48 Infectious Diseases, Part II

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This chapter includes discussions of selected viral, fungal, zoonotic, and mycobacterial infections.

VIRAL INFECTIONS

Human Parvovirus Infection

Human parvovirus (HPV) is a small DNA virus that replicates in human precursor red blood cells.

Primary infection most commonly occurs in school-aged children (5–15-years old) in the late winter and spring. At least 60% of adults are seropositive and immune to infection. Transmission is by respiratory spread and rarely by transfusion of blood from an acutely infected person. Vertical transmission during pregnancy is also possible. The secondary attack rate is approximately 50% with household contact and 20% to 30% with school exposure.

Most infections with HPV are asymptomatic. *Erythema infectiosum (slapped cheek or fifth disease) is the most recognizable form of infection.* This is characterized by an intensely erythematous rash on the cheeks, with mild systemic signs of illness developing approximately 1 week after a mild prodrome of fever, headache, and myalgias. A systemic, lace-like maculopapular rash, which may be pruritic, may also appear on the trunk and extremities (see Fig. 1.20). The rash is often evanescent for weeks, changing with varying temperature and exposure to sunlight.

The appearance of the rash in erythema infectiosum signifies an immune response to the infection. *Therefore, children with the rash are not contagious.*

Other manifestations of HPV infection include:

- Arthritis
- Transient aplastic crisis in children with hemolytic anemia
- Chronic bone marrow infection in immunodeficient persons
- Fetal hydrops

Transient aplastic crisis occurs in persons who depend on rapid red cell production and whose hemoglobin levels are low, such as those who have hemolytic anemia associated with sickle cell disease. The aplastic crisis typically lasts 7 to 10 days, and children may require red blood cell transfusions to prevent or treat congestive heart failure. Children with aplastic crisis are highly contagious, and should be placed in droplet isolation when hospitalized.

Chronic bone marrow failure can develop in an immunodeficient child, resulting in severe anemia and, at times, thrombocytopenia and neutropenia. Intravenous immunoglobulin therapy may be effective.

Human Herpesvirus 6 Infection

Human herpesvirus 6 (HHV-6) is a ubiquitous herpesvirus that is now known to be the cause of exanthem subitum (roseola). Like all herpesviruses, HHV-6 causes a primary infection and then establishes latency. The distribution of HHV-6 is worldwide and nonseasonal, and primary infection most often occurs in children between the ages of 6 months and 2 years. Almost all children are seropositive for the virus by the age of 2 years. Transmission is thought to be from asymptomatic salivary shedding.

Classic roseola develops in approximately 20% of children infected with HHV-6. It is characterized by a high fever that lasts for 3 to 7 days, often associated with toxicity, followed by an erythematous maculopapular rash. It is now clear that HHV-6 is a very common cause of *febrile illness without rash* or localizing signs in children aged 6 to 18 months. Other clinical features of HHV-6 infection include:

- Cervical and occipital adenopathy
- Respiratory symptoms and otitis media
- Gastrointestinal symptoms
- Bulging fontanelle
- Febrile seizures

Febrile seizures are thought to occur in approximately 15% of children who have a primary infection with HHV-6. Reactivation of the virus in immunocompromised persons may result in hepatitis, pneumonitis, and encephalitis.

Human Immunodeficiency Virus Infection in Children

Perinatal Transmission

Most cases of human immunodeficiency virus (HIV) infection in children are the result of perinatal transmission. The overall transmission rate from an infected mother to

her infant if neither the mother nor the infant is treated with antiretroviral therapy ranges from 14% to 27% in developed countries. Transmission can occur:

- *In utero* (30% of cases)
- At the time of delivery (70% of cases)
- Postpartum (rarely)

Transmission *in utero* is associated with early onset of disease in the infant and decreased survival. By definition, infants infected *in utero* have a blood culture positive for HIV or evidence of HIV DNA on polymerase chain reaction (PCR) testing within 7 days of birth. A large maternal viral load and a low count of $CD4^+$ lymphocytes in the mother are risk factors for *in utero* transmission.

Peripartum transmission accounts for most cases of infection. The clinical course of these infants is much more variable. By definition, they do not have evidence of HIV on blood culture or PCR testing within the first 7 days of life. Risk factors for peripartum transmission include advanced maternal disease (large viral load, low count of $CD4^+$ lymphocytes), prolonged rupture of membranes, obstetric complications, and first-born twin.

Postpartum transmission occurs mainly through breast-feeding, mostly by mothers with acute seroconversion. Breast-feeding remains the recommended method of feeding in developing countries, whereas in the United States, breast-feeding is contraindicated if the mother is infected, given the availability of safe alternatives and the risk for transmission.

The *perinatal transmission of HIV can be reduced by two thirds* when the pregnant mother is treated with oral zidovudine beginning in the second trimester of pregnancy and intravenous zidovudine during delivery, and the infant is treated with oral zidovudine for the first 6 weeks of life. The transmission rate can be reduced further when mothers are treated more aggressively with antiretroviral agents during pregnancy. Other approaches utilizing shorter duration of antiretroviral agents in the mother at the time of delivery, using nevirapine therapy alone or in combination with other antiretroviral agents in the mother, and a single dose of nevirapine in the infant at birth, offer some benefit, but are less effective than the 3-part zidovudine regimen or combination antiretroviral therapy during pregnancy. Cesarean delivery prior to rupture of membranes in mothers receiving zidovudine decreases the risk of perinatal transmission (2%), as compared to mothers on zidovudine therapy undergoing vaginal delivery (7%). However, the additional benefits of cesarean delivery in mothers who have low HIV viral loads (<1,000/mL) are unknown and may not outweigh the added risk of an operative delivery for the infected woman.

Diagnosis

HIV infection is difficult to diagnose in young infants because maternal antibodies may persist until 18 months of age. Therefore, tests that reveal the presence of HIV antibodies are *not* useful for infants. *The detection of HIV DNA by PCR is the most reliable test for diagnosing HIV infection in a young infant.* Culture of HIV from the blood may also be utilized but is less sensitive and more cumbersome to perform than PCR detection tests. Antibody tests, such as enzyme immunoassay and Western blot, are reliable in older children (>18 months) unless they are severely malnourished or hypogammaglobulinemic and unable to mount an antibody response.

Clinical Features

The clinical features of HIV infection in children include:

- Failure to thrive
- Recurrent invasive bacterial infections
- Chronic lymphadenopathy
- Parotitis
- Recurrent diarrhea
- Oral candidiasis
- Hepatosplenomegaly
- Opportunistic infections
- Central nervous system disease, including developmental delay
- Lymphoid interstitial pneumonitis

Common opportunistic infections in children infected with HIV include:

- *Pneumocystis* pneumonia (PCP)
- Candidiasis of the lower respiratory tract or esophagus
- Chronic diarrhea secondary to cryptosporidiosis or isosporiasis
- Cytomegalovirus disease and retinitis
- Severe herpes simplex virus and varicella-zoster virus infections
- Invasive fungal infections
- Mycobacterial infections

PCP is one of the most common serious opportunistic infection in HIV-infected infants and children. It generally develops between 3 and 6 months of life and may be the presenting manifestation of HIV infection. An acute presentation in which tachypnea and oxygen desaturation lead to respiratory failure is not uncommon in these infants. Mortality from PCP infection in HIV-infected infants is high despite specific therapy. Trimethoprim/sulfamethoxazole is the drug of choice for the treatment of PCP in infants and children.

General Care of the Child Infected with Human Immunodeficiency Virus

Children with HIV infection should be allowed and encouraged to attend school. The physician and family are not required to reveal the diagnosis to the school or teachers. All schools should implement routine infection control procedures for managing exposure to blood or blood-containing fluids, regardless of the source of the blood. Schools should

notify all parents when contagious diseases such as varicella and measles are reported in a school.

Most routine childhood vaccines should be administered to HIV-infected children at the appropriate age. Measles-mumps-rubella vaccine should be administered unless the child has immunosuppression, defined as a low count ($<500/mm^3$) or low percentage ($<15\%$) of $CD4^+$ lymphocytes. Varicella vaccine should be considered for the HIV-infected child who is asymptomatic or mildly symptomatic and whose count and percentage of $CD4^+$ lymphocytes are normal.

Prevention of Opportunistic Infections

PCP prophylaxis with trimethoprim/sulfamethoxazole is recommended for all infants with suspected or proven HIV infection:

- Prophylaxis should be initiated at 4 to 6 weeks of age for all HIV-exposed infants until the diagnosis is excluded.
- Children 1 to 5 years infected with HIV should continue PCP prophylaxis unless the count and percentage of $CD4^+$ lymphocytes is greater than 500 cells/uL or greater than 15%, respectively.
- Children 5 years and older, who are infected with HIV, should continue PCP prophylaxis unless the count and percentage of $CD4^+$ lymphocytes is greater than 200 cells/uL or greater than 15%.

Tuberculosis prophylaxis should be utilized for HIV-infected persons whose tuberculin skin test results are positive without evidence of active disease. Varicella-zoster immunoglobulin should be given to an HIV-infected child who is exposed to varicella. Immune globulin is indicated for the HIV-infected child who is exposed to measles, regardless of immunization status.

Antiretroviral Therapy

Antiretroviral therapy is indicated for most HIV-infected children. Recommendations regarding antiretroviral therapy are rapidly changing. In general, treatment is indicated for children who are symptomatic, have evidence of immunosuppression, or are less than 12 months of age. Treatment should consist of at least three antiretroviral agents, which is more effective than monotherapy. A protease inhibitor or a non-nucleoside reverse transcriptase inhibitor should be part of the regimen whenever possible. The desired goal of therapy is to decrease the viral load in the blood to undetectable levels.

FUNGAL INFECTIONS

Infections Caused by Dimorphic Pathogenic Fungi

Histoplasma, Blastomyces, and *Coccidioides* can cause localized and disseminated disease in normal and immunocompromised hosts, but most frequently cause asymptomatic infection. *Sporothrix schenckii* causes lymphocutaneous and cutaneous disease, usually without systemic signs and symptoms. The epidemiology and major clinical features of the dimorphic pathogenic fungi are summarized in Table 48.1.

Histoplasma capsulatum infection is endemic in the Ohio, Mississippi, and Missouri river valleys, and the skin test results of more than 50% of persons living in areas of

TABLE 48.1
EPIDEMIOLOGY AND CLINICAL FEATURES OF DIMORPHIC PATHOGENIC FUNGI

Organism	Epidemiology	Clinical Features of Symptomatic Infection
Histoplasma capsulatum	Ohio and Mississippi river valleys Bat or bird droppings; Caves	Acute influenza-like pulmonary illness Hilar adenopathy, mediastinal mass Disseminated disease in infants: fever, hepatosplenomegaly, adenopathy, pancytopenia
Blastomyces dermatitidis	Southeastern and central states Uncommon in children	Acute pneumonia Cutaneous and bone involvement Chronic forms common
Coccidioides immitis	Southwestern United States	Acute pneumonia Disseminated disease with meningitis Bone and cutaneous involvement Hypersensitivity reactions (erythema nodosum, arthralgias/arthritis)
Sporothrix schenckii	Missouri and Mississippi river valleys Contaminated rosebushes, barberry, grass species Disease of gardeners, farmers	Lymphocutaneous or cutaneous disease Papule at inoculation site Ulcers and nodules along lymphatic chain Satellite lesions

endemicity are positive for the organism. *H. capsulatum* can be found in caves, attics, old buildings, and animal roosts. Person-to-person or animal-to-human transmission does not occur.

Ninety-five percent of infections are asymptomatic. Symptomatic infection may present with pulmonary, cutaneous, or disseminated disease. Most pulmonary disease is mild and brief and may be accompanied by hilar adenopathy and a mediastinal mass. More severe disease can develop, and may be accompanied by erythema nodosum, hepatosplenomegaly, and migratory arthritis. Disseminated disease may be acute, subacute, or chronic and most commonly involves the liver, spleen, lymph nodes, adrenal glands, and bone marrow. Eighty percent of cases of disseminated disease occur in immunosuppressed hosts, especially patients with malignancy and HIV infection. An acute form of histoplasmosis, most common in infants, manifests as overwhelming infection associated with high fever, hepatosplenomegaly, lymphadenopathy, pneumonia, and pancytopenia.

The diagnosis can be established histologically by demonstrating the organism or culturing it from peripheral blood, bone marrow aspirates, or bronchoalveolar lavage fluid. Immunodiffusion and complement fixation serologic techniques are often utilized for diagnostic purposes.

Patients with chronic pulmonary involvement, disseminated disease, or complications of infection are treated with antifungal therapy. Amphotericin B remains the most frequently utilized agent for initial therapy.

Coccidioides immitis can be found in the soil in the southwestern United States, including New Mexico, Arizona, and the central valley of California, regions where infection is endemic. The organism is acquired most often by inhalation. Person-to-person transmission does not occur.

Sixty percent of infections are asymptomatic. Most symptomatic infections manifest as pulmonary or disseminated disease. Pulmonary disease can range from mild flu-like illness to severe pneumonia that generally presents with fever, cough, and chest pain. A transient maculopapular skin rash occurs early in the infection in about half of symptomatic children. Hypersensitivity reactions, especially erythema nodosum, arthritis, and arthralgias, may develop during the course of the infection. Pulmonary infiltrates with perihilar adenopathy and pleural effusions are common radiographic findings. Disseminated disease may develop a few weeks to a few months after the initial infection. The risk of disseminated disease is significantly higher in infants, Filipinos, African Americans, Hispanics, and immunocompromised persons. Meningitis is the most important feature of disseminated disease, and is associated with significant morbidity and mortality. *Coccidioides* meningitis can be acute or indolent, and may mimic tuberculous meningitis. Examination of the spinal fluid reveals a mononuclear pleocytosis with decreased levels of glucose and elevated levels of protein.

The diagnosis may require skin testing and serologic assays of blood and spinal fluid.

Antifungal therapy is reserved for persons who have severe pulmonary and disseminated infection or who are at increased risk for disseminated disease. Amphotericin B remains the drug of choice for most infections. Fluconazole may be helpful in meningitis, and has been utilized for suppressive therapy, because recurrence of meningitis is not uncommon.

Opportunistic Fungal Infections

Candida species are dimorphic yeast organisms that not uncommonly colonize the mouth and the gastrointestinal and genitourinary tracts of humans. Their ability to cause disease depends on the host's ability to deal with them. The organisms are common causes of nosocomial infections, especially in:

- Premature neonates
- Children with malignancies or in whom central venous catheters have been placed
- Organ transplant recipients
- Persons with immunodeficiency syndromes

Manifestations of infection are both local and disseminated.

Cryptococcus neoformans is an encapsulated budding yeast that can be found in avian habitats, especially pigeon roosting sites. This yeast causes disease almost exclusively in immunocompromised patients. A subacute or chronic meningitis is the most common manifestation of infection in children. Headaches, mental status changes, vomiting, and meningeal signs are common. Cerebrospinal fluid (CSF) examination reveals a lymphocytic pleocytosis with an increased protein level, decreased glucose level, and elevated opening pressures. India ink examination may demonstrate the capsule of the organism, and aids in the diagnosis. Latex particle agglutination in specimens of serum and CSF fluid is more sensitive and specific diagnostically. A combination of amphotericin B and flucytosine is used to treat cryptococcal meningitis.

Aspergillus species are found in air, soil, water, and decaying vegetation. They can cause hypersensitivity reactions and both noninvasive and invasive disease. Allergic bronchopulmonary aspergillosis occurs in atopic children with a history of asthma and cystic fibrosis. Wheezing, pulmonary infiltrates, eosinophilia, elevated levels of immunoglobulin E (IgE) and IgG antibodies to *A. fumigatus*, and elevated IgE concentrations are characteristic.

Predisposing factors for invasive aspergillosis include:

- Corticosteroid therapy
- Neutropenia
- Cytotoxic chemotherapy
- Acute organ rejection

Invasive pulmonary aspergillosis is an acute life-threatening infection characterized by invasion of blood vessels, infarction, necrosis, and hematogenous dissemination to the brain, heart, liver, and other organs. Sinusitis, ocular infection, and endocarditis are other manifestations of invasive *Aspergillus* infection.

The mucormycoses are a group of opportunistic fungal infections associated with vessel invasion, tissue necrosis, and thrombosis. The organisms are easily isolated from soil and commonly found on fruit and bread mold. Infection is limited to children with risk factors, including poorly controlled diabetes with acidosis, malignancy, neutropenia, uremia, and burns. Rhinocerebral disease is the most common form in children and manifests with pain, facial swelling and tenderness, proptosis, and altered mental status. Rhinocerebral disease is seen mainly in children with diabetic ketoacidosis and is associated with a high mortality rate. Cranial nerve involvement and cavernous sinus thrombosis are not uncommon. Treatment involves surgical resection of the involved tissue, correction of the metabolic abnormalities, and administration of amphotericin B.

TICK-BORNE AND ZOONOTIC INFECTIONS

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF), caused by *Rickettsia rickettsii*, is the most prevalent rickettsial disease in the United States. It is most common in the southeastern and south central regions of the United States. Ticks, wild animals, and dogs serve as reservoirs of infection, and a tick bite is the usual mode of transmission. Children younger than 15 years account for two thirds of cases, and the disease is most common in spring and summer.

R. rickettsii causes a vasculitis that clinically manifests with fever, headache, rash, myalgias, toxicity, and changes in mental status. *The rash can be maculopapular or petechial and usually begins peripherally on the wrist and ankle and spreads centripetally.* The palms and soles are commonly involved. Leukopenia, thrombocytopenia, anemia, elevated levels of aminotransferases and bilirubin, and hyponatremia are common laboratory findings.

A definitive diagnosis often cannot be made until the second week of illness because serologic assays are not sensitive early in the course of the disease. Fluorescent or peroxidase-tagged antibody tests of specimens from skin lesions can provide a rapid and highly specific diagnosis.

The differential diagnosis of RMSF includes:

- Meningococcemia
- Ehrlichiosis
- Atypical measles
- Enteroviral infection
- Henoch-Schönlein purpura
- Leptospirosis

Because the diagnosis often cannot be confirmed until the second week of the illness, a high index of suspicion and presumptive therapy is required. The institution of antimicrobial therapy within 6 days of the onset of illness is associated with low mortality. *Doxycycline* is the treatment of choice for children of any age. Severe morbidity and mortality from cardiac failure, vascular collapse, and renal failure can occur and are usually related to a delayed diagnosis.

Ehrlichiosis

Human monocytic ehrlichiosis is caused by *Ehrlichia chaffeensis*; human granulocytic ehrlichiosis is caused by *Anaplasma* (formerly *Ehrlichia*) *phagocytophila* and *Ehrlichia ewingii*. Both forms of ehrlichiosis are transmitted by a tick bite; known reservoirs include the white-tailed deer and white-footed mouse. *E. chaffeensis* infections occur mainly in the southeastern and south central regions of the United States; most cases of human granulocytic ehrlichiosis have occurred in Wisconsin, Minnesota, Connecticut, and New York. The infections generally develop in spring and summer, and adults appear to be at greatest risk, although infection with *E. chaffeensis* is common in children. Immunocompromised individuals appear to be at greatest risk for severe infection.

The clinical features of the two types of human *Ehrlichia* infection are similar and also quite similar to the clinical features of RMSF. Rash is less common in ehrlichiosis, whereas anemia, leukopenia, and thrombocytopenia are more common in ehrlichiosis than in RMSF.

The identification of intraleukocytic inclusions (morulae) in peripheral blood monocytes (Fig. 48.1) or granulocytes and acute and convalescent serologic titers are used to confirm the diagnosis.

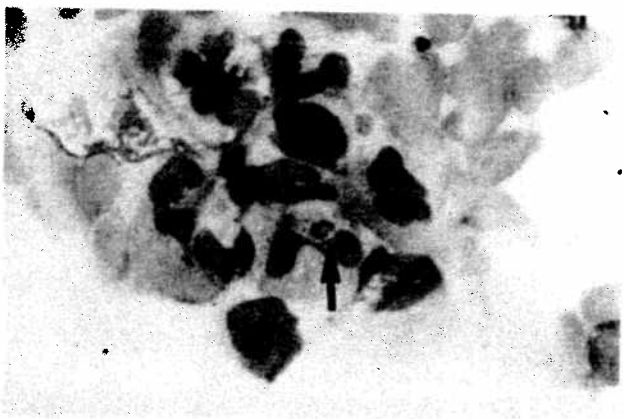

Figure 48.1 Peripheral blood smear showing an intraleukocytic inclusion (morula), characteristic of *Ehrlichia* infection. (See color insert.)

Doxycycline is the drug of choice for the treatment of ehrlichiosis in children of any age.

Tularemia

The etiologic agent of tularemia is *Francisella tularensis*, a small gram-negative coccobacillus. Important reservoirs of infection include rabbits, hares, and ticks. The most important route of transmission is a tick bite, but transmission can also result from direct contact with infected animals, aerosolization of the organism, or ingestion of contaminated water or meat. Infection is most common in the central states of Arkansas, Missouri, Tennessee, and Texas between the months of April and September.

The ulceroglandular form is the most common form of infection and is characterized by fever, regional lymphadenopathy, and skin lesions, usually an ulcer or papule at the site of inoculation. Pharyngitis, myalgias, vomiting, and hepatosplenomegaly may be present. Other forms of disease may also occur (glandular, pneumonic, oculoglandular), depending on the portal of entry of the organism.

A history of exposure to the organism (*tick bite, close contact with rabbits*) along with the characteristic clinical picture should lead the examiner to suspect tularemia. Serologic testing may be helpful diagnostically.

Streptomycin is the drug of choice, with gentamicin an effective alternative.

Leptospirosis

Leptospira organisms are spirochetes found in many wild and domestic mammals, including dogs, rats, and livestock. Transmission to humans results from contact with water and soil infected with the organism or from direct contact with infected animals. *Contaminated farm ponds and animal slaughterhouses* are settings where transmission occurs.

Subclinical infection is most common, but clinical illness can manifest in either an anicteric (milder) or icteric (severe) form. Anicteric disease accounts for 90% of cases and presents with an abrupt onset of fever, headache, myalgia, and subconjunctival suffusion; a second phase of disease often follows, characterized by fever, rash, uveitis, and meningitis. The organism can be recovered from the blood and spinal fluid in the first phase of illness, and from the urine in the second phase. Icteric leptospirosis, also known as *Weil syndrome*, occurs in 10% of cases and is characterized by severe illness with liver and renal failure, hemorrhage, and myocarditis.

Special laboratory techniques are required to recover the organism. Serologic assays are utilized in confirming the diagnosis.

Most cases are self-limited. Patients with severe disease requiring hospitalization should be treated with intravenous penicillin. Amoxicillin and doxycycline (for children 8 years of age and older) are alternative therapies for patients with mild disease.

Lyme Disease

Borrelia burgdorferi is the etiologic agent of Lyme disease. Infected ticks serve as the vectors of transmission. Reservoirs include the white-footed mouse, birds, lizards, and deer. In the United States, most cases of Lyme disease are seen in the northeastern states, upper Midwest (Minnesota and Wisconsin), and northern California. Most cases occur between April and October.

The clinical manifestations can be categorized as:

- *Early localized disease*, occurring 3 days to 4 weeks after a tick bite
- *Early disseminated disease*, developing 4 weeks to 8 weeks after infection
- *Late disease*, occurring 2 months to several years after infection

In *early localized disease, erythema migrans* (Fig. 48.2) develops at the site of the tick bite, which may or may not be recalled. Erythema migrans begins as an erythematous papule that expands to become an annular lesion measuring 3 to 15 cm, often with central clearing but occasionally with a vesicular center. Multiple small lesions may also be present. Biopsy of the lesion with special culture media often reveals the organism. The lesion is frequently confused with ringworm, a spider bite, or nummular eczema. Nonspecific symptoms, such as fever, malaise, and arthralgias, may be present at this stage. Antibodies to *B. burgdorferi* are consistently absent at this stage of infection and remain so in persons who receive treatment at this stage. Although most untreated persons recover completely without further disease, late manifestations of Lyme disease develop in approximately 20% of untreated cases.

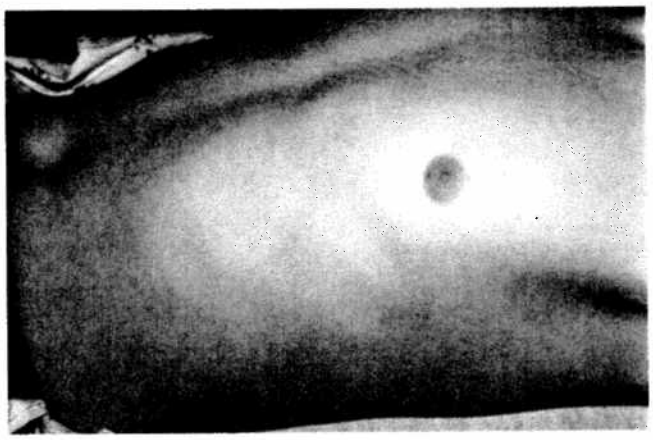

Figure 48.2 Erythema migrans in an adolescent with Lyme disease. Note the annular lesion with central clearing, characteristic of the rash. (See color insert.)

TABLE 48.2
TREATMENT OF LYME DISEASE IN CHILDREN

Stage of Illness	Treatment Recommendations
Early localized disease	
≥8 years old	Doxycycline 100 mg orally b.i.d. for 14–21 days, *or* Amoxicillin 25–50 mg/kg/day for 14–21 days
All ages	Amoxicillin as above (Cefuroxime axetil or erythromycin is alternative for penicillin-allergic children)
Early disseminated and late disease	
Meningitis	Ceftriaxone 75–100 mg/kg IV or IM for 30–60 days, *or* Penicillin G 300,000 U/kg/day IV for 30–60 days
Isolated cranial nerve palsy	Same oral regimen as for early disease but for 21–28 days
Carditis	Same as for meningitis, but for 14–28 days
Arthritis	Same oral regimen as for early disease but for 28 days
Persistent or recurrent arthritis	Ceftriaxone 75 mg/kg IV or IM for 14–21 days, *or* Penicillin G 300,000 U/kg/day IV for 14–28 days, *or* same oral regimen as for early disease

IV, intravenous; IM, intramuscular.

Features of *early disseminated disease* include:

- Multiple circular lesions
- Flu-like illness
- Neuritis (seventh cranial nerve palsy)
- Aseptic meningitis
- Carditis

Meningitis develops in a small percentage of untreated persons and manifests as headache, photophobia, and neck stiffness. The CSF fluid is aseptic with a lymphocytic pleocytosis, mildly elevated protein level, and normal glucose level. The diagnosis can be confirmed by demonstrating the intrathecal production of specific antibodies. *Seventh cranial nerve palsy* is more common than meningitis and is self-limited. Treatment does not alter the course of the neuritis but prevents late complications of infection. *Carditis* is quite uncommon, occurring in fewer than 5% of infected persons, and usually manifests as a transient alternating heart block.

Lyme *arthritis* is by far the most frequent manifestation of *late disease*. Lyme arthritis is characterized by involvement of the knee in more than 90% of cases and may be monoarticular or pauciarticular. The course may be chronic and intermittently flaring. Encephalopathy and polyneuropathies occur very rarely.

Early in the course of infection the diagnosis can be made clinically based on the appearance of the characteristic rash in a patient from an area in which Lyme disease is endemic. Routine serologic tests are *not* indicated in children with typical symptoms. Serologic tests can be helpful in diagnosing later stages of Lyme disease when the appropriate clinical features are present. This should be accomplished using an enzyme immunoassay and *confirmed* by Western immunoblot testing. When serologic tests are considered, only reference laboratories should be utilized. Serologic studies are not recommended for children with nonspecific symptoms whose probability of having Lyme disease is low, because these tests are nonspecific.

The treatment recommendations for children with Lyme disease are summarized in Table 48.2. When children are treated according to these recommendations, the outcome is excellent. Prolonged (beyond the periods specified in Table 48.2) or repeated courses of antimicrobial therapy for Lyme disease are *not* indicated. Chemoprophylaxis following a tick bite, even for people living in areas of endemicity, is not routinely recommended.

MYCOBACTERIAL DISEASE IN CHILDREN

Tuberculosis

Epidemiology

Mycobacterium tuberculosis, an acid-fast bacillus, is the usual etiologic agent of tuberculosis. Tuberculosis, although rare in the United States, can cause devastating infection, especially in infants and young children. Foreign-born and homeless persons, residents of correctional facilities, first-generation immigrants from high-risk countries, and people living in urban, low-income areas have the highest rates of infection. The organism is transmitted when droplet nuclei produced by an adult or postpubertal adolescent with cavitary, pulmonary disease are inhaled. Children with pulmonary tuberculosis are *not* usually contagious because the organism burden is small, they do not have cavitary disease, and cough is minimal or nonexistent. Therefore, for every child in whom tuberculosis is diagnosed, a contagious adult contact must be sought vigorously.

The development of a positive result of a tuberculin skin test, which normally occurs between 2 and 12 weeks after

initial infection, indicates likely *infection* in an individual. A person with a positive tuberculin skin test result who has no physical findings of disease and normal findings on a chest radiograph has *latent tuberculous infection*. Tuberculosis *disease* is defined by the presence of pulmonary or extrapulmonary manifestations of *M. tuberculosis* in a person with infection.

Clinical Manifestations

Most infected children are asymptomatic. The interval between infection and disease may be several weeks to many years. *Infants and postpubertal adolescents with recent exposure to infectious adults are at highest risk for progression to disease.* Other persons at high risk for progression to disease include recent skin test converters and those who are immunodeficient or who are receiving immunosuppressive therapy.

Early disease (1–6 months after infection) in children can present with lymphadenopathy and pulmonary or extrapulmonary manifestations. Hilar, mediastinal, cervical, and supraclavicular lymph nodes may be involved. Pulmonary findings may include lobar or segmental involvement, pleural effusion, or miliary disease (Fig. 48.3). Extrapulmonary disease includes miliary tuberculosis and meningitis. Late disease (months to years after infection) represents reactivation of latent infection and may involve the middle ear, mastoids, bones, joints, and skin.

Meningitis and miliary tuberculosis are especially common in infants and young children. *Tuberculous meningitis* is most commonly characterized by a gradual onset during 2 to 3 weeks. Fever, listlessness, and irritability are common initially. These are followed by nuchal rigidity, signs of increased intracranial pressure, cranial nerve palsies (especially of nerves III, VI, and VII), and seizures. Without therapy, neurologic progression to altered consciousness and posturing occurs. The CSF findings most commonly include white blood cells 50 to 500/mm^3 (neutrophils early, lymphocyte predominance later), hypoglycorrhachia, and an elevated protein level.

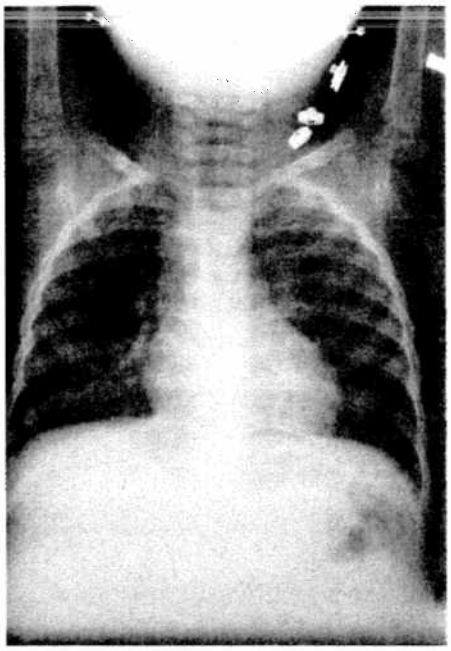

Figure 48.3 Miliary tuberculosis in an infant.

Diagnosis

Tuberculin skin testing is utilized to screen for tuberculosis infection in asymptomatic persons. The 5-tuberculin unit Mantoux intradermal skin test is the *only* recommended skin test and should be placed and interpreted by well-trained professionals. The American Academy of Pediatrics recommends that only infants, children, and adolescents with factors that put them at high risk for tuberculosis be tested on a regular basis. These include:

- Children infected with HIV or living with an HIV-infected person: annual testing.
- Incarcerated adolescents: annual testing.
- Children exposed to persons at high risk for tuberculosis, including homeless, incarcerated, or institutionalized persons: testing recommended every 2 to 3 years.
- Children whose parents have emigrated from an area of endemicity or who have no risk factors but live in an area where the prevalence of tuberculosis is high should be considered for skin testing at the time of school entry and before adolescence.

Children at highest risk for tuberculosis should undergo immediate tuberculin skin testing. These include:

- Children who have contact with persons having confirmed or suspected active tuberculosis
- Children with clinical or radiographic features of tuberculosis
- Immigrants from regions of endemicity
- Children returning from areas of endemicity

The size of the induration produced by a skin test, in addition to the specific epidemiologic and clinical factors of the patient being tested, determine how the test result is interpreted:

- *An induration of 15 mm or larger is considered a positive test result in children who are 4 years of age or older, and have no risk factors for tuberculosis.*
- An induration of 10 mm or larger is considered a positive test result in children who are younger than 4 years or have any chronic conditions, or whose exposure to tuberculosis disease is deemed to be increased.
- An induration of 5 mm or larger is considered a positive result in children who:
  - Have been in close contact with individuals who have had or suspected to have had tuberculosis
  - Are suspected of having tuberculous disease

- Are immunocompromised (including those with HIV infection)

Because approximately 10% of healthy children with culture-confirmed tuberculosis do not react to the tuberculin skin test, a negative test result never rules out tuberculosis. Previous vaccination with Bacillus Calmette-Guérin (BCG) vaccine should never be a contraindication to skin testing. The interpretation of skin test results in children previously vaccinated with BCG vaccine should be the same as in those who have not received BCG vaccine.

Children who have a positive tuberculin skin test result should be evaluated with a complete physical examination and chest radiography. Children who are well, have normal physical examination findings, and negative findings on chest radiography are considered to have latent tuberculous infection. In children suspected of having clinical or radiographic features of tuberculous disease, appropriate cultures and smears should be taken from suspected sources of infection. Early morning gastric aspirates provide the best chance of recovery of *M. tuberculosis* organisms in the young child with or suspected of having pulmonary tuberculosis. Pleural fluid, sputum, and CSF fluid can be cultured for *M. tuberculosis* as the clinical situation warrants.

Prophylaxis and Treatment

Children who are found to have latent tuberculosis infection and have never been treated with antituberculosis therapy should be given isoniazid prophylaxis for 9 months (12 months if coinfected with HIV). This effectively prevents progression to disease.

The treatment of tuberculosis disease should be based on a knowledge of the resistance patterns of the organism in the geographic area where the infection occurred. In general, three or four antituberculosis medications should be used initially to treat the disease. When drug resistance is suspected, four drugs should be used initially. Isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin are the drugs most commonly utilized for the treatment of tuberculosis. Ethambutol is less frequently utilized in infants and young children because it can cause a reversible optic neuritis. Monitoring children for optic neuritis requires monthly tests for visual acuity, visual fields, and red–green color discrimination, which is difficult if not impossible in young children. The adverse effects of the commonly utilized antituberculosis agents are listed in Table 48.3.

TABLE 48.3
ADVERSE EFFECTS AND DRUG INTERACTIONS OF COMMONLY UTILIZED ANTITUBERCULOUS AGENTS

Drug	Adverse Effects/Drug Interactions
Isoniazid	Hepatitis (rare in children) Peripheral neuritis (from inhibition of pyridoxine metabolism) Increases serum phenytoin levels
Rifampin	Orange discoloration of body fluids Influenza-like reaction Hepatitis (especially in combination with isoniazid) Decreases serum levels of cyclosporine, digoxin, and theophylline
Pyrazinamide	Hyperuricemia Hepatotoxicity
Streptomycin	Vestibular and auditory toxicity Renal toxicity
Ethambutol	Optic neuritis Gastrointestinal toxicity

Infection with Nontuberculous Mycobacteria

Cervical lymphadenitis is the most common clinical feature of nontuberculous mycobacterial infection in healthy children. *Mycobacterium avium* complex and *Mycobacterium scrofulaceum* are the species most often causing lymphadenitis. These infections most frequently occur in toddlers and are characterized by a subacute or chronic presentation. The insidious onset of a painless, firm, unilateral cervical adenitis is typical. Unlike tuberculosis, these infections are most common in children who live in rural areas and have no risk factors for tuberculosis. Tuberculin skin testing not infrequently reveals reactions of less than 10 mm. Treatment for these infections should consist of complete excision of the lymph node.

Disseminated infection with nontuberculous mycobacteria occurs almost exclusively in immunocompromised persons. Persons with altered cell-mediated immunity, including those with HIV infection, are at greatest risk. *M. avium* complex organisms are the nontuberculous mycobacteria most commonly isolated from these patients. Features of disseminated infection include fever, weight loss, diarrhea, and night sweats. Disseminated infection caused by *M. avium* complex requires therapy with multiple drugs.

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REVIEW EXERCISES

QUESTIONS

1. A 10-month-old infant is seen in your office with a history of fever up to 39.44°C (103°F) for the past 3 days. The child is playful, and the physical examination findings are unremarkable except for fever. No ill contacts are in the home and she does not attend a child care center. Of the following, the *most* likely virus causing this child's fever is:
a) Parvovirus
b) HHV-6
c) Herpes simplex virus
d) Epstein-Barr virus (EBV)
e) Cytomegalovirus

2. A 30-year-old teacher calls your office seeking advice. She is 10 weeks pregnant, and an outbreak of *slapped cheek* disease has occurred in her school, with some of the cases in her classroom. Which of the following would be the *best* advice to this teacher?
a) Advise her that the risk to the fetus is low.
b) Recommend ultrasonography to look for hydrops fetalis in the beginning of her third trimester.
c) Recommend referral to a high-risk obstetric service to follow serial ultrasonograms and prepare for *in utero* transfusions.
d) Recommend that she take a leave of absence from work until the outbreak is over.

3. A 6-month-old infant born to a woman with HIV infection is seen in your office with a 3-day history of upper respiratory infection symptoms and cough. A high fever has developed today, and on examination she is mildly tachypneic but has no other focal findings. Chest radiograph reveals a fine, diffuse infiltrate. Appropriate interventions at this point would include all of the following, *except*:
a) Obtaining a nasopharyngeal swab and performing direct fluorescent antibody testing for respiratory syncytial virus, adenovirus, parainfluenza virus, and influenza virus
b) Obtaining a blood culture from the infant and commencing ceftriaxone therapy
c) Administering high-dose intravenous trimethoprim/sulfamethoxazole to the infant
d) Sending a sample of the infant's serum for HIV antibody testing

4. A 3-year-old boy has had swollen lymph nodes in the left anterior cervical chain for several weeks. He has had low-grade fever but no other significant illness. He lives in a suburban area, is not in child care, and has no known exposure to anyone with tuberculosis. The induration of his purified protein derivative test measures 9 mm. His chest radiographic findings are normal. The *best* therapy for this child is:
a) Course of isoniazid, rifampin, and pyrazinamide
b) Biopsy of the node mass for culture
c) Course of clarithromycin and rifampin
d) Excision of the lymph node

5. A 3-year-old Filipino girl from Arizona presents with a 3-week history of headaches, increasing confusion, and fever. Her past medical history is unremarkable. Examination of her spinal fluid reveals 52 lymphocytes/mm^3, a protein level of 90 mg/dL, and a glucose level of 35 mg/dL. The organism *most* likely to cause this clinical picture is:
a) *C. immitis*
b) *H. capsulatum*
c) *S. schenckii*
d) *C. neoformans*

6. Fever, headache, severe myalgias, and a dark rash on the hands and arms develop in a 12-year-old boy during a 5-day period after his return from a trip to North Carolina. On physical examination, he is febrile at 39°C (102.2°F) and has meningismus and a petechial rash on his upper extremities bilaterally. Laboratory findings reveal a white blood cell count of 3,000/mm^3, platelet count of 90,000/mm^3, and serum sodium concentration of 129 mEq/L. Which is *true* concerning the diagnosis in this child?
a) Serum serologic testing performed early in the course of the illness is not likely to demonstrate evidence of this infection.
b) Ceftriaxone is effective therapy.
c) Bone marrow examination is required to reveal the cause.
d) Supportive therapy without antibiotics is the mainstay of management.

ANSWERS AND EXPLANATIONS

1. b.

Of the choices listed, HHV-6 is the most likely etiologic agent. Although HHV-6 is the etiologic agent of exanthem subitum (roseola), the virus is also a very common cause of fever in infants without a rash. In a study from Rochester, New York, HHV-6 was isolated from 14% of febrile infants younger than 2 years presenting to an emergency department. Parvovirus is uncommon in young infants and generally does not cause high fever. Herpes simplex virus is a very uncommon cause of fever without a source. EBV and cytomegalovirus may produce febrile illness without other findings in infants and children but are statistically less common than HHV-6.

2. a.

Infection with HPV can result in erythema infectiosum, also called *"slapped cheek" disease* because of the characteristic rash it produces. School-age children are at greatest risk for infection with this organism. HPV has also been associated with the development of nonimmune hydrops fetalis when it infects pregnant women. However, the risk for hydrops fetalis is estimated to be low given that approximately 50% of women are seropositive for HPV before pregnancy, the transmission rate to susceptible contacts is 30% to 50%, and the estimated risk for fetal loss once infection occurs is 2% to 10%. Children with erythema infectiosum are not contagious at the time the rash appears, and asymptomatic infection is very common. For all these reasons, excluding pregnant women from the workplace where HPV is prevalent is *not* recommended.

3. d.

For a 6-month-old infant born to an HIV-infected mother and presenting with fever and a diffuse pneumonitis, PCP should certainly be included in the differential diagnosis, and because of the potential severity and mortality of this infection, empiric high-dose trimethoprim/sulfamethoxazole therapy (trimethoprim component 20 mg/kg/day) is indicated. Viral agents, including respiratory syncytial virus, influenza virus, parainfluenza virus, and adenovirus, may cause fever and a diffuse pneumonitis in healthy and immunocompromised persons. It is important to include bacterial pneumonia in the differential diagnosis of any ill infant with pneumonia. In addition, HIV-infected infants frequently become infected with bacterial pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Therefore, therapy with ceftriaxone after appropriate blood cultures have been obtained is warranted. Serologic testing for HIV antibodies is not appropriate in this infant, whose mother is known to be infected with HIV, because placentally transferred maternal antibodies will be present. HIV infection can be diagnosed in the infant by utilizing nucleic acid detection assays (PCR DNA).

4. d.

Lymphadenitis caused by nontuberculous mycobacteria is the most likely diagnosis in this child, who has a subacute cervical lymphadenitis, a purified protein derivative test induration measuring 9 mm, a chest radiograph negative for Lymphadenitis, and no risk factors for tuberculosis. The best course of action when a patient has adenitis caused by nontuberculous mycobacteria is complete excision of the node. Medical therapy with antituberculous therapy is not effective; biopsy of the lymph node may be complicated by fistulous tract formation; although many species of nontuberculous mycobacteria are susceptible *in vitro* to clarithromycin and rifampin, no evidence indicates that treatment with these agents will be of benefit.

5. a.

The spinal fluid findings reveal a lymphocytic meningitis, which can be fungal or tuberculous. The epidemiologic clues to the diagnosis include the following: this girl is from Arizona, where *C. immitis* infection is endemic; she is a Filipino, so that her risk for disseminated disease with *C. immitis* is greatly increased, and she is previously healthy. *C. neoformans* can cause a similar clinical picture, but infection with this agent occurs almost exclusively in immunocompromised persons.

6. a.

Fever, myalgias, meningismus, and a petechial rash developing over a 5-day period in a child with a recent history of travel to the southeastern United States are likely to be manifestations of RMSF, caused by *R. rickettsii*. The differential diagnosis must take into account the possibility of meningococcemia, an acute life-threatening infection. The time course in this patient is more consistent with the diagnosis of RMSF; meningococcemia is more likely than RMSF to progress over a 12- to 24-hour period. The results of serum serologic testing performed early in the course of the illness are likely to be negative in patients with RMSF; they are often not positive until the second week of the illness. Therefore, therapy must be instituted based on a high index of suspicion. The outcome depends on the prompt institution of antimicrobial therapy (within 6 days of the illness). The drug of choice for children of all ages is doxycycline. Ceftriaxone may be added if the diagnosis of meningococcemia is suspected, but this agent has no activity against *R. rickettsii*.