

CHAPTER 96

Fever Without a Focus

Core body temperature is normally maintained within 1–1.5°C in a range of 37–38°C. Normal body temperature is generally considered to be 37°C (98.6°F; range, 97–99.6°F). Normal diurnal variation exists, with maximum temperature in the late afternoon. Rectal temperatures higher than 38°C (>100.4°F) generally are considered abnormal, especially if associated with other symptoms.

Normal body temperature is maintained by a complex regulatory system in the anterior hypothalamus. The development of fever begins with the release of endogenous pyrogens into the circulation as the result of infection, inflammatory processes, or malignancy. Microbes and microbial toxins act as **exogenous pyrogens** by stimulating release of **endogenous pyrogens**, including cytokines such as interleukin 1 (IL-1), IL-6, tumor necrosis factor, and interferons. These cytokines reach the anterior hypothalamus, liberating arachidonic acid, which is metabolized to prostaglandin E₂. Elevation of the hypothalamic thermostat occurs via a complex interaction of complement and prostaglandin E₂ production. Antipyretics (acetaminophen, ibuprofen, aspirin) inhibit hypothalamic cyclooxygenase, decreasing production of prostaglandin E₂. Aspirin is associated with Reye syndrome in children and is not recommended as an antipyretic. The response to antipyretics does not distinguish bacterial from viral infections.

The **pattern of fever** in children may vary, depending on age and the nature of the illness. Neonates may not have a febrile response and may instead be hypothermic despite significant infection, whereas older infants and children younger than 5 years of age may have an exaggerated febrile response with temperatures of up to 105°F (40.6°C) in response to either a serious bacterial infection or an otherwise benign viral infection. Fever to this degree is unusual in older children and adolescents and suggests a serious process. The fever pattern does not reliably distinguish fever caused by infectious microorganisms from that resulting from malignancy, autoimmune diseases, or drugs.

Children with fever without a focus present a diagnostic challenge that includes identifying bacteremia and sepsis. **Bacteremia**, the presence of bacteria in the bloodstream, may be primary or secondary to a focal infection. **Sepsis** is the systemic response to infection that is manifested by hyperthermia or hypothermia, tachycardia, tachypnea, and shock (see Chapter 40). Children with septicemia and signs of central nervous system (CNS) dysfunction (irritability, lethargy), cardiovascular impairment (cyanosis, poor perfusion), or disseminated intravascular coagulation (petechiae, ecchymosis) are readily recognized as **toxic appearing** or **septic**. Most febrile illnesses in children may be categorized as follows:

- **Fever of short duration** accompanied by localizing signs and symptoms, in which a diagnosis can often be established by clinical history and physical examination

- **Fever without localizing signs (fever without a focus)**, frequently occurring in children younger than 3 years of age, in which a history and physical examination fail to establish a cause
- **Fever of unknown origin (FUO)**, defined as daily fever for more than 14 days without an identified etiology despite history, physical examination, and routine laboratory tests, or after 1 week of intense evaluation

FEVER IN INFANTS YOUNGER THAN 2 MONTHS OF AGE

Fever or **temperature instability** in infants younger than 2 months of age is associated with a higher risk of **serious bacterial infections** than in older infants. These younger infants usually exhibit only fever and poor feeding, without localizing signs of infection. Most febrile illnesses in this age group are caused by common viral pathogens, but serious bacterial infections include **bacteremia** (most commonly caused by group B streptococcus [GBS], *Escherichia coli*, and *Listeria monocytogenes* in neonates; and *Streptococcus pneumoniae*, *Haemophilus influenzae* type b [Hib], nontyphoidal *Salmonella*, and *Neisseria meningitidis* in 1- to 3-month-old infants), **urinary tract infection (UTI)** (*E. coli*), **pneumonia** (*S. pneumoniae*, GBS, or *Staphylococcus aureus*), **meningitis** (GBS, *E. coli*, *L. monocytogenes*, *S. pneumoniae*, *N. meningitidis*, Hib, herpes simplex virus [HSV], enteroviruses), **bacterial diarrhea** (*Salmonella*, *Shigella*, *E. coli*), and **osteomyelitis** or **septic arthritis** (*S. aureus* or GBS).

Differentiating between viral and bacterial infections in young infants is difficult, but emerging studies demonstrate that doing so may be possible with the examination of inflammatory markers and gene expression profiles. Febrile infants younger than 2 months of age who appear ill, especially if follow-up is uncertain, and all febrile infants younger than 4 weeks of age should be admitted to the hospital for empirical antibiotics pending culture results. After blood, urine, and cerebrospinal fluid cultures are obtained, broad-spectrum parenteral antibiotics (typically ampicillin with a third-generation cephalosporin such as cefepime or ceftazidime, or with gentamicin) are administered. The choice of antibiotic depends on the pathogens suggested by localizing findings. The possibility of neonatal HSV should also be considered in febrile children younger than 4 weeks, and empirical acyclovir begun in those in whom neonatal HSV is a concern. Well-appearing febrile infants 4 weeks of age and older without an identifiable focus and with certainty of follow-up are at a low risk of developing a serious bacterial infection (0.8% develop bacteremia, and 2% develop a serious localized bacterial infection). Specific criteria identifying these low-risk infants include age older than 1 month, well appearing without a focus of infection, no history of prematurity or prior antimicrobial therapy, a white blood cell (WBC) count of 5,000–15,000/μL, normal urinalysis, procalcitonin below 1.7 ng/mL, and spinal fluid, if obtained, with less than 5–10 WBC/μL. Fecal leukocyte testing and chest radiograph can be considered in infants with diarrhea or respiratory signs. Low-risk infants may be followed as outpatients without empirical antibiotic treatment, or alternatively, may be treated with intramuscular ceftriaxone. Regardless of antibiotic treatment, close follow-up for at least 72 hours, including re-evaluation in 24 hours or immediately with any clinical change, is essential.

FEVER IN CHILDREN 2 MONTHS TO 3 YEARS OF AGE

A common problem is the evaluation of a febrile but well-appearing child 2 months to 3 years of age without localizing signs of infection. Although most of these children have self-limited viral infections, some have **occult bacteremia** (bacteremia without identifiable focus) or UTIs, and a few have severe and potentially life-threatening illnesses. It is difficult, even for experienced clinicians, to differentiate patients with occult bacteremia from those with benign illnesses.

Observational assessment is a key part of the evaluation. Descriptions of normal appearance and **alertness** include *child looking at the observer and looking around the room*, with eyes that are *shiny or bright*. Descriptions that indicate severe impairment include *glassy eyes* and *stares vacantly into space*. Observations, such as *sitting, moving arms and legs on table or lap*, and *sits without support* reflect normal motor ability, whereas *no movement in caregiver's arms* and *lies limply on table* indicate severe impairment. Normal behaviors, such as *vocalizing spontaneously*, *playing with objects*, *reaching for objects*, *smiling*, and *crying with noxious stimuli*, reflect **playfulness**; abnormal behaviors reflect **irritability**. Normally, crying children are **consolable** and *stop crying when held by*

the caregiver, whereas severe impairment is indicated by *continual cry despite being held and comforted*.

Children between 2 months and 3 years of age are at increased risk for infection with organisms with polysaccharide capsules, including *S. pneumoniae*, Hib, *N. meningitidis*, and nontyphoidal *Salmonella*. Effective phagocytosis of these organisms requires opsonic antibody. Transplacentally acquired maternal immunoglobulin G (IgG) initially provides immunity to these organisms, but as the maternal IgG gradually dissipates, the risk of infection increases. In the United States, use of conjugate Hib and *S. pneumoniae* vaccines has dramatically reduced the incidence of these infections, and determining the child's immunization status is essential to evaluate the risk of these infections. An approach to evaluating these children is outlined in Fig. 96.1.

Most episodes of fever in children younger than 3 years of age have a demonstrable source of infection elicited by history, physical examination, or a simple laboratory test. In this age group, the most commonly identified serious bacterial infection is a UTI. A blood culture to evaluate for occult bacteremia, and urinalysis and urine culture to evaluate for a UTI, should be considered for all children younger than 3 years of age with ongoing fever without localizing signs. Stool culture or molecular testing should be obtained in those with diarrhea

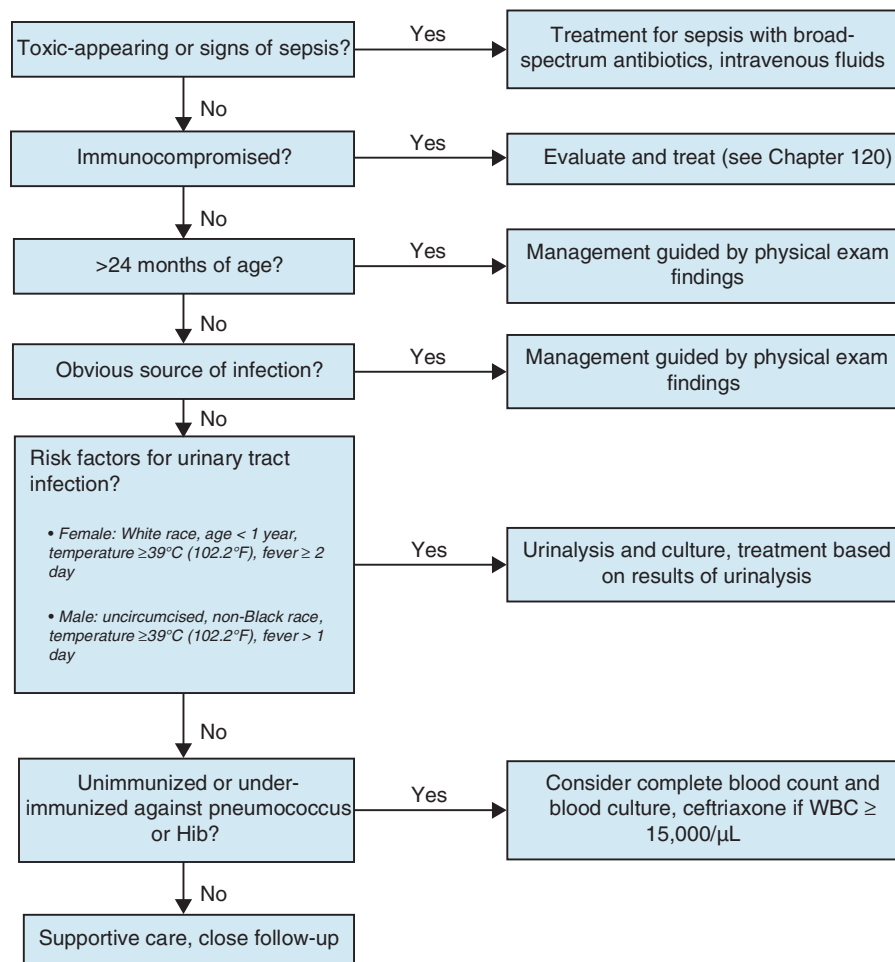


FIGURE 96.1 Algorithm for evaluation and management of fever in infants and children older than 2 months. Hib, *Haemophilus influenza* type b; WBC, white blood cell count. (Modified from Aronson PL, Neuman MI. Fever in the older child. In: Kliegman RM, St. Geme III JW, eds. *Nelson Textbook of Pediatrics*. 21st ed. Philadelphia: Elsevier; 2020 [fig. 203.3].)

marked by blood or mucus. Ill-appearing children should be admitted to the hospital and treated with empirical antibiotics.

Approximately 0.2% of well-appearing febrile children 3–36 months of age vaccinated against *S. pneumoniae* and Hib and without localizing signs have occult bacteremia. Signs associated with occult bacteremia include temperature of 102.2°F (39°C) or greater, WBC count of 15,000/mm³ or more, and elevated absolute neutrophil count, band count, erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP). No combination of demographic factors (socioeconomic status, race, gender, and age), clinical parameters, or laboratory tests in these children reliably predicts occult bacteremia. Occult bacteremia in otherwise healthy children is usually transient and self-limited but may progress to serious localizing infections. Well-appearing children usually are followed as outpatients without empirical antibiotic treatment. Regardless of antibiotic treatment, close follow-up for at least 72 hours, including re-evaluation in 24 hours or immediately with any clinical change, is essential. Children with a positive blood culture require immediate re-evaluation, repeat blood culture, consideration for lumbar puncture, and empirical antibiotic treatment.

Children with **sickle cell disease** have both impaired splenic function and properdin-dependent opsonization that places them at increased risk for bacteremia due to encapsulated

organisms, especially during the first 5 years of life. Children with sickle cell disease and fever who appear seriously ill, have a temperature of 104°F (40°C) or above, or WBC count less than 5,000/mm³ or more than 30,000/mm³ should be hospitalized and treated empirically with antibiotics. Other children with sickle cell disease and fever should have blood culture, empirical treatment with ceftriaxone, and close outpatient follow-up. Osteomyelitis resulting from *Salmonella* or *S. aureus* is more common in children with sickle cell disease; blood culture is not always positive in the presence of osteomyelitis.

FEVER OF UNKNOWN ORIGIN

FUO is defined as a daily temperature greater than 100.4°F (38°C) lasting for more than 14 days without an obvious cause or a fever documented by a health care provider for which the cause could not be identified after at least 8 days of workup despite a complete history, physical examination, and routine screening laboratory evaluation. It is important to distinguish persistent fever from recurrent or periodic fevers, which often represent serial acute illnesses.

The initial FUO evaluation requires a thorough history and physical examination supplemented with a few screening laboratory tests (Fig. 96.2). Additional laboratory and imaging tests are

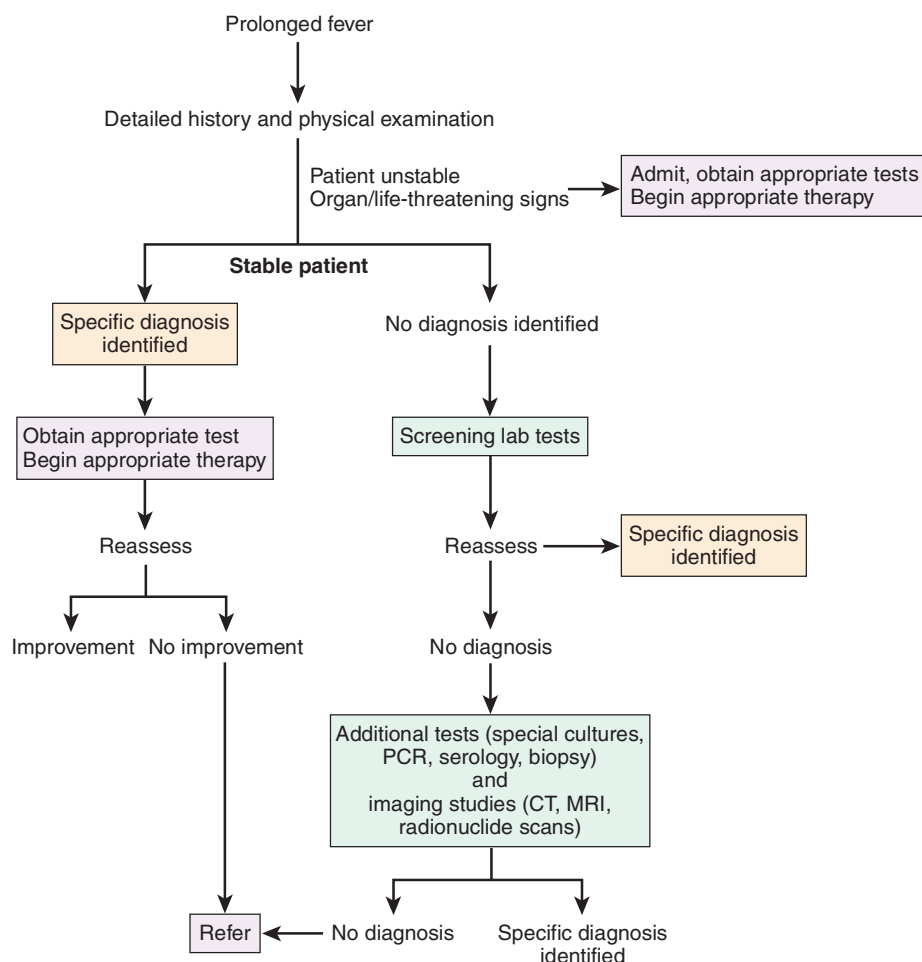


FIGURE 96.2 Approach to the evaluation of fever of unknown origin in children. Screening laboratory tests include complete blood count with and differential, erythrocyte sedimentation rate, C-reactive protein, basic metabolic panel, hepatic transaminase levels, urinalysis, and cultures of urine and blood. Chest radiograph should be included for patients with pulmonary symptoms. CT, Computed tomography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PET, position emission tomography; WBC, white blood cells.

guided by abnormalities on initial evaluation. Important historical elements include the impact the fever has on the child's health and activity; weight loss; the use of drugs, medications, or immunosuppressive therapy; a history of unusual, severe, or chronic infection suggesting immunodeficiency (see [Chapter 72](#)); immunizations; exposure to unprocessed or raw foods; a history of pica and exposure to soil-borne or water-borne organisms; exposure to industrial or hobby-related chemicals; blood transfusions; domestic or foreign travel; exposure to animals; exposure to ticks or mosquitoes; ethnic background and family history; recent surgical procedures or dental work; tattooing and body piercing; and sexual activity.

The etiology of most occult infections causing FUO is an unusual presentation of a common disease. Sinusitis, endocarditis, intraabdominal abscesses (perinephric, intrahepatic, subdiaphragmatic), and CNS lesions (tuberculoma, cysticercosis, abscess, toxoplasmosis) may be relatively asymptomatic. **Infections** are the most common cause of FUO in children, accounting for approximately 40–50% of FUO episodes, followed by **inflammatory diseases** (about 20% of all episodes), **malignancy** (about 10% of all episodes), and other etiologies ([Table 96.1](#)). Approximately 15% of children with FUO have no diagnosis. Fever eventually resolves in many of these cases, usually without sequelae, although some may develop definable signs of rheumatic disease over time. Common infections causing FUO in patients with known or newly diagnosed **immunodeficiency** include viral hepatitis, Epstein-Barr virus, cytomegalovirus, *Bartonella henselae*, ehrlichiosis, *Salmonella*, and tuberculosis.

Factitious fever or fever produced or feigned intentionally by the patient (**Munchausen syndrome**) or the parent of

a child (**Munchausen syndrome by proxy**) is an important consideration, particularly if family members are familiar with health care practices (see [Chapter 22](#)). Fever should be recorded in the hospital by a reliable individual who remains with the patient when the temperature is taken. Continuous observation over a long period and repetitive evaluation are essential.

Screening tests for FUO include complete blood count with WBC and differential, ESR, CRP, procalcitonin, basic metabolic panel, hepatic transaminase levels, urinalysis, and cultures of urine and blood. Chest radiograph should be included for patients with pulmonary symptoms. Additional tests for FUO may include throat culture, stool culture or molecular testing, tuberculin skin test or interferon- γ release assay, HIV, Epstein-Barr virus, cytomegalovirus, and *B. henselae* antibodies. Consultation with infectious disease, immunology, rheumatology, or oncology specialists should be considered. Further tests may include lumbar puncture for cerebrospinal fluid analysis and culture; evaluation for rheumatic disease with antinuclear antibody, rheumatoid factor, ferritin, and serum complement (C3, C4, CH₅₀); uric acid and lactate dehydrogenase; computed tomography or magnetic resonance (often with positron emission tomography [PET] scan) imaging of the chest, abdomen, and head; and bone marrow biopsy for cytology and culture.

PEARLS FOR PRACTITIONERS

See *Infectious Diseases: Pearls for Practitioners* at the end of this section.

TABLE 96.1 Causes of Fever of Unknown Origin in Children

INFECTIONS	
Localized Infections	
Abscesses: abdominal, brain, dental, hepatic, pelvic, perinephric, rectal, subphrenic, splenic, periappendiceal, psoas, pyomyositis	<i>Francisella tularensis</i> (tularemia)
Cholangitis	Gonococcemia (chronic)
Discitis	Leptospirosis
Infective endocarditis	<i>Listeria monocytogenes</i> (listeriosis)
Mastoiditis	Lyme disease (<i>Borrelia burgdorferi</i>)
Osteomyelitis	Lymphogranuloma venereum
Pneumonia	Meningococcemia (chronic)
Pyelonephritis	<i>Mycoplasma pneumoniae</i>
Septic arthritis	Psittacosis
Sinusitis	Relapsing fever (<i>Borrelia recurrentis</i> , other <i>Borrelia</i>)
Bacterial Diseases	
Actinomycosis	Salmonellosis
<i>Bartonella henselae</i> (cat-scratch disease)	<i>Spirillum minus</i> (rat-bite fever)
Brucellosis	<i>Streptobacillus moniliformis</i> (rat-bite fever)
<i>Campylobacter</i>	Syphilis
<i>Chlamydia</i> / <i>Chlamydophila</i>	Tuberculosis
	Whipple disease
	Yersiniosis
Viral Diseases	
	Cytomegalovirus

Continued

TABLE 96.1 Causes of Fever of Unknown Origin in Children —cont'd

Hepatitis viruses	MALIGNANCIES
HIV (and associated opportunistic infections)	Atrial myxoma
Infectious mononucleosis (Epstein-Barr virus)	Cholesterol granuloma
Rickettsial Diseases	Ewing sarcoma
Anaplasmosis	Hepatoma
Ehrlichiosis	Hodgkin disease
Q fever (<i>Coxiella burnetii</i>)	Inflammatory pseudotumor
Rocky Mountain spotted fever	Leukemia
Tick-borne typhus	Lymphoma
Fungal Diseases	Neuroblastoma
Blastomycosis (extrapulmonary)	Pheochromocytoma
Coccidioidomycosis (disseminated)	Wilms tumor
Histoplasmosis (disseminated)	MISCELLANEOUS
Parasitic Diseases	Addison disease
Extraintestinal amebiasis	Anhidrotic ectodermal dysplasia
Baylisascaris	Autonomic neuropathies
Babesiosis	Castleman disease
Malaria	Chronic active hepatitis
Toxoplasmosis	Cyclic neutropenia
Trichinosis	Diabetes insipidus (central and nephrogenic)
Trypanosomiasis	Fabry disease
Visceral larva migrans (<i>Toxocara</i>)	Factitious fever
INFLAMMATORY DISEASES	Familial dysautonomia
Autoimmune lymphoproliferative syndrome	Familial Mediterranean fever
Behçet syndrome	Granulomatous hepatitis
Chronic recurrent multifocal osteomyelitis	Hemophagocytic syndromes
Drug fever	Hypertriglyceridemia
Granulomatosis with polyangiitis	Hypothalamic-central fever
Hypersensitivity pneumonitis	Ichthyosis
Juvenile dermatomyositis	Infantile cortical hyperostosis
Juvenile idiopathic arthritis (systemic onset, Still disease)	Kikuchi-Fujimoto disease
Inflammatory bowel disease (Crohn disease, ulcerative colitis)	Metal fume fever
Kawasaki disease	Pancreatitis
Polyarteritis nodosa	Periodic fever syndromes
Rheumatic fever	Poisoning
Sarcoidosis	Postoperative (pericardiotomy, craniectomy)
Serum sickness	Pulmonary embolism
Systemic lupus erythematosus	Thrombophlebitis
Weber-Christian disease	Thyrotoxicosis

Modified from Steenhoff AP. Fever of unknown origin. In: Kliegman RM, St Geme III JW, eds. Nelson Textbook of Pediatrics. 21st ed. Philadelphia: Elsevier; 2020.

CHAPTER 97

Infections Characterized by
Fever and Rash

Rashes are a common manifestation of many infections; this chapter describes five common childhood viral exanthems characterized by fever and rash. Rash distribution and appearance provide important clues to the differential diagnosis, including other infectious agents (Table 97.1).

MEASLES (RUBEOLA)

Etiology

Measles (rubeola) is highly contagious and is caused by a single-stranded RNA paramyxovirus with one antigenic type. Humans are the only natural host. The measles virus infects the upper respiratory tract and regional lymph nodes and is spread systemically during a brief, low-titer primary viremia. A secondary viremia occurs within 5–7 days as virus-infected monocytes spread the virus to the respiratory tract, skin, and other organs. The virus is present in respiratory secretions, blood, and the urine of infected individuals. It is transmitted by droplets or via the airborne route and is extremely contagious. Infected persons are contagious from 1–2 days before onset of symptoms—from about 5 days before to 4 days after the appearance of rash; immunocompromised persons can have prolonged excretion of contagious virus.

Epidemiology

Measles remains endemic in regions of the world where measles vaccination is not readily available and is responsible for about 20 million infections and 150,000 deaths annually. There have typically been fewer than 100 cases of measles reported annually in the United States; however, outbreaks have occurred resulting from imported virus after international travel, and in 2019 there were almost 1,300 measles cases in the United States, the highest number in a decade. Infections of nonimmigrant children may occur during outbreaks among those too young to be vaccinated or in communities with low immunization rates. Most young infants are protected by transplacentally acquired maternal antibody until the end of their first year.

Clinical Manifestations

Measles infection is divided into four phases: incubation, prodromal (catarrhal), exanthematous (rash), and recovery. The incubation period is 8–12 days from exposure to symptom onset and a mean of 14 days (range: 7–21) from exposure to rash onset. The manifestations of the 3-day prodromal period are cough, coryza, conjunctivitis, and the pathognomonic **Koplik spots** (gray-white, sand-grain-sized dots on the buccal mucosa opposite the lower molars) that last 12–24 hours. The conjunctiva may reveal a characteristic transverse line of inflammation along the eyelid margin (**Stimson line**). The classic symptoms of cough, coryza, and conjunctivitis continue to occur during the secondary viremia of the exanthematous phase, which often is accompanied by high fever

TABLE 97.1 Differential Diagnosis of Fever and Rash

LESION	PATHOGEN OR DISEASE
MACULAR OR MACULOPAPULAR RASH	
Viruses	Adenovirus
	Measles
	Rubella
	Roseola (HHV-6 or HHV-7)
	Erythema infectiosum (fifth disease, parvovirus B19)
	Epstein-Barr virus
	Enteroviruses
	Parechoviruses
	HBV (papular acrodermatitis or Gianotti-Crosti syndrome)
	HIV
Bacteria	Erythema marginatum (rheumatic fever)
	Scarlet fever (group A streptococcus)
	Erysipelas (group A streptococcus)
	<i>Arcanobacterium haemolyticum</i>
	Secondary syphilis
	Leptospirosis
	<i>Pseudomonas aeruginosa</i>
	Meningococcal infection (early)
	<i>Salmonella typhi</i> (typhoid fever, “rose spots”)
	Lyme disease (erythema migrans)
Rickettsiae	<i>Mycoplasma pneumoniae</i>
	Rocky Mountain spotted fever (early)
	Typhus (scrub, endemic)
	Ehrlichiosis
	Kawasaki disease
	Rheumatoid arthritis
	Drug reaction
DIFFUSE ERYTHRODERMA	
Bacteria	Scarlet fever (group A streptococcus)
	Staphylococcal scalded skin syndrome
	Toxic shock syndrome (<i>Staphylococcus aureus</i> , group A streptococcus)
Fungi	<i>Candida albicans</i>
Other	Kawasaki disease
URTICARIAL RASH	
Viruses	Epstein-Barr virus
	HBV
	HIV
Bacteria	<i>M. pneumoniae</i>
	Group A streptococcus
Other	Drug reaction
	Serum sickness
VESICULAR, BULLOUS, PUSTULAR	
Viruses	Herpes simplex viruses
	Varicella-zoster virus
	Coxsackievirus

(Continued)

TABLE 97.1 Differential Diagnosis of Fever and Rash—cont'd

LESION	PATHOGEN OR DISEASE
Bacteria	Staphylococcal scalded skin syndrome
	Staphylococcal bullous impetigo
	Group A streptococcal crusted impetigo
Rickettsiae	Rickettsialpox
Other	Toxic epidermal necrolysis
	Erythema multiforme
	Stevens-Johnson syndrome
PETECHIAL-PURPURIC	
Viruses	Adenovirus
	Atypical measles
	Congenital rubella
	Congenital cytomegalovirus
	Enterovirus
	Papular-purpuric gloves and socks (parvovirus B19)
	HIV
	Hemorrhagic fever viruses
	SARS-CoV-2
Bacteria	Sepsis (meningococcal, gonococcal, pneumococcal, <i>Haemophilus influenzae</i> type b)
	Infective endocarditis
	Ecthyma gangrenosum (<i>P. aeruginosa</i>)
	<i>Vibrio vulnificus</i>
Rickettsiae	Rocky Mountain spotted fever
	Epidemic typhus
	Ehrlichiosis
Other	Vasculitis
	Thrombocytopenia
	Henoch-Schönlein purpura
	Acute hemorrhagic edema of infancy
	Malaria
NECROTIC ESCHAR	
Bacteria	<i>Bacillus anthracis</i>
	<i>Francisella tularensis</i>
Fungi	<i>Aspergillus</i> , <i>Mucor</i>
ERYTHEMA NODOSUM	
Viruses	Epstein-Barr virus
	HBV
Bacteria	Group A streptococcus
	<i>Mycobacterium tuberculosis</i>
	<i>Yersinia</i>
	Cat-scratch disease (<i>Bartonella henselae</i>)
Fungi	Coccidioidomycosis
	Histoplasmosis
Other	Sarcoidosis
	Inflammatory bowel disease
	Estrogen-containing oral contraceptives
	Systemic lupus erythematosus
	Behçet disease

HBV, Hepatitis B virus; HHV, human herpesvirus.

(40–40.5°C [104–105°F]). The macular rash begins on the head (often above the hairline) and spreads over most of the body in a cephalad-to-caudal pattern over 24 hours. Areas of the rash are often confluent. The rash fades in the same pattern, and illness severity is related to the extent of the rash. It may be petechial or hemorrhagic (**black measles**). As the rash fades, it undergoes brownish discoloration and desquamation. Generalized lymphadenopathy may be noted with the rash, with cervical nodes being most prominent. Mesenteric lymphadenopathy with abdominal pain may be noted with the rash. Otitis media, pneumonia, and diarrhea are more common in infants. Liver involvement is more common in adults.

The term **modified measles** describes mild cases of measles occurring in persons with partial protection against measles. Modified measles occurs in persons vaccinated before 12 months of age or with co-administration of immune serum globulin, in infants with disease modified by transplacentally acquired antibody, or in persons receiving immunoglobulin.

Laboratory and Imaging Studies

Routine laboratory findings are nonspecific and do not aid in diagnosis. Leukopenia is characteristic. In patients with acute encephalitis, the cerebrospinal fluid reveals an increased protein, a lymphocytic pleocytosis, and normal glucose levels. Measles virus culture is not generally available, though identification of measles RNA via reverse transcriptase-polymerase chain reaction (PCR) may be available through state public health departments or the Centers for Disease Control and Prevention (CDC). Serologic testing for immunoglobulin M (IgM) antibodies that appear within 1–2 days of the rash and persist for 1–2 months in unimmunized persons confirms the clinical diagnosis, though IgM antibodies may be present only transiently in immunized people. Suspected cases should be **reported immediately** to the local or state health department.

Differential Diagnosis

The constellation of fever, rash, cough, and conjunctivitis is highly suggestive of measles. Koplik spots are pathognomonic but not always present at the time the rash is most pronounced. Confirmation is by diagnostic antibody increases in acute and convalescent sera. Measles must be differentiated from rubella, roseola, enteroviral or adenoviral infection, infectious mononucleosis, toxoplasmosis, meningococcemia, scarlet fever, rickettsial disease, Kawasaki disease, serum sickness, and drug rash.

Treatment

Routine supportive care includes maintaining adequate hydration and antipyretics. High-dose vitamin A supplementation improves the outcome of infants with measles in developing countries. The World Health Organization recommends routine administration of vitamin A for 2 days to children with acute measles, regardless of country of residence.

Complications and Prognosis

Otitis media is the most common complication of measles infection. Interstitial (measles) pneumonia can occur, or pneumonia may result from secondary bacterial infection

with *Streptococcus pneumoniae*, *Staphylococcus aureus*, or group A streptococcus. Persons with impaired cell-mediated immunity may develop **giant cell (Hecht) pneumonia**, which is usually fatal. Myocarditis and mesenteric lymphadenitis are infrequent complications.

Encephalomyelitis occurs in 1–3 per 1,000 cases and usually occurs 2–5 days after the onset of the rash. Early encephalitis probably is caused by direct viral infection of brain tissue, whereas later onset encephalitis is a demyelinating, and probably an immunopathologic, phenomenon. **Subacute sclerosing panencephalitis (SSPE)** is a late neurologic complication of slow measles infection that is characterized by progressive behavioral and intellectual deterioration and eventual death. It occurs in approximately 1 in every million cases of measles, an average of 8–10 years after measles. There is no effective treatment.

Deaths most frequently result from bronchopneumonia or encephalitis, with much higher risk in persons with malignancy, severe malnutrition, age under 5 years, or immunocompromise (such as HIV infection). Late deaths in adolescents and adults usually result from SSPE. Other forms of measles encephalitis in immunocompetent persons are associated with a mortality rate of approximately 15%, with 20–30% of survivors having serious neurologic sequelae.

Prevention

Live measles vaccine prevents infection and is recommended as measles, mumps, and rubella (MMR) for children at 12–15 months and 4–6 years of age. The MMRV (MMR combined with varicella vaccine) is an alternative vaccine for children 12 months to 12 years of age, provided there are no contraindications, but is associated with a higher rate of febrile seizures following administration. The second dose of MMR is not a booster dose but significantly reduces the primary vaccine failure rate, from less than 5% to less than 1%. Contraindications to measles vaccine include immunocompromised states or an immunosuppressive course of corticosteroids (>2 mg/kg/day or >20 mg/day for those weighing >10 kg, for >14 days), pregnancy, or recent administration of immunoglobulin (within 3–11 months, depending on dose). MMR vaccination is recommended for all HIV-infected persons without evidence of severe immunosuppression (low age-specific CD4 T lymphocytes), children with cancer in remission who have not received chemotherapy in the previous 3 months, and children who have not received immunosuppressive corticosteroids in the previous month. Susceptible household contacts with a chronic disease or who are immunocompromised should receive **postexposure prophylaxis** with measles vaccine within 72 hours of measles exposure or immunoglobulin within 6 days of exposure.

RUBELLA (GERMAN OR 3-DAY MEASLES)

Etiology

Rubella, also known as **German measles** or **3-day measles**, is caused by a single-stranded RNA virus with a glycolipid envelope and is a member of the togavirus family. Humans are the only natural host. Rubella virus invades the respiratory epithelium and disseminates via a primary viremia. After replication in the reticuloendothelial system, a secondary viremia ensues, and the virus can be isolated from peripheral blood

monocytes, cerebrospinal fluid, and urine. Rubella virus is most contagious through direct or droplet contact with nasopharyngeal secretions from 2 days before until 5–7 days after rash onset, although the virus may be present in nasopharyngeal secretions from 7 days before until 14 days after the rash.

Infection **in utero** results in significant morbidity from **congenital rubella syndrome (CRS)** with associated ophthalmologic, cardiac, and neurologic manifestations (see [Chapter 66](#)). Maternal infection during the first trimester results in fetal infection with generalized vasculitis in more than 90% of cases. Infants with CRS may shed the virus in nasopharyngeal secretions and urine for more than 12 months after birth and transmit it to susceptible contacts.

Epidemiology

In unvaccinated populations, rubella usually occurs in the spring, with epidemics occurring in cycles of every 6–9 years. Approximately 25–50% of cases are subclinical. Fewer than 20 cases of rubella occur annually in the United States. Outbreaks occasionally occur in nonvaccinated groups from internationally imported cases. Transplacentally acquired antibody is protective during the first 6 months of life.

Clinical Manifestations

The incubation period for postnatal rubella is typically 16–18 days (range: 14–21 days). The mild catarrhal symptoms of the prodromal phase of rubella may go unnoticed. The characteristic signs of rubella are retroauricular, posterior cervical, and posterior occipital lymphadenopathy accompanied by an erythematous, maculopapular, discrete rash. The rash begins on the face and spreads to the body, lasting for 3 days, and is less prominent than that of measles. Rose-colored spots on the soft palate, known as **Forchheimer spots**, develop in 20% of patients and may appear before the rash. Other manifestations of rubella include mild pharyngitis, conjunctivitis, anorexia, headache, malaise, and low-grade fever. Polyarthritides, usually of the hands, may occur, especially among adult females, but usually resolves without sequelae. Paresthesias and tendinitis may occur.

Laboratory and Imaging Studies

Routine laboratory findings are nonspecific and generally do not aid in diagnosis. The white blood cell count usually is normal or low, and thrombocytopenia rarely occurs. Diagnosis is confirmed by serologic testing for IgM antibodies (typically positive 5 days after symptom onset) or by a fourfold or greater increase in specific IgG antibodies in paired acute and convalescent sera. CRS cases can have detectable IgM until 3 months of age and stable or rising IgG titers over the first 7–11 months of age. False-positive IgM results can occur. Cases of suspected CRS and postnatal rubella infection should be reported to the local and state health departments.

Differential Diagnosis

The rash must be differentiated from measles, roseola, enteroviral or adenoviral infection, infectious mononucleosis, toxoplasmosis, scarlet fever, rickettsial disease, Kawasaki disease, serum sickness, and drug rash.

Treatment

There is no specific therapy for rubella, and treatment is supportive.

Complications and Prognosis

Other than CRS (see Chapter 66) arising from rubella infection during pregnancy, complications are rare. Death rarely occurs with rubella encephalitis.

Prevention

Live rubella vaccine prevents infection and is recommended as MMR for children at 12–15 months and at 4–6 years of age. After vaccination, rubella virus is shed from the nasopharynx for several weeks, but it is not communicable. In children, rubella vaccine rarely is associated with adverse effects, but in postpubertal females it causes arthralgias in 25% of vaccinated individuals and acute arthritis-like symptoms in 10% of vaccinated individuals. These symptoms typically develop 1–3 weeks after vaccination and last 1–3 days.

Contraindications to rubella vaccine include immunocompromised states or an immunosuppressive course of corticosteroids (>2 mg/kg/day or >20 mg/day for those weighing >10 kg, for >14 days), pregnancy, or recent administration of immunoglobulin (within 3–11 months, depending on dose). Vaccine virus has been recovered from fetal tissues, although no cases of CRS have been identified among infants born to women inadvertently vaccinated against rubella during pregnancy. Nevertheless, women are cautioned to avoid pregnancy for 28 days after receiving the rubella-containing vaccine. All pregnant women should have prenatal serologic testing to determine their immune status to rubella, and susceptible mothers should be vaccinated after delivery and before hospital discharge.

Susceptible, nonpregnant persons exposed to rubella should receive rubella vaccination. Immunoglobulin is not recommended for postexposure prophylaxis of susceptible, pregnant women exposed to rubella.

ROSEOLA INFANTUM (EXANTHEM SUBITUM)

Etiology

Roseola infantum (exanthem subitum, sixth disease) is caused primarily by human herpesvirus type 6 (HHV-6) in most cases, and by HHV-7 in 10–30% of cases. HHV-6 and HHV-7 are large, enveloped double-stranded DNA viruses that are members of the herpesvirus family. Two species of HHV-6 (HHV-6A and HHV-6B) exist, with almost all postnatal infections caused by HHV-6B. These viruses infect mature mononuclear cells and cause a relatively prolonged (3–5 days) viremia during primary infection. They can be detected in the saliva of healthy adults, which suggests, as with other herpesviruses, the development of lifelong latent infection and intermittent viral shedding.

Epidemiology

Transplacentally acquired antibody protects most infants until 6 months of age. The incidence of infection increases

as maternally derived antibody levels decline. By 12 months of age, approximately 60–90% of children have antibodies to HHV-6, and essentially all children are seropositive by 2–3 years of age. The virus is likely acquired from asymptomatic adults who periodically shed these viruses. HHV-6 is a major cause of acute febrile illnesses in infants and may be responsible for up to 20% of visits to the emergency department for children 6–18 months of age.

Clinical Manifestations

Roseola is characterized by high fever (often $>40^{\circ}\text{C}$) with an abrupt onset that lasts 3–5 days. A maculopapular, rose-colored rash erupts coincident with defervescence, although it may be present earlier. The rash usually lasts 1–3 days but may fade rapidly and is not present in all infants with HHV-6 infection. Upper respiratory symptoms, nasal congestion, erythematous tympanic membranes, and cough may occur. Gastrointestinal symptoms are described. Roseola is associated with approximately one third of febrile seizures. Roseola caused by HHV-6 and HHV-7 are clinically indistinguishable, although HHV-6-associated roseola typically occurs in younger infants. Reactivation of HHV-6 following bone marrow transplantation may result in bone marrow suppression, hepatitis, rash, and encephalitis.

Laboratory and Imaging Studies

Routine laboratory findings are nonspecific and do not aid in diagnosis. Encephalitis with roseola is characterized by pleocytosis ($30\text{--}200$ cells/ mm^3) with mononuclear cell predominance, elevated protein concentration, and normal glucose concentration. Serologic testing showing a fourfold rise in acute and convalescent sera or documentation of HHV-6 DNA by PCR in the cerebrospinal fluid is diagnostic. PCR has also been used to detect HHV-6 in blood but may not be able to differentiate latent, reactivation, or primary infection. A rising viral titer is indicative of reactivation or primary infection. HHV-6 may also integrate in human chromosomes making viral PCR on white blood cells difficult to interpret.

Differential Diagnosis

The pattern of high fever for 3–5 days without significant physical findings followed by onset of rash with subsequent defervescence is characteristic. Many febrile illnesses may be easily confused with roseola during the preeruptive stage. Serious infections must be excluded, although most children are alert, behave normally, and continue with their usual daily activities.

Treatment

There is no specific therapy for roseola. Routine supportive care includes maintaining adequate hydration and antipyretics. In immunocompromised hosts, use of ganciclovir or foscarnet can be considered.

Complications and Prognosis

The prognosis for roseola is excellent. A few deaths have been attributed to HHV-6, usually in cases complicated by encephalitis or virus-associated **hemophagocytosis syndrome**.

Prevention

No preventative measures are available.

ERYTHEMA INFECTIONOSUM (FIFTH DISEASE)

Etiology

Erythema infectiosum (fifth disease) is caused by the human parvovirus B19, a single-stranded DNA virus producing a benign viral exanthem in healthy children. The viral affinity for red blood cell progenitor cells makes it an important cause of aplastic crisis in patients with hemolytic anemias, including sickle cell disease, spherocytosis, and thalassemia. Parvovirus B19 also causes fetal anemia and hydrops fetalis after primary infection during pregnancy. The cell receptor for parvovirus B19 is the **erythrocyte P antigen**, a glycolipid present on erythroid cells. The virus replicates in actively dividing erythroid stem cells, leading to cell death that results in erythroid aplasia and anemia.

Epidemiology

Erythema infectiosum is common. Parvovirus B19 seroprevalence is only 2–9% in children younger than 5 years of age but increases to 15–35% in children 5–18 years and 30–60% in adults. Community epidemics usually occur in the spring. The virus is transmitted by respiratory secretions and by blood product transfusions.

Clinical Manifestations

The incubation period is typically 4–14 days and, rarely, may last 21 days. Parvovirus B19 infections usually begin with a mild, nonspecific illness characterized by fever, malaise, myalgias, and headache. In some cases, the characteristic rash appears 7–10 days later. Erythema infectiosum is manifested by rash, low-grade or no fever, and occasionally pharyngitis and mild conjunctivitis. The rash appears in three stages. The initial stage is typically a **“slapped cheek” rash** with circumoral pallor. An erythematous symmetric, maculopapular, truncal rash appears 1–4 days later, then fades as central clearing takes place, giving a distinctive **lacy, reticulated rash** that lasts 2–40 days (mean: 11 days). This rash may be pruritic, does not desquamate, and may recur with exercise, bathing, rubbing, or stress. Adolescents and adults may experience myalgia, significant arthralgias or arthritis, headache, pharyngitis, coryza, and gastrointestinal upset.

Children with shortened erythrocyte life span (e.g., sickle cell disease) may develop a **transient aplastic crisis**, which is characterized by ineffective erythroid production typically lasting 7–10 days (see [Chapter 150](#)). Most children with parvovirus B19-induced transient aplastic crisis have multiple symptoms, including fever, lethargy, malaise, pallor, headache, gastrointestinal symptoms, and respiratory symptoms. The reticulocyte count is extremely low, and the hemoglobin level is lower than usual for the patient. Transient neutropenia and thrombocytopenia also commonly occur. Parvovirus may also cause hepatitis, myocarditis, and the papular-purpuric gloves and socks syndrome.

Persistent parvovirus B19 infection may develop in children with immunodeficiency, causing severe anemia resulting from pure red blood cell aplasia. These children do not display the typical manifestations of erythema infectiosum.

Laboratory and Imaging Studies

Hematologic abnormalities occur with parvovirus infection, including reticulocytopenia lasting 7–10 days, mild anemia, thrombocytopenia, lymphopenia, and neutropenia. Parvovirus B19 can be detected by PCR and by electron microscopy of erythroid precursors in the bone marrow. Serologic tests showing specific IgM antibody to parvovirus are diagnostic, demonstrating an infection that probably occurred in the prior 2–4 months. Parvovirus PCR of blood and cerebrospinal fluid is also available, primarily for use in severe illness or immunocompromised patients.

Differential Diagnosis

The diagnosis of erythema infectiosum in children is established on the basis of the clinical findings of typical facial rash with absent or mild prodromal symptoms, followed by a reticulated rash over the body that waxes and wanes. The differential diagnosis includes measles, rubella, scarlet fever, enteroviral or adenoviral infection, infectious mononucleosis, Kawasaki disease, systemic lupus erythematosus, serum sickness, and drug reaction.

Treatment

There is no specific therapy other than routine supportive care. Transfusions may be required for transient aplastic crisis. Intrauterine transfusion has been performed for hydrops fetalis associated with fetal parvovirus B19 infection. Intravenous immunoglobulin may be used for immunocompromised persons with severe anemia or chronic infection.

Complications and Prognosis

The prognosis for erythema infectiosum is excellent. Fatalities associated with transient aplastic crisis are rare. Parvovirus B19 is not teratogenic, but in utero infection of fetal erythroid cells may result in fetal heart failure, hydrops fetalis, and fetal death. Of the approximately 50% of women of childbearing age susceptible to parvovirus B19 infection, 30% of exposed women develop infection, with 25% of exposed fetuses becoming infected and 10% of these culminating in fetal death.

Prevention

The greatest risk is to pregnant women. Effective control measures are limited. The exclusion of affected children from school is not recommended because children generally are not infectious by the time the rash is present. Good handwashing and hygiene are practical measures that should help reduce transmission.

VARICELLA-ZOSTER VIRUS INFECTION (CHICKENPOX AND ZOSTER)

Etiology

Chickenpox and zoster are caused by varicella-zoster virus (VZV), an enveloped, icosahedral, double-stranded DNA virus that is a member of the herpesvirus family. Humans are the only natural host. **Chickenpox (varicella)** is the manifestation of primary infection. VZV infects susceptible

individuals via the conjunctivae or respiratory tract and replicates in the nasopharynx and upper respiratory tract. It disseminates by a primary viremia and infects regional lymph nodes, the liver, the spleen, and other organs. A secondary viremia follows, resulting in a cutaneous infection with the typical vesicular rash. After resolution of chickenpox, the virus persists in latent infection in the dorsal root ganglia cells. **Zoster (shingles)** is the manifestation of reactivated latent infection of endogenous VZV. Chickenpox is highly communicable in susceptible individuals, with a secondary attack rate of more than 90%. The period of communicability ranges from 2 days before to 7 days after the onset of the rash, when all lesions are crusted.

Epidemiology

In the prevaccine era, the peak age of occurrence was 5–10 years, with peak seasonal infection in late winter and spring. In the postvaccine era, the incidence of varicella has declined in all age groups, with the peak incidence now in 10- to 14-year-olds. Transmission is by direct contact, droplet, and air. Zoster, however, is contagious by direct contact. Only 5% of cases of zoster occur in children younger than 15 years of age. The incidence and severity of zoster are increased in immunocompromised persons.

Clinical Manifestations

The incubation period of varicella is generally 14–16 days, with a range of 10–21 days after exposure. Prodromal symptoms of fever, malaise, and anorexia may precede the rash by 1 day. The characteristic rash appears initially as small red papules that rapidly progress to nonumbilicated, oval, teardrop-like vesicles on an erythematous base. The fluid progresses from clear to cloudy, and the vesicles ulcerate, crust, and heal. New crops appear for 3–4 days, usually beginning on the trunk followed by the head, the face, and, less commonly, the extremities. There may be a total of 100–500 lesions, with all forms of lesions being present at the same time. Pruritus is universal and marked. Lesions may be present on mucous membranes. Lymphadenopathy may be generalized. The severity of the rash varies, as do systemic signs and fever, which generally abate after 3–4 days.

The preeruption phase of zoster includes intense localized and burning pain and tenderness (**acute neuritis**) along a dermatome, accompanied by malaise and fever. In several days, the eruption of papules, which quickly vesiculate, occurs in the dermatome or in two adjacent dermatomes. Groups of lesions occur for 1–7 days and then progress to crusting and healing. Thoracic and lumbar regions are typically involved. Lesions generally are unilateral and are accompanied by regional lymphadenopathy. In one third of patients, a few vesicles occur outside the primary dermatome. Any branch of cranial nerve V may be involved, which also may cause corneal and intraoral lesions. Involvement of cranial nerve VII may result in facial paralysis and ear canal vesicles (**Ramsay Hunt syndrome**). Ophthalmic zoster may be associated with ipsilateral cerebral angiitis and stroke. Immunocompromised persons may have unusually severe, painful herpes zoster that involves multiple cutaneous regions and, potentially, visceral dissemination (to liver, lungs, and central nervous system).

Postherpetic neuralgia, defined as pain persisting longer than 1 month, is uncommon in children.

Laboratory and Imaging Studies

Laboratory testing confirmation for diagnosis is usually unnecessary. PCR of vesicular fluid is the current diagnostic method of choice, and genotyping to distinguish vaccine and wild-type strains is available through the CDC. Detection of varicella-specific antigen in vesicular fluid by immunofluorescence using monoclonal antibodies or demonstration of a fourfold antibody increase of acute and convalescent sera is also diagnostic but not as sensitive as PCR.

Differential Diagnosis

The diagnosis of varicella and zoster is based on the distinctive characteristics of the rash. **Eczema herpeticum**, or **Kaposi varicelliform eruption**, is a localized, vesicular eruption caused by herpes simplex virus (HSV) that develops on skin affected by underlying eczema or trauma. The differentiation between zoster and HSV infection may be difficult because HSV may cause eruption that appears to be in a dermatomal distribution. Coxsackievirus A infection has a vesiculopustular appearance, but lesions are usually localized to the extremities and oropharynx. A previously healthy patient with more than one recurrence probably has HSV infection, which can be confirmed by viral culture or PCR.

Treatment

Symptomatic therapy of varicella includes nonaspirin antipyretics, cool baths, and careful hygiene. Routine oral administration of acyclovir is not recommended in otherwise healthy children with varicella. The decision to use antiviral medications, the route, and the duration of treatment depend on host factors and the risk for severe infection or complications. Early therapy with antivirals (especially within 24 hours of rash onset) in immunocompromised persons is effective in preventing severe complications, including pneumonia, encephalitis, and death from varicella. Acyclovir or valacyclovir may be considered in those at risk of severe varicella, such as unvaccinated persons older than 12 years; those with chronic cutaneous or pulmonary disease; receiving short-course, intermittent, or aerosolized corticosteroids; or receiving long-term salicylate therapy. The dose of acyclovir used for VZV infections is much higher than that for HSV.

Antiviral treatment of zoster accelerates cutaneous healing, hastens the resolution of acute neuritis, and reduces the risk of postherpetic neuralgia. Oral famciclovir and valacyclovir have much greater oral bioavailability than acyclovir and are recommended for treatment of zoster in adults. Valacyclovir is approved for use in children 2 years and older, and acyclovir is available for use in all age groups.

Complications and Prognosis

Secondary infection of skin lesions by streptococci or staphylococci is the most common complication. These infections may be mild, resembling impetigo, or life-threatening with

toxic shock syndrome or necrotizing fasciitis. Pneumonia is uncommon in healthy children but occurs in 15–20% of healthy adults and immunocompromised persons. Myocarditis, pericarditis, orchitis, hepatitis, ulcerative gastritis, glomerulonephritis, and arthritis may complicate varicella. Reye syndrome may follow varicella; thus salicylate use is contraindicated during varicella infection.

Neurologic complications frequently include postinfectious encephalitis, cerebellar ataxia, nystagmus, and tremor. Less common neurologic complications include Guillain-Barré syndrome, transverse myelitis, cranial nerve palsies, optic neuritis, and hypothalamic syndrome.

Primary varicella can be a fatal disease in immunocompromised persons as a result of visceral dissemination, encephalitis, hepatitis, and pneumonitis. The mortality rate approaches 15% in children with leukemia who do not receive prophylaxis or therapy for varicella (see [Chapter 72](#)).

A severe form of neonatal varicella may develop in newborns of mothers with primary varicella (but not shingles) occurring 5 days before to 2 days after delivery. The fetus is exposed to a large inoculum of virus but is born before the maternal antibody response develops and can cross the placenta. These infants should be treated as soon as possible with varicella-zoster immunoglobulin (VZIG) or intravenous immunoglobulin if VZIG is unavailable, to attempt to prevent or ameliorate the infection.

Primary varicella usually resolves spontaneously. The mortality rate is much higher for persons older than 20 years of age and for immunocompromised persons. Zoster usually is self-limited, especially in children. Advanced age and severity of pain at presentation and at 1 month are predictors of prolonged pain. Scarring is more common with zoster because of the involvement of the deeper layers of the skin.

Prevention

Children with chickenpox should not return to school until all vesicles have crusted. A hospitalized child with chickenpox and immunocompromised patients with zoster should be isolated in a negative-pressure room to prevent transmission. Zoster transmission can be minimized by covering the affected area.

A live, two-dose attenuated varicella vaccine is recommended for all children. The first dose should be administered at age 12–15 months and the second dose at 4–6 years. The varicella vaccine is 85% effective in preventing any disease and 97% effective in preventing moderately severe and severe disease. Transmission of vaccine virus from a healthy vaccinated individual is rare but possible.

Passive immunity can be provided by VZIG, which is indicated within 96 hours of exposure for susceptible individuals at increased risk for severe illness, such as immunocompromised children and some hospitalized preterm infants. Administration of VZIG does not eliminate the possibility of disease in recipients and prolongs the incubation period up to 28 days.

PEARLS FOR PRACTITIONERS

See *Infectious Diseases: Pearls for Practitioners* at the end of this section.