Neonatal Infections

Pathogenesis and Epidemiology

As many as 2% of fetuses are infected in utero, and up to 10% of infants have infections in the 1st mo of life.

(1) Infectious agents can be transmitted from the mother to the fetus or newborn infant by diverse modes. (2) Newborn infants are less capable of responding to infection because of 1 or more immunologic deficiencies. (3) Coexisting conditions often complicate the diagnosis and management of neonatal infections. (4) The clinical manifestations of newborn infections vary and include subclinical infection, mild to severe manifestations of focal or systemic infection. (5) Maternal infection that is the source of transplacental fetal infection is often undiagnosed during pregnancy because the mother was either asymptomatic or had nonspecific signs and symptoms at the time of acute infection. (6) A wide variety of etiologic agents infect the newborn, including bacteria, viruses, fungi, protozoa, and mycoplasmas. (7) Immature, very low birthweight (VLBW) newborns have improved survival but remain in the hospital for a long time in an environment that puts them at continuous risk for acquired infections.

Modes of Transmission and Pathogenesis

PATHOGENESIS OF INTRAUTERINE INFECTION

Intrauterine infection is a result of clinical or subclinical maternal infection with a variety of agents (cytomegalovirus [CMV], Treponema pallidum, Toxoplasma gondii, rubella virus, varicella virus, parvovirus B19) by hematogenous transplacental transmission to the fetus. Transplacental infection may occur at any time during gestation, and signs and symptoms may be present at birth or be delayed for months or years. Infection may result in early spontaneous abortion, congenital malformation, intrauterine growth restriction, premature birth, stillbirth, acute or delayed disease in the neonatal period, or asymptomatic persistent infection with sequelae later in life. In some cases, no apparent effects are seen in the newborn infant.

The timing of infection during gestation affects the outcome. First trimester infection may alter embryogenesis, with resulting congenital malformations (congenital rubella). Third trimester infection often results in active infection at the time of delivery (toxoplasmosis, syphilis). Infections that occur late in gestation may lead to a delay in clinical manifestations until some time after birth (syphilis).

Maternal infection is a necessary prerequisite for transplacental infection. For some etiologic agents (rubella), maternal immunity is effective and antibody is protective for the fetus. For other agents (CMV), maternal antibody may ameliorate the outcome of infection or have no effect.

PATHOGENESIS OF ASCENDING BACTERIAL INFECTION

In most cases, the fetus or neonate is not exposed to potentially pathogenic bacteria until the membranes rupture and the infant passes through the birth canal and/or enters the extraterine environment. The human birth canal is colonized with aerobic and anaerobic organisms that may result in ascending amniotic infection and/or colonization of the neonate at birth. Vertical transmission of bacterial agents that infect the amniotic fluid and/or vaginal canal may occur in utero or more commonly
during labor and/or delivery. Chorioamnionitis results from microbial invasion of amniotic fluid, often as a result of prolonged rupture of the chorioamniotic membrane. Amniotic infection may also occur with apparently intact membranes or with a relatively brief duration of membrane rupture. The term chorioamnionitis refers to the clinical syndrome of intrauterine infection, which includes maternal fever, with or without local or systemic signs of chorioamnionitis, (uterine tenderness, foul smelling vaginal discharge/amniotic fluid, maternal leukocytosis, maternal and/or fetal tachycardia). Chorioamnionitis may also be asymptomatic, only diagnosed by amniotic fluid analysis or pathologic examination of the placenta. Histologic chorioamnionitis is inversely related to gestational age at birth and directly related to duration of membrane rupture. Greater than 24 hr was once considered prolonged rupture of membranes because microscopic evidence of inflammation of the membranes is uniformly present when the duration of rupture exceeds 24 hr. At 18 hr of membrane rupture, however, the incidence of early-onset disease with group B streptococcus (GBS) increases significantly; longer than 18 hr is the appropriate cutoff for increased risk of neonatal infection. Difficult or traumatic delivery and premature delivery are also associated with an increased frequency of neonatal infection.

Bacterial colonization does not always result in disease. Factors influencing which colonized infant will develop disease are not well understood but include prematurity, underlying illness, invasive procedures, inoculum size, virulence of the infecting organism, the innate immune system and host response, and transplacental maternal antibodies. Aspiration or ingestion of bacteria in amniotic fluid may lead to congenital pneumonia or systemic infection, with manifestations becoming apparent before delivery (fetal distress, tachycardia), at delivery (perinatal asphyxia), or after a latent period of a few hours (respiratory distress, shock). Aspiration or ingestion of bacteria during the birth process may lead to infection after an interval of 1–2 days.

Resuscitation at birth, particularly if it involves endotracheal intubation, insertion of an umbilical vessel catheter, or both, is associated with an increased risk of bacterial infection. Explanations include the presence of infection at the time of birth or acquisition of infection during the invasive procedures associated with resuscitation.

**PATHOGENESIS OF LATE-ONSET POSTNATAL INFECTIONS**

After birth, neonates are exposed to infectious agents in the nursery or in the community. Postnatal infections may be transmitted by direct contact with hospital personnel, the mother, or other family members; from breast milk (HIV, CMV); or from inanimate sources such as contaminated equipment. The most common source of postnatal infections in hospitalized newborns is hand contamination of health care personnel. Most cases of meningitis result from hematogenous dissemination. Less often, meningitis results from contiguous spread as a result of contamination of open neural tube defects, congenital sinus tracts, or penetrating wounds from fetal scalp sampling or internal fetal electrocardiographic monitors. Abscess formation, ventriculitis, septic infarcts, hydrocephalus, and subdural effusions are complications of meningitis that occur more often in newborn infants than in older children.

**Etiology of Fetal and Neonatal Infection**

A number of agents may infect newborns in utero, intrapartum, or postpartum. Intrauterine transplacental infections of significance to the fetus and/or newborn include syphilis, rubella, CMV, toxoplasmosis, parvovirus B19, and varicella.
Although HSV, HIV, hepatitis B virus (HBV), hepatitis C virus, and tuberculosis (TB) can each result in transplacental infection, the most common mode of transmission for these agents is intrapartum during labor and delivery with passage through an infected birth canal (HIV, HSV, HBV) or postnatal from contact with an infected mother or caretaker (TB).

Any microorganism inhabiting the genitourinary or lower gastrointestinal tract may cause intrapartum and postpartum infection. The most common bacteria are GBS, enteric organisms, gonococci, and chlamydiae. The more common viruses are CMV, HSV, and HIV.

Congenital pneumonia may be caused by CMV, rubella virus, and T. pallidum and, less commonly, by the other agents producing transplacental infection. Microorganisms causing pneumonia acquired during labor and delivery include GBS, gram-negative enteric aerobes, *Listeria monocytogenes*, genital *Mycoplasma*, *Chlamydia trachomatis*, CMV, HSV, and *Candida* species.

The bacteria responsible for most cases of nosocomial pneumonia typically include staphylococcal species, gram-negative enteric aerobes, and occasionally, *Pseudomonas*. Fungi are responsible for an increasing number of systemic infections acquired during prolonged hospitalization of preterm neonates. Respiratory viruses cause isolated cases and outbreaks of nosocomial pneumonia. These viruses, usually endemic during the winter months and acquired from infected hospital staff or visitors to the nursery, include respiratory syncytial virus, parainfluenza virus, influenza viruses, and adenovirus. Respiratory viruses are the single most important cause of community-acquired pneumonia and are usually contracted from infected household contacts.

The most common bacterial causes of neonatal meningitis are GBS, *E. coli*, and *L. monocytogenes*. *S. pneumoniae*, other streptococci, non-typable *Haemophilus influenzae*, both coagulase-positive and coagulase-negative staphylococci, *Klebsiella*, *Enterobacter*, *Pseudomonas*, *T. pallidum*, and *Mycobacterium tuberculosis* may also produce meningitis.

**Epidemiology of Early- and Late-Onset Infections**

The terms early-onset infection and late-onset infection refer to the age at onset of infection in the neonatal period. Originally divided arbitrarily as infections occurring before and after 1 wk of life, it is more useful to separate early- and late-onset infections according to peripartum pathogenesis. Early-onset infections are acquired before or during delivery. Late-onset infections are acquired after delivery in the normal newborn nursery, neonatal intensive care unit (NICU), or the community. The age at onset depends on the timing of vertical transmission and the virulence of the infecting organism. Pyogenic early infections such as GBS are usually clinically apparent within the 1st 24 hr of life. Late, late-onset infections (onset after 1 mo of life) occur, particularly in VLBW preterm infants or term infants requiring prolonged neonatal intensive care for other chronic problems.

The incidence of GBS sepsis by intrapartum antibiotics.

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The incidence of meningitis in newborn infants is 0.2–0.4 cases per 1,000 live births and is higher in preterm infants. Bacterial meningitis may be associated with sepsis or may occur as a local meningeal infection. Meningitis develops in fewer than 20% of newborn infants with early-onset invasive bacterial infections. One third of VLBW infants with late-onset meningitis have negative blood cultures. The discordance in blood and cerebrospinal fluid (CSF) cultures suggests that meningitis may be underdiagnosed among VLBW infants and emphasizes the need for culture of CSF in such infants when late-onset sepsis is suspected.

PREMATURITY

The most important neonatal factor predisposing to infection is prematurity or LBW. Preterm infants have a 3- to 10-folds higher incidence of infection than full-term normal birthweight infants. Possible explanations include: (1) Maternal genital tract infection is considered to be an important cause of preterm labor, with an increased risk of vertical transmission to the newborn. (2) The frequency of intra-amniotic infection is inversely related to gestational age. (3) Premature infants have documented immune dysfunction. (4) Premature infants often require prolonged intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry or impair barrier and clearance mechanisms.

NOSOCOMIAL INFECTIONS

Nosocomial (hospital-acquired) infections are responsible for significant morbidity and late mortality in hospitalized newborns. Many define nosocomial infections as infections occurring after 3 days of life, which are not directly acquired from the mother's genital tract. The Centers for Disease Control and Prevention (CDC) defines a nosocomial infection as any infection occurring after admission to the NICU that was not transplacentally acquired. Rates of nosocomial infection in healthy term infants who are either rooming in with their mothers or staying in the well baby nursery are low (<1%). The majority of nosocomial infections occur in preterm or term infants who require intensive care. Risk factors for nosocomial infection in these infants include prematurity, LBW, invasive procedures, indwelling vascular catheters, parenteral nutrition with lipid emulsions, endotracheal tubes, ventricular shunts, alterations in the skin and/or mucous membrane barriers, frequent use of broad-spectrum antibiotics, and prolonged hospital stay. Most nosocomial infections are bloodstream infections associated with an intravascular catheter. Other serious infections are pneumonia, meningitis, omphalitis, and necrotizing enterocolitis.

VLBW infants (under 1,500 g birthweight) have nosocomial infection rates of 20–25%. Rates increase with decreasing gestational age and birthweight. The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network has reported rates of 43% for infants 401–750 g; 28% for those 751–1,000 g; 15% for those 1,001–1,250 g; and 7% for those 1,251–1,500 g. The National Nosocomial Infection Surveillance System (NNISS) monitors device-associated nosocomial infection rates. Rates are inversely related to birthweight and range from 11.4 infections/1,000 device days for infants under 1,000 g to 3.8 infections/1,000 device days for those over 2,500 g. The widespread differences in practice regarding the inclusion of lumbar puncture in the diagnostic evaluation of an infant with suspected sepsis make it more difficult to determine rates of late-onset meningitis.

Various bacterial and fungal agents colonize hospitalized infants, health care workers, and visitors. Pathogenic agents can be transmitted by direct contact or indirectly via
contaminated equipment, intravenous fluids, medications, blood products, or enteral feedings. Colonization of the infant’s skin, umbilicus, and respiratory or gastrointestinal tract with pathogenic agents often precedes the development of infection. Antibiotic use interferes with colonization by normal flora, thereby facilitating colonization with more virulent pathogens.

Coagulase-negative staphylococci are the most frequent neonatal nosocomial pathogens. Among a cohort of 6,215 VLBW infants in the NICHD Neonatal Research Network, gram-positive agents were associated with 70%, gram-negative with 18%, and fungi with 12% of cases of late-onset sepsis. Coagulase-negative staphylococcus, the single most common organism, was isolated in 48% of these infections. The emergence of nosocomial bacterial pathogens resistant to multiple antibiotics is a growing concern. Among NICU patients, methicillin-resistant S. aureus, vancomycin-resistant enterococci, and multidrug-resistant gram-negative pathogens are particularly alarming. Organisms responsible for all categories of neonatal sepsis and meningitis may change with time.

Viral organisms may also cause nosocomial infection in the NICU and include respiratory syncytial virus, varicella, influenza, rotavirus, and enteroviruses. For viral as well as bacterial agents, nursery outbreaks may occur in addition to individual cases. Hospital infection control policies are essential to prevent and/or contain nursery outbreaks.

The mean age at onset of the 1st episode of late-onset nosocomial sepsis is 2–3 wk, independent of the infecting pathogen. Nosocomial infections increase the risk of adverse outcomes, including prolonged hospitalization and mortality.

Active surveillance for nosocomial infection is essential in monitoring overall rates of infection, rates of infection with specific pathogens, and antibiotic susceptibility patterns and in identifying clusters of cases or true infectious outbreaks. Surveillance is based on the ongoing review of nursery infections and data from the microbiology laboratory; routine surveillance to detect colonization is not indicated. Culture results should indicate the bacterial isolate and the antimicrobial sensitivity pattern. Assessment of other microbial markers (biotype, serotype, DNA fingerprint) is helpful in epidemics. During epidemics, investigation of possible reservoirs of infection, modes of transmission, and risk factors is necessary. Identification of colonized infants and nursery personnel is also helpful.

Infections acquired after discharge from the nursery are usually community acquired. They have the same epidemiologic considerations as other community-acquired infections in infants and children, except for protection provided by maternal antibody.

**Diagnosis**

The maternal history may provide important information about maternal exposure to infection, maternal immunity (natural or acquired), maternal colonization, and obstetric risk factors (prematurity, prolonged ruptured membranes, maternal chorioamnionitis). Sexually transmitted infections (STIs) that infect a pregnant woman are of particular concern to the fetus and newborn because of the possibility for intrauterine or perinatal transmission. All pregnant women and their partners should be queried about a history of STIs. Women should also be counseled about the need for timely diagnosis and therapy for infections during pregnancy. The CDC recommends the following screening tests and appropriate treatment of infected
mothers: (1) All pregnant women should be offered voluntary and confidential HIV testing at the 1st prenatal visit. For women at high risk of infection during pregnancy (multiple sexual partners or STIs during pregnancy, intravenous drug use), repeat testing in the 3rd trimester is recommended. (2) A serologic test for syphilis should be performed on all pregnant women at the 1st prenatal visit. Repeat screening early in the 3rd trimester and again at delivery is recommended for women who had positive serology in the 1st trimester and for those at high risk for infection during pregnancy. (3) A serologic test for hepatitis B surface antigen (HBsAg) should be performed at the 1st prenatal visit and repeated late in pregnancy in those who are initially negative but at high risk for infection. (4) A maternal genital culture for C. trachomatis should be performed at the 1st prenatal visit. Young women (under 25 yr) and those at increased risk for infection (new or multiple partners during pregnancy) should be retested during the 3rd trimester. (5) A maternal genital culture for Neisseria gonorrhoeae should be performed at the 1st prenatal visit for women at risk and for those who live in areas with a high prevalence of gonorrhea. Repeat testing in the 3rd trimester is recommended for those at continued risk. (6) Evaluation for bacterial vaginosis should be considered at the 1st prenatal visit for asymptomatic women at high risk for preterm labor. (7) The CDC has recommended universal screening for rectovaginal GBS colonization of all pregnant women at 35–37 wk gestation and a screening-based approach to selective intrapartum antibiotic prophylaxis against GBS.

**SUSPECTED INTRAUTERINE INFECTION**

The acronym TORCH refers to toxoplasmosis, other agents (syphilis, etc.), rubella, CMV, and HSV. Although the term may be helpful in remembering some of the etiologic agents of intrauterine infection, the TORCH battery of serologic tests has a poor diagnostic yield, and appropriate specific diagnostic studies should be selected for each etiologic agent under consideration. CMV and HSV require culture or polymerase chain reaction (PCR) methods, whereas syphilis, toxoplasmosis, and rubella are diagnosed by specific serologic methods.

In most cases of suspected fetal infection, concern is not raised until the pregnant woman has been ill for several weeks or, in retrospect, after delivery. At this time, the maternal immune response to the suspected pathogen may no longer reflect an acute infection; that is, the specific IgM response is no longer detectable and the IgG response has already reached a plateau. Many of the pathogen-specific IgM serologic assays require considerable skill to perform and tend to be less reliable than the more common IgG assays. As a result, IgM assays can be either falsely negative or falsely positive.

Neonatal antibody titers are often difficult to interpret because IgG is acquired from the mother by transplacental passage and determination of neonatal IgM titers to specific pathogens is technically difficult to perform and not universally available. IgM titers to specific pathogens have high specificity but only moderate sensitivity; they should not be used to preclude infection. Paired maternal and fetal-neonatal IgG titers with higher newborn IgG levels or rising IgG titers during infancy may be used to diagnose some congenital infections (syphilis). Total cord blood IgM or IgA (neither are actively transported across the placenta to the fetus) and the presence of IgM-rheumatoid factor in neonatal serum are nonspecific tests for intrauterine infection.

If the likelihood of maternal infection with a known teratogenic agent is high, fetal ultrasound examination is recommended. If the examination demonstrates either a
physical abnormality or delayed growth for gestational age, examination of a fetal
blood sample may be warranted. Cordocentesis can provide a sufficient sample for
both total and pathogen-specific IgM assays or for PCR or culture. The total IgM
value is important because the normal fetal IgM level is <5 mg/dL. Any elevation in
total IgM may indicate an underlying fetal infection. Specific IgM antibody tests are
available for CMV, T. pallidum, parvovirus B19, and toxoplasmosis. IgM tests are
useful only when the results are strongly positive. A negative pathogen-specific IgM
finding does not rule out that pathogen as a cause of fetopathy.

If maternal serologic studies point to a specific pathogen, it is sometimes possible to
detect the organism in amniotic fluid or fetal blood (culture, PCR). Amniocentesis can
be performed and the fluid sent for analysis. The presence of CMV, Toxoplasma, or
parvovirus in amniotic fluid indicates that the fetus is infected and at high risk, but it
does not always mean that the fetus will have severe sequelae. In contrast, HSV and
varicella-zoster virus (VZV) are rarely isolated from amniotic fluid samples. CMV,
Toxoplasma, and parvovirus can also be identified from cordocentesis sampling.

Parvovirus does not grow in the cell cultures commonly available in the virology
laboratory. An IgM response is not always detectable in women with primary
infection. When fetal parvovirus infection is suspected, testing of fetal blood or
amniotic fluid by PCR is recommended in addition to testing for a specific IgM
response in the fetus. PCR may also be used for the diagnosis of toxoplasmosis,
CMV, HSV, rubella, and syphilis.

Neonatal infections with CMV, Toxoplasma, rubella, HSV, and syphilis present a
diagnostic dilemma because:

(1) their clinical features overlap and may initially be indistinguishable;

(2) disease may be inapparent;

(3) maternal infection is often asymptomatic;

(4) special laboratory studies may be needed;

(5) appropriate treatment of toxoplasmosis, syphilis, and HSV, which may reduce
significant long-term morbidity, is predicated on an accurate diagnosis.

Common shared features that should suggest the diagnosis of an intrauterine infection
include intrauterine growth restriction, hematologic involvement (anemia,
neutropenia, thrombocytopenia, petechiae, purpura), ocular signs (chorioretinitis,
cataracts, keratoconjunctivitis, glaucoma, microphthalmos), CNS signs
(microcephaly, aseptic meningitis, hydrocephaly, intracranial calcifications), other
organ system involvement (pneumonia, myocarditis, nephritis, hepatitis with
hepatosplenomegaly, jaundice), and nonimmune hydrops. Diagnostic studies in
newborns with suspected chronic intrauterine infection should specifically test for
each diagnostic consideration. Systemic infections with CMV, HSV, and
enteroviruses frequently involve the liver; if these infections are suspected, liver
function tests should be performed. Neonatal HSV meningitis may be confirmed by
isolation of the virus (or more often by PCR) from CSF or another site (skin, eye,
mouth).
SUSPECTED BACTERIAL OR FUNGAL INFECTIONS

Bacterial or fungal infection is diagnosed by isolating the etiologic agent from a normally sterile body site (blood, CSF, urine, joint fluid). Obtaining 2 blood culture specimens by venipuncture from different sites avoids confusion caused by skin contamination and increases the likelihood of bacterial detection. Samples should be obtained from an umbilical catheter only at the time of initial insertion. A peripheral venous sample should also be obtained when blood is drawn for culture from central venous catheters. Bacterial antigen detection kits are available for a variety of organisms (GBS, S. pneumoniae) but are infrequently used because they are not as sensitive as blood cultures and false-positive results can occur. They may be helpful in the diagnosis of meningitis in the presence of previous antibiotic therapy. DNA probes and PCR technology are available for a number of viral and bacterial agents.

Documentation of a positive blood culture is the first diagnostic criterion that must be met for sepsis. It is important to note, however, that some patients with bacterial infection may have negative blood cultures (“clinical infection”), and other approaches to identification of infection are needed. A variety of diagnostic markers of infection are being evaluated. Although the total WBC count and differential and the ratio of immature to total neutrophils have limitations in sensitivity and specificity, an immature-to-total neutrophil ratio of $\geq 0.2$ suggests bacterial infection. Neutropenia is more common than neutrophilia in severe neonatal sepsis, but neutropenia also occurs in association with maternal hypertension, preeclampsia, and intrauterine growth restriction. Thrombocytopenia is a nonspecific indicator of infection. Tests to demonstrate an inflammatory response include C-reactive protein, procalcitonin, haptoglobin, fibrinogen, inflammatory cytokines (including IL-6, IL-8, and TNF-α), and cell surface markers.

When the clinical findings suggest an acute infection and the site of infection is unclear, additional studies should be performed, including blood cultures, lumbar puncture, urine examination, and a chest x-ray. Urine should be collected by catheterization or suprapubic aspiration; urine culture for bacteria can be omitted in suspected early-onset infections because hematogenous spread to the urinary tract is rare at this point. Stains of endotracheal secretions in infants with early-onset pneumonia may demonstrate intracellular bacteria, and cultures may reveal either pathogens or upper respiratory tract flora. Careful examination of the placenta can be helpful in the diagnosis of both chronic and acute intrauterine infections.

Diagnostic evaluation is indicated for asymptomatic infants born to mothers with chorioamnionitis. The probability of neonatal infection correlates with the degree of prematurity and bacterial contamination of the amniotic fluid. In an asymptomatic term infant whose mother has chorioamnionitis, 2 blood cultures should be performed and presumptive treatment initiated. There is controversy over whether a lumbar puncture is necessary for all term infants with suspected early-onset sepsis. If the blood culture result is positive or if the infant becomes symptomatic, lumbar puncture should definitely be performed. If the mother has been treated with antibiotics for chorioamnionitis, the newborn's blood culture result may be negative, and the clinician must rely on clinical observation and other laboratory tests.

The diagnosis of pneumonia in a neonate is usually presumptive; microbiologic proof of infection is generally lacking because lung tissue is not easily cultured. Although some clinicians rely on the results of bacteriologic culture of material obtained from the trachea as “proof” of cause, interpretation of such cultures has many pitfalls.
These cultures often reflect upper respiratory tract commensal organisms and may have no etiologic significance. Even cultures performed on material obtained by bronchoalveolar lavage in a neonate are unreliable because the small bronchoscopes used in neonates cannot be protected from contamination as they are introduced into the distal airways. The diagnosis of meningitis is confirmed by examination of CSF and identification of a bacterium, virus, or fungus by culture, antigen, or the use of PCR. The importance of the lumbar puncture (LP) as part of the diagnostic evaluation of the neonate with suspected sepsis has been the subject of debate; clinical practice varies. For term infants with suspected early-onset sepsis, many clinicians start with a blood culture and a complete blood count, because 70–85% of term neonates with bacterial meningitis have positive results on blood culture. Examination and culture of CSF are undertaken in term infants with symptoms and/or bacteremia. Many clinicians defer the LP in severely ill infants with suspected early-onset infection because of the fear of respiratory and/or cardiovascular compromise. In these situations, blood culture should be performed and treatment initiated for presumed meningitis until lumbar puncture can be safely performed.

### Treatment

Treatment of suspected bacterial infection is determined by the pattern of disease and the organisms that are common for the age of the infant and the flora of the nursery. Once appropriate cultures have been obtained, intravenous or, less often, intramuscular antibiotic therapy should be instituted immediately. Initial empirical treatment of early-onset bacterial infections should consist of ampicillin and an aminoglycoside (usually gentamicin). Nosocomial infections acquired in a NICU are more likely to be caused by staphylococci, various Enterobacteriaceae, Pseudomonas species, or Candida species. Thus, an antistaphylococcal drug (methicillin or nafcillin for S. aureus or, more often, vancomycin for coagulase-negative staphylococci or methicillin-resistant S. aureus) should be substituted for ampicillin. A history of recent antimicrobial therapy or the presence of antibiotic-resistant infections in the NICU suggests the need for a different aminoglycoside agent (amikacin). When the history or the presence of necrotic skin lesions suggests Pseudomonas infection, initial therapy should be piperacillin, ticarcillin, carbenicillin, or ceftazidime and an aminoglycoside. The use of antifungal therapy should be considered in VLBW infants who have had previous antibiotic therapy, may have mucosal colonization with C. albicans, and are at high risk for invasive diseaseful to ensure therapeutic levels and minimize toxicity if administered for more than 2–3 days.

The sequelae of intrauterine infections with specific pathogens are described in their respective chapters. In general, complications of bacterial or fungal infections may be divided into those related to the inflammatory process per se and those that underlie neonatal problems such as respiratory distress and fluid and electrolyte abnormalities.

Complications of bacteremic infections include endocarditis, septic emboli, abscess formation, septic joints with residual disability, and osteomyelitis and bone destruction. Recurrent bacteremia is rare (<5% of patients). Candidemia may lead to vasculitis, endocarditis, and endophthalmitis, as well as abscesses in the kidneys, liver, lungs, and brain. Sequelae of sepsis may result from septic shock, DIC, or organ failure.

Mortality rates from the sepsis syndrome depend on the definition of sepsis. In adults, the mortality rate approaches 50%, and the rate in newborn infants is probably at least that high. Reported mortality rates in neonatal sepsis are as low as 10% because all
bacteremic infections are included in the definition. Several studies have documented that the sepsis case fatality rate is highest for gram-negative and fungal infections.

The case fatality rate for neonatal bacterial meningitis is between 20 and 25%. Many of these cases have associated sepsis. Risk factors for death or for moderate or severe disability include a duration of seizures for more than 72 hr, coma, necessity for the use of inotropic agents, and leukopenia. Immediate complications of meningitis include ventriculitis, cerebritis, and brain abscess. Late complications of meningitis occur in 40–50% of survivors and include hearing loss, abnormal behavior, developmental delay, cerebral palsy, focal motor disability, seizure disorders, and hydrocephalus. CT has demonstrated cerebritis, brain abscess, infarct, subdural effusions, cortical atrophy, and diffuse encephalomalacia in newborns surviving meningitis. A number of these sequelae may be encountered in infants with sepsis but without meningitis as a result of cerebritis or septic shock. Extremely low birthweight infants (<1,000 g) with sepsis are at increased risk for poor neurodevelopmental and growth outcomes in early childhood.

A number of intrauterine infections are preventable through maternal immunization, including hepatitis B, rubella, and VZV. CMV vaccines are under study. Toxoplasmosis is preventable with appropriate diet and avoidance of exposure to cat feces. Malaria during pregnancy can be minimized with chemoprophylaxis. Congenital syphilis is preventable by timely diagnosis and appropriate early treatment of infected pregnant women.

Neonatal tetanus can be prevented by maternal tetanus immunization and proper care of the umbilical cord. Aggressive management of suspected maternal chorioamnionitis with antibiotic therapy during labor, along with rapid delivery of the infant, reduces the risk of early-onset neonatal sepsis. Vertical transmission of GBS is significantly reduced by selective intrapartum chemoprophylaxis. Neonatal infection with Chlamydia can be prevented by identification and treatment of infected pregnant women. Mother-to-child transmission of HIV is significantly reduced by maternal antiretroviral therapy during pregnancy, labor, and delivery, cesarean section delivery prior to rupture of membranes, and antiretroviral treatment of the infant after birth.

**PREVENTION OF NOSOCOMIAL INFECTION**

Principles for the prevention of nosocomial infection include adherence to universal precautions with all patient contact, avoiding nursery crowding and limiting nurse-to-patient ratios, strict compliance with handwashing, meticulous neonatal skin care, minimizing the risk of catheter contamination, decreasing the number of venipunctures and heelsticks, reducing the duration of catheter and mechanical ventilation days, encouraging appropriate advancement of enteral feedings, providing education and feedback to nursery personnel, and ongoing monitoring and surveillance of nosocomial infection rates in the NICU.