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Neonatal Sepsis

Epidemiology and Management

Robert S. Baltimore

Yale University School of Medicine, New Haven, Connecticut, USA

Contents

Abstract

Neonatal sepsis is uncommon (2–4 per 1000 live births in developed countries), but the rate increases dramatically in premature newborns and those born to mothers with infections or prolonged rupture of the fetal membranes. While infections caused by organisms contracted from the mother at birth have decreased in the past two decades, there has been an increase in nosocomial infections. Today, most infants with sepsis have been

hospitalized in neonatal intensive care units for weeks or months because of extreme prematurity, or because of a congenital malformation or surgical condition. Antimicrobial therapy is usually begun prior to the isolation of a pathogen and is based upon knowledge of the likely microbes in the particular clinical situation.

The number of antimicrobial agents that can be safely used in neonates is relatively small, and dose administration usually needs to be adjusted based upon birthweight and post-gestational age. The decision whether to treat with antimicrobials should be made with consideration of the history, physical examination, and laboratory data. One should also consider the effects of the use of antimicrobials on the flora of the care unit. Bacterial resistance in the resident flora of the unit has become a major problem where there has been indiscriminate use of broad-spectrum agents.

Neonatal sepsis generally refers to systemic symptomatic bacterial, fungal, and viral infections that, on earliest presentation, may be associated with any gradation of symptoms, from only subtle feeding disturbances to frank septic shock. Infections in newborns often present with sepsis, with or without focal signs of infection.

Focal signs and symptoms in neonates due to localized infections may be clinically imperceptible, and thus difficult to differentiate on initial presentation from generalized or bloodstream infections. Often the early signs of neonatal sepsis are nonspecific, such as temperature instability, lethargy, poor feeding, and unexplained hyperbilirubinemia.

1. Epidemiology of Neonatal Infections

The rate of sepsis in infants born at any hospital varies according to the economic standards, availability of prenatal care, and variations in perinatal risk factors. The rate of neonatal sepsis has been 2–4 per 1000 live births since 1980 in the US, with a worldwide range of 1–8 per 1000 live births; higher rates are reported in developing countries. Low birthweight and male gender are associated with a higher rate of sepsis. Today, in developed countries most neonatal sepsis occurs in premature infants (table I).

Table I. Birthweight-specific sepsis rate within the first 30 days of life for infants born at Yale New Haven Hospital, 1978–1988 (reproduced from Gladstone et al.,[1] with permission from Lippincott Williams and Wilkins)

Birthweight (g)	No. of infants	No. of cases of sepsis per 1000 live births
600–999	406	86
1000–1499	618	45
1500–2499	2269	14
>2500	50 280	1
All infants >600	53 573	2.7

Neonatal infections are usually classified according to time and mode of onset (table II). They are grouped into three categories: (i) congenital infection, acquired *in utero* by vertical transmission with onset before birth; (ii) early-onset neonatal infections, acquired by vertical transmission in the perinatal period, either shortly before or during the process of birth; and (iii) late-onset neonatal infections, acquired by horizontal transmission in the nursery. Opinion differs as to what is the appropriate age for differentiating between early- and late-onset infections; the range is 2–7 days of age. The exact time period defined as early-onset infection is not very important, as 80–90% of infections in the first week of life have their onset in the first 2 days of life.[1-3]

Infections that have an onset within the first month of life are considered to be neonatal infections. A change in practice since the early 1980s is that neonatal intensive care units now frequently provide continuing care for severely premature and chronically ill infants up to several months of age, sometimes for up to 1 year of age. The term late, late-onset infections may be used to indicate nosocomial infections acquired in a neonatal intensive care unit with onset at age >1 month of age.[1,5]

1.1 Early-Onset Infections

Several risk factors for early-onset postnatal infections have a very strong influence on infection rates (table II). Healthy full-term infants born without incident or complications actually have the lowest incidence of infection, including nosocomial infections, of any population of hospitalized patients (table I). Infants at increased risk of early-onset postnatal infections are those with one or more of the following risk factors: prematurity, birth to a mother with an infection, birth to a mother who has had stress due to a complication of the pregnancy or delivery, and rupture of membranes for >6 hours. Prolonged premature rupture of the membranes often results in amnionitis, with the risk of early-onset

Table II. Relationship between time of onset of neonatal infection and mode of transmission of infection (reproduced from Baltimore,[4] with permission from Elsevier)

Time of onset	Age at onset of infection	Mode of transmission of infection	Major risk factors	Most common organisms
Prenatal	Prior to birth	Transplacental or ascending	Maternal infection, usually primary infection Prolonged premature rupture of membranes	Cytomegalovirus Syphilis *Toxoplasma gondii* Maternal vaginal flora HIV
Early-onset	Birth to 2–5 days	Maternal flora transmitted peripartum	Prolonged premature rupture of membranes Prematurity Septic or traumatic delivery Fetal anoxia Male gender Maternal infection (especially urogenital) Maternal poverty, pre-eclampsia, cardiac disease, diabetes mellitus	*Escherichia coli* Group B streptococcus *Klebsiella pneumoniae* *Enterococcus* spp. *Listeria monocytogenes* Other enteric Gram-negative bacilli
Late-onset	>2–5 to 30 days	Nosocomial	Intravascular catheters Endotracheal intubation Assisted ventilation Surgery (including necrotizing enterocolitis) Contact with hands of colonized personnel Contact with contaminated equipment	Those causing early onset sepsis *Staphylococcus aureus* Coagulase-negative staphylococci *Pseudomonas aeruginosa* *Candida* spp.
Late, late-onset	>30 days	Nosocomial	Indwelling intravascular devices Extreme prematurity Bronchopulmonary dysplasia Short gut syndrome Complex congenital malformations Previous broad spectrum antibacterial therapy	*Staphylococcus aureus* Coagulase-negative staphylococci *Pseudomonas aeruginosa* *Candida* spp. Resistant Gram-negative bacilli

infection increasing with longer duration of rupture. Otherwise, healthy full-term infants born to mothers with amnionitis have a rate of infection of only approximately 1%, compared with 20–25% for premature infants born to mothers with amnionitis. Compared with full-term infants, premature infants are also at greater risk of an invasive infection if born to a mother with a peripartum infection. Maternal factors that relate to poverty and poor prenatal care, and chronic diseases such as cardiac disease and diabetes mellitus, appear to have some independent effect on neonatal infection rates, but they are also risk factors for premature birth.[4,6]

Since the early 1970s when group B streptococcus emerged as a major cause of neonatal sepsis and meningitis, group B streptococci and *Escherichia coli* have accounted for approximately 60–80% of cases of early-onset neonatal sepsis and meningitis (table III). Since perinatal prophylaxis has been encouraged, the rate of group B streptococcal infections has fallen; the Centers for Disease Control and Prevention (CDC) has predicted that an 80% drop is possible (figure 1).[7] All of the major types of group B streptococci (types Ia, Ib, Ia/c, II, III, IV, and V) may colonize women and may cause early-onset sepsis in the neonate manifested by sepsis, with or without meningitis, or pneumonia. Type III strains appear to have special virulence properties for the development of meningitis, and cause >85% of cases of early-onset meningitis and most late-onset group B streptococcal infections, which most often present as meningitis and sepsis.

Of the >100 capsular serotypes of *E. coli*, K1 serotype strains cause >75% of cases of *E. coli* neonatal meningitis, and are the most common and most severe cause of neonatal *E. coli* sepsis. Thus, the K1 carbohydrate is a virulence factor. Transplacentally passed IgG antibodies for group B streptococci and *E. coli* act as opsonins. It is not completely clear what the pathogenic mechanisms and susceptibility factors for early-onset sepsis are; however, immunologic immaturity is certainly important. The neonate is deficient in humoral and cellular immunity, as well as in complement and phagocytic activity, and has poor skin and mucosal barriers to infection.

Table III. Bacteria and fungi causing neonatal sepsis

Organism	No. of participants (%)		
	Yale 1979–1988[1]a	NICHD Network 1991–1993[8]b	Ohio State University 1986–1997[9]c
Gram-positive bacterial species			
Group B streptococci	37	31	9
Group D streptococci	8	0	4
non-grouped and other streptococci	0	7	0
Viridans streptococci	3	9	0
Streptococcus pneumoniae	1	0	<1
Staphylococcus aureus	3	3	4
coagulase-negative staphylococci	8	7	47
Listeria monocytogenes	1	0	0
Gram-negative aerobic bacteria			
Escherichia coli	20	16	10
Klebsiella and *Enterobacter* spp.	3	5	8
Pseudomonas aeruginosa	3	0	2
Haemophilus spp.	5	11	3
Salmonella spp.	1	0	<1
Gram-negative anaerobic bacteria	3	0	0
Fungi	1	1	11
Others	1	10	1
Total number of patients	147	147	433
Mortality rate	16%	26%	12%

a Age of infants included in the study was birth to 30 days.

b Age of infants included in the study was birth to 3 days.

c Age of infants included in the study was birth to death or discharge.

NICHD = National Institute of Child Health and Human Development.

1.2 Late-Onset Infections

While early-onset neonatal infections are usually associated with the transmission of organisms from mother-to-infant, either before or during parturition, late-onset infections are usually due to organisms acquired after birth and are, therefore, nosocomial infections. Nosocomial infections in the nursery are an important and growing problem. As the technology for managing very premature and very sick infants has improved, the population of surviving immunocompromised infants who require invasive life support measures such as mechanical ventilation, intravascular catheters, total parenteral nutrition, and surgical drains has increased (table II). The liberal use of broad-spectrum antibacterials increases the risk of acquisition of pathogens by interfering with the development of normal flora.[2] Recently, there has been a reduction of early-onset infections due to perinatal prophylaxis of mothers with suspected amnionitis or colonization with group B streptococci, but in highly specialized referral neonatal intensive care units there is an increase in late-onset nosocomial infections.[11,12]

The microbial causes of late-onset neonatal sepsis have changed over time as they are heavily influenced by newer developments in the care for very low birthweight newborns. These trends are important to recognize because they provide the basis for rational empiric antimicrobial therapy. Certain species emerge and cause an increased proportion of infections for a limited period of time, such as the increase in *Staphylococcus aureus* in the late 1950s and early 1960s, and the emergence of group B streptococci in the early 1970s. The increase in coagulase-negative staphylococci and *Candida* spp. over the past two decades appears to be due to the increased survival among extremely premature infants, the use of parenteral nutrition, and frequent use of broad-spectrum

antibacterials. In many institutions coagulase-negative staphylococci are now the most common cause of all cases of neonatal bacteremia (table III and table IV).[12-14] The importance of coagulase-negative staphylococci in nosocomial neonatal infections is primarily as a cause of bloodstream infections, which in turn is the most common site of neonatal nosocomial infections.[14] Continuous surveillance of the microbiologic epidemiology and antimicrobial susceptibilities should be routine for all neonatal intensive care units.

The risk of acquiring nosocomial viral infections appears to depend mostly on the chances of contact with another person infected with the virus. This contrasts with the risk factors for sepsis due to bacterial and fungal infections that are related to birthweight and healthcare processes. Community activity of respiratory and gastrointestinal viruses, and the absence of effective barriers to prevent spread within the unit, appear to be the most important risk factors.

Overall, nosocomial infection rates in tertiary care neonatal intensive care units are similar to those for other intensive care units, at approximately 20 infections per 100 discharges. This number includes sepsis, focal infections, and various viral infections.

Any condition that causes a newborn to have a long stay in the nursery increases the opportunity for late-onset nosocomial infections. Therefore, the risk factors for late-onset infections cannot be separated from those for early-onset infections because the most common reason for prolonged neonatal hospitalization is prematurity.

2. Pathogenesis

Pathogenesis of sepsis in a newborn, as with epidemiologic characteristics, is divided into two categories: infections transmitted from mother to infant (early-onset), and nosocomial infections transmitted to an infant after birth by contact with contaminated personnel or hospital equipment (late-onset).

2.1 Prenatal-Onset and Early-Onset Infections

The fetus and the environment within the amniotic membranes are normally sterile. Transmission of infection to the infant before birth is resisted by the placental barrier, but occasionally infection reaches the fetus directly or through the maternal bloodstream. In practice, it is uncommon to be able to prove that this was the route of bacterial or fungal infection other than in cases of congenital syphilis. Occasionally, histology of the placenta will suggest infection, but this must be differentiated from nonspecific inflammatory findings. There may be bacterial or fungal ascending infection by contamination of the amniotic fluid with organisms from the mother's vaginal flora. Ascending infection may occur as a consequence of frank rupture of the membranes or inapparent tears that later seal. If the fetus ingests these organisms by swallowing contaminated amniotic fluid, the organisms may invade the upper and lower respiratory and gastrointestinal tracts before birth. Signs of infection following ascending infection may be present at delivery, within hours of birth, or less commonly, within several days.

Perinatal transmission of pathogens may take place during the birth process. The skin and upper respiratory tract of a neonate may become contaminated with organisms from the mother's cervical, vaginal, or fecal flora by contact or aspiration during the process of delivery. The mechanisms by which colonization, which is common, becomes invasive infection, which is less common, are not well understood. Occasionally the route of infection is apparent, i.e. when the umbilical cord stump is contaminated and omphalitis accompanies sepsis, or when instruments are used in the respiratory tract, as in endotracheal intubation.

It is presumed that the major susceptibility factor for invasive infection is the weaker immune function of neonates, especially premature neonates, compared with older children or adults. Maternally-derived IgG antibody is an important component of protection. Late in the third trimester, IgG antibody is actively trans-

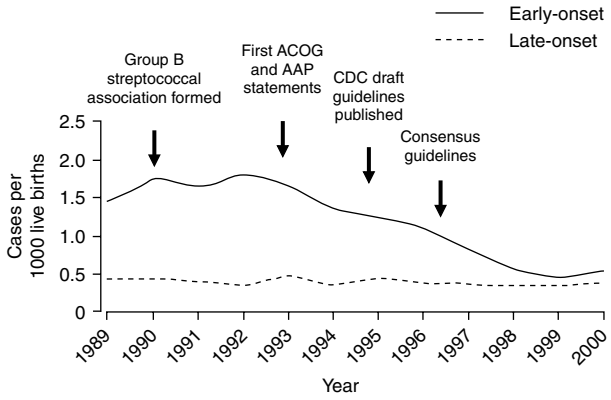

Fig. 1. Incidence of early- and late-onset invasive group B streptococcal disease in selected Active Bacterial Core surveillance areas, 1989-2000, and activities for prevention of group B streptococcal disease[7] (reproduced from Schrag et al.,[10] with permission from the Massachusetts Medical Society [Copyright© 2000]) **AAP** = American Academy of Pediatrics; **ACOG** = American College of Obstetricians and Gynecologists; **CDC** = Centers for Disease Control and Prevention.

Table IV. Distribution of organisms causing late-onset bloodstream infections

Species	Total (%)	
	CDC study of three hospitals 1989–91[12]	NICHD study 1996[13]
Coagulase-negative staphylococci	43	55
Candida spp.	13	7
Escherichia coli	11	4
Group B streptococci	9	14
Other Gram-negative bacterial species	9	2
Other species	15	18

CDC = Centers for Disease Control and Prevention; **NICHD** = National Institute of Child Health and Human Development.

ported from the mother across the placenta. If the infant is born prematurely, the transmission of IgG antibodies is decreased and the neonate is susceptible to those pathogens. Serologic studies of mother–infant pairs have shown that a major susceptibility factor to infection with group B streptococcus type III, the cause of most group B streptococcal neonatal sepsis and almost all group B streptococcal meningitis, is lack of antibody to major virulence antigen, the type III capsular carbohydrate.[15] Approximately 15–30% of delivering mothers have rectal or vaginal colonization with strains of group B streptococcus, and 50% or more of infants born to these mothers have colonization of the skin, mucous membranes, or gastrointestinal tract. It appears that newborns heavily colonized with group B streptococcus at multiple sites are more likely to develop invasive infection than newborns with limited colonization; however, only approximately 0.1% will have invasive group B streptococcal infection – these infants clearly have a lower concentration of antibody to the capsular carbohydrates than the 99.9% who do not have invasive infections.[15,16]

Susceptibility of the neonate to infection caused by exogenous organisms may be due to the inadequacy of physical barriers. The neonate has thinner skin than an older child does, and in premature infants the skin may be parchment-like with little subcutaneous tissue. Lack of gastric acidity results in easy colonization by environmental organisms, which may also cause invasive infections.

Unusual pathogens that colonize or infect the vagina or other parts of the mother's genital tract may be the cause of neonatal sepsis due to *Haemophilus influenzae, Streptococcus pneumoniae, Listeria monocytogenes, Salmonella* spp., *Mycoplasma hominis, Candida* spp., and others. Introduction of pathogens into the lower genital tract from the outside can occur shortly before or during birth. Faulty examining technique may introduce organisms during an obstetric examination or when monitoring equipment is used. Scalp electrodes have been determined to be the mode of introduction of new pathogens, as well as spread of vaginal organisms to the tissues of the emerging newborn even when there has been no apparent deviation from accepted techniques.

2.2 Late-Onset Infections

The mode of acquisition of late-onset neonatal infections is similar to that of nosocomial infections involving patients of all ages. However, while nosocomial infections in older children and adults involve the individual's own skin, respiratory, and gastrointestinal flora, a neonate is born sterile and acquires surface flora in the nursery. Normal flora confers resistance to colonization with new organisms and is an important constituent of host resistance to infection. A long hospitalization, especially with prolonged or repeated exposure to antimicrobials may have an influence on the nature of this flora. In a neonatal intensive care unit a newborn acquires atypical flora that make the infant more susceptible to invasive infection. Colonization of the skin, gastrointestinal and respiratory tracts with flora acquired from the mother, nursery personnel or inanimate objects precedes late-onset infections.

If an infection is due to organisms commonly associated with early-onset infections it may be impossible to determine whether the organisms were acquired from the mother or the nursery environment. It is unclear why infants colonized with organisms at birth may suddenly develop severe infections caused by these organisms many days or weeks later.

Late-onset infections caused by organisms commonly found on the skin, such as *S. aureus*, coagulase negative staphylococci, viridans streptococci, and *Candida* spp., may follow colonization either at birth or after birth. The major risk factors for infections caused by these species are the use of intravascular catheters, the presence of surgical wounds and drains, congenital malformations, and the use of invasive life-support equipment. Although these medical and surgical support measures are responsible for the improvement in survival of low birthweight and otherwise ill neonates, they predispose to infection by interfering with normal barriers.

Indwelling catheters allow for a pathway between the skin and the cannulated blood vessel. The infusion fluid is a medium that

facilitates the growth of certain organisms, which may normally be of low pathogenicity. Use of these fluids is a risk factor for infections due to coagulase-negative staphylococci, as well as certain fungi. *Malassezia furfur*, a lipophilic yeast that frequently colonizes infants in newborn intensive care units, has occasionally been encountered in neonates receiving lipid emulsion intravenously. Other lipophilic fungi have rarely been isolated from the blood of infants receiving intravenous lipid emulsion.

3. Diagnosis

The diagnosis of neonatal sepsis is considered likely on the basis of abnormal findings on physical examination, or a combination of risk factors plus abnormal laboratory data that indicate that sepsis is highly likely. In either case, empiric antimicrobial therapy directed against likely organisms is begun immediately after cultures are obtained. Antibacterial therapy is discontinued or adjusted after culture results are known in 2–3 days. Cultures of blood, cerebrospinal fluid, and urine are generally positive within 48 hours of incubation if infection is due to any of the usual neonatal bacterial or fungal pathogens.

3.1 Laboratory Evaluation

3.1.1 Leukocyte Counts

The white blood cell count (WBC) and differential count are useful for assessing a neonate who may have sepsis, and for evaluating a neonate being treated for proven sepsis. The marrow reserves of leukocytes in a newborn are relatively smaller compared with those of older children and adults, and leukopenia occurs more frequently as a sign of overwhelming infection. Although the diagnosis of sepsis should not be based solely on the results of WBC and differential count, this information is helpful when added to other clinical and epidemiologic information to determine which infants should be empirically treated because of the strong likelihood of sepsis. The normal peripheral WBC count of newborns is from 5000–20 000/mm^3,[17] (5–20 $\times$ 10^9/L), but even values outside this range still have a poor specificity for predicting sepsis. There is some evidence that the absolute neutrophil count, determined by multiplying the WBC count by the fraction of neutrophils plus bands in the differential, is more predictive of sepsis than is the total WBC count. Neutrophil concentrations outside the normal range support an impression of sepsis or a high risk of sepsis.

In an attempt to increase the specificity of WBC parameters as an indicator of sepsis, the ratio of the concentration of immature cells of the neutrophilic series (bands, metamyelocytes, and myelocytes) to total cells of the neutrophil series, known as the I : T ratio, has been used. An increased concentration of immature neutrophil series cells and an I : T ratio of >0.2 have been reported to have moderately increased specificity for sepsis. The I : T ratio takes into consideration the normative values over the first days of life.[17] It is frequently used and has only moderate sensitivity but good negative predictive value if normal.

3.1.2 Other Screening Laboratory Tests

In practice, so many low birthweight infants who do not have infection receive antibacterials, that there is concern about the deleterious effects of so much unnecessary antibacterial use. These concerns have led to attempts to develop screening systems to target those newborns much more likely to benefit from antibacterial treatment. Newborns with symptoms consistent with sepsis should be treated empirically after appropriate cultures, chest radiograph, and laboratory tests have been performed. For symptomatic newborns, laboratory tests need not be used in making the decision for treatment, which should not be withheld while waiting for the results of tests that have been ordered.

Acute phase reactants such as C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and concentrations of certain cytokines, have each been reported to have moderate positive and negative predictive values. The quantitative CRP test is moderately sensitive for bacteremia if there are serial determinations in the first days of life. Several studies have also suggested that decrease of the CRP during treatment for sepsis is a good determinant of effectiveness of treatment and can be used to shorten the length of therapy. Recent studies have shown that interleukin (IL)-6, IL-8, and CD11b, which is a member of the β-integrin family of adhesion proteins, are moderately sensitive assays for predicting neonatal bacteremia, but have great potential in use as screening tests to exclude bacteremia.

Procalcitonin is a prohormone of calcitonin. There has been considerable interest in measuring procalcitonin as a method to differentiate bacterial from viral infections, and as an early indicator of neonatal sepsis. Some studies have shown that it has higher specificity for neonatal bacterial sepsis than CRP or IL-6.[18-22] Clinical studies demonstrating improvement of care using this test are lacking. While all of these tests of acute phase reactants may be useful, it is not clear which test is the most useful in the first hours

after birth when decisions to begin empiric antibacterial treatment are usually necessary, but their use may allow shortened courses of antibacterials.[23-30]

In addition to the use of single tests for determining which newborns would benefit from empiric treatment for sepsis, a panel of tests have been used that are only useful for newborns without any symptoms. While all these tests are not required, some newborn units will test asymptomatic newborns with standard blood, urine, and cerebrospinal fluid cultures, plus a radiograph of the chest, WBC count, I : T ratio, CRP, ESR, and cytokine markers as a sepsis screen. One earlier study[29] showed that of 30 proven cases of sepsis among 376 newborns, 28 occurred among the 71 newborns with positive screens, and only two newborns with proven sepsis had negative screens, giving a screen sensitivity of 93%, specificity of 88%, and positive predictive accuracy of 39%. Newborns with a negative screen were at low risk and did not need to be treated empirically with antibacterials.[30] Some centers use laboratory screens, and others have been unwilling to withhold antibacterial treatment from newborns with risk factors such as low birthweight, perinatal asphyxia, or prolonged rupture of the membranes. There is no clear standard of practice at this time.

3.1.3 Microbiologic Evaluation

Cultures of a newborn being evaluated for sepsis should routinely include one or more blood cultures, urine culture, and cerebrospinal fluid culture. While most infectious diseases consultants recommend a lumbar puncture, in some centers the cerebrospinal fluid culture is not routinely performed on asymptomatic infants unless central nervous system infection is suspected or if there have been other positive cultures.[6,31] Sometimes the fragile condition of the neonate precludes the performance of a lumbar puncture. Other cultures, such as joint fluid, bone, and peritoneal fluid, are not performed routinely, but should be performed if there is evidence of focal infection. Although a single blood culture is fairly sensitive for diagnosing sepsis, the chances of a contaminant growing in a blood culture are high enough that concordance or discordance between two cultures is helpful to determine whether the organism was a true cause of sepsis. Concordant positive results indicate a higher probability of sepsis, and discordant results indicate a higher probability that the isolate is a contaminant; therefore, two blood cultures obtained by venipuncture from separate sites are recommended if this will not delay treatment.

The use of superficial cultures, such as cultures of skin, umbilicus, and gastric contents, may be helpful in determining if organisms have been transferred from mother to newborn, if obtained immediately after birth. These cultures may indicate that the infant is colonized with these organisms and should not be interpreted as indicating invasive infection. Negative surface cultures do not indicate absence of infection risk as there may be technique problems with culturing and processing. The value of such cultures, especially if taken after a few days of life, is dubious.

Urine cultures are useful, especially when a blood culture grows a pathogen and the specific focus of infection needs to be clarified. Cultures of urine or cerebrospinal fluid taken during the course of antibacterial treatment are not useful in determining if a focus existed at the time antibacterial treatment was begun. There is little question that blood, urine, and cerebrospinal fluid are the minimal cultures for the evaluation of a neonate older than 2 days of age who develops new signs of infection.

Urine cultures should be obtained by urethral catheterization or suprapubic bladder aspiration. Bagged urine from a neonate is frequently contaminated with skin flora.

3.1.4 Tests for Bacterial Antigens

It is possible to detect the free soluble antigens produced by bacteria multiplying in bodily fluids such as blood, urine, and cerebrospinal fluid, using particle agglutination. Attempts to detect *E. coli* and group B streptococcus in neonatal infections have looked promising in some studies, but recent data suggest the tests have sufficiently poor sensitivity and specificity to render treatment decisions on the basis of their results alone unwise. At this time newer tests for group B streptococci are being developed, but they have been de-emphasized in management strategies until improved tests that are currently under study become available.

3.1.5 Viral Detection Methods

The availability of viral cultures in the evaluation of an ill newborn varies considerably from institution-to-institution. Either congenital viral infection or perinatally-acquired viral infection with herpes simplex, varicella-zoster, and enteroviruses may present as neonatal sepsis. Postnatal community-acquired viral infections may occur in newborns in the first few days of life, and in neonates with chronic underlying illnesses who may be resident in the hospital for many weeks. Respiratory viruses such as adenoviruses, respiratory syncytial virus, influenza viruses, and parainfluenza viruses may be transmitted by respiratory spread to newborns from the mother or healthcare workers, and can be detected by viral culture or rapid tests using direct immunofluorescence. Viral detection tests are indicated whenever there is an

outbreak of a nonbacterial respiratory infection in a nursery. They are also useful in the routine evaluation of infants with suspected respiratory tract infection. Tests for herpes simplex virus, cytomegalovirus, and enteroviruses, which may mimic neonatal sepsis, using genomic tests such as polymerase chain reaction, are available in many reference laboratories and some hospital diagnostic laboratories. These are most useful when the turnaround time is sufficiently short that they can be used for therapeutic decision-making. Viral diarrheal agents may also affect neonates, but the availability of tests for these agents and their applicability for infants is currently limited.

3.1.6 Diagnostic Imaging

Radiologic examination of neonates is important in the evaluation of the lower respiratory tract for evidence of pneumonia, and of the gastrointestinal tract for evidence of necrotizing enterocolitis (NEC).

NEC is a disease of stressed neonates characterized by breakdown of the intestinal mucosal barrier. The exact pathogenesis is unknown, but intestinal ischemia probably plays an important role. It is manifested by intramural air (pneumatosis intestinalis), ileus, and intestinal distention, and may progress to intestinal necrosis and perforation. If there is perforation, peritonitis ensues and sepsis may accompany peritonitis. Abdominal radiographs in early NEC show nonspecific distention, and as the disease progresses, pneumatosis intestinalis, fixed loops of distended bowel, portal vein gas, and pneumoperitoneum (which would be evidence of perforation) occur.

The chest and abdomen of a neonate are usually imaged in a single film. A chest radiograph is important in the evaluation for congenital heart disease, which may cause congestive heart failure and symptoms suggestive of sepsis. Infants believed to have clinically significant congenital cardiac disease should also have a cardiac ultrasonographic examination interpreted by a pediatric cardiologist.

Radiographs of the abdomen by plain radiography, as well as cross-table lateral images, may reveal the nonspecific finding of fixed, dilated loops of intestine, as seen in NEC. Pneumatosis intestinalis with or without the finding of intrahepatic portal air, which is seen most easily on cross-table lateral images, confirms the diagnosis of NEC, but it is not always present and is not necessary for the diagnosis.

4. Treatment

Treatment of neonatal sepsis encompasses antimicrobial therapy, adjunctive therapy, and supportive therapy. The empiric or definitive antibacterials chosen should be the most efficacious and specific drug that can be safely used for neonates. Adjunctive pharmaceutical agents to enhance host defenses against infection may also be used. Sustaining organ function by treating shock and acidosis, and by using life-support measures such as assisted ventilation, fluid resuscitation, and inotropic agents as a part of aggressive neonatal care, is of critical importance.

4.1 Antibacterial Treatment

The use of antibacterial agents in neonates is based on limited information compared with pharmacologic and safety data available for other populations. There is also concern about housing a large number of ill infants receiving antibacterials in an enclosed unit and what effect that may have on the development of resistance in the resident microbial flora. At any time, one-third or more of infants in a neonatal intensive care unit may be receiving broad-spectrum antibacterials.[32] Because there is little evidence that routine culture methods frequently fail to confirm sepsis in infants who actually have sepsis, and only 1 **:** 20, or fewer, who are treated for sepsis actually have a blood or spinal fluid isolated of bacteria or fungi, it appears that a large number of infants who are treated with antimicrobials receive no benefit from them. Antimicrobial use should be designed to minimize undesirable adverse effects. The number of antibacterials frequently used for the treatment of neonatal sepsis is relatively small, and an attempt is made to use agents that appear to be least associated with inducing resistance in the bacterial flora of the patient population.

4.2 Antimicrobial Therapy for Early-Onset Sepsis

Administration of antibacterials for early-onset infections to treat newborns who have risk factors is frequently begun before the infecting organism is identified (table V and table VI) as waiting for the results of cultures would result in unacceptably high morbidity and mortality. Thus, many schemas have been developed for empiric antibacterial treatment of infants with multiple epidemiologic risk factors or nonspecific signs and laboratory test abnormalities, plus epidemiologic risk factors. These schema depend on the recognition of known risk factors, the possibility that severe infection may present as temperature instability or other subtle changes in vital signs, unexplained hyperbilirubine-

Table V. Guidelines for empiric antibacterial treatment for presumed neonatal sepsis (with or without meningitis) in the first month of life (reproduced from Baltimore,[4] with permission from Elsevier)

Clinical setting	Recommended regimen	Alternative regimens
Early-onset sepsis	Ampicillin plus gentamicin[a]	Ampicillin plus cefotaxime
Late-onset sepsis (up to 1 month)		
readmission to hospital from the community	Ampicillin plus cefotaxime (or ceftriaxone[b])	Ampicillin plus gentamicin[a], with or without cefotaxime (or ceftriaxone[b])
occurring in the hospital, with no intravenous catheter(s)	Ampicillin plus gentamicin[a]	Ampicillin plus cefotaxime (or ceftriaxone[b])
occurring in the hospital, with intravascular catheter(s) in place	Oxacillin or vancomycin[a] plus gentamicin[a]	Vancomycin[a] plus cefotaxime (or ceftriaxone[b])

a Adjust dose according to concentration of the antibacterial in the blood once a steady state has been achieved.

b Ceftriaxone can displace bilirubin from albumin, thus intensifying hyperbilirubinemia, and may also cause deposition of sludge in the gall bladder; therefore, it should be used with caution in newborns.

mia, vomiting, or changes in feeding. Empiric treatment is designed to provide adequate antimicrobial activity against the likely organisms (table III and table IV). An infant suspected of having infection, but without focal signs, has therapy directed at the common causes of bacteremia and meningitis because experience demonstrates that these are the most likely types of infection to present without focal findings. If pneumonia or a urinary tract infection is present, therapy is aimed at the most common causes of these infections.

Empiric treatment of sepsis is generally accomplished by a combination of a broad-spectrum penicillin and an aminoglycoside, or a broad-spectrum penicillin and an extended-spectrum (third-generation) cephalosporin (table V). Most experts continue to recommend the combination of a penicillin (usually ampicillin) and an aminoglycoside, usually gentamicin. The advantages of this combination are low cost, considerable experience, low rate of development of bacterial resistance, and low toxicity when there is proper monitoring of blood aminoglycoside levels. Group B streptococci and *Listeria* spp. are susceptible to ampicillin, as are many strains of *E. coli* and *Proteus* spp. In nurseries where Gram-negative bacilli with acquired plasmid or chromosomal resistance to the aminoglycosides are not prevalent, gentamicin is active against *E. coli, Klebsiella*, *Proteus*, most *Enterobacter* spp., and *Pseudomonas aeruginosa*. Species commonly resistant to gentamicin include *Acinetobacter* spp., many strains of *Enterobacter cloacae*, some strains of *Serratia* spp., and *Flavobacterium* spp. These resistant species are rarely associated with early-onset sepsis. If a cluster of cases of sepsis caused by these organisms producing an extended spectrum β-lactamase (ESBL) is known to be occurring, alternative empiric therapy regimens employing carbapenems (i.e. meropenem or imipenem/cilastin) should be considered. ESBLs are β-lactamases that hydrolyze extended-spectrum cephalosporins with an oxyimino side chain. These include ceftazidime, ceftriaxone, cefotaxime, and the oxyimino-monobactam, aztreonam. *In vitro*, ESBLs appear susceptible to the β-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam, and this property is used for *in vitro* confirmation of the presence of ESBLs; However, β-lactamase inhibitor combinations cannot be relied on consistently for therapy of these organisms.

Extended-spectrum cephalosporins may provide greater activity against many of the pathogens, including Gram-negative bacilli resistant to gentamicin. The third-generation cephalosporins most used in neonates (cefotaxime and ceftriaxone) have excellent CNS penetration in the presence of inflammation; however, extended-spectrum cephalosporins are less active against Gram-positive cocci than the first- or second-generation cephalosporins, and their activity against group B streptococci is not as good as that of penicillin or ampicillin. They are inactive against *Enterococcus* spp. and *Listeria* spp., which are not infrequent causes of neonatal sepsis in many large centers. For these reasons, ampicillin is added to the cephalosporin when it is used empirically for neonatal sepsis or meningitis. Ceftriaxone has a similar spectrum of activity to cefotaxime and a longer half-life, but it has the potential to displace bilirubin from albumin-binding sites, and should not be used in infants with hyperbilirubinemia. When there is a high rate of use of these broad-spectrum cephalosporin agents, the prevalent flora in the neonatal intensive care unit may include strains of bacteria resistant to cephalosporins; therefore, there is an advantage in only using them when they are of proven or theoretical superiority.[36,37] If a diagnosis of Gram-negative bacillary

meningitis is based on Gram stain or culture of the cerebrospinal fluid, it is reasonable to use the combination of ampicillin and an extended-spectrum cephalosporin empirically as a first choice, although it has not been shown that this combination results in a superior outcome for neonatal meningitis compared with ampicillin and gentamicin.

Occasionally, isolates of Gram-negative rod pathogens are recovered that are resistant to cephalosporins and aminoglycosides. The carbapenems imipenem and meropenem have been used in neonates. Of the two, meropenem is preferred because of considerably less CNS irritation causing seizures. One problem with this class is the high frequency of fungal superinfection that follows its use.

The aminoglycoside of choice may, in some circumstances, be an agent other than gentamicin. Tobramycin has greater activity against *P. aeruginosa*, but this is an uncommon cause of neonatal infections. Some gentamicin-resistant isolates will be susceptible to amikacin. The third-generation cephalosporin ceftazidime can be safely used in neonates and generally has excellent activity against *P. aeruginosa* and other relatively resistant bacilli, but should not be used if there is demonstration of bacterial ESBL production.

4.3 Antimicrobial Therapy for Late-Onset Sepsis

Infants likely to have late-onset infections are most likely to be residents of the intensive care nursery with associated risk factors. Empiric antibacterial therapy for late-onset neonatal sepsis should take into consideration the resident flora of the nursery, especially isolates from previously infected neonates, and the particular risk factors of the individual patient (table V and table VI). It is appropriate to use the same empiric treatment as for early-onset sepsis, such as ampicillin plus an aminoglycoside if there have been no intravascular catheters in place, if the infant has not been treated for a previous infection, and there have not been isolates of gentamicin-resistant Gram-negative aerobic bacilli in the unit. However, many infants believed to have late-onset sepsis have specific risk factors and another regimen is often more appropriate. The most common bacterial isolates causing catheter-associated infections are *S. aureus* and coagulase-negative staphylococci. Although penicillinase-resistant semisynthetic penicillins, such as oxacillin and nafcillin, are usually the agents of choice for treating staphylococci, resistance to this class, commonly referred to as methicillin-resistant *S. aureus* (MRSA), is occurring more frequently in many institutions. Also, of the two, coagulase-negative staphylococci more commonly cause symptomatic infection of very low birthweight infants, and this species is more likely to have methicillin resistance; therefore, it is reasonable to use vancomycin for empiric treatment of late-onset infections in institutions with large numbers of MRSA. Generally, an aminoglycoside is added, usually gentamicin, for empiric coverage of Gram-negative bacilli. If new symptoms of infection develop while the infant is receiving gentamicin, either amikacin or an expanded spectrum (third-generation) cephalosporin is substituted for gentamicin. Blanket use of vancomycin for all cases of late-onset sepsis is generally not warranted because it is toxic compared with the penicillins, including the penicillinase-resistant penicillins, and has activity only against aerobic Gram-positive bacteria. Similarly, antibacterials active against gentamicin-resistant bacteria should be used only when there is a high risk of resistant pathogens. Frequent use of such agents in an enclosed nursery population promotes the emergence and persistence of even more resistant strains of bacteria.[2] The recommendations for empiric therapy in table V should be followed only when there are no unusual factors or clues to the cause of infection. Neonates with a specific focus of infection require individualization.

Persistently positive blood cultures can be a problem when treating catheter-associated infections due to staphylococci. This is usually due to adherence of bacteria enmeshed in fibrin adhering to the catheter, and is best managed by removing all intravascular catheters. For added antibacterial activity, some practitioners add rifampin (rifampicin) to either a semi-synthetic penicillin or vancomycin, although there is a lack of data demonstrating effectiveness. Newer antibacterials, such as quinupristin/dalfopristin, and linezolid, have activity against MRSA, but data on their use in neonates is lacking. Since both have significant adverse effects in older individuals they are not recommended at this time unless conventional antibacterial therapy fails.

Neonates who have been discharged from hospital and, due to fever, are readmitted for treatment of presumed sepsis or meningitis, should be treated empirically with a third-generation cephalosporin (usually cefotaxime or ceftriaxone) plus ampicillin. This combination is active against the usual causes of nonhospital-acquired sepsis, such as group B streptococci, enterococci, *Listeria* spp., *S. aureus*, and Gram-negative bacilli. If these infants are hospitalized in a regular infant unit as opposed to a neonatal intensive care unit, there will be a lower prevalence of antibacteri-

Table VI. Dosages and administration intervals of parenteral antibacterials for the treatment of neonatal infections (reproduced from Baltimore,[4] with permission from Elsevier)

Antibacterial	Dosage (mg/kg/dose)[a]				
	birthweight <1200g	birthweight 1200–2000g		birthweight >2000g	
	age 0–4 weeks	age 0–7 days	age >7 days	age 0–7 days	age >7 days
Penicillins					
Penicillin G (benzylpenicillin)[b]					
meningitis	50 000U q12h	50 000U q12h	75 000U q8h	50 000U q8h	50 000U q6h
other infections	25 000U q12h	25 000U q12h	25 000U q8h	25 000U q8h	25 000U q6h
Ampicillin[b]					
meningitis	50 q12h	50 q12h	50 q8h	50 q8h	50 q6h
other infections	25 q12h	25 q12h	25 q8h	25 q8h	25 q6h
Ticarcillin, ticarcillin/clavulanate	75 q12h	75 q12h	75 q8h	75 q8h	75 q6h
Piperacillin[c], piperacillin/tazobactam[c]	75 q12h	75 q12h	75 q8h	75 q12h	75 q8h
Penicillinase-resistant penicillins (nafcillin, oxacillin)					
meningitis	50 q12h	50 q12h	50 q8h	50 q8h	50 q6h
other infections	25 q12h	25 q12h	25 q8h	25 q8h	25 q6h
Cephalosporins					
Cephalothin	20 q12h	20 q12h	20 q8h	20 q8h	20 q6h
Cefazolin	20 q12h	20 q12h	20 q12h	20 q12h	20 q8h
Cefotaxime	50 q12h	50 q12h	50 q8h	50 q12h	50 q8h
Ceftazidime	50 q12h	50 q12h	50 q8h	50 q12h	50 q8h
Ceftriaxone[d]	50 q24h	50 q24h	50 q24h	50 q24h	75 q24h
Other β-lactams					
Aztreonam[e]	30 q12h	30 q12h	30 q8h	30 q8h	30 q6h
Imipenem[c], meropenem[c]	20 q18–24h	20 q12h	20 q12h	20 q12h	20 q8h
Aminoglycosides					
Gentamicin[f]	2.5 q18–24h	2.5 q12–18h	25 q8–12h	2.5 q12h	2.5 q8h
Tobramycin[f]	2.5 q18–24h	2.5 q12–18h	2.5 q8–12h	2.5 q12h	2.5 q8h
Amikacin[f]	7.5 q18–24h	7.5 q18–24h	7.5 q8–12h	10 q12h	10 q8h

Continued next page

Table VI. Contd

Antibacterial	Dosage (mg/kg/dose)[a]				
	birthweight <1200g	birthweight 1200–2000g		birthweight >2000g	
	age 0–4 weeks	age 0–7 days	age >7 days	age 0–7 days	age >7 days
Others					
Clindamycin	5 q12h	5 q12h	5 q8h	5 q8h	5 q6h
Metronidazole[c]	7.5 q48h	7.5 q24h	7.5 q12h	7.5 q12h	15 q12h
Vancomycin[f]	15 q24h	15 q12–18h	15 q8–12h	15 q12h	15 q8h
Chloramphenicol[d,f]	25 q24h	25 q24h	25 q24h	25 q24h	25 q12h
Antifungal agents	No age specified				
Amphotericin B	0.5–1.0 mg/kg once daily				
Amphotericin B liposome and amphotericin B lipid complex	1–5 mg/kg once daily				
Flucytosine[g]	50–150 mg/kg/day divided q6h				
Fluconazole[h]	6 mg/kg once daily				

a Doses in this table were assembled from Young and Mangum,[33] Nelson and Bradley,[34] The Medical Letter,[35] and Baltimore.[4] These dosages are for parenteral (intravenous or intramuscular) administration.

b Some authorities recommend higher doses – penicillin up to 100 000 U/kg/dose for meningitis and 50 000 U/kg/dose for other infections; ampicillin up to 100 mg/kg/dose for meningitis and 50 mg/kg/dose for other infections.

c Tolerability and efficacy in infants has not been established.

d Should not be administered to neonates with hyperbilirubinemia, especially those born prematurely.

e Safety and efficacy in infants younger than 9 months of age have not been established.

f Administration should be guided by laboratory determination of serum antibacterial concentrations once a steady state has been reached. These doses are a guideline for beginning therapy.

g Safety and efficacy in infants and children younger than 12 years of age have not been established. There are limited data on administration for neonates. The dose for older infants is indicated.

h There are limited data on administration for neonates.

q*x*h = every *x* hours.

al use, less antibacterial pressure, and the risk of development of resistant strains of bacteria will be lower than in the neonatal unit.

4.4 Duration of Antibacterial Treatment

While data indicating an optimal duration of therapy for neonatal sepsis do not exist, some useful guidelines are available.[4,6]

Empiric antibacterial therapy for sepsis should be stopped if cultures are sterile after 2–3 days, as cultures of blood, urine, and cerebrospinal fluid are usually positive after 2 days of incubation. This may not be possible if the infant or mother were treated with antibacterials that might interfere with recovery of an organism from a culture, and the infant appears to respond to antibacterials after a clinical diagnosis of sepsis. Although blood cultures are usually positive in neonatal bacterial sepsis, false negative results can occur if antibacterials were given prenatally to the mother, if a small volume of blood was drawn for culture, or due to poor handling of the specimen.

For infants with proven bacteremia without meningitis, or another focus of infection and a prompt bacteriologic and clinical response to therapy, 7–10 days of antibacterial treatment are sufficient. If a focus exists, the duration of therapy is generally 7–10 days, or a length of time which is appropriate for the focus of infection, whichever is longer. For bacterial meningitis, 2–3 weeks of antibacterial therapy is recommended for meningitis caused by group B streptococci or *Listeria* spp. For meningitis caused by Gram-negative bacilli, a minimum of 3 weeks of antibacterial therapy is recommended.

4.5 Adverse Drug Reactions

Antibacterials recommended for the treatment of neonatal sepsis can generally be safely used if delivered in the recommended doses and monitored appropriately. Listed below are the major adverse drug reactions and interactions.[33,38]

4.5.1 Penicillins

Penicillins can generally be safely used in neonates, and allergic problems such as drug rashes are rare. When blood levels are very high there may be CNS irritation resulting in seizures. The antipseudomonal penicillins such as ticarcillin and mezlocillin may inactivate aminoglycosides if they are mixed in the same solution. Gentamicin, tobramycin, and amikacin should not be mixed in the same solution with penicillins.

4.5.2 Cephalosporins

Cephalosporins, like penicillins, have a very good tolerability record in neonates, and true allergic problems are uncommon. Ceftriaxone competes with bilirubin for albumen binding sites, thus raising the free serum bilirubin, and should be avoided in young neonates. Ceftriaxone may also cause the development of biliary sludge, resulting in biliary obstruction.

4.5.3 Vancomycin

Vancomycin is occasionally responsible for nephrotoxicity and ototoxicity, but if either of these disorders occur it is usually when vancomycin is combined with other nephrotoxic or ototoxic drugs, such as aminoglycosides, loop diuretics, or amphotericin B. Vancomycin may cause phlebitis, but this is less common than was seen in the past when the drug was marketed in a form which was less pure. Vancomycin infusion may be associated with the so-called 'red man' syndrome of fever, flushing, tachycardia, and pruritus. Slowing the infusion rate usually controls this problem. Blood levels should be obtained in those with changing renal function and prolonged therapy. While peak levels (drawn 30 minutes after the end of a 1 hour infusion) should be 30–40 μg/mL, they are rarely indicated. Trough doses drawn just before the next dose should be 5–10 μg/mL.

4.5.4 Aminoglycosides

Aminoglycosides are associated with nephrotoxicity and ototoxicity. Keeping the blood levels in a nontoxic range can reduce the risk of these problems. Transient reversible renal tubular dysfunction is the most common problem. Infants may develop loss of renal concentrating ability along with proteinuria, usually after more than 5 days of treatment. Toxicity is additive with amphotericin B, loop diuretics, and vancomycin. In neonates receiving gentamicin or tobramycin, blood levels should be obtained if therapy is to be continued beyond 48 hours. Some experts recommend 4 mg/kg doses and extended intervals. In the first week of life, if using a scheduled interval of every 24 hours or longer, obtain a blood level 4 hours before the third dose. For older infants on a multiple doses per day schedule, obtain the peak level 30 minutes after the end of infusion of the third dose, and a trough level immediately before the fourth dose. Trough levels of 0.5–1.5 μg/mL are 'safe'. If the level is 1.6–2.0 μg/mL the dose interval should be extended by 12 hours, and if the level is >2 the next dose should be held until the level is ≤1.5 μg/mL. Peak levels, if obtained, should be in the range of 5–10 μg/mL, and up to 12 μg/mL for pseudomonal infections.[4,33,39]

4.6 Supportive Therapy

The use of agents to support or enhance the immune system during the treatment of neonatal sepsis is controversial. For many agents that aid the immune response of neonates there are studies showing benefit and other studies showing no benefit. Some small studies have suggested benefit from exchange transfusion, WBC transfusion when there is severe neutropenia and bone marrow failure, intravenous immunoglobulin (IVIG), and specific immune serum globulin preparations. While WBC transfusions appear to reduce the mortality rate in some studies,[40] the logistics for providing them in a safe and timely manner has been difficult at most centers. The use of hematopoietic growth factors such as granulocyte-colony stimulating factor (G-CSF)[41] and granulocyte monocyte-colony stimulating factor (GM-CSF)[42] in newborns with sepsis and neutropenia appears potentially promising, but data are still limited and results are inconclusive. A recent review of myeloid colony stimulating factors in neonatal sepsis concludes that there is insufficient evidence of benefit from G-CSF or GM-CSF to recommend either as routine adjunctive treatment for neonates with sepsis. If they are indeed beneficial, larger and well controlled additional studies will be required to demonstrate improved survival.[43] Despite lack of a good response in some studies,[44] a meta-analysis[45] suggests that IVIG (750 mg/kg as a single dose) is beneficial in decreasing the morbidity of neonatal sepsis. Some agents that have been useful for older children and adults have not been tested in neonates. Drotrecogin alfa (activated protein C) is beneficial in adults and older children with severe sepsis. There are no reports of its use in neonates and it is presently not approved for this use.[46] There is some evidence that corticosteroids are beneficial in reducing neurologic sequelae childhood and adult meningitis, but studies to demonstrate whether they are either beneficial or associated with an adverse outcome in neonates are not available and their use in this situation cannot be endorsed.

4.7 Group B Streptococcus Intrapartum Prophylaxis

Group B streptococcal disease has, until recently, been the most frequent life-threatening cause of neonatal sepsis and meningitis in the developed world. In the US strategies for selective intrapartum antimicrobial prophylaxis recommended by the CDC, the American College of Obstetrics and Gynecology, and the American Academy of Pediatrics, have resulted in dramatic reductions in incidence of early-onset disease. While two strategies were initially recommended, one based only on risk factors and the second based on the combination of prenatal culture screening at 35–37 weeks' gestation and risk factors, the latter method is now preferred.[7] The recommended maternal regimen of intrapartum prophylaxis is penicillin G (benzylpenicillin) 5 million units (alternative: ampicillin 2g) intravenously at the onset of labor, followed by penicillin G 2.5 million units (alternative: ampicillin 1g) intravenously every 4 hours until delivery. Clindamycin (900mg every 8 hours) or erythromycin (500mg every 6 hours) intravenously until delivery are recommended as alternatives for women with hypersensitivity to penicillin. Maternal fever during labor, suggesting chorioamnionitis, in addition to being a risk factor for neonatal disease, requires broad-spectrum antibacterial therapy of the mother.

4.8 Infants Born to Mothers Who Received Peripartum Antibacterials

Current obstetric practice emphasizes the use of antibacterial treatment to reduce the incidence of early onset sepsis in newborns when mothers have evidence of chorioamnionitis or other urogenital tract infections, while mothers who are colonized with group B streptococci receive intrapartum prophylaxis with penicillin or ampicillin.[7] Since antibacterials administered to the mother cross the placenta and give rise to significant antibacterial concentrations in the infant, physicians treating newborns are presented with several challenges. For symptomatic infants born to mothers receiving antibacterials, should the usual antibacterials be used for empiric treatment, or should alternatives be used? If symptomatic infants are treated with antibacterials and clinically improve, but all cultures are sterile, can antibacterials be discontinued or should they be continued for some predetermined duration? There is a range of opinion among neonatologists and infectious diseases specialists concerning treatment in these situations. A compromise recommended by many experts is based on the presence of symptoms and risk factors. Infants with signs or symptoms of sepsis, or whose mothers received antibacterials for suspected chorioamnionitis, should have a complete evaluation for sepsis, including complete blood count (CBC), cultures of the blood, urine, and cerebrospinal fluid, and be treated as for sepsis for 7–10 days, even if cultures are negative. Infants who are asymptomatic who have risk factors for sepsis (e.g. fever, prematurity, prolonged premature rupture of membranes, maternal infection) should have a complete sepsis evaluation, including CBC, cultures of the blood,

urine, and cerebrospinal fluid (at the discretion of the physician), and treatment with broad-spectrum antibacterials for 48 hours. After 48 hours, a decision about the length of treatment is made on the basis of initial evaluation, culture reports, and clinical course. Asymptomatic infants with no risk factors should be observed for 48 hours without antibacterial treatment, and evaluated and treated if symptoms develop (see figure 2).[7]

4.9 Treatment of Candidemia

Treatment of candidemia in a newborn usually begins with amphotericin B. In general, it is recommended to use an initial treatment dose of 0.2–0.3 mg/kg once daily, increasing the dose by 0.25 mg/kg each day over 2–3 days to a maximum of 0.5–1.0 mg/kg/day.[47] Very ill infants may be treated initially with a full treatment dose of 0.75–1.0 mg/kg daily. Many infants with candidemia respond to a dose lower than 1 mg/kg/day, with doses of 0.3–0.4 mg/kg/day reported to result in successful eradication of the organism. The maximum dose should be used for infants with evidence of focal infection in organs, especially those with meningitis. If there is evidence of endocarditis, the lesion may have to be excised surgically from the cardiac valve, but survival of these infants without surgery has been described.[48] The optimal duration of treatment of neonatal candidemia has not been determined and experts differ in their recommendations. Although amphotericin B is often dosed by the total amount of amphotericin B per kilogram of bodyweight for the treatment of deep-tissue fungal infections, candidemia can often be treated according to the duration of the dose effective in eliminating the organism. For candidemia without evidence of tissue invasion, treatment for 2 weeks beyond the last positive blood culture is usually curative. When infection has disseminated to organs, or the patient has had meningitis, a longer duration will be necessary; a total dose of 25–30 mg/kg is recommended, which will require treatment for about 1 month at a dosage of 1 mg/kg/day.[49] If the organism is relatively resistant to amphotericin B, or if eradication is unsuccessful with 1.0 mg/kg/day, the use of higher doses (up to 1.5 mg/kg/day) or the use of liposomal amphotericin B 5 mg/kg/day have been reported anecdotally. Whether liposomal amphotericin preparations are advantageous for all neonates with candidemia is unknown at this time. For the treatment of meningitis, the addition of flucytosine (50–150 mg/kg/day orally, in four divided doses) is recommended, but experience is limited in neonates. In some cases, intrathecal amphotericin B may be required to eradicate the organism.

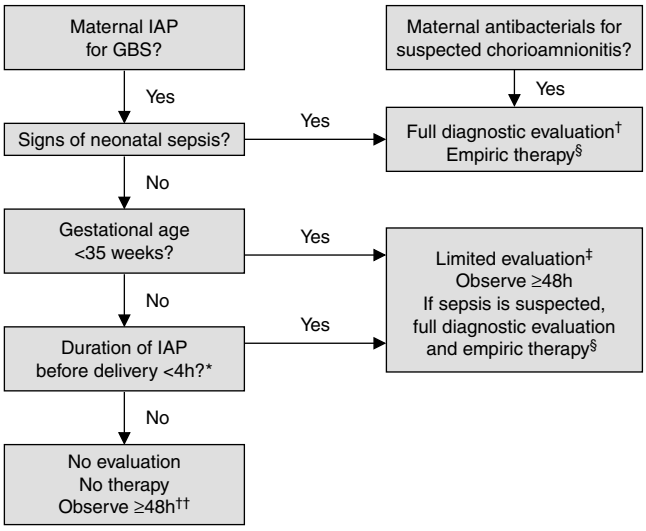

Fig. 2. Algorithm for the management of a newborn whose mother received IAP agents for prevention of early-onset GBS disease or suspected chorioamnionitis.[7] If no maternal intrapartum prophylaxis for GBS was administered despite an indication being present, data are insufficient on which to recommend a single management strategy. **CBC** = complete blood cell count; **GBS** = group B streptococcal; **IAP** = intrapartum prophylaxis. **†** = includes CBC and differential, blood culture, and chest radiograph if respiratory abnormalities are present. When signs of sepsis are present, a lumbar puncture, if feasible, should be performed; **§** = duration of therapy varies depending on results of blood culture, cerebrospinal fluid findings, if obtained, and the clinical course of the infant. If laboratory results and clinical course do not indicate bacterial infection, duration may be as short as 48 hours; **‡** = CBC with differential and blood culture; ***** = applies only to penicillin, ampicillin, or cefazolin, and assumes recommended administration regimens; **††** = a healthy-appearing infant who was ≥38 weeks' gestation at delivery, and whose mother received ≥4 hours of intrapartum prophylaxis before delivery, may be discharged home after 24 hours if other discharge criteria have been met and a person able to comply fully with instructions for home observation will be present. If any one of these conditions is not met, the infant should be observed in the hospital for at least 48 hours, and until criteria for discharge are achieved.

5. Conclusions

The presentation and treatments available for neonatal sepsis have changed over the years. Before the 1970s, survival of infants with severe respiratory distress syndrome was rare, as was the survival of very low birthweight infants. With the development of infant respiratory assistance equipment, intravenous alimentation, and selective intrapartum prophylactic antibacterials, the survival of low birthweight infants has increased dramatically. Along with these changes have come shifts in the presentation of neonatal sepsis to older infants, infections associated with life support devices, and etiologic micro-organisms that are frequently resistant to first-line antibacterials. Improved survival of unwell new-

born infants will follow the development of new adjunctive supports, therapies, and methods of preventing nosocomial infections.

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Correspondence and offprints: Dr *Robert S. Baltimore*, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520-8064, USA.