McCracken Jr., Personal communication, (1976).
[745] S.S. Namnyak, B. Holmes, S.E. Fathalla, Neonatal meningitis caused by *Achromobacter xylosoxidans*, J. Clin. Microbiol. 22 (1985) 470–471.
[746] Y.R. Hearn, R.M. Gander, *Achromobacter xylosoxidans*: An unusual neonatal pathogen, Am. J. Clin. Pathol. 96 (1991) 211–214.
[747] J. Molina-Cabrillana, et al., Outbreak of *Achromobacter xylosoxidans* pseudobacteremia in a neonatal care unit related to contaminated chlorhexidine solution, Eur. J. Clin. Microbiol. Infect. Dis. 26 (2007) 435–437.
[748] G.G. Christo, et al., *Acinetobacter* sepsis in neonates, Indian Pediatr. 30 (1993) 1413–1416.
[749] A. Mishra, et al., *Acinetobacter* sepsis in newborns, Indian Pediatr. 35 (1998) 27–32.
[750] N. Mittal, et al., Outbreak of *Acinetobacter* spp septicemia in a neonatal ICU, Southeast Asian J. Trop. Med. Public Health 34 (2003) 365–366.
[751] A. Kilic, et al., *Acinetobacter septicus* sp. nov. association with a nosocomial outbreak of bacteremia in a neonatal intensive care unit, J. Clin. Microbiol. 46 (2008) 902–908.
[752] A. Simmonds, et al., Outbreak of *Acinetobacter* infection in extremely low birth weight neonates, Pediatr. Infect. Dis. J. 28 (2009) 210–214.
[753] A. Kadanali, M.A. Tasyaran, S. Kadanali, Anthrax during pregnancy: case reports and review, Clin. Infect. Dis. 36 (2003) 1343–1346.
[754] N. Manickam, A. Knorr, K.L. Muldrew, Neonatal meningoencephalitis caused by *Bacillus cereus*, Pediatr. Infect. Dis. J. 27 (2008) 843–846.
[755] C. Larsson, et al., Complications of pregnancy and transplacental transmission of relapsing-fever borreliosis, J. Infect. Dis. 194 (2006) 1367–1374.
[756] P.W. Melkert, H.V. Stel, Neonatal *Borrelia* infections (relapsing fever): report of 5 cases and review of the literature, East. Afr. Med. J. 68 (1991) 999–1005.
[757] S. Chheda, S.M. Lopez, E.P. Sanderson, Congenital brucellosis in a premature infant, Pediatr. Infect. Dis. J. 16 (1997) 81–83.
[758] I. Giannacopoulos, et al., Transplacentally transmitted congenital brucellosis due to *Brucella abortus*, J. Infect. 45 (2002) 209–210.
[759] J.K. Lee, Two outbreaks of *Burkholderia cepacia* nosocomial infection in a neonatal intensive care unit, J Paediatr Child Health 44 (2008) 62–66.
[760] O. Kahyaoglu, B. Nolan, A. Kumar, *Burkholderia cepacia* sepsis in neonates, Pediatr. Infect. Dis. J. 14 (1995) 815–816.
[761] C. Doit, et al., Outbreak of *Burkholderia cepacia* bacteremia in a pediatric hospital due to contamination of lipid emulsion stoppers, J. Clin. Microbiol. 42 (2004) 2227–2230.
[762] F.C. Abbink, J.M. Orendi, A.J. de Beaufort, Mother-to-child transmission of *Burkholderia pseudomallei*, N. Engl. J. Med. 344 (2001) 1171–1172.
[763] R. Krishnaswamy, et al., Early onset neonatal sepsis with *Campylobacter jejuni*: a case report, Eur. J. Pediatr. 150 (1991) 277–278.
[764] J.D. Feldman, E.N. Kontaxis, M.P. Sherman, Congenital bacteremia due to *Capnocytophaga*, Pediatr. Infect. Dis. 4 (1985) 415–416.
[765] J.R. Rosenman, J.K. Reynolds, M.B. Kleiman, *Capnocytophaga canimorsus* meningitis in a newborn: an avoidable infection, Pediatr. Infect. Dis. J. 22 (2003) 204–205.
[766] C. Edwards, C.H. Yi, J.L. Currie, Chorioamnionitis caused by *Capnocytophaga*: case report, Am. J. Obstet. Gynecol. 173 (1995) 244–245.
[767] R. Berner, et al., Fatal sepsis caused by *Corynebacterium amycolatum* in a premature infant, J. Clin. Microbiol. 35 (1997) 1011–1012.
[768] M.S. Platt, Neonatal *Hemophilus vaginalis* (*Corynebacterium vaginalis*) infection, Clin. Pediatr. (Phila) 10 (1971) 513–516.
[769] K. Vohra, et al., Neonatal sepsis and meningitis caused by *Edwardsiella tarda*, Pediatr. Infect. Dis. J. 7 (1988) 814–815.
[770] O.A. Okubadejo, K.O. Alausa, Neonatal meningitis caused by *Edwardsiella tarda*, BMJ 3 (1968) 357–358.
[771] E.E. Mowbray, et al., Maternal colonization and neonatal sepsis caused by *Edwardsiella tarda*, Pediatrics 111 (2003) e296–e298.
[772] K.M. Dahl, J. Barry, R.L. DeBiasi, *Escherichia hermannii* infection of a cephalohematoma: case report, review of the literature, and description of a novel invasive pathogen, Clin. Infect. Dis. 35 (2002) e96–e98.
[773] H.G. Ginsberg, R.S. Daum, *Escherichia hermannii* sepsis with duodenal perforation in a neonate, Pediatr. Infect. Dis. J. 6 (1987) 300–302.
[774] M.S. Tekerekoglu, et al., Analysis of an outbreak due to *Chryseobacterium meningosepticum* in a neonatal intensive care unit, New Microbiol. 26 (2003) 57–63.
[775] T.G. Abrahamsen, P.H. Finne, E. Lingaas, *Flavobacterium meningosepticum* infections in a neonatal intensive care unit, Acta Paediatr. Scand. 78 (1989) 51–55.
[776] R.A. Amaya, F. Al-Dossary, G.J. Demmler, *Gardnerella vaginalis* bacteremia in a premature neonate, J. Perinatol. 22 (2002) 585–587.
[777] T.K. Venkataramani, H.K. Rathbun, *Corynebacterium vaginale* (*Hemophilus vaginalis*) bacteremia: clinical study of 29 cases, Johns Hopkins Med. J. 139 (1976) 93–97.
[778] S.L. Orlicek, D.F. Welch, T.L. Kuhls, Septicemia and meningitis caused by *Helicobacter cinaedi* in a neonate, J. Clin. Microbiol. 31 (1993) 569–571.
[779] C. Thompson, et al., *Lactobacillus acidophilus* sepsis in a neonate, J. Perinatol. 21 (2001) 258–260.
[780] S.M. Cox, et al., Lactobacillemia of amniotic fluid origin, Obstet. Gynecol. 68 (1986) 134–135.
[781] H.O. Gsell Jr., et al., [Intrauterine leptospirosis pomona: 1st reported case of an intrauterine transmitted and cured leptospirosis], Dtsch. Med. Wochenschr. 96 (1971) 1263–1268.
[782] Y. Shaked, et al., Leptospirosis in pregnancy and its effect on the fetus: case report and review, Clin. Infect. Dis. 17 (1993) 241–243.
[783] P. Yossuck, et al., *Leuconostoc* spp sepsis in an extremely low birth weight infant: a case report and review of the literature, W. V. Med. J. 105 (2009) 24–27.
[784] G. Janow, et al., *Leuconostoc* septicemia in a preterm neonate on vancomycin therapy: case report and literature review, Am. J. Perinatol. 26 (2009) 89–91.
[785] A.K. Sinha, et al., Early onset *Morganella morganii* sepsis in a newborn infant with emergence of cephalosporin resistance caused by depression of AMPC beta–lactamase production, Pediatr. Infect. Dis. J. 25 (2006) 376–377.
[786] S. Dutta, A. Narang, Early onset neonatal sepsis due to *Morganella morganii*, Indian Pediatr. 41 (2004) 1155–1157.
[787] M. Casanova–Roman, A. Sanchez–Porto, M. Casanova–Bellido, Early–onset neonatal sepsis caused by vertical transmission of *Morganella morganii*, Scand. J. Infect. Dis. 34 (2002) 534–535.
[788] A. Hata, et al., *Mycoplasma hominis* meningitis in a neonate: case report and review, J. Infect. 57 (2008) 338–343.
[789] R. Duran, et al., *Ochrobactrum anthropi* bacteremia in a preterm infant with meconium peritonitis, Int. J. Infect. Dis. 13 (2009) e61–e63.
[790] N.Y. Aly, et al., *Pantoea agglomerans* bloodstream infection in preterm neonates, Med. Princ. Pract. 17 (2008) 500–503.
[791] C.M. Thompson, et al., Neonatal septicemia and meningitis due to *Pasteurella multocida*, Pediatr. Infect. Dis. J. 3 (1984) 559.
[792] D. Cohen-Adam, et al., *Pasteurella multocida* septicemia in a newborn without scratches, licks or bites, Isr. Med. Assoc. J. 8 (2006) 657–658.
[793] K. Fujita, et al., Neonatal *Plesiomonas shigelloides* septicemia and meningitis: a case and review, Acta Paediatr. Jpn. 36 (1994) 450–452.
[794] C. Terpeluk, et al., *Plesiomonas shigelloides* sepsis and meningoencephalitis in a neonate, Eur. J. Pediatr. 151 (1992) 499–501.
[795] J. Billiet, et al., *Plesiomonas shigelloides* meningitis and septicaemia in a neonate: report of a case and review of the literature, J. Infect. 19 (1989) 267–271.
[796] Z. Kassim, et al., Isolation of *Proteus mirabilis* from severe neonatal sepsis and central nervous system infection with extensive pneumocephalus, Eur. J. Pediatr. 162 (2003) 644–645.
[797] C.P. Darby, E. Conner, C.U. Kyong, *Proteus mirabilis* brain abscess in a neonate, Dev. Med. Child. Neurol. 20 (1978) 366–368.
[798] H. Velvis, N. Carrasco, S. Hetherington, Trimethoprim-sulfamethoxazole therapy of neonatal *Proteus mirabilis* meningitis unresponsive to cefotaxime, Pediatr. Infect. Dis. 5 (1986) 591–593.
[799] P. Lumbiganon, et al., Neonatal melioidosis: a report of 5 cases, Pediatr. Infect. Dis. J. 7 (1988) 634–636.
[800] M. Lloyd-Puryear, et al., Meningitis caused by *Psychrobacter immobilis* in an infant, J. Clin. Microbiol. 29 (1991) 2041–2042.
[801] A.C. Kimura, et al., Outbreak of *Ralstonia pickettii* bacteremia in a neonatal intensive care unit, Pediatr. Infect. Dis. J. 24 (2005) 1099–1103.
[802] J.H. Shin, et al., *Rothia dentocariosa* septicemia without endocarditis in a neonatal infant with meconium aspiration syndrome, J. Clin. Microbiol. 42 (2004) 4891–4892.
[803] J.W. Ruderman, K.P. Stoller, J.J. Pomerance, Bloodstream invasion with *Shigella sonnei* in an asymptomatic newborn infant, Pediatr. Infect. Dis. 5 (1986) 379–380.
[804] J.A. Aldrich, R.P. Flowers 3rd, F.K. Hall, *Shigella sonnei* septicemia in a neonate: a case report, J. Am. Osteopath. Assoc. 79 (1979) 93–98.
[805] E.E. Moore, Shigella sonnei septicaemia in a neonate, BMJ 1 (1974) 22.
[806] C. Gras-Le Guen, et al., Almond oil implicated in a *Staphylococcus capitis* outbreak in a neonatal intensive care unit, J. Perinatol. 27 (2007) 713–717.
[807] M. Langbaum, F.G. Eyal, *Stomatococcus mucilaginosus* septicemia and meningitis in a premature infant, Pediatr. Infect. Dis. J. 11 (1992) 334–335.
[808] A. Bose, J.K. Philip, M. Jesudason, Neonatal septicemia caused by *Vibrio cholerae* O:139, Pediatr. Infect. Dis. J. 19 (2000) 166.
[809] J.A. Kerketta, et al., Non-01 *Vibrio cholerae* septicemia and meningitis in a neonate, Indian. J. Pediatr. 69 (2002) 909–910.
[810] E.C. Thompson, *Yersinia enterocolitica* sepsis in a 3-week-old child, J. Natl. Med. Assoc. 86 (1994) 783–785.
[811] M. Challapalli, D.G. Cunningham, *Yersinia enterocolitica* septicemia in infants younger than three months of age, Pediatr. Infect. Dis. J. 12 (1993) 168–169.
[812] M.E. White, et al., Plague in a neonate, Am. J. Dis. Child. 135 (1981) 418–419.