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39

Fever

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Two-thirds of all children visit a physician for fever before they reach the age of 2 years. Fever in the pediatric population is usually grouped into 4 categories:

- Fever in the neonate
- Fever with localizing signs
- Fever without source (FWS)
- Fever of unknown origin (FUO)

PATHOPHYSIOLOGY OF FEVER

Temperature is controlled by the thermoregulatory center, located in the preoptic area of the anterior hypothalamus. The thermoregulatory center receives input from peripheral receptors and the temperature of the blood bathing the hypothalamus and acts on autonomic, endocrine, and behavioral mechanisms to maintain the body temperature at a particular set point. The hypothalamic set point normally maintains body temperature around 37°C, but there can be significant variation among individuals. Normal temperatures range from 36-37.8°C, depending on the time of day, with the peak in the afternoon (5-7 P.M.) and the trough in the early morning (2-6 A.M.). Although the circadian rhythm is not well established in infancy, it becomes more reliable by the 2nd year of life.

The febrile response not only produces an elevation in body temperature but also causes physiologic changes that enhance the individual's ability to eliminate infection. Production of acute-phase reactants and alterations in metabolism and endocrine function are examples of these changes. **Acute-phase reactants**—proteins that are produced in response to infection or injury—include ceruloplasmin, C-reactive protein, haptoglobin, amyloid A, complement, and fibrinogen. Hormones and cytokines, some of which are endogenous pyrogens, regulate the production of acute-phase proteins. Exogenous pyrogens, such as bacteria or endotoxins, generate the production of endogenous pyrogens, which play a vital role in prostaglandin-related set point elevation and regulation of acute-phase responses.

Fever results when the thermoregulatory set point is elevated above the normal set point; the hypothalamus then generates physiologic changes involving endocrine, metabolic, autonomic, and behavioral processes. Diversion of blood from peripheral vessels to central vessels causes coolness of the extremities but helps increase core temperature. Shivering increases metabolic activity and heat production. The affected patient may feel cold and seek a warmer environment or add clothing to feel warmer and prevent heat loss. Once these processes have resulted in increasing the core temperature to match the elevated set point, the thermoregulatory center works to maintain the temperature as it does during normothermia. The thermoregulatory point returns to normal once the infection is resolved. The hypothalamus then produces physiologic changes to decrease the core temperature; these include sweating, dilation of cutaneous blood vessels, and the sensation of feeling hot, which may lead to behaviors such as removing clothing or seeking a cooler environment.

Fever has both positive and negative effects. High body temperatures may impair the reproduction and survival of some invading microorganisms by decreasing required nutrients, such as free iron, or by increasing immunologic responses such as phagocytosis. However, at extremely high temperatures, immunologic responses may be impaired. Fever increases the basal metabolic rate by 10-12% for each degree Celsius elevation of temperature. This increases oxygen consumption, carbon dioxide production, and fluid and caloric needs. Fluid requirements increase 100 mL/m^2/day for each 1°C rise in temperature above 37.8°C.

Heat illness must be distinguished from fever as a cause for elevated body temperature. In heat illness, there is an unregulated rise in body temperature, despite the fact that the hypothalamic set point is normal. It can result from excessive heat production or inadequate heat dissipation. Temperatures may reach extreme heights and can result in multiorgan dysfunction and death. Restoration of normal body temperature in heat illness is mandatory (Table 39.1).

FEVER WITHOUT SOURCE

A child with fever of recent onset with no obvious historical or physical explanation for the fever is said to have fever without source (FWS). Bacterial pathogens account for a small but clinically significant number of cases. The risk of bacterial infection decreases with increasing age and is highest for infants less than 3 months of age, compared to infants and toddlers 3-36 months of age, and even lower for children over the age of 36 months. Most of the patients in all age groups have a self-limited viral illness. The challenge is to identify which children have fever caused by bacterial pathogens, or other pathogens requiring treatment, in order to avoid the morbidity and mortality associated with delayed treatment, balanced against the risks of testing or treatment when neither is needed. Bacterial infection must be considered in immunocompromised patients or those with central lines or shunts. Studies in adults suggest that patients with high fever (>105°F) and rigors have a higher risk of bacterial infection; exceptions to this include influenza and adenoviral infections.

TABLE 39.1 Causes of Hyperthermia

Excessive Heat Production
Exertion
Heat stroke (exertion)
Malignant hyperthermia (anesthesia induced)
Neuroleptic malignant syndrome
Catatonia
Tetanus
Status epilepticus
Delirium
Endocrine disorders (hyperthyroidism, pheochromocytoma)
Drugs (cocaine, amphetamines, ephedrine, phencyclidine, tricyclic antidepressants, LSD, lithium, thyroid hormone, salicylates)

Diminished Heat Dissipation
Heat stroke
Occlusive dressings
Dehydration
Extensive burns (including severe sunburn)
Anhidrotic ectodermal dysplasias
Anticholinergic-like drugs (atropine, antihistamines, phenothiazines, tricyclic antidepressants)
Autonomic neuropathy
Spinal cord level paralysis (spinal crisis)
Possible overbundling (especially in a warm environment)
Therapeutic hyperthermia

Hypothalamic Dysfunction*
Stroke
Encephalitis
Granulomatous processes (sarcoid, tuberculosis, eosinophilic)
Trauma
Central: idiopathic
Phenothiazines
Hemorrhage

*Usually associated with hypothermia.
LSD, lysergic acid diethylamide.

◆ History

A detailed history may reveal a potential source for infection. A complete history addresses several important issues: (1) onset and duration of fever; (2) degree of temperature; (3) by what method and in which anatomic site the temperature was taken; (4) medications given, including antipyretics, antibiotics, or home remedies; (5) environmental exposures; (6) associated symptoms; (7) ill contacts; (8) recent immunizations, and (9) recent travel. Inquiry into the child's medical history may reveal important information such as recurrent febrile illnesses, primary or acquired immunodeficiency, or medications such as chemotherapy that alter host defenses.

Fever: Temperature Measurement

Rectal temperature measurement is considered to be the gold standard for children 3 years of age or younger. The most widely accepted definition of fever is rectal temperature of 38°C (100.4°F) or higher. It is important to consider that infants, especially those younger than 2 months of age, may have a blunted febrile (or hypothermic) response to infection. Hence, lack of fever should not be used as a criterion for ruling out infection in infants. Although rectal temperature measurement is the gold standard, it should be avoided in neutropenic immunocompromised patients, in whom rectal manipulation may seed the blood with bacteria.

Oral thermometry can be considered for cooperative patients who are older than 4-5 years of age. **Axillary temperatures** are commonly done and tympanic membrane and temporal artery temperatures are newer modalities with some studies examining their reliability. Axillary temperatures are less precise than rectal temperatures. There is a correlation between axillary and rectal temperature measurements; the axillary temperature is usually 0.5-0.85°C *lower*. **Tympanic membrane thermometers** are often inaccurate in children. **Temporal artery temperature** measurement correlates well with rectal temperature in some studies, but has been shown to be inferior when patients are febrile. It can be considered in settings when children are not likely to be febrile and are over 3 months of age. *When detection of fever is critical for diagnosis and management, rectal temperatures should be used in the child 3 years of age and younger.*

◆ Physical Examination

Many children will have a source for fever identified on their history and/or physical examination. If no focus of infection is found on the physical examination, the clinician must rely on history and observation to determine the appropriate next steps. The child may appear ill or well. Ill-appearing children are typically lethargic or irritable. They may show signs of shock, including weak peripheral pulses, tachycardia, poor perfusion, respiratory distress, mottling, cyanosis, or decreased mental status (Table 39.2). After thorough clinical and laboratory evaluation, ill-appearing children should be admitted to the hospital, and will likely need empiric antibiotic treatment.

Observational Scales

Infants and children with fever without source who do not appear ill create important decision processes in terms of evaluation and management. The physician's ability to make a hypothesis about the child's degree of illness, on the basis of observation, is critical in the evaluation. An objective scoring measure may be used in an effort to assess serious illness in young febrile children. The Acute Illness Observation Scale (AIOS) (Table 39.3), also known as the Yale Observation Score, is a 6-item predictive model graded on a scale of 1-5. Use of the AIOS in conjunction with the history and physical examination has a higher sensitivity for identifying serious illness than history and physical examination alone. The AIOS is most useful in patients younger than 24-36 months; *it has not been shown to provide sufficient data to identify serious illness in 4- to 8-week-old infants, and has not been evaluated in infants less than 4 weeks old.*

◆ Differential Diagnosis

Most children who present with fever without source (FWS) are subsequently determined to have a self-limited benign viral infection. In 1 study in 2-36 month old children who presented with FWS, 76% had 1 or more known pathogenic viruses found; 57% had adenovirus, human herpesvirus 6 (HHV-6: roseola), enterovirus, or parechovirus detected. Other identifiable viruses include respiratory syncytial virus, parainfluenza viruses, influenza viruses, varicella (chickenpox), human metapneumovirus and parvovirus (fifth disease/erythema infectiosum). Measles, mumps, and rubella are uncommon in developed countries but have been reported in epidemics following imported cases or in underimmunized communities. Although rapid testing for viral pathogens is often readily available, a detailed investigation to identify a viral pathogen is not necessary unless the confirmation of a viral infection will change the acute diagnostic plan; treatment with antivirals is an option (HSV, influenza) if the fever is prolonged and evolves into FUO or if there is end-organ involvement, as in hepatitis, myocarditis, encephalitis, or meningitis.

Most viral infections do not have simultaneous co-infection with a bacterial pathogen. Exceptions include croup due to parainfluenza

TABLE 39.2 International Consensus Definitions for Pediatric Sepsis

Infection	Suspected or Proven Infection or a Clinical Syndrome Associated with High Probability of Infection
SIRS	Two of 4 criteria, 1 of which must be abnormal temperature or abnormal leukocyte count: 1. Core temperature >38.5°C (101.3°F) or <36°C (96.8°F) (rectal, bladder, oral, or central catheter) 2. Tachycardia: Mean heart rate >2 SD above normal for age in absence of external stimuli, chronic drugs or painful stimuli or Unexplained persistent elevation over 0.5–4 hr or In children <1 yr old, persistent bradycardia over 0.5 hr (mean heart rate <10th percentile for age in absence of vagal stimuli, β-blocker drugs, or congenital heart disease) 3. Respiratory rate >2 SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anesthesia 4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophils
Sepsis	**SIRS Plus a Suspected or Proven Infection**
Severe sepsis	Sepsis plus 1 of the following: 1. Cardiovascular organ dysfunction, defined as: Despite >40 mL/kg of isotonic intravenous fluid in 1 hr: • Hypotension <5th percentile for age or systolic blood pressure <2 SD below normal for age *or* • Need for vasoactive drug to maintain blood pressure or • 2 of the following: • Unexplained metabolic acidosis: base deficit >5 mEq/L • Increased arterial lactate: >2 times upper limit of normal • Oliguria: urine output <0.5 mL/kg/hr • Prolonged capillary refill: >5 sec • Core to peripheral temperature gap >3°C (5.4°F) 2. ARDS as defined by the presence of a Pa_{O_2}/Fi_{O_2} ratio ≤300 mm Hg, bilateral infiltrates on chest radiograph, and no evidence of left heart failure *or* Sepsis plus 2 or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic)
Septic shock	Sepsis plus cardiovascular organ dysfunction as defined above
MODS	Presence of altered organ function such that homeostasis cannot be maintained without medical intervention

ARDS, acute respiratory distress syndrome; Fi_{O_2}, fraction of inspired oxygen; MODS, multiple organ dysfunction syndrome; Pa_{O_2}, partial pressure arterial oxygen; SIRS, systemic inflammatory response syndrome.

From Turner DA, Cheifetz IM. Shock. In: Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:522, Table 70.7.

virus, which may predispose to bacterial tracheitis and influenza, which may predispose to bacterial pneumonia. The sequence may be biphasic with viral symptoms followed by improvement, followed by worsening symptoms of the bacterial superinfection, or both phases may not be apparent as the child demonstrates no improvement or deterioration. Respiratory syncytial virus (RSV) may predispose patients to otitis media.

Noninfectious conditions manifesting with FWS are extremely rare. Historical clues (recurrences, chronicity) or systemic signs usually indicate malignancy or rheumatic disorders. If the history and physical examination are not suggestive, these diagnoses need not be pursued. Heat-related illness or drug ingestion may be considered if supported by the history. Fever caused by immunizations may not be accompanied by other signs or symptoms, but the history should suggest immunization as the cause.

Urinary Tract Infections (UTIs)

UTIs are the most common serious bacterial infection in children less than 36 months of age who present with FWS. UTIs are almost always occult in children younger than 24 months because the symptoms, except for fever, are nonspecific or nonexistent. UTI occurs in 7% of febrile children younger than 2 years. The prevalence of UTI varies by height of the fever, duration of the fever, age, gender, race, and circumcision status. Children with fever greater than 39°C are at a higher risk of UTIs. Boys with fever for more than 2 days and girls with fever for more than 1 day are more likely to have a UTI. Higher rates of UTIs are found in girls, especially those younger than 12 months of age. For febrile boys younger than 3 months of age, 20.1% of those who are uncircumcised have a UTI; for circumcised boys the rate is 2.4%. UTI rates are higher among white infants than among black infants and among children with abnormal genitourinary tract anatomy or neurogenic bladder.

Urine specimens should be obtained from the following children with FWS: those with a history of UTI, those with a history of urinary tract anomalies or vesicoureteral reflux, all infants younger than 2 months, girls younger than 12-24 months, uncircumcised boys younger than 12 months, and circumcised boys younger than 6 months. There is an age-associated risk of bacteremia with UTIs, particularly in infants. The incidence of bacteremia in patients younger than 2 months with UTI is 10%. The incidence of bacteremia in patients younger than 2 months with UTI ranges from 4-15% depending on the setting. Opinions regarding when to obtain blood cultures in infants with UTI differ, but a reasonable approach would be to obtain blood cultures in children younger than 2-6 months with suspected UTI, and in older infants with UTI if they are ill-appearing (urosepsis).

Bacteremia

Occult bacteremia is defined by the presence of a positive blood culture for pathogenic bacteria in a febrile patient who does not appear extremely ill and who has no focus of infection, excluding otitis media. Following the introduction of the 7-valent pneumococcal vaccine in 2007, invasive pneumococcal disease decreased dramatically. Pneumococcal bacteremia decreased from 80% of the cases of bacteremia to 30%. *Most cases of bacteremia in children were not occult.* Bacteremic children were either ill or had a focus of infection, such as a UTI. In 1 study, the rate of occult bacteremia after 2007 was 0.25%. After the 13-valent pneumococcal vaccine was introduced in 2010, the incidence of invasive pneumococcal disease in children less than 5 years old decreased again with 1 state-based population study showing incidence rates dropping from 46/100,000 to 23/100,000 with the age group most involved being children 2-23 months of age. *Escherichia coli* is the most common cause of bacteremia in children aged less than 12 months, all due to UTIs. Other less common causes of bacteremia in young

TABLE 39.3 Acute Illness Observation Scale

Observation Item	1 Normal	3 Moderate Impairment	5 Severe Impairment
Quality of cry	Strong with normal tone *or* Content and not crying	Whimpering *or* Sobbing	Weak *or* Moaning *or* High-pitched
Reaction to parent stimulation	Cries briefly, then stops *or* Content and not crying	Cries off and on	Continual cry *or* Hardly responds
State variation	If awake → stays awake *or* If asleep and stimulated → wakes up quickly	Eyes close briefly → awakens *or* Awakes with prolonged stimulation	Falls asleep *or* Will not rouse
Color	Pink	Pale extremities *or* Acrocyanosis	Pale *or* Cyanotic *or* Mottled *or* Ashen
Hydration	Skin normal, eyes normal *and* Mucous membranes moist	Skin, eyes normal *and* Mouth slightly dry	Skin doughy *or* Skin tented *and* Dry mucous membranes *and/or* Sunken eyes
Response (talk, smile) to social overtures	Smiles *or* Alert (≤2 mo)	Brief smile *or* Alert briefly (≤2 mo)	No smile; face anxious, dull, expressionless *or* No alertness (≤2 mo)

From McCarthy PL, Sharpe MR, Spiesel SZ, et al. Observation scales to identify serious illness in febrile children. *Pediatrics*. 1982;70:802.

children are *N. meningitidis*, nontyphoidal *Salmonella*, *Staphylococcus aureus*, and group A streptococcus. *Neisseria meningitidis* bacteremia is frequently associated with serious sequelae. Children with *N. meningitidis* bacteremia are much more likely to progress to meningitis than are those with *S. pneumoniae* bacteremia. Nontyphoidal *Salmonella* bacteremia is often accompanied or preceded by enteritis. In some instances, particularly in young infants, the diarrhea is mild or even absent. The prevalence of *Salmonella* bacteremia among patients with *Salmonella enteritis* has been reported to be between 2% and 45%; fever is not always present. *Salmonella* infection seldom causes serious complications in patients with normal host defenses and resolves spontaneously. *Infants younger than 3 months, malnourished, and immunocompromised individuals are exceptions.*

◆ Role of Diagnostic Testing in Patients with Fever Without Source

Evaluation is usually divided into 4 different age ranges: younger than 1 month, 1-3 months, 3-36 months, and older than 36 months. Testing for each individual age group is based on risks for diseases and prevalence of pathogens.

Complete Blood Count and Other Markers of Inflammation

The white blood cell (WBC) count is the most commonly used test in young children with FWS. Complete blood count (CBC) is less useful as a marker for invasive disease caused by *E. coli* than by *S. pneumoniae*, thus its utility has declined with the reduction of the incidence of invasive pneumococcal disease. Similarly, band counts are less commonly used, except in the 29-60 day old infant as part of identifying a low-risk cohort. A WBC count of 5,000-15,000 is generally considered normal for children over 1 month of age. A WBC count less than 15,000/mm^3 or even leukopenia may be found in children with *N. meningitidis* bacteremia. A minority of children with occult nontyphoidal *Salmonella* bacteremia have been found to have a WBC count exceeding 15,000/mm^3. C-reactive protein (CRP) and procalcitonin combined with a urine dipstick (the lab score) can be used to screen for bacterial infection. This combination of tests has been validated for children 7 days to 36 months of age.

Polymerase Chain Reaction (PCR)

PCR is useful in identifying the cause of fever for common viruses such as respiratory syncytial virus, influenza viruses, parainfluenza viruses, enteroviruses, parechovirus, adenoviruses, or herpes simplex virus.

Additional methods available or in development that may be helpful to identify serious bacterial infections and distinguish bacterial from viral infections utilize molecular microbiology methods. **Gene expression profiles** of the patient's peripheral blood leukocytes demonstrate different biosignatures of RNA production that may differentiate bacterial from viral infections. This method does not identify the

specific pathogen. **Rapid multiplex PCR** combined with standard blood culture methods may identify a specific pathogen much sooner (~20 hours) than standard blood culture techniques. Specific bacteria may be identified using **16S ribosomal RNA** bacterial gene detection. This method does not require bacterial growth. 16S rRNA detection may be helpful when antibiotics were administered before the sample was obtained, and in patients with ventilator-associated pneumonia or bacteria that grow poorly or are present in effusions or tissues (heart valves).

Blood Cultures

Blood cultures are the gold standard for determination of bacteremia. Although blood cultures do not provide immediate results, methods allow for continuous and more rapid detection of bacterial growth. Blood cultures are easy to perform and provide essential information in the diagnosis and management of patients with possible bacteremia. Preliminary blood culture results are typically available within 24 hours, with positive identification of most organisms within 48 hours.

False-negative blood culture results may be due to prior treatment with antibiotics, missing an episode of bacteremia if it is intermittent, and inoculation of too little blood into the culture media. Alternatively, too much blood inoculated into the blood culture bottle may yield a false-negative result because of ongoing killing of bacteria by neutrophils. Three to 5 mL of blood should be added to each blood culture bottle. False-positive results may be due to inadequate skin preparation, leading to contamination with skin flora.

Urinalysis and Urine Culture

A positive urine culture was once considered the gold standard; current recommendations include a urinalysis that has pyuria (defined as >5 WBCs/high-power field [hpf] on the microscopic examination or a positive leukocyte esterase on dipstick) and a positive urine culture for a uropathogen in an appropriately collected specimen. Fifty to 100,000 colonies of a single organism is considered positive (see Chapter 18). Children should have a catheterized urine specimen obtained, unless they are toilet-trained and can supply a clean voided specimen. Suprapubic aspiration is acceptable but requires technical expertise, and parents often perceive it as unsuitably invasive; it may be the only alternative for boys with severe phimosis. The use of plastic receptacles attached to the perineum should be discouraged because contamination from skin and fecal flora commonly occurs.

Lumbar Puncture

Lumbar puncture is indicated if the patient is younger than 28 days or if a diagnosis of sepsis, meningitis, or encephalitis is considered, regardless of the child's age. Normal cerebrospinal fluid (CSF) findings, including chemistry, cell count with differential, Gram stain, PCR, and culture, help exclude the diagnosis of meningitis. Less than 1% of children with normal preliminary CSF results have a positive culture; in most of these, the pathogen is *N. meningitidis*. Thus, even in the presence of normal preliminary CSF results, close follow-up is essential.

Chest Radiographs

Chest radiographs are usually normal in children who have FWS. Respiratory signs or symptoms, such as tachypnea, retractions, crackles, wheezing, rhonchi, nasal flaring, grunting, cough, or hypoxia, may predict chest radiograph findings consistent with pneumonia. In practice, pneumonia can often be diagnosed solely on the basis of the clinical findings of fever, tachypnea, and crackles; chest radiographs are not always necessary. However, chest radiographs may be useful in evaluating for the presence of pleural effusion or other complications of pneumonia.

Stool Cultures

Most acute diarrhea and fever is caused by viral pathogens in developed countries. Obtaining a stool culture is indicated if bacterial enteritis is indicated by the presence of risk factors in the history, such as blood in the stool or certain exposures (petting zoos) (see Chapter 11).

◆ Evaluation and Management

Children Younger Than 3 Months

Febrile infants younger than 3 months have a higher incidence of serious bacterial infections than older infants. The relatively high incidence of bacterial disease probably results from a combination of factors unique to this age group: decreased opsonin activity; decreased macrophage function; decreased neutrophil function; poor immunoglobulin G antibody response to encapsulated bacteria; and susceptibility to bacterial pathogens such as group B streptococci (GBS), gram-negative enteric organisms, and *Listeria monocytogenes*. The incidence of early-onset group B streptococcal infections has decreased with routine screening and the intrapartum treatment of GBS-positive pregnant women; the incidence of late-onset GBS (>1 week) has not decreased. *E. coli* is the most common organism causing bacterial infections in neonates and young infants.

In very young infants, clinical evaluation alone is inadequate for excluding serious bacterial infections. Management of febrile infants **younger than 28 days** includes a sepsis evaluation and hospitalization for parenteral antimicrobial therapy pending culture results. The reasoning for this conservative approach lies in the difficulty in evaluating the behavioral state of neonates, the rapid clinical deterioration of infants with bacterial infections, the immature neonatal immune system, and the possibility of life-threatening viral infections caused by herpes simplex viruses (HSV) or enteroviruses. Sepsis evaluation should include culture of the CSF, blood, and urine; a complete blood cell count with differential; examination of the CSF for cells, protein, and glucose; and urinalysis. A chest radiograph should be considered if the patient has signs or symptoms of a respiratory infection. Testing (blood and CSF PCR for HSV) and treatment for possible HSV infection should be considered in ill-appearing infants, those with a seizure prior to presentation, and those with a vesicular rash consistent with HSV.

A combination of clinical evaluation and laboratory studies can be used to define a specific population of infants **aged 29-60 days** who do not appear ill and are at low risk for bacterial infections. Infants at low risk for bacterial infections are those who are previously healthy with no focus of bacterial infection on physical examination and who have negative laboratory screening results. A number of prospective studies have contributed to the development of specific low-risk screening criteria (Table 39.4). The age groups included vary by study, ranging from 0-90 days to 29-56 days. Because there are differences in study criteria used to define infants at low risk for bacterial infections the most conservative values have been used in the guidelines presented in this chapter. Negative laboratory screening results consist of a WBC count of 5000-15,000/mm^3; fewer than 1500 bands/mm^3 or a band-to-neutrophil ratio of less than 0.2; fewer than 10 WBCs/hpf and no organisms on urinalysis; and fewer than 8 WBCs/hpf and no organisms on CSF Gram stain. Some experts also include a negative chest radiograph and, when diarrhea is present, a stool examination with fewer than 5 WBCs/hpf.

Most experts suggest that febrile infants 29-60 days old who meet the low-risk criteria and have access to close follow-up can be managed as outpatients. Blood, urine, and CSF cultures should be obtained before empirical antibiotic treatment so that viral and bacterial causes

may be distinguished. An alternative strategy is to manage such infants as outpatients, without empirical antibiotic therapy, after blood, CSF, and urine cultures are obtained. Although most of the original studies on outpatient management of febrile infants included infants aged 2-3 months, many experts agree that infants aged 2-3 months can be managed safely according to the guidelines for infants and children aged 3-36 months (Table 39.4).

Regardless of whether the clinician chooses to treat the patient with empiric antibiotics, all low-risk infants should be re-evaluated within 24 hours. Those who appear ill or who have positive culture results should be admitted for parenteral antibiotics. If a child appears well and all culture results are negative, close follow-up should be continued and a 2nd return visit made in 24 hours.

Children Aged 3 to 36 Months

The risk of bacteremia for children with FWS in this age group has decreased with the routine use of pneumococcal vaccines. The most common occult bacterial infection in this age group is UTI. For children in this age group who appear ill, a full sepsis evaluation should be undertaken (Table 39.5).

TABLE 39.4 Low-Risk Criteria in a Child 1–3 Mo Old with Fever

Boston Criteria

Infants are at low risk if they appear well, have a normal physical examination, and have a caretaker reachable by telephone, and if laboratory tests are as follows:

- CBC: <20,000 WBC/μL
- Urine: negative leukocyte esterase
- CSF: leukocyte count less than 10×10^6/L

Philadelphia Protocol

Infants are at low risk if they appear well and have a normal physical examination, and if laboratory tests are as follows:

- CBC: <15,000 WBC/μL; band: total neutrophil ratio <0.2
- Urine: <10 WBC/hpf; no bacteria on Gram stain
- CSF: <8 WBC/μL; no bacteria on Gram stain
- Chest radiograph: no infiltrate
- Stool: no RBC; few to no WBC

Pittsburgh Guidelines

Infants are at low risk if they appear well and have a normal physical examination, and if laboratory tests are as follows:

- CBC: 5,000–15,000 WBC/μL; peripheral absolute band count <1,500/μL
- Urine (enhanced urinalysis): 9 WBC/μL and no bacteria on Gram stain
- CSF: 5 WBC/μL and negative Gram stain; if bloody tap, then WBC:RBC ≤1 : 500
- Chest radiograph: no infiltrate
- Stool: 5 WBC/hpf with diarrhea

Rochester Criteria

Infants are at low risk if they appear well and have a normal physical examination, and if laboratory findings are as follows:

- CBC: 5,000–15,000 WBC/μL; absolute band count ≤1,500/μL
- Urine: <10 WBC/hpf at ×40
- Stool: <5 WBC/hpf if diarrhea

CBC, complete blood count; CSF, cerebrospinal fluid; hpf, high-powered field; RBC, red blood cell; WBC, white blood cell.
From Nield LS, Kamat D. Fever without a focus. In: Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:1281, Table 177.2.

Screening urinalysis (UA) for UTI should be considered in children with a history of UTI, children with a history of urinary tract anomalies or vesicoureteral reflux, girls younger than 12-24 months, especially when the temperature is greater than 39.0°C, uncircumcised boys younger than 12 months, and circumcised boys younger than 6 months. Blood cultures are recommended for children with probable UTIs who are less than 6 months of age. A febrile child with moderate leukocyte esterase on urine dipstick testing or pyuria on an appropriately collected specimen should be treated presumptively for a UTI. Urine cultures should be obtained for any patient with a suspected UTI. The choice of antibiotics should be guided by knowledge of the common pathogens that cause UTIs and by patterns of antibiotic sensitivity in the community. Hospitalization should be considered for the child who is vomiting, is dehydrated, or appears ill; for those in whom compliance is likely to be poor; and for any patient with underlying renal or urologic anomalies.

Examination and culture of the CSF are the only tests to exclude the diagnosis of meningitis and encephalitis. They should be considered in any child in whom the diagnosis of sepsis, meningitis or encephalitis is suspected on the basis of the history, observation, and physical examination findings. Outpatient management of children with FWS is acceptable for those with a low probability of meningitis, good follow-up, and reliable caregivers. Blood cultures should be obtained for all children in whom sepsis or meningitis is suspected. Empiric treatment with antibiotics should be considered in those suspected of sepsis or meningitis after appropriate cultures are obtained.

In summary, management of children aged 3-36 months with fever is based on clinical experience and numerous study results:

- Child who appears ill on initial evaluation or on follow-up: Admit to the hospital for parenteral antibiotics after appropriate laboratory evaluation.
- Well-appearing children with FWS should be screened for UTIs, based on their number of risk factors. Risk factors for girls are: age <12 months, white race, temperature greater than 39°C, and fever for 2 or more days. Girls 2-24 months of age with 1 or more of these risk factors have a greater than 1% probability of having a UTI, and should be screened for a UTI.

  For boys, the risk factors are uncircumcised status, nonblack race, temperature greater than 39°C, and fever for over 24 hours. All uncircumcised boys less than 12 months old, even if they don't have other risk factors, should be screened for a UTI. For boys who are circumcised, 2 or more of the other risk factors increases the risk to over 1% and they should be screened.
- Child with positive blood culture: Reevaluation should occur in any child whose blood culture is presumptively positive. If the blood is found to contain *N. meningitidis* or *Haemophilus influenzae* (which has been rare since the advent of *H. influenzae b* immunization), a CSF sample and a repeat blood culture should be obtained, and the child should be admitted to the hospital for parenteral antibiotics, pending the results of the cultures. The child with occult pneumococcal bacteremia who appears well and is afebrile when returning for a follow-up may be managed as an outpatient with parenteral ceftriaxone followed by oral antibiotics according to the sensitivity of the organism. Because of the concern of pneumococcal resistance to penicillin, a 2nd dose of intramuscular ceftriaxone may be given until sensitivity results are available. If the culture is positive for nontyphoidal *Salmonella* organisms and the child is younger than 3 months, full sepsis evaluation and intravenous antibiotics are recommended. Oral antibiotics and close follow-up are recommended for older children with *Salmonella* bacteremia.
- Child with positive urine culture: If the child is afebrile and appears well, treatment with oral antibiotics is recommended, according to the sensitivity of the organism.

TABLE 39.5 Management of Fever Without Source

Group	Management
Any toxic-appearing child 0–36 mo and temperature ≥38°C (100.4°F)	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child <1 mo and temperature ≥38°C (100.4°F)	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child 1–3 mo and temperature ≥38°C (100.4°F)	**Two-Step Process** 1. Determine risk based on history, physical examination, and laboratory studies. Low risk: • Uncomplicated medical history • Normal physical examination • Normal laboratory studies • Urine: negative leukocyte esterase, nitrite and <10 WBC/hpf • Peripheral blood: 5,000–15,000 WBC/mm^3; <1,500 bands or band: total neutrophil ratio <0.2 • Stool studies if diarrhea (no RBC and <5 WBC/hpf) • CSF cell count (<8 WBC/μL) and negative Gram stain • Chest radiograph without infiltrate 2. If child fulfills all low-risk criteria, administer no antibiotics, ensure follow-up in 24 hr and access to emergency care if child deteriorates. Daily follow-up should occur until blood, urine, and CSF cultures are final. If any cultures are positive, child returns for further evaluation and treatment. If child does not fulfill all low-risk criteria, hospitalize and administer parenteral antibiotics until all cultures are final and definitive diagnosis determined and treated
Child 3–36 mo and temperature 38–39°C (100.4–102.2°F)	Reassurance that diagnosis is likely self-limited viral infection, but advise return with persistence of fever, temperatures >39°C (102.2°F), and/or new signs and symptoms
Child 3–36 mo and temperature >39°C (102.2°F)	**Two-Step Process** 1. Determine immunization status 2. If received conjugate pneumococcal and *Haemophilus influenzae* type b vaccines, obtain urine studies (urine WBC, leukocyte esterase, nitrite, and culture) for all girls, all boys <6 mo old, all uncircumcised boys <2 yr, all children with recurrent urinary tract infections If did not receive conjugate pneumococcal and *H. influenzae* type b vaccines, manage according to the 1993 Guidelines (see Baraff et al. *Ann Emerg Med.* 1993;22:1198-1210.)

*Other tests may include chest radiograph, stool studies, herpes simplex virus polymerase chain reaction.
CSF, cerebrospinal fluid; hpf, high-powered field; RBC, red blood cell; WBC, white blood cell.
From Nield LS, Kamat D. Fever without a focus. In: Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016: Table 177.3.)

Children Older Than 36 Months

Evaluation and management of ill-appearing children older than 36 months with fever without source are similar to those of younger children. For children in this age group who do not appear ill, no screening diagnostic tests are indicated. Close attention should be paid to environmental exposures and ill contacts because of the high likelihood of increased contacts in this school-aged cohort.

CENTRAL NERVOUS SYSTEM INFECTIONS

Bacterial Meningitis

Bacterial meningitis is usually a disease of infants and young children. The attack rate is highest between the ages of 3 and 8 months; 66% of cases occur in children younger than 5 years of age. Bacterial meningitis is seen during all seasons; however, there may be a seasonal correlation between the presence of preceding respiratory pathogens in the upper respiratory tract and the subsequent development of bacterial meningitis. Bacterial meningitis usually occurs sporadically. Clusters of cases have been noted in day care centers, colleges, and other closed communities. Bacterial meningitis occurs more frequently in children with traumatic fractures of the cribriform plate or paranasal sinuses or with a cochlear implant (pneumococci); in children who have undergone neurosurgical procedures such as ventricular shunts (*S. aureus*, *S. epidermidis*, *Corynebacterium* species); in children with congenital or acquired immunodeficiencies (pneumococci, *L. monocytogenes*, meningococci); in children with anatomic or functional asplenia (pneumococci, meningococci); and in children with sickle hemoglobinopathies (pneumococci). There may be a genetic predisposition in some groups to the development of meningitis, inasmuch as there is an increased incidence of *H. influenzae* type b meningitis in Navahos and Eskimos.

Bacterial meningitis manifests in 2 patterns. In the 1st, the symptoms develop slowly over several days, the initial symptoms being those of a nonspecific illness. The signs and symptoms of meningitis develop subsequently. In the 2nd pattern, the disease develops suddenly and quickly, the 1st indications of illness being the signs and symptoms of meningitis and/or sepsis.

The manifestations of meningitis depend on the child's age. In infants, the findings are usually nonspecific and may be subtle; they include vomiting, diarrhea, irritability, lethargy, poor appetite, respiratory distress, seizures, hypothermia, and jaundice. Only 50% of affected infants have fever; some present only with fever. It is uncommon for affected young infants to have a stiff neck; only 30% have a bulging fontanel.

Older children present with more specific meningeal signs. They complain of a headache that is described as being severe, generalized, deep-seated, and constant. They complain about neck stiffness, caused by inflammation of the cervical dura and reflex spasm of the extensor muscles of the neck. There is pain and limitation of motion on flexion

of the neck, but lateral movement of the neck may be normal and pain-free. They also complain of nausea, vomiting, anorexia, and photophobia.

On examination, they demonstrate irritability, mental confusion or altered consciousness, nuchal rigidity, and, occasionally, hyperesthesia and ataxia. The clinician demonstrates nuchal rigidity by feeling resistance and observing a painful response while flexing the patient's neck. The stiffness may not be recognized until the end of flexion. The neck usually can be rotated without symptoms. In the child who is crying and tensing the muscles, nuchal rigidity may be demonstrated if the examiner places 1 hand under the occiput of the supine patient and lifts the child. If the neck does not flex, it is stiff. Alternatively, a sitting child may be observed following an object as it falls to the floor. The child who flexes the neck to look at the object does not have nuchal rigidity. In the presence of meningitis, flexion of the neck causes spontaneous flexion of the legs at the hips and knees, the **Brudzinski sign** (Fig. 39.1). The **Kernig sign** is elicited when the patient lies supine and, with the knee flexed, the leg is flexed at the hip. The knee is then extended. A positive sign is present if this movement is limited by contraction of the hamstrings and causes pain. Absence of nuchal rigidity is found in 1.5% of older children with meningitis; it may be absent in children who have overwhelming infections, are deeply comatose, or who have focal or global neurologic impairment.

As many as 15% of children with bacterial meningitis initially present in a **comatose** or semicomatose state (see Chapter 31). Because

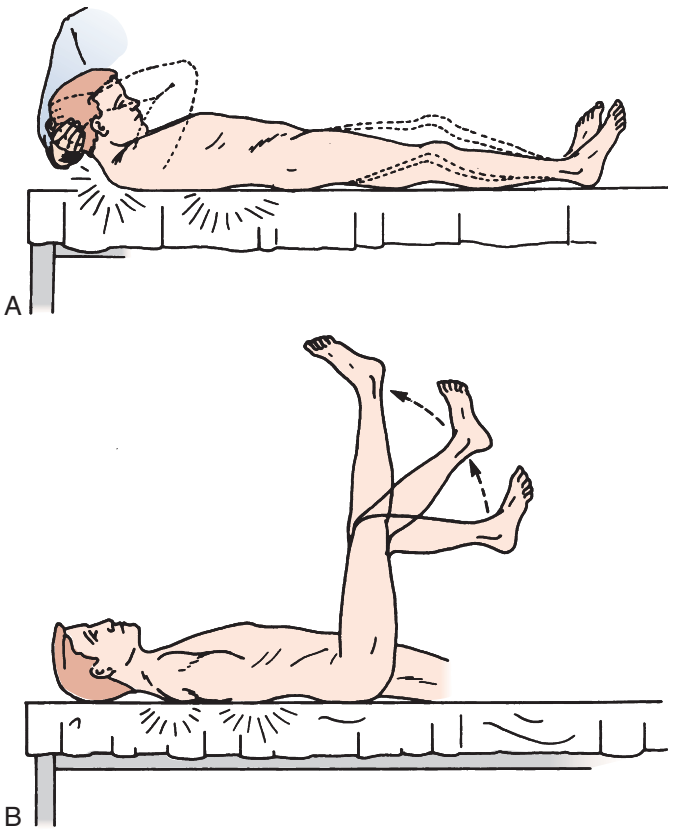

FIGURE 39.1 *A,* Brudzinski sign. The patient lies supine, and the head is passively elevated from the table by the examiner. The patient complains of neck and low back discomfort and attempts to relieve the meningeal irritation by involuntary flexion of the knees and hips. *B,* Kernig sign. The patient lies supine, with the hips and knees flexed. The knees are then gradually extended. Complaints of pain in the lower back, neck, and/or head are suggestive of meningeal irritation. (From Reilly BM. *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991:95.)

of the short duration and inconsistent development of increased intracranial pressure, **papilledema** is usually not seen at presentation. When it is present, venous sinus thrombosis, subdural effusion, or an intracranial abscess must be considered. **Seizures** occur before hospital admission in up to 20% of affected patients.

Children with meningitis may also present with cutaneous findings. Although commonly associated with meningococcal disease, purpura, petechiae, or a diffuse nonspecific maculopapular rash may be present in meningitis caused by any of the common bacterial pathogens (see Chapter 40).

Septic arthritis may be seen simultaneously with bacterial meningitis. This has been assumed to be caused by simultaneous localizing infection after a primary bacteremia. Reactive arthritis caused by immune complex deposition is also seen with bacterial meningitis. This arthritis affects 1 large joint and appears 5-7 days after treatment for meningitis has started. In general, arthritis occurring acutely with meningitis should be assumed to be infectious (see Chapter 33).

Various eye disorders have also been described with acute bacterial meningitis, including transient cataracts, paralysis of the extraocular muscles, pupillary dysfunction, dendritic ulcers, endophthalmitis, cortical blindness, and conjunctivitis.

Recurrent episodes of bacterial meningitis rarely occur. Potential etiologies include congenital CSF fistulas (inner ear, dermal sinus, neuroenteric cysts, lumbosacral sinus tracts), traumatic or surgical CSF fistula (skull fracture, postoperative nasal surgery, cochlear implant), immunodeficiency states and parameningeal infections (mastoiditis, sinusitis, craniofacial osteomyelitis).

◆ Diagnostic Studies

Lumbar Puncture and Cerebrospinal Fluid Analysis

The definitive diagnosis of meningitis is based on examination of the cerebrospinal fluid (CSF). The CSF is usually obtained via a lumbar puncture (spinal tap). The lumbar puncture is performed by introducing a small-bore, short-beveled, spinal needle with a stylet into the subarachnoid space at the L3-L4 or L4-L5 level (Figs. 39.2 to 39.4). A needle with a stylet is used to minimize the risk of introducing a nest of epidermal cells into the subarachnoid space that may later grow into a cord-compressing epidermoid tumor. Approximately 3 mL of fluid is removed for analysis.

There are a few **contraindications** for the performance of a lumbar puncture. The 1st is cardiorespiratory compromise. Performance of the lumbar puncture requires that the child be held in flexion to open the intervertebral spaces. In seriously ill children or children with significant underlying cardiac or pulmonary disease, this positioning may be enough to cause respiratory compromise. The lumbar puncture may need to be postponed, be performed cautiously with continuous oxygen saturation monitoring, or performed with the patient in the sitting position.

Second, children with **increased intracranial pressure** from a focal central nervous system (CNS) lesion, such as brain abscess or tumor, or from illnesses associated with cerebral edema have a high risk of cerebral herniation after a lumbar puncture. If signs or symptoms of increased intracranial pressure are present, the lumbar puncture should be postponed until the increased pressure is lowered with appropriate treatment. *If a lumbar puncture is delayed, appropriate antibiotic therapy should be initiated without further delay.* Third, a lumbar puncture should not be done if the spinal needle must pass through an area of infection on its way to the subarachnoid space. To do so might introduce pathogens into the CNS that could cause meningitis.

Epidural hematomas causing lower limb paralysis may be a complication of lumbar punctures in children with bleeding disorders. Therefore, in children with hemophilia, disseminated intravascular

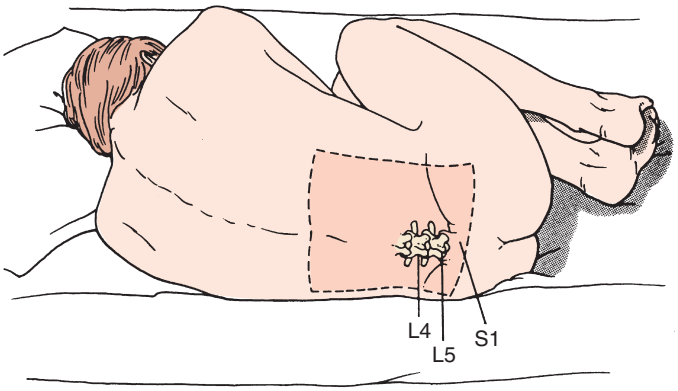

FIGURE 39.2 Lateral decubitus position for a lumbar puncture. L4-L5 position is determined by a vertical line drawn between the superior iliac crests. (From Davidson RI. Lumbar puncture. In: Vander Salm TJ, Cutler BS, Wheeler HB, eds. *Atlas of Bedside Procedures*. 2nd ed. Boston: Little, Brown; 1992:443.)

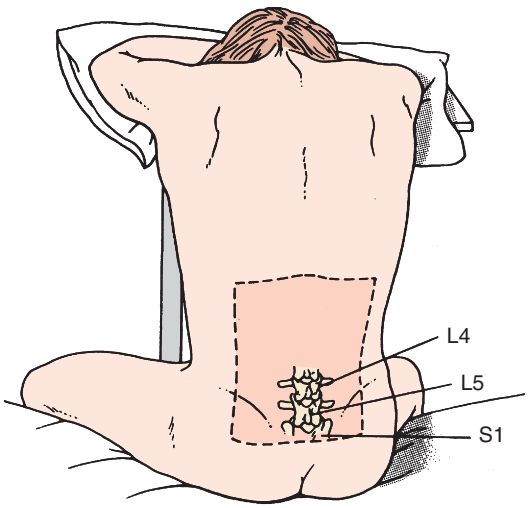

FIGURE 39.3 Sitting position for a lumbar puncture. (From Davidson RI. Lumbar puncture. In: Vander Salm TJ, Cutler BS, Wheeler HB, eds. *Atlas of Bedside Procedures*. 2nd ed. Boston: Little, Brown; 1992:443.)

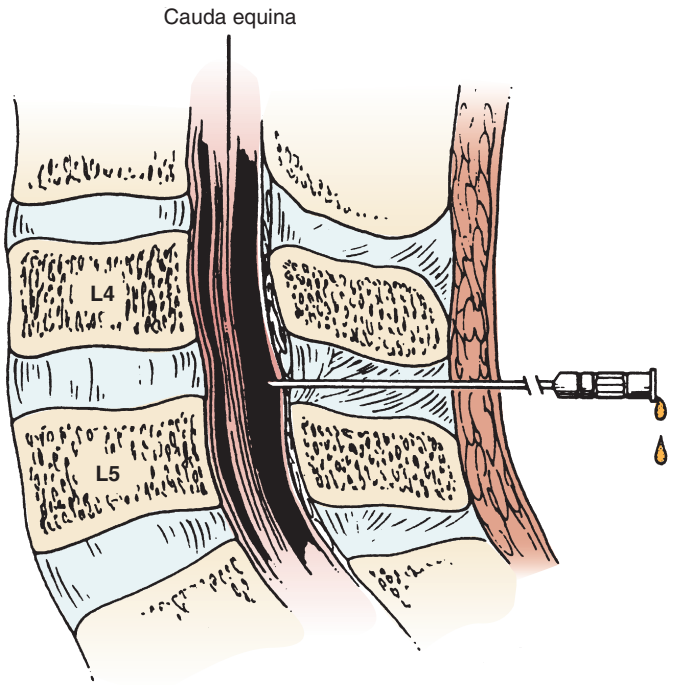

FIGURE 39.4 The needle and stylet are advanced into the subarachnoid space. On penetration into the space, the examiner often feels a give or pop after moving through the dura. After the needle enters into the subarachnoid space, the clinician removes the stylet and collects the cerebrospinal fluid. (From Davidson RI. Lumbar puncture. In: Vander Salm TJ, Cutler BS, Wheeler HB, eds. *Atlas of Bedside Procedures*. Boston: Little, Brown; 1992:447.)

coagulopathy, or thrombocytopenia, lumbar puncture should be postponed until the bleeding disorder is corrected, and extra care should be taken to avoid a traumatic lumbar puncture. Such children should be monitored after the procedure for the development of neurologic deficits. *Empirical therapy may be started while the coagulopathy is corrected.*

Other, rarer complications of lumbar puncture include cortical blindness from compression of the posterior cerebral artery against the tentorium cerebelli, causing ischemic infarction of the occipital lobes. Cervical spinal cord infarction, with respiratory arrest and flaccid tetraplegia, may occur if intracranial hypertension causes herniation of the cerebellar tonsils through the foramen magnum with resulting compression of the anterior spinal artery or its penetrating branches. Post–lumbar puncture headache may occur in up to 10% of older children and adults; it is presumably caused by persistent CSF leakage at the lumbar puncture site.

The CSF is examined for red blood cells (RBCs), white blood cells (WBCs) and differential, glucose, protein, and the presence (by culture, by Gram stain or other stain, or by antigen or DNA-PCR testing for specific agents) of pathogenic organisms. Opening pressure measurements are obtained with the head of the bed flat and with the child relaxed and in the lateral decubitus position with the back no longer tightly flexed. The upper limit of normal value in children 1-18 years of age is less than 25 cm of water. Opening pressure is less than 5 cm H_2O in premature infants and less than 10 cm H_2O in normal newborns. Opening pressure measurements are elevated if the lumbar puncture is performed with the patient in the sitting position and if the patient is combative or performing the Valsalva maneuver. Obstructive hydrocephalus, hyperventilation, or removal of fluid can all lead to lowering of the measurement. Children with bacterial meningitis usually have a mean opening pressure of 18 ± 7 cm H_2O.

Normal CSF is clear and colorless (Table 39.6). Blood in the CSF indicates a traumatic lumbar puncture or a CNS hemorrhage. Obtaining a RBC count on tubes 1 and 3 may differentiate the 2 conditions because the count is unchanged in CNS hemorrhage but may decline in traumatic taps. Centrifugation of the CSF sample may also help differentiate between a traumatic tap and a CNS hemorrhage. When blood has been present in the CSF for several hours, the CSF is xanthochromic after centrifugation. However, if the blood was recently mixed with CSF, as in the case of a traumatic tap, the supernatant is clear. Xanthochromic CSF can also be caused by icterus or an elevated CSF protein concentration.

The normal values for WBCs in the CSF are shown in Table 39.6. Most children with bacterial meningitis have a WBC count of at least $1000/mm^3$ in their CSF, but, in general, more than $6/mm^3$ in children after the neonatal period is considered abnormal. Normal values for neonates are 0-18 (mean: 6) WBCs in the CSF.

An absolute neutrophil count exceeding $3/mm^3$ (neutrophils may be as high as 35%) is also considered abnormal and evidence of a

TABLE 39.6 Cerebrospinal Fluid Findings in Central Nervous System Disorders

Condition	Pressure (mm H_2O)	Leukocytes (mm^3)	Protein (mg/dL)	Glucose (mg/dL)	Comments
Normal	50–80	<5, ≥75% Lymphocytes	20–45	>50 (or 75% serum glucose)	
Common Forms of Meningitis					
Acute bacterial meningitis	May be elevated (100–300)	100–10,000 or more; usually 300–2,000; PMNs predominate	Usually 100–500	Decreased, usually <40 (or <50% serum glucose)	Organisms usually seen on Gram stain and recovered by culture
Partially treated bacterial meningitis	Normal or elevated	5–10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time	Usually 100–500	Normal or decreased	Organisms may be seen on Gram stain. Pretreatment may render CSF sterile. Organism detected by antigen or PCR tests
Viral meningitis or meningoencephalitis	Normal or slightly elevated (80–150)	Rarely >1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand. PMNs early but mononuclear cells predominate through most of the course	Usually 50–200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15–20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on CT or MRI scans or EEG. HSV and enteroviruses may be detected by PCR of CSF
Uncommon Forms of Meningitis					
Tuberculous meningitis	Usually elevated	10–500; PMNs early, but lymphocytes predominate through most of the course	100–3,000; may be higher in presence of CSF block	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms almost never seen on smear. Organisms may be recovered in culture of large volumes of CSF. *Mycobacterium tuberculosis* may be detected by PCR of CSF; elevated ADA and gamma interferon
Fungal meningitis	Usually elevated	5–500; PMNs early but mononuclear cells predominate through most of the course. Cryptococcal meningitis may have no cellular inflammatory response	25–500	<50; decreases with time if treatment is not provided	Budding yeast may be seen. Organisms may be recovered in culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection
Syphilis (acute) and leptospirosis	Usually elevated	50–500; lymphocytes predominate	50–200	Usually normal	Positive CSF serology. Spirochetes not demonstrable by usual techniques of smear or culture; dark-field examination may be positive
Amebic (*Naegleria*) meningoencephalitis	Elevated	1,000–10,000 or more; PMNs predominate	50–500	Normal or slightly decreased	Mobile amebas may be seen by hanging-drop examination of CSF at room temperature

TABLE 39.6 Cerebrospinal Fluid Findings in Central Nervous System Disorders—cont'd

Condition	Pressure (mm H_2O)	Leukocytes (mm^3)	Protein (mg/dL)	Glucose (mg/dL)	Comments
Brain Abscesses and Parameningeal Focus					
Brain abscess	Usually elevated	5–200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach >100,000	75–500	Normal unless abscess ruptures into ventricular system	No organisms on smear or culture unless abscess ruptures into ventricular system
Subdural empyema	Usually elevated	100–5,000; PMNs predominate	100–500	Normal	No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid
Cerebral epidural abscess	Normal to slightly elevated	10–500; lymphocytes predominate	50–200	Normal	No organisms on smear or culture of CSF
Spinal epidural abscess	Usually low, with CSF block	10–100; lymphocytes predominate	50–400	Normal	No organisms on smear or culture of CSF
Chemical (drugs, dermoid cysts, myelography dye)	Usually elevated	100–1,000 or more; PMNs predominate	50–100	Normal or slightly decreased	Epithelial cells may be seen within CSF by use of polarized light in some children with dermoids
Noninfectious Causes					
Sarcoidosis	Normal or elevated slightly	0–100; mononuclear	40–100	Normal	No specific findings
Systemic lupus erythematosus with CNS involvement	Slightly elevated	0–500; PMNs usually predominate; lymphocytes may be present	100	Normal or slightly decreased	No organisms on smear or culture. Positive neuronal and ribosomal P protein antibodies in CSF
Tumor, leukemia	Slightly elevated to very high	0–100 or more; mononuclear or blast cells	50–1,000	Normal to decreased (20–40)	Cytology may be positive
Acute disseminated encephalomyelitis	Normal or elevated	~100 lymphocytes	Normal to elevated	Normal	MRI adds to diagnosis
Autoimmune encephalitis	Normal	~100 lymphocytes	Normal to elevated	Normal	Anti-NMDAR antibody positive

CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; HSV, herpes simplex virus; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; PCR, polymerase chain reaction; PMN, polymorphonuclear neutrophils; ADA, adenosine deaminase.
From Prober CG, Srinivas NS, Mathew R. CNS infections. In: Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016, Table 603.1.

bacterial infection. Although there are case reports of children with proven, usually rapidly fulminant meningococcal bacterial meningitis who do not have CSF pleocytosis, the CSF of 98% of children with meningitis has pleocytosis and more than 50% neutrophils. It takes 200-400 WBCs/mm^3 to turn CSF turbid.

On occasion, the spinal needle is advanced too far and passes through the subarachnoid space and penetrates the richly vascularized ventral epidural space. Blood is thereby introduced into the subarachnoid space, and the CSF appears bloody. This occurrence is often called a traumatic tap. It is then difficult to know whether the WBCs seen on examination of the CSF are caused by CSF pleocytosis or are peripheral blood WBCs contaminating the CSF. To aid in this determination, the ratio of WBCs to RBCs in the CSF is compared with the ratio of WBCs to RBCs in the patient's peripheral blood. A higher ratio in the CSF indicates the presence of CSF pleocytosis. When the CSF ratio is at least 10 times higher than the blood ratio, bacterial meningitis is indicated, with a sensitivity of 88% and a specificity of 90%. Conversely, the negative predictive value for the presence of bacterial meningitis of a less than 10-fold difference between the ratios is 99%. Traumatic taps usually do not alter the CSF glucose, Gram stain, or culture findings, which are often abnormal with bacterial meningitis. When there is doubt about the validity of the cell count after a bloody tap, the lumbar puncture should be repeated after several hours by introducing the spinal needle 1 intervertebral space above the original tap site.

In normal CSF, the glucose concentration is two-thirds that of serum glucose concentration. The CSF glucose concentration is low in most infected infants and younger children and in 45% of school-aged children with bacterial meningitis. In children older than 2 months of age, a CSF/serum glucose ratio of less than 0.4 is 80% sensitive and 98% specific for the presence of bacterial meningitis. The presence of RBCs in a CSF sample that is promptly analyzed does not affect the glucose concentration.

The normal CSF protein concentration is less than 45 mg/dL in children older than 2 months. The mean CSF protein concentration is 90 (range, 20-170) in full-term infants and 115 (range, 65-150) in preterm infants.

The CSF protein concentration is elevated in more than 90% of younger children with bacterial meningitis but in only 60% of infected school-aged children. Every 1000 RBCs in the CSF (from a traumatic tap) increases the protein concentration by approximately 1 mg/dL.

The presence of bacterial pathogens in the CSF should be investigated. Microscopic examination of a Gram-stained sample of the fluid is performed first. The sensitivity of this test is directly related to the number of organisms in the CSF and is inversely related to the age of the patient. The Gram stain identification of certain organisms, such as *H. influenzae*, may be problematic. A decision whether to treat a child for bacterial meningitis should not be based on the Gram stain alone; the definitive diagnosis is based on the CSF culture. Rapid diagnostic tests for bacterial antigens in CSF, including countercurrent immunoelectrophoresis and latex particle agglutination, suffer from variations in sensitivity and specificity that limit their value in clinical practice.

Some patients will have been treated with antibiotics before the lumbar puncture is performed. When the CSF from such a child is examined, organisms may not be seen on Gram stain or recovered on culture. However, abnormalities of CSF cell count (including elevated leukocytes), protein concentration, and glucose concentration usually continue to suggest the diagnosis of bacterial meningitis. In this setting, presumptive treatment for bacterial meningitis is initiated. If an organism is identified by culture or antigen detection, definitive antibiotic treatment is administered. If no organism is identified, the decision to continue treatment depends on the clinical suspicion of bacterial meningitis and the exclusion of other causes of aseptic meningitis (Tables 39.7 and 39.8). Newer laboratory techniques that utilize PCR to detect bacterial pathogens are being developed and may be useful in the diagnosis of bacterial meningitis in patients who have been treated with antibiotics before lumbar puncture.

Computed Tomography

Routine computed tomography (CT) of the head is not indicated in children with suspected meningitis. Even though children with bacterial meningitis have increased intracranial pressure, most CT scans are normal. In addition, most lumbar punctures do not result in cerebral herniation in patients with meningitis. CT should be reserved for children who show clinical signs of herniation or cerebral edema and for those who may have an intracranial mass causing signs and symptoms similar to meningitis.

Other Laboratory Tests

Usually, the peripheral blood WBC and platelet counts are elevated with bacterial meningitis. A low WBC count and thrombocytopenia may also be seen; these are associated with overwhelming infection and a poor outcome. The sensitivity (70%), specificity (54%), and negative predictive value (81%) of the differential WBC count are too low to render the differential WBC examination useful in making the diagnosis of bacterial meningitis.

Blood cultures may be useful in identifying the bacterial pathogen of meningitis. However, a negative blood culture may be found in up to 33% of children with meningococcal meningitis, 20% of children with pneumococcal cases, and 10% of patients with *H. influenzae* type b meningitis. These numbers increase with prior antibiotic therapy. In addition, there is a negative correlation between the length of illness before diagnosis and the rate of positive blood cultures. A bacterial meningitis score has been developed to attempt to distinguish between bacterial and aseptic (nonbacterial) meningitis in patients with CSF pleocytosis. The risk of bacterial meningitis is low if *none* of the following criteria are present: history of a seizure with the illness, blood neutrophil count $\geq 10 \times 10^9$ cells/L, positive CSF Gram stain, CSF protein ≥80 mg/dL, or CSF neutrophil count $\geq 1 \times 10^9$ cells/L. This diagnostic tool is 99% sensitive and 62% specific for bacterial meningitis. It should only be applied to non–ill-appearing children older than 2 months without petechiae, purpura, or other concerning findings on examination who have not been pretreated with antibiotics.

Aseptic Meningitis

Aseptic meningitis is an inflammatory process of the meninges, most often characterized by acute signs and symptoms of meningeal irritation; CSF pleocytosis, usually with a predominance of mononuclear cells; a normal or, less frequently, elevated CSF protein concentration; normal or, less often, low CSF glucose concentration; and no organisms demonstrable by Gram stain or bacterial cultures. There are many causes of aseptic meningitis (see Table 39.7). The most common cause is viral infection; up to 90% of cases are caused by enteroviruses and arbovirus. The definitive diagnosis is made by identifying the organism in the CSF. However, this is not always possible, and other causes must be excluded by history, presence or absence of associated symptoms, and appropriate laboratory tests (Tables 39.7 and 39.8).

Viral Meningitis

Enteroviral meningitis occurs most often during the summer and early fall months. Transmission is via the fecal-oral route, and young children exhibit increased transmission of the viruses and more severe disease in comparison with other age groups. Initially, patients may have a respiratory tract infection, a nonspecific febrile illness, or vomiting and diarrhea. Viral infection of the meninges occurs 7-10 days after initial exposure. The clinical course may be biphasic. Virus from the oropharynx can be cultured only during the 1st 5-7 days of the illness but may be excreted in stool for 6-8 weeks.

Children with viral meningitis present with fever, nuchal rigidity, irritability, headache, and vomiting. Less common symptoms are anorexia, drowsiness, photophobia, myalgia, and malaise. As in bacterial meningitis, affected young infants often lack meningeal signs. In addition, children may have an altered sensorium, but focal neurologic signs are rare. Seizures are more common in infants.

The number of WBCs in the CSF varies from zero to several thousand (Table 39.6). Up to 75% of *initial (early in the illness)* CSF specimens contain a predominance of polymorphonuclear cells. Mononuclear cells predominate by 2 days after the onset of symptoms. Of children with enteroviral meningitis, 18% may have decreased CSF glucose concentrations, whereas 12% may have elevated CSF protein. Treatment of enteroviral meningitis is supportive. Admission to the hospital may be required while bacterial meningitis is being ruled out and for intravenous hydration. Analgesics and antipyretics may also be indicated. The lumbar puncture performed to diagnose viral meningitis is often helpful in ameliorating the acute symptoms. The mechanism for this is not clear.

The outcome is quite good for patients in whom common viral pathogens cause aseptic meningitis. Sequelae in older children are rare. Adverse outcomes are more common (but unusual) in children who have viral meningitis during the 1st year of life. Speech and language development may be affected. Treatment and outcome for the other types of aseptic meningitis depend on the underlying cause.

Tuberculous Meningitis

Tuberculous meningitis is an important treatable cause of aseptic meningitis. During the primary pulmonary tuberculous infection and

TABLE 39.7 Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis

Viruses
Enteroviruses (coxsackievirus, echovirus, poliovirus, enterovirus)
Parechovirus
Arboviruses: Eastern equine, Western equine, Venezuelan equine, St. Louis encephalitis, Powassan and California encephalitis, West Nile virus, Colorado tick fever
Herpes simplex (types 1, 2)
Human herpesvirus (types 6, 7)
Varicella–zoster virus
Epstein–Barr virus
Parvovirus B19
Cytomegalovirus
Adenovirus
Variola (smallpox)
Measles
Mumps
Rubella
Influenza A and B
Parainfluenza
Rhinovirus
Rabies
Lymphocytic choriomeningitis
Rotaviruses
Coronaviruses
Human immunodeficiency virus type 1

Bacteria
Mycobacterium tuberculosis
Leptospira species (leptospirosis)
Treponema pallidum (syphilis)
Borrelia species (relapsing fever)
Borrelia burgdorferi (Lyme disease)
Nocardia species (nocardiosis)
Brucella species
Bartonella species (cat-scratch disease)
Rickettsia rickettsiae (Rocky Mountain spotted fever)
R. prowazekii (typhus)
Ehrlichia canis
Coxiella burnetii
Mycoplasma pneumoniae
M. hominis
Chlamydia trachomatis
C. psittaci
C. pneumoniae
Partially treated bacterial meningitis

Bacterial Parameningeal Focus
Sinusitis
Mastoiditis
Brain abscess
Subdural–epidural empyema
Cranial osteomyelitis

Fungi
Coccidioides immitis (coccidioidomycosis)
Blastomyces dermatitidis (blastomycosis)
Cryptococcus neoformans (cryptococcosis)
Histoplasma capsulatum (histoplasmosis)
Candida species
Other fungi (*Alternaria, Aspergillus, Cephalosporium, Cladosporium, Dreschlera hawaiiensis, Paracoccidioides brasiliensis, Petriellidium boydii, Sporotrichum schenckii, Ustilago* species, Zygomycetes)

Parasites (Eosinophilic)
Angiostrongylus cantonensis
Gnathostoma spinigerum
Baylisascaris procyonis
Strongyloides stercoralis
Trichinella spiralis
Toxocara canis
Taenia solium (cysticercosis)
Paragonimus westermani
Schistosoma species
Fasciola species

Parasites (Noneosinophilic)
Toxoplasma gondii (toxoplasmosis)
Acanthamoeba species
Naegleria fowleri
Malaria

Postinfectious
Vaccines: rabies, influenza, measles, poliovirus
Demyelinating or allergic encephalitis

Systemic or Immunologically Mediated
Bacterial endocarditis
Autoimmune encephalitis
Kawasaki disease
Systemic lupus erythematosus
Vasculitis, including polyarteritis nodosa
Sjögren syndrome
Mixed connective tissue disease
Rheumatoid arthritis
Behçet syndrome
Polyangiitis with granulomatosis
Lymphomatoid granulomatosis
Granulomatous arteritis
Sarcoidosis
Familial Mediterranean fever
Vogt–Koyanagi–Harada syndrome

Malignancy
Leukemia
Lymphoma
Metastatic carcinoma
Central nervous system tumor (e.g., craniopharyngioma, glioma, ependymoma, astrocytoma, medulloblastoma, teratoma)

Continued

TABLE 39.7 Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis—cont'd

Drugs	Miscellaneous
Intrathecal injections (contrast media, serum, antibiotics, antineoplastic agents)	Heavy metal poisoning (lead, arsenic)
Nonsteroidal antiinflammatory agents	Foreign bodies (shunt, reservoir)
OKT3 monoclonal antibodies	Subarachnoid hemorrhage
Carbamazepine	Postictal state
Azathioprine	Postmigraine state
Intravenous immune globulins	Mollaret syndrome (recurrent)
Antibiotics (trimethoprim-sulfamethoxazole, sulfasalazine, ciprofloxacin, isoniazid)	Intraventricular hemorrhage (neonate)
	Familial hemophagocytic syndrome
	Post neurosurgery
	Dermoid–epidermoid cyst

Data from Cherry JD. Aseptic meningitis and viral meningitis. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 4th ed. Philadelphia: WB Saunders; 1998:450; and from Davis LE. Aseptic and viral meningitis. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Disease*. New York: Churchill Livingstone; 1997:329.

subsequent lymphohematogenous spread to extrapulmonary sites, tubercle bacilli produce local microscopic granulomas in the CNS and meninges. If this primary CNS infection is not contained by host defense mechanisms (T lymphocytes, monocytes), or if host defense mechanisms fail at a later period, tuberculous meningitis may result. Meningitis occurs weeks to months after the primary pulmonary process.

The symptoms of tuberculous meningitis are insidious and subacute (weeks to months). Stage 1 is a prodrome with nonspecific manifestations (apathy, poor school function, irritability, weight loss, fever, night sweats, nausea); stage 2 is heralded by the onset of neurologic signs (headache, cranial neuropathy, nuchal rigidity, signs of increased intracranial pressure); and stage 3 manifests with altered levels of consciousness (lethargy, stupor, coma). Meningismus is not present in all patients.

The diagnosis is supported by a history of contacts with adults with known active tuberculosis, a chronic cough, or human immunodeficiency virus (HIV) disease or by a history of immigration, poverty, or homelessness. In addition, the patient's chest radiograph is consistent with active or, more often, quiescent tuberculosis (parenchymal-hilar node calcifications, infiltrates, hilar adenopathy, and, in rare cases, endobronchial or cavitary lesions), and the patient's tuberculin skin test yields a positive result (see Chapter 2). Cranial CT or magnetic resonance imaging (MRI) may show the most intense meningeal inflammation around the base of the brain or inflammatory mass lesions (tuberculomas). The CSF results (Table 39.6) include profound hypoglycorrhachia, a high CSF protein, lymphocyte- or monocyte-predominant cells (usually 500 cells/mm^3), increased opening pressure, and, on occasion, tubercle organisms on acid-fast staining. PCR amplification of *Mycobacterium tuberculosis* DNA aids in making a more rapid diagnosis than does culture of CSF, sputum, or gastric aspirates, which traditionally requires 2-6 weeks. The differential diagnosis depends on the stage of the illness.

Encephalitis

Encephalitis is inflammation of the brain parenchyma, whereas meningoencephalitis is inflammation of the brain accompanied by inflammation of the meninges. Meningoencephalitis is distinguished from aseptic meningitis by evidence of brain parenchymal involvement, including behavior or personality changes; altered level of consciousness (including agitation or coma); generalized seizures; focal neurologic signs, including focal seizures and focal motor defects (hemiparesis or ataxia); or movement disorders.

Enteroviruses and arboviruses cause most cases of infectious encephalitis in children. Enterovirus encephalitis, uncommon without meningeal involvement, is suggested by epidemic occurrence and presence of typical prodrome or associated findings (Table 39.8); prompt diagnosis is by PCR for enterovirus in CSF, blood, throat, or stool specimens. A CSF or blood specimen is preferred because PCR may identify enterovirus in throat and especially stool for weeks after the primary infection has resolved. Arbovirus encephalitis is suggested by mosquito or tick exposure and epidemic occurrence and is diagnosed by findings of arbovirus immunoglobulin M in CSF or blood or by paired serologic findings for immunoglobulin G.

Infections with herpes simplex virus (HSV) occur throughout the year. In neonates, HSV encephalitis usually occurs between 7 and 21 days of age; may produce focal or generalized CNS disease; and may occur with or without conjunctivitis, oral mucosal involvement, vesicles on skin, or disseminated disease (hepatitis, pneumonia, septic appearance). After the neonatal period, HSV encephalitis is usually isolated to the CNS and classically produces necrotizing encephalitis with a focus in the temporal lobe. Symptoms in persons with HSV encephalitis range broadly from those suggesting mild aseptic meningitis to the presence of status epilepticus and coma and then death. In addition to neutrophils and monocytes, CSF examination may show increased numbers of erythrocytes and elevated protein. CT, MRI, and an electroencephalogram (EEG) may suggest a temporal lobe focus. Specific diagnosis is by PCR of CSF for herpes simplex DNA. CSF culture is usually negative. In the appropriate clinical setting, presumptive therapy with intravenous acyclovir, 60 mg/kg/day given every 8 hours, is indicated while the results of PCR of CSF for HSV are awaited.

Autoimmune encephalitis. Anti-D-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a novel and relatively common form of encephalitis. Data from the California Encephalitis Project showed that anti-NMDAR encephalitis was the most common identifiable cause of encephalitis in their cohort, which included patients from 6 months to 30 years. Most of the cases occurred in children and adolescents. Patients present with similar features as viral encephalitis, but seizures, language dysfunction, psychosis, autonomic dysfunction, movement disorders, and EEG abnormalities are more common in these patients.

FEVER OF UNKNOWN ORIGIN

In adults, FUO is defined as an illness lasting more than 3 weeks, a fever higher than 38.3°C (101°F) on several occasions, and uncertainty

TABLE 39.8 Characteristics of the Most Common Causes of Aseptic Meningitis Syndrome

Organism	Age Group Serology	Season	Prodrome	Clinical Characteristics	Epidemiologic Characteristics	Agent Identification	Serologic Diagnosis
Common							
Enteroviruses	Infants, young children	Summer, fall	None, or mild GI or pharyngitis syndrome for 1–3 days	Exanthem, myopericarditis, conjunctivitis, pleurodynia, hand–foot–mouth disease, herpangina, myositis, hepatitis	Epidemic	Culture or PCR of CSF, blood, throat, stool	Enterovirus serologic study
Arboviruses	Children, elderly	Summer, early fall	Fever, rash, malaise for 1–5 days	Encephalitis or aseptic meningitis	Geographic area, contact with insect vector, encephalitis in community or animals	PCR of CSF	IgM, paired IgG
Herpes simplex type 2	Young adults	Year round	Genital vesicles for 1–7 days	Associated primary herpes lesions	Sexual exposure	Culture of genital lesions; PCR of CSF	IgM, paired IgG
Borrelia burgdorferi (Lyme disease)	Children, adults	Spring–late fall	Erythema migrans; secondary symptoms weeks to months later	Facial palsy or other cranial nerve palsy; radiculitis; heart block	Endemic area, deer tick exposure (often unrecognized)	PCR of CSF	IgG, IgM: EIA with Western blot confirmation
Less Common							
Mumps	5- to 9-year-olds	Late winter–spring	Parotitis, orchitis: 2–10 days	Parotitis, orchitis, oophoritis, pancreatitis	Exposure to mumps or vaccination	PCR of CSF, throat	IgM, paired IgG
HIV	Young adults	Year round	Fever, arthralgias, maculopapular rash, pharyngitis, adenopathy	Same as prodrome; meningitis may occur 1–5 days into the illness	2–6 wk after sexual or blood exposure	Blood PCR for HIV, RNA, or DNA	IgG (EIA) negative at this stage
Lymphocytic choriomeningitis virus	Older children, young adults	Fall, early winter	Fever and flulike syndrome, 5–21 days	Orchitis, alopecia	Exposure to mice, hamsters	PCR of CSF, blood	IgG
Mycobacterium tuberculosis	Infants (primary infection), young adults (reactivation)	Year round	Fever	Pneumonia, basilar inflammation with cranial nerve palsy and intracranial hypertension	History of tuberculosis or exposure, HIV risk factors	Culture, PCR of CSF for mycobacteria	None
Leptospira	Young adults	Late summer, early fall	Hepatitis and hematuria, 1–7 days	Conjunctivitis, splenomegaly, jaundice, nephritis, rash	Exposure to animals, water contaminated with animal urine	Culture of blood, CSF, urine	Paired IgG
Fungal	Premature infant, young adult	Year round	Fever	Basilar inflammation on CT or MRI, cranial nerve findings	Endemic area (blastomycosis, histoplasmosis) Immunodeficiency (cryptococcosis) Prematurity (candidal disease)	Culture of CSF for fungus, meningeal biopsy	Specific IgG
Mycoplasma organisms	Children, young adults	Fall, winter	Fever, malaise, sore throat, cough	Cough, rash, hemolytic anemia	Family or community epidemic	PCR of CSF, nasopharyngeal secretions	IgM

CSF, cerebral spinal fluid; CT, computed tomography; EIA, enzyme immunoassay; GI, gastrointestinal; HIV, human immunodeficiency virus; IgG and IgM, immunoglobulins G and M; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

Modified from Connolly KJ, Hammer SM. The acute aseptic meningitis syndrome. *Infect Dis Clin North Am.* 1990;4:599-622; and from Davis LE. Aseptic and viral meningitis. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Disease*. New York: Churchill Livingstone; 1997:331.

TABLE 39.9 Summary of Definitions and Major Features of the Four Subtypes of Fever of Unknown Origin

	Classic FUO	Health Care–Associated FUO	Immune-Deficient FUO	HIV-Related FUO
Definition	>38.0°C, >3 wk, >2 visits or 3 days in hospital	>38.0°C, >3 days, not present or incubating on admission	>38.0°C, >3 days, negative cultures after 48 hr	38.0°C, >3 wk for outpatients, >3 days for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Leading causes	Infections, cancer, inflammatory conditions, undiagnosed, habitual hyperthermia	Health care–associated infections, postoperative complications, drug fever	Majority due to infections, but cause documented in only 40–60%	HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, degree and duration of neutropenia; drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum, lower limb deep veins	Wounds, drains, devices, sinuses, lungs, venous thrombosis urine	Skin folds, IV sites, lungs, sinuses, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, CT scan bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

FUO, fever of unknown origin; CMV, cytomegalovirus; CXR, chest radiograph; HIV, human immunodeficiency virus; IV, intravenous.
Modified from Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practices of Infectious Diseases*. 7th ed. Philadelphia: Churchill Livingstone; 2010:780, Table 51.1.

of diagnosis after a 1-week study in the hospital (Table 39.9). In pediatrics, the defined duration of fever is variable, from 8 days to 3 weeks (average, 2 weeks). This may be dependent on the age of the patient, with shorter periods of fever in young infants and more traditional adult standards in adolescent patients. FUO is defined as a temperature higher than 38°C (100.4°F) daily for at least 8-14 days and no diagnosis after an initial evaluation. The initial evaluation recommended varies but always includes a noncontributory history and physical examination, and nondiagnostic initial laboratory and radiologic tests. In accordance with this definition, the differential diagnosis for FUO in children is large (Table 39.10).

Most children with FUO have an infectious disease; in a systematic review of studies of children with FUO, 51% of children had an infectious cause, 9% had a collagen vascular cause and 6% had a malignancy. There were 11% identified as otherwise miscellaneous which included Kawasaki disease and inflammatory bowel disease; 23% were without a formal diagnosis. Infections identified included urinary tract infections (UTI) and tuberculosis in all children; and osteomyelitis and bartonellosis in developed countries and brucellosis and typhoid in developing countries. Often patients with an FUO have atypical manifestations of common childhood bacterial or viral diseases rather than unusual or uncommon disorders.

◆ Evaluation

The evaluation of a child with FUO centers on a detailed history and physical examination. Taking the history should be repeated because parents often remember important details after the initial interview. The physical examination findings may also change during the course of the investigation revealing important clues (Fig. 39.5, Table 39.11).

◆ History

The history should include the time of day of the fever, who measured the temperature, and the instrument that was used to measure the temperature. Increased temperatures after exercise and in the afternoon often represent normal variations. The appearance of the

TABLE 39.10 Diagnostic Considerations of Fever of Unknown Origin in Children

Abscesses
Abdominal
Brain
Dental
Hepatic
Pelvic
Perinephric
Rectal
Subphrenic
Psoas

Bacterial Diseases
Actinomycosis
Bartonella henselae (cat-scratch disease)
Brucellosis
Campylobacter
Francisella tularensis (tularemia)
Listeria monocytogenes (listeriosis)
Meningococcemia (chronic)
Mycoplasma pneumoniae
Rat bite fever (*Streptobacillus moniliformis*; streptobacillary form of rat bite fever)
Salmonella
Tuberculosis
Whipple disease
Yersiniosis
Chlamydia
Lymphogranuloma venereum
Psittacosis

Localized Infections
Cholangitis
Infective endocarditis
Mastoiditis
Osteomyelitis
Diskitis
Pneumonia
Pyelonephritis
Sinusitis

Spirochetes
Borrelia burgdorferi (Lyme disease)
Relapsing fever *(Borrelia recurrentis)*
Leptospirosis
Rat bite fever (*Spirillum minus*; spirillary form of rat bite fever)
Syphilis

Fungal Diseases
Blastomycosis (extrapulmonary)
Coccidioidomycosis (disseminated)
Histoplasmosis (disseminated)

Rickettsiae-like organisms
Q fever
Rocky Mountain spotted fever
Tick-borne typhus
Anaplasmosis
Ehrlichosis

Viruses
Cytomegalovirus
Hantavirus
Hepatitis viruses
Human immunodeficiency virus
Epstein–Barr virus

Parasitic Diseases
Amebiasis
Babesiosis
Giardiasis
Malaria
Toxoplasmosis
Trichinosis
Trypanosomiasis
Visceral larva migrans *(Toxocara)*

Rheumatologic Diseases
Behçet syndrome
Juvenile dermatomyositis
Juvenile idiopathic arthritis
Rheumatic fever
Systemic lupus erythematosus
Vasculitis

Hypersensitivity Diseases
Drug fever
Hypersensitivity pneumonitis
Serum sickness
Weber–Christian disease

Neoplasms
Atrial myxoma
Cholesterol granuloma
Hodgkin disease
Inflammatory pseudotumor
Leukemia
Lymphoma
Pheochromocytoma
Neuroblastoma
Wilms tumor

Granulomatous Diseases
Crohn disease
Granulomatous hepatitis
Sarcoidosis
Polyangiitis with granulomatosis

Familial and Hereditary Diseases
Anhidrotic ectodermal dysplasia
Autonomic neuropathies
Fabry disease
Familial dysautonomia
Familial Hibernian fever
Familial Mediterranean fever and the many other autoinflammatory diseases (see Chapter 41)
Hypertriglyceridemia
Ichthyosis
Sickle cell crisis
Spinal cord/brain injury

Continued

TABLE 39.10 Diagnostic Considerations of Fever of Unknown Origin in Children—cont'd

Miscellaneous	
Addison disease	Infantile cortical hyperostosis
Allergic Alveolitis	Inflammatory bowel disease
Castleman disease	Kawasaki disease
Chronic active hepatitis	Kikuchi–Fujimoto disease
Cyclic neutropenia	Metal fume fever
Diabetes insipidus (nonnephrogenic and nephrogenic)	Pancreatitis
Factitious fever	Periodic fever syndromes
Hemophagocytic syndromes	Poisoning
Hypereosinophilia syndromes	Pulmonary embolism
Hypothalamic-central fever	Thrombophlebitis
	Thyrotoxicosis, thyroiditis

TABLE 39.11 Examples of Subtle Physical Findings Having Special Significance in Patients with Fever of Unknown Origin

Body Site	Physical Finding	Diagnosis
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis, vasculitis
Oropharynx	Ulceration Tender tooth	Disseminated histoplasmosis, SLE, Behçet syndrome, IBD Periapical abscess
Fundi or conjunctivae	Choroid tubercle Petechiae, Roth spot	Disseminated granulomatosis* Endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective endocarditis, rheumatic fever
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis*
Rectum	Perirectal fluctuance, tenderness Perianal skin tags, fistula	Abscess IBD
Genitalia	Testicular nodule Epididymal nodule	Periarteritis nodosa, tumor Disseminated granulomatosis*
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis; malignancy, autoimmune disease
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis, bronchiectasis

*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, and syphilis.
SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease.
Modified from Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practices of Infectious Diseases.* 7th ed. Philadelphia: Churchill Livingstone; 2010:785, Table 51.8.

child while febrile is also important. Increased temperature without sweating might be seen in a child with ectodermal dysplasia or factitious fever.

The pattern of fever should be noted (Fig. 39.6). Sustained fever, intermittent fever, and relapsing fever have been associated with different disease states. Sustained or remittent fever remains elevated with little variation during the day and has been associated with enteric (typhoid) fever, tularemia, and rickettsial diseases such as typhus and Rocky Mountain spotted fever. Intermittent fever normalizes at least once a day and is associated with tuberculosis, abscesses, lymphomas, juvenile idiopathic arthritis (JIA), and some forms of malaria. Children with relapsing fever have afebrile days between febrile episodes. Relapsing fever has been associated with rat bite fever, *Borrelia* species infection, malaria, brucellosis, subacute bacterial endocarditis, African trypanosomiasis, lymphomas, and Lyme disease. Saddle-back or double-hump fever lasts a few days, is followed by an afebrile day or 2, and then returns. It has been associated with some viruses and dengue fever. Double quotidian fever (2 fever spikes each day) occurs in kala-azar, malaria, and gonococcal endocarditis. Periodic fevers occur as acute febrile episodes separated by prolonged afebrile, healthy periods. Diseases to consider include cyclic neutropenia, familial Mediterranean fever, and the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA). Periodic fever syndromes have different prevalence patterns in different ethnic groups and different inheritance patterns. A detailed family history is particularly important when these diagnoses are considered (see Chapter 41).

Unfortunately, neither the fever pattern nor the duration is specific for a particular cause. Fevers lasting for more than 1 year are not usually infectious; factitious fever, rheumatic or granulomatous disorders, familial diseases, or malignancies need to be considered in these patients.

A history of rash is important for diagnosing Lyme disease, JIA, and acute rheumatic fever (see Chapter 40). A history of pica is associated with visceral larva migrans and toxoplasmosis. Exposure to domestic and wild animals should be identified to exclude zoonoses (see Chapter 40). The food history should be detailed and should include water sources, use of game meats, cooking practices, and consumption of unpasteurized, raw milk, or soft cheese.

Travel history is critically important in the establishment of a differential diagnosis. Areas visited, accommodations, activities,

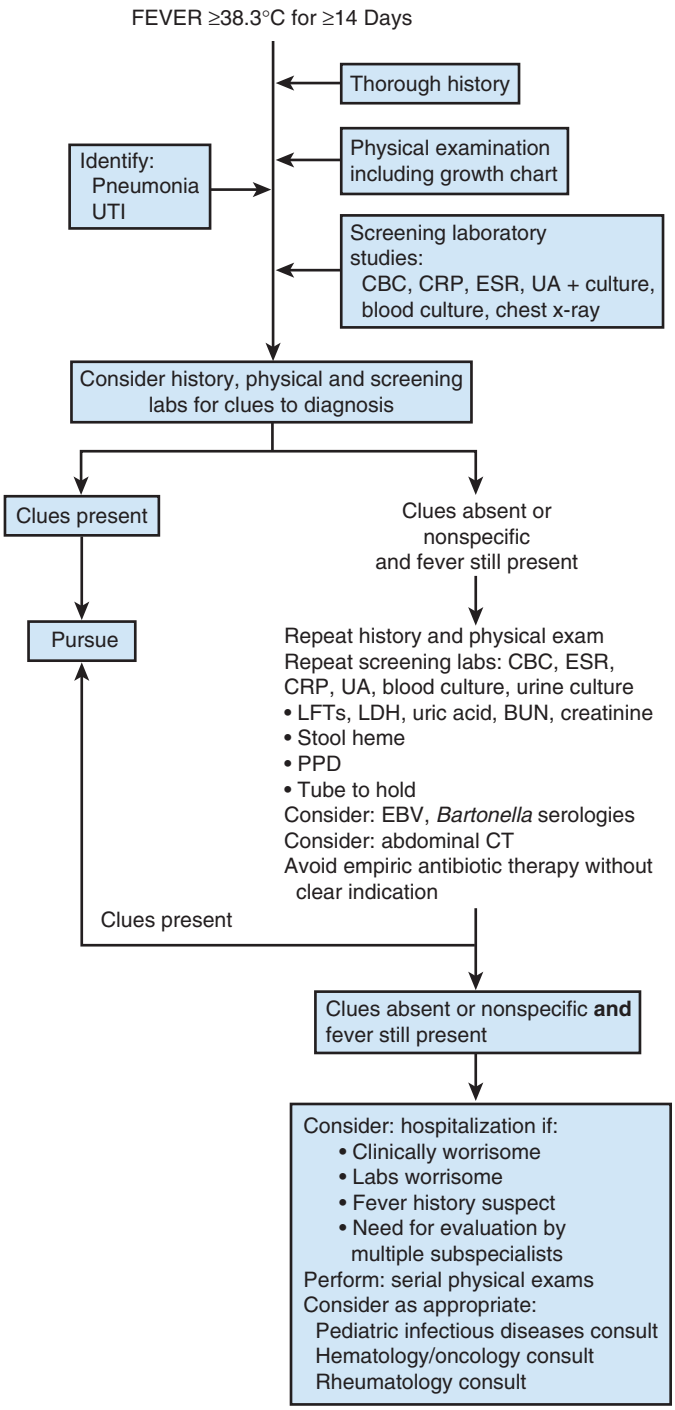

FIGURE 39.5 Approach to the evaluation of fever of unknown origin (FUO). BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; CRP, C-reactive protein; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; LFT, liver function test; PPD, purified protein derivative; UA, urinalysis; UTI, urinary tract infection.

prophylactic treatments, animal and insect exposures, and water and food sources should be reviewed. Coccidioidomycosis, histoplasmosis, malaria, Lyme disease, and Rocky Mountain spotted fever have regional distributions. Children who have traveled to or have emigrated from developing countries are at increased risk for endemic diseases and *M. tuberculosis* (Table 39.12).

Previous medical records should be reviewed. Weight loss is important for diagnosing many chronic diseases such as lymphoma, tuberculosis, and inflammatory bowel disease. Poor weight gain and growth, with or without gastrointestinal symptoms, may be the only historical clue to inflammatory bowel disease (see Chapter 11). HIV risk factors in the parents and child should be reviewed. Past and current medications should also be reviewed. The review of systems may reveal heat intolerance, palpitations, tremors, and declining quality of schoolwork in a child with hyperthyroidism. A history of severe head trauma may be associated with hypothalamic dysfunction and central fevers.

◆ Physical Examination

Whenever possible, the patient should be examined during a febrile episode. A high fever in the absence of an increased pulse may be present in a patient with factitious fever. To verify this diagnosis, the temperature of freshly voided urine may be recorded. Tremor, tachycardia, palpitations, exophthalmos, lid lag, eyelid retraction, and smooth, flushed skin with diaphoresis are suggestive of hyperthyroidism.

Eyes

The ophthalmologic examination should include assessment of visual acuity, extraocular motion, visual field integrity, and gaze, as well as inspection of external structures and ophthalmoscopic examination (see Chapter 32). Conjunctivitis, iritis-uveitis-scleritis, or both may be seen in a variety of infectious conditions, including Epstein–Barr virus (EBV) infection, leptospirosis, rickettsial infection, and cat-scratch disease. Conjunctivitis, uveitis, or both occur with Kawasaki disease, systemic lupus erythematosus (SLE), polyarteritis nodosa, and JIA. Sarcoidosis may be associated with conjunctival and uveal tract nodules. A thorough ophthalmoscopic evaluation (and, if needed, slit-lamp examination) should be performed. Sarcoidosis may be accompanied by vascular occlusions, hemorrhages, vascular sheathing, and preretinal inflammatory exudates. Cytomegalovirus (CMV) produces chorioretinitis associated with white infiltrates near vessels and confluent depigmented areas. Histoplasmosis causes small atrophic spots and, in rare cases, focal granulomas of the retina and choroid. *Toxoplasma gondii* is a common cause of recurrent retinochoroiditis. Retinal changes also occur with bacterial endocarditis. Tuberculosis can cause formation of choroidal tubercles and also ulcerative palpebral conjunctival lesions. Slit-lamp examination may also reveal iridocyclitis in JIA, Behçet syndrome, and inflammatory bowel disease.

Ears, Nose, and Throat

The frontal and maxillary sinuses should be palpated for tenderness. The nares should be inspected for inflamed mucosa and purulent discharge. Tympanic membranes should be viewed and insufflated (see Chapter 4). The mouth should be checked for lesions, inflammation, and tooth tenderness. Behçet syndrome may manifest with oral aphthous lesions. Inspection of teeth and gums may reveal a dental abscess. Exudative and nonexudative pharyngitis is associated with EBV infection, tularemia, leptospirosis, and CMV. PFAPA syndrome is characterized by periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy. *Candida* infection in the mouths of children older than 2 years may result from immunodeficiency such as HIV or from the use of inhaled steroids.

Neck

The neck should be examined for adenopathy or thyroid enlargement (see Chapter 36). The rest of the lymphatic system should be carefully examined. A single tender node may be seen with cat-scratch disease. Generalized adenopathy can be seen in CMV infection, EBV infection, and systemic JIA (see Chapter 33).

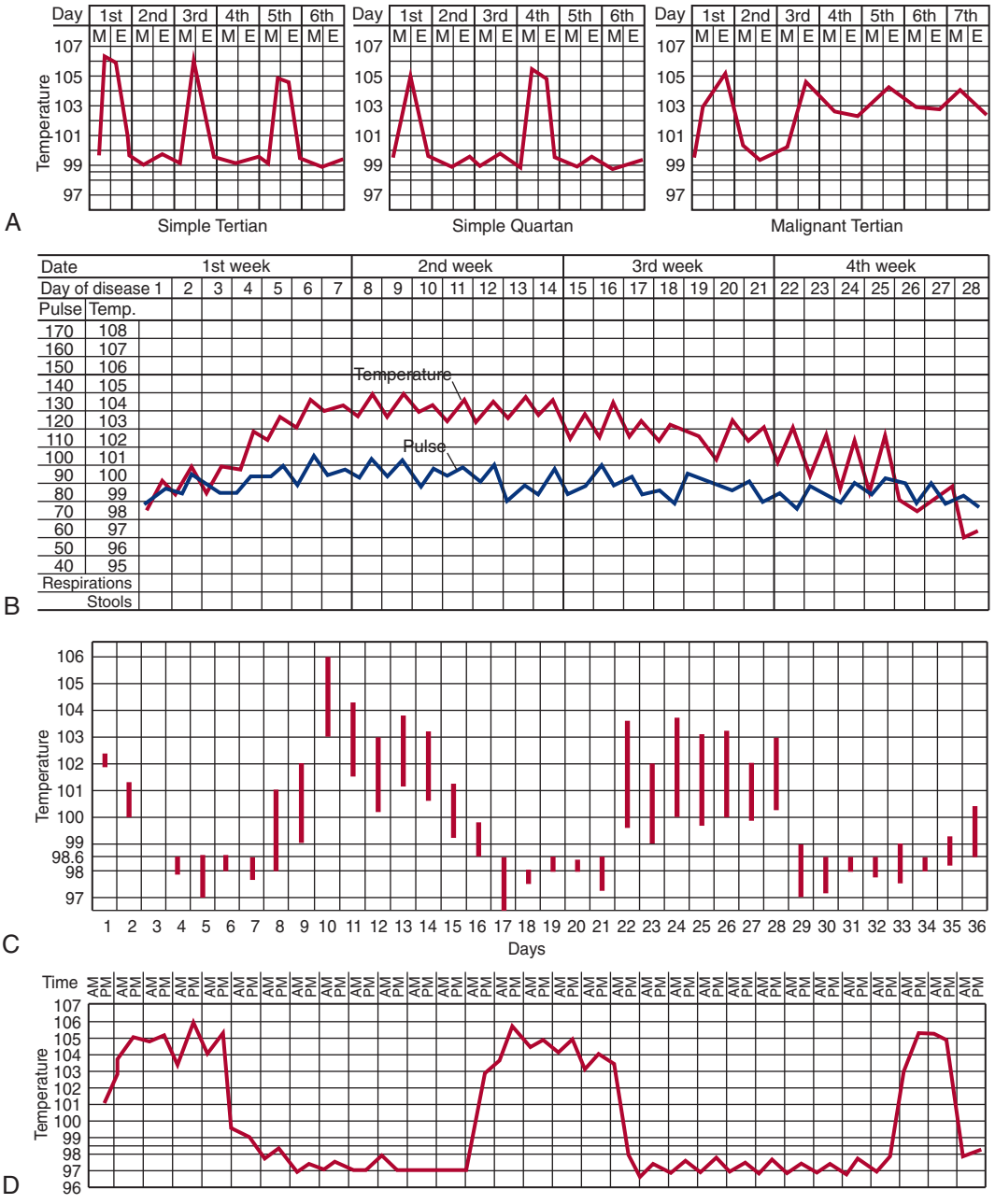

FIGURE 39.6 Distinctive Fever Patterns. *A,* Malaria. *B,* Typhoid fever (demonstrating relative bradycardia). *C,* Hodgkin disease (Perl-Ebstein pattern). *D,* Borreliosis (relapsing fever pattern). (Data from Woodward TE. The fever pattern as a clinical diagnostic aid. In: Mackowiak PA, ed. *Fever: Basic Mechanisms and Management*. 2nd ed. Philadelphia: Lippencott-Raven; 1997:215-236.)

Heart, Lungs, and Abdomen

Careful auscultation of the heart and lungs is essential. A mitral or aortic regurgitant murmur may be the initial finding of endocarditis or of carditis in children with acute rheumatic fever. A pericardial friction rub may also suggest JIA, SLE, rheumatic fever, malignancy, or viral pericarditis. The abdomen must be carefully palpated for evidence of masses or hepatosplenomegaly (see Chapters 14 and 17). Abdominal tenderness may be present with abdominal abscesses, hepatosplenomegaly, and inflammatory bowel disease. A rectal examination should be performed, and stool should be tested for occult blood. Sexually active girls should have a pelvic examination. Pain on movement of the uterus during the pelvic examination may indicate pelvic inflammatory disease.

Musculoskeletal Evaluation

The musculoskeletal examination should include assessments of strength and of active and passive range of motion and evaluation for warmth, tenderness, or swelling of joints. Irritability and pain on palpation over a bone or disuse pseudoparalysis may be the 1st clue to osteomyelitis. Bone pain may also result from neoplastic infiltration of the bone marrow or sickle cell anemia. Unexplained fever, arthralgias, and arthritis may be present with acute rheumatic fever, JIA, Lyme disease, Kawasaki disease, SLE, polyarteritis nodosa, and Behçet syndrome (see Chapter 33). Myalgias occur commonly with viral diseases such as influenza, and may be present with rickettsial diseases, polyarteritis nodosa, Takayasu arteritis, and dermatomyositis.

TABLE 39.12 Causes of Fever in the Returned Traveler

Diagnosis	%
Malaria	30–40
Hepatitis	3–6
Respiratory infection*	2–11
Urinary tract infection/pyelonephritis	2–4
Dysentery	4–5
Dengue fever	2–6
Enteric fever	1–2
Tuberculosis	1–2
Rickettsial infection	~1
Acute HIV infection	<1
Amebic liver abscess	<1
Other miscellaneous infections	4–9
Miscellaneous noninfectious causes	1–6
Undiagnosed	~25

*Includes upper respiratory tract infection, pneumonia, and bronchitis.
HIV, human immunodeficiency virus.
Modified from Suh KN, Kozavsky PE, Keystone JS. Evaluation of fever in the returned traveler. *Travel Med.* 1999;83:997-1017.

Skin

The skin must be inspected for evidence of rashes and other lesions (see Chapter 40). JIA may manifest with an evanescent, salmon-colored macular rash over the trunk and joints that may appear and disappear rapidly and be evident only during febrile periods. Dermatomyositis is characterized by a heliotropic rash of the upper eyelids and an erythematous eruption (vasculitis) over the extensor surfaces (Gottron sign). SLE may manifest with a butterfly rash over the nose and malar regions, signs of photosensitivity in sun-exposed areas, or vasculitis. The rash of Kawasaki disease is erythematous and may manifest in many forms; it is most commonly a diffuse maculopapular rash. In Rocky Mountain spotted fever, there are macular erythematous spots on the wrists, ankles, or forearms that may become maculopapular and expand centripetally to the proximal extremities and torso; palms and soles may be involved and petechiae may develop later in the course of the illness. Endocarditis may be associated with splinter hemorrhages or Janeway lesions (painless, small, erythematous or hemorrhagic lesions on the palms and soles). Lyme disease usually manifests with erythema migrans. This rash begins at the site of the tick bite and is erythematous with a pale center. The rash radiates out from the bite in a circular manner and persists for weeks; satellite secondary lesions may also appear.

Tularemia, salmonellosis, listeriosis, and EBV infections may feature generalized maculopapular rashes.

◆ Diagnostic Studies

Laboratory evaluation should proceed in a stepwise, focused manner with emphasis on identifying serious illnesses with defined interventions (see Fig. 39.5). Initial studies should include a complete blood cell count with differential, erythrocyte sedimentation rate (ESR) measurement, CRP, blood cultures, urinalysis, urine culture, tuberculin skin tests with controls (anergy panel) or gamma interferon release assay, and chest radiograph. Because EBV infection is common in childhood, viral-specific antibody titers may also be obtained at the initial evaluation (see Chapter 36). Further studies should be directed by information obtained from detailed histories and physical examinations.

Specific serologic studies aid in the diagnosis of CMV, toxoplasmosis, brucellosis, tularemia, hepatitis A, B, and C, and leptospirosis. Biopsies of lymph nodes, the skin, the liver, or bone marrow may be indicated. Radiologic studies that may be of benefit if directed by the history, physical examination findings, and initial laboratory study results include sinus CT, abdominal imaging, or total body MRI (to evaluate for occult osteomyelitis, malignancy, histiocytic disorders).

The complete blood cell count with differential is neither specific nor diagnostic, except in rare circumstances, such as seeing lymphoblasts on the blood smear. Approximately 30% of patients have abnormal white blood cell counts; 46% may have a left shift, lymphocytosis, atypical lymphocytes, or blasts. An elevated ESR or CRP indicates inflammation. The ESR is usually (70-90% of the time) high in children with FUO caused by infectious pathogens, malignancies, and rheumatic diseases. Of patients with an ESR less than 10 mm/hr, 90% have a self-limited viral disease.

Urinalysis and urine culture identify occult infections, particularly in young girls. The urinalysis may also be abnormal in patients with endocarditis and rheumatic and other inflammatory disorders.

Unexpected consolidations, calcifications, interstitial changes, perihilar adenopathy, or cardiomegaly (heart failure, pericarditis) may be found on chest radiographs. Chest films are abnormal in 10-15% of patients with FUO. CT of the chest may reveal abnormalities not detected by a chest x-ray.

Specialized radiologic studies performed without specific diagnostic clues from the history, physical examination findings, or initial laboratory evaluation results have a low yield. Whole body MRI is another technique that may be useful in children with FUO. It is helpful in identifying abnormal areas in bones, such as with occult osteomyelitis.

Cause

Infections

A wide variety of infections have been identified in children with FUO including subacute bacterial endocarditis, urinary tract infections (UTI), sinusitis, abscesses, osteomyelitis, and rheumatic fever.

Bacterial endocarditis. Bacterial endocarditis is rare in children; incidence increases with advancing age and history of preexisting heart disease (see Chapter 8). A new murmur or a change in the characteristic of an existing murmur may not be initially evident. Vegetations also may not be visible initially by transthoracic echocardiography; a transesophageal approach is much more sensitive. Serial blood cultures with anaerobic and aerobic media are necessary for definitive diagnosis.

Urinary tract infection. Both upper and lower urinary tract infections may be asymptomatic, and leukocytes may not always be present in urine (see Chapter 18). Sterile pyuria may be present with tuberculosis, nongonococcal urethritis, viral cystitis, Kawasaki disease, reactive arthritis, interstitial nephritis, and other rheumatic diseases. Renal ultrasonography may show areas of decreased echogenicity, enlarged echogenic kidneys, and renal or perinephric abscesses. Kidneys may be enlarged with acute pyelonephritis. A CT scan with contrast may show infected parenchyma as a nonenhancing lucency. Nuclear medicine renal scans also identify active areas of infection and old scars.

Sinusitis. Factors that decrease the size and patency of the ostium, or impair the mucociliary transport system predispose a child to sinusitis. Ethmoid and maxillary sinuses are present at birth. The frontal sinuses usually appear near 5 or 6 years of age but may be asymmetric or absent. Sphenoid sinuses may be seen radiographically by 9 years of age. Prolonged nasal congestion, headache, purulent nasal discharge, sore throat, daytime cough, tender teeth, and halitosis may be present

in children with sinusitis. CT studies may be helpful. Rhinoscopy may show purulent material at the ostium of an infected sinus. Infectious complications of sinusitis include dural space empyema or brain abscesses.

Abscesses. Hepatic, renal, perinephric, pelvic, and subphrenic abscesses may present with FUO. Internal jugular thrombophlebitis may manifest with prolonged fever and severe neck pain. Liver abscess may manifest with right upper quadrant tenderness and hepatomegaly. Blood cultures and liver function study results are often normal. The diagnosis may be made with MRI, CT with contrast, or ultrasonography. The diagnosis of perinephric abscesses is made with CT with contrast or ultrasonography. CT or ultrasound guidance may be used to direct percutaneous drainage of many abscesses. Pelvic abscesses should be suspected in children with FUO who have abdominal, rectal, or pelvic tenderness.

Osteomyelitis. Osteomyelitis usually follows bacteremia, but it sometimes follows penetrating injury. Tenderness to palpation over the infected site is common. Abnormalities in plain films appear late (2 weeks). MRI is the imaging modality of choice. The blood or bone culture is often positive, and the ESR is often elevated. Suppurative myositis may mimic osteomyelitis and manifest as an FUO.

Rheumatic fever. Acute rheumatic fever may cause FUO; the diagnosis is made by fulfillment of the Jones criteria, updated in 2015 (see Chapter 8). Initially, a child may present with polyarthralgia and an increased ESR. Elbows, wrists, knees, and ankles are frequently involved. The later migratory nature of the true arthritis differentiates rheumatic fever from JIA.

Bacterial Syndromes

Bacterial syndromes that cause FUO in children include agents of the following:

- Lyme disease
- Cat-scratch disease
- Q fever
- Rat bite fever
- Tularemia
- Brucellosis
- Leptospirosis

Lyme disease. Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is transmitted by the *Ixodes dammini* and *I. pacificus* ticks. The usual manifestation of early Lyme disease is with erythema migrans, an erythematous, annular, expanding rash with central clearing. The rash resolves 1-30 days (usually 2 weeks) after exposure. Patients may exhibit fever, chills, fatigue, headaches, malaise, myalgias, arthralgias, and lymphadenopathy. Early disseminated Lyme disease follows 2-8 weeks after exposure; facial nerve palsy, peripheral neuropathy, cardiac conduction defects, myocarditis, and aseptic meningitis may occur. Diagnosis is made clinically in early localized Lyme disease because serology lacks sensitivity and specificity during early infection and because erythema migrans is so specific for Lyme disease. Diagnosis of early disseminated Lyme disease requires a typical clinical illness, exposure to ticks known to carry *B. burgdorferi* and serologic evidence of infection with a 2-tier testing strategy. The initial test is an enzyme-linked immunosorbent assay (ELISA) or immunofluorescent (IFA) test. If this result is equivocal or positive, a Western immunoblot is performed. Western blot should not be performed if the ELISA is negative or has not been performed because it lacks specificity in this setting.

Cat-scratch disease. Cat-scratch disease is a febrile illness associated with cats (usually kittens) and, more rarely, dogs. *Bartonella henselae*, which may be transmitted by the cat flea and by cat saliva, is the etiologic agent. After a scratch or bite, a papule forms and may persist from days to months. Regional lymphadenopathy with 1 or more nodes occurs proximal to the skin site 1-9 weeks after inoculation. The node or nodes become enlarged and tender and may have overlying erythema. The lymphadenopathy usually resolves after 2 months but may last up to 3 years. Affected children may have adenopathy with fever, headache, malaise, anorexia, sore throat, and conjunctivitis (see Chapter 36).

Q fever. Q fever is caused by *Coxiella burnetii*, formerly classified as a rickettsia. It manifests with headache, fever, chills, malaise, and, on occasion, respiratory symptoms. Hepatic, cardiac, and CNS involvement may occur. Rash is usually not seen. Domestic farm animals, cats, rodents, and marsupials may be infected. Pasteurization destroys the organism in milk. Diagnosis is made by serologic testing.

Rat bite fever. Rat bite fever is a relapsing fever caused by *Streptobacillus moniliformis* or *Spirillum minus*. *S. moniliformis* is a pleomorphic gram-negative bacillus transmitted by rat bite or by contaminated food or water. In 1-10 days after exposure, patients may exhibit fever, chills, malaise, and muscle aches. A rash may form on the extremities; arthralgias and arthritis may occur. Complications include abscesses, pneumonia, endocarditis, myocarditis, and meningitis. Diagnosis is made by blood culture or culture of other infected fluid, such as abscess aspiration.

Tularemia. *Francisella tularensis* is the causative agent of tularemia. The disease is spread by contact with wild animals, such as rabbits and squirrels, and by insects that bite these animals, such as mosquitoes, ticks, and deer flies, as well as by contaminated water. A maculopapular nodule forms at the portal of entry and later becomes ulcerated. The child may present with fever, chills, and headache. Lymphadenopathy, pharyngitis, conjunctivitis, hepatosplenomegaly, and pneumonia may also occur. Diagnosis is made by serologic study.

Brucellosis. Brucellosis is caused by gram-negative coccobacilli: *Brucella abortus*, *B. melitensis*, *B. suis*, or *B. canis*. The microorganisms are found in sheep, goats, cattle, swine, and dogs. Infection may occur by airborne spread or by ingestion of meat or milk. The child may present with fever, chills, malaise, headache, arthralgias, or myalgias. Pneumonia, cardiac involvement, and CNS involvement occur in rare cases. Diagnosis is made by special culture techniques and serologic study.

Leptospirosis. Leptospirosis is caused by members of the spirochete genus *Leptospira*. Infection is spread by contact with the urine of wild or domestic animals. In 1-2 weeks after exposure, patients experience the abrupt onset of fever, chills, nausea, vomiting, headache, and occasionally conjunctival suffusion and rash. Liver, renal, and CNS involvement may also occur. Diagnosis is made by special culture techniques and serologic testing.

Fungal Infections

Fungal causes of FUO include:

- Blastomycosis
- Histoplasmosis
- Coccidioidomycosis
- Cryptococcoses

Blastomyces dermatitidis is a saprophytic fungus with both yeast and mycelial forms; it is found in the soil all over the world but is common in the Americas. It is endemic in the Southeast and Midwest regions of North America. Infections with this fungus may be disseminated or pulmonary. The diagnosis is made by visualization of single-budding yeast in clinical material, culture on Sabouraud agar, or serologic tests.

Histoplasma capsulatum is a yeast found in soil in the Ohio River valley and other locations in the United States that causes pulmonary and disseminated disease. Diagnosis is made by the demonstration of the microorganism in biopsy specimens or by complement-fixing antibody.

Coccidioides immitis is found in soil in the southwestern United States. Infections in humans are associated with a febrile pulmonary disease characterized by cough, rash, and chest pain. Diagnosis is usually made serologically.

Cryptococcus neoformans is often found in pigeon droppings and can cause a variety of diseases. The diagnosis is made by culture or by identification of encapsulated yeast in collected specimens.

Chlamydial Infection

Psittacosis and lymphogranuloma venereum are chlamydial causes of FUO. *Chlamydia psittaci* may be transmitted by infected birds and produces respiratory illness with fever. Cardiac, liver, CNS, and thyroid involvement are rare. Diagnosis is made serologically. *C. trachomatis* is a sexually transmitted organism that causes urogenital infections, perihepatitis, invasive lymphadenopathy (lymphogranuloma venereum), neonatal conjunctivitis, and neonatal pneumonia. Diagnosis is by cell culture and rapid antigen tests.

Rickettsial Infections

Rocky mountain spotted fever. Rocky Mountain spotted fever manifests with fever, headache, intense myalgias, and abdominal symptoms. A characteristic rash is usually present by the 6th day of illness. The rash covers the palms, wrists, soles, and ankles and progresses from macular to petechial. The disease can last up to 3 weeks. Many end organs, including the heart, kidneys, and CNS, can be involved. Transmission of the causative agent, *Rickettsia rickettsii*, occurs by tick bite. Diagnosis is made by PCR testing of blood.

Ehrlichiosis and Anaplasmosis. These infections are caused by *Ehrlichia chaffeensis*, *Anaplasma phagocytophilia*, and *E. ewingii* and are transmitted by the Lone Star tick. Anaplasmosis is caused by Anaplasma phagocytophilia and is transmitted by the black legged deer tick. These illnesses are usually seen in the southeastern and upper Midwestern United States, respectively, and have manifestations similar to that of Rocky Mountain spotted fever. The patient presents with headache, myalgias, fever, chills, nausea, vomiting, weight loss, thrombocytopenia, and leukopenia. Rash is inconsistent but may be seen after 1 week. Pulmonary and renal complications can occur. Mental status changes are less frequent. Diagnosis is confirmed by PCR.

Viral Infections

Cytomegalovirus infection. CMV may cause a mononucleosis-like syndrome in children. Generalized or cervical adenopathy may be seen along with fatigue, malaise, fever, hepatosplenomegaly, and abdominal pain (see Chapter 36). A morbilliform rash may also be present. Retinitis, hepatitis, colitis, and pneumonia may occur in children with impaired immune systems. The virus is transmitted by contact with secretions. Infection is diagnosed by culture (nasopharyngeal, blood, urine) or by the detection of specific immunoglobulin G and immunoglobulin M antibodies.

Infectious mononucleosis. Infectious mononucleosis is typically caused by EBV and may manifest with fever, exudative pharyngitis, malaise, and fatigue (see Chapter 36). The appearance of rash is sometimes preceded by amoxicillin therapy, but rash may occur without antibiotic administration. Tender lymphadenopathy and hepatosplenomegaly may occur. The diagnosis may be made by nonspecific tests (heterophile antibody or Monospot) in older patients, but these studies are unreliable for young children. Specific antibody tests against viral capsid antigen, early antigen, and nuclear antigen are recommended in younger children. Treatment is supportive.

Human immunodeficiency virus infection. Infection with HIV or associated opportunistic infections or associated malignancies is another cause of FUO in children.

Parasites

FUO in children may be caused by parasitic infections, including (1) babesiosis, (2) toxoplasmosis, and (3) toxocariasis.

Babesiosis is caused by *Babesia microtia* and is a parasite of rodents transmitted to humans by tick bite. Infection may result in fever, chills, nausea, vomiting, night sweats, myalgias, and arthralgias. Identification of the organism in a thick smear of red blood cells is diagnostic.

T. gondii is a protozoan parasite. Children become infected from eating contaminated, undercooked meat or from exposure to the feces of domestic cats. Most infections acquired postnatally are asymptomatic but children may develop a mononucleosis-like illness (see Chapter 36).

Toxocariasis (previously visceral larva migrans) results from ingestion of larvae of *Toxocara canis* or from *T. cati* shed in dog and cat feces, respectively. Infection results in fever, intense eosinophilia, hepatomegaly, and hypergammaglobulinemia. Lung, heart, and CNS involvement is rare. The eye may become infected. Diagnosis is presumed with increased eosinophils and hypergammaglobulinemia, and elevated titers of isohemagglutinin to A and B blood group antigens.

Infections in Children Who Live in or Have Traveled to Developing Countries

In a child who has traveled to or lives in a developing country, consideration must be given to the area, water sources, and activities. Some causes of FUO to consider include malaria, hepatitis, typhoid fever, tuberculosis, and amebic liver abscess (Table 39.12).

Malaria

Malaria is transmitted by the bite of an infected mosquito carrying 1 of the 5 species of the *Plasmodium* genus that cause disease in humans. The patient experiences chills, rigors, high fever, diaphoresis, and headaches. The incubation period varies among species, from 1 week to several months. Demonstration of the parasite on thick peripheral blood smear is diagnostic. Risk for malaria can be checked for areas of the world on www.cdc.gov/malaria.

Hepatitis

Hepatitis A may be contracted by ingestion of contaminated food or water. Hepatitis B and C viruses are transmitted through blood products or sexual contact. Diagnosis is by serologic testing. Symptoms can include fever, malaise, jaundice, hepatomegaly, nausea, and anorexia. Hepatitis B and C can become chronic (see Chapter 15).

Typhoid Fever (Enteric Fever)

Enteric fever is caused by infection with 3 serovars of *S. enterica*, which includes *S. typhi*. After ingestion of contaminated water or food, incubation lasts from 1-6 weeks. Persistent fever, headache, malaise, anorexia, and rose spots are clinical hallmarks of enteric fever. Diagnosis is by blood culture.

Tuberculosis

Tuberculosis may manifest as FUO in children (see Chapters 2 and 36). Affected children may have pulmonary or extrapulmonary disease. The signs and symptoms of pulmonary disease may vary greatly from weight loss, tuberculin skin test conversion, and low-grade fever to mass effect from mediastinal lymphadenopathy and fulminant disseminated pulmonary involvement with miliary infiltrates or, in rare cases, cavitation. Nonpulmonary tuberculosis more commonly manifests as FUO, inasmuch as positive chest radiograph findings and pulmonary signs may initiate an early work-up for tuberculosis. Hematogenous spread may cause liver, heart, or renal involvement. Ingested bacilli may result in gastrointestinal tuberculosis. The diagnosis requires demonstration of

acid-fast bacilli from sputum, gastric aspirate, or the affected organ. Skin testing may yield negative results even with positive controls.

Amebiasis

Intestinal infection with *Entamoeba histolytica* may produce invasion of the mucosal lining and spread to other organs such as the liver. Amebic liver abscess may manifest with fever, weight loss, right upper quadrant pain, and anorexia. The patient may have painful hepatomegaly without splenomegaly. The abscess may be localized with abdominal ultrasonography or CT. Diagnosis is by serologic study.

Rheumatic Causes of Fever of Unknown Origin

Rheumatic diseases as a cause of FUO are the 2nd most common identified cause of FUO after infections. In a systematic review, the most common causes were JIA and SLE (see Chapter 33).

Juvenile Idiopathic Arthritis

JIA is a diagnosis that requires time to identify all of its manifestations and to exclude other entities. JIA is defined by arthritis of unknown origin that begins in a child younger than 16 years and persists for a minimum of 6 weeks. JIA is divided into 3 subtypes: systemic, polyarticular, and oligoarticular. The systemic form often manifests with prolonged high fever. Affected children often have a daily fever and may have a fine macular rash, arthralgias, arthritis, hepatosplenomegaly, or pericardial involvement. Polyarticular JIA may manifest with arthritis, low-grade fever, morning stiffness, anorexia, and weight loss.

Polyarteritis

Polyarteritis is a necrotizing vasculitis that may manifest with myalgia, arthralgia, fever, vasculitic skin lesions, and abdominal pain. Cardiac, CNS, and renal involvement may also occur. The ESR usually is markedly elevated. Biopsy and the presence of antibodies to proteinase 3 and myeloperoxidase (antineutrophil cytoplasmic antibodies) are helpful.

Systemic Lupus Erythematosus

SLE may manifest with fever, photosensitivity, mouth sores, weight loss, rash, myalgias, malaise, and hepatosplenomegaly. Patients may also have serositis and renal involvement. Laboratory tests that are helpful include lupus erythematosus cell preparation and those for antinuclear antibody, anti-Smith antibody, anti-ribonuclear protein antibody, anti-Ro (Sjögren syndrome type A) antibody, and anti-La (Sjögren syndrome type B) antibody.

Behçet Syndrome

Behçet syndrome is very rare in children but may manifest with FUO. Patients may have aphthous stomatitis, arthritis, genital ulcers, uveitis, and erythema nodosum.

Neoplasms

Hodgkin disease, lymphoma, neuroblastoma, and leukemia may all manifest as FUO. In young children, leukemia, neuroblastoma, and lymphoma should be suspected, whereas in adolescents, Hodgkin disease and Ewing sarcoma are more common as causes of FUO.

Hodgkin Disease

Hodgkin disease may manifest with firm, nontender adenopathy, fever, night sweats, and weight loss. Diagnosis is made through biopsy.

Lymphoma

Non-Hodgkin lymphoma may manifest as painless adenopathy, cough or dyspnea from a mediastinal mass, abdominal mass, nerve compression, bone pain, fever, and weight loss. Diagnosis is by biopsy.

Neuroblastoma

Neuroblastoma may manifest as abdominal, thoracic, or pelvic masses; spinal cord compression; bone pain; hypertension; hepatomegaly; diarrhea; and fever (see Chapter 17). Diagnosis is aided by radiologic studies and urinary catecholamine measurements and is confirmed by biopsy.

Leukemia

Both acute lymphocytic leukemia and acute nonlymphocytic leukemia may manifest with lethargy, pallor, bleeding, fever, bone pain, lymphadenopathy, and arthralgias. Diagnosis is made by blood smear and bone marrow biopsy.

Pheochromocytoma

Pheochromocytomas are rare catecholamine-secreting tumors; 10% occur in children. These tumors manifest with paroxysmal or sustained hypertension, headache, excessive sweating, fever, hyperglycemia, and palpitations. The tumors are usually in the adrenal medulla, but 35% of those occurring in children are multiple or extraadrenal. Diagnosis is made by measuring urinary or plasma metanephrine or catecholamine levels. Localization of tumor is by CT, MRI, or iodine 131-metaiodobenzylguanidine scanning.

Miscellaneous Causes of Fever of Unknown Origin

Genetic Diseases (See Chapter 41)

Familial Mediterranean fever is an autosomal recessive trait seen in Sephardic Jews and people of Middle Eastern descent. The fever may be accompanied by joint, abdominal, and chest pain. Anhidrotic ectodermal dysplasia is an X-linked recessive disorder associated with decreased ability to sweat, dental abnormalities, and sparse hair. Eyebrows and eyelashes may be absent. Fever may result from the inability of the body to cool itself. Diagnosis is made by skin biopsy that shows an absence of eccrine glands.

Drug Fever

Drug fever is a diagnosis of exclusion. Some drugs are more likely than others to cause drug fever (α-methyldopa, quinidine, penicillins). There is no characteristic fever pattern. There is a highly variable lag time between the initiation of the drug and the onset of fever, and there is an infrequent association with rash or eosinophilia. Some drugs may cause fever by virtue of physiologic side effects. Anticholinergic drugs may decrease sweating and diminish the body's ability to cool itself. Chronic salicylate intoxication can cause increased heat production by uncoupling oxidative phosphorylation.

Kawasaki Disease

Kawasaki disease may manifest with a variety of signs, including rash; lymphadenopathy; conjunctival hyperemia; strawberry tongue; erythematous lips; swelling of hands and feet; arthralgia; arthritis; myocarditis; late desquamation of hands, feet, and perineal area; and sterile pyuria. Fever may be high and spiking. Diagnosis is by fulfillment of clinical criteria (see Chapter 40).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD; ulcerative colitis, Crohn disease) may manifest with FUO. Ulcerative colitis may manifest with bloody diarrhea, fever, fecal urgency, and straining (see Chapter 11). Pyoderma gangrenosum, arthritis, and erythema nodosum can also be seen. Crohn disease (regional enteritis) may manifest with abdominal pain, fever, anorexia, and growth failure. Diarrhea may develop later. Arthritis, erythema nodosum, and finger clubbing may also occur. Diagnosis of IBD is by endoscopy and histology.

Thyrotoxicosis

Hyperthyroid states may manifest with FUO. Children usually have multiple symptoms, such as irritability, tremor, eyelid lag, and exophthalmos. Diagnosis is made from thyroid function studies.

Factitious Disorders

Factitious fever may be a form of factitious disorder imposed on self (formerly Munchausen syndrome) or medical child abuse (formerly Munchausen syndrome by proxy) (see Chapter 26). A variety of techniques have been used to falsely elevate a recorded temperature. A mercury thermometer may be rubbed between hands or placed near a light bulb. Hot liquids may be placed in the mouth before an oral temperature is taken. Hot rectal douches have also been reported to raise a rectally taken temperature. Even with pathologic fevers, there is some circadian rhythm to the temperature curve; with factitious fever there is no rhythm. In addition, there is usually no vasoconstriction, sweating, tachypnea, or tachycardia. If factitious fever is suspected, the temperature should be obtained while the patient is observed. The temperature of freshly voided urine can also be recorded.

Other patients may produce actual diseases that cause true fevers, such as by injecting infected pyogenic material subcutaneously or intravenously or by taking toxic levels of thyroid hormone. Once the diagnosis is documented, psychiatric care is indicated.

Patients in Whom No Diagnosis Is Made

If no diagnosis is made, most patients are clinically well and asymptomatic on follow-up. Some may be determined to be healthy from the start; most are in good health at follow-up, whereas few have symptoms at the end of evaluation. Some may have relapses of fever for a few months. JIA, inflammatory bowel disease, and PFAPA syndrome may not be immediately diagnosed but usually manifest typical symptoms and signs within 2 years of the onset of the FUO.

SUMMARY AND RED FLAGS

Many children with fever will have a source identified on their initial history and physical examination. Red flags include patients with symptoms or signs of sepsis (tachycardia, hypotension) or meningitis or encephalitis (fever, headache, irritability, altered mental status and for the older child, meningismus). Affected infants with meningitis are more likely than older children to have subtle and nonspecific symptoms.

A child with fever of recent onset with no adequate historical or physical explanation for the fever is said to have fever without source (FWS). Because of the high volume of children with FWS, it is important to have a reliable system for individual patient evaluation and management. Although the majority of patients with FWS have a self-limited viral illness, 5-10% have an invasive bacterial infection, with young infants at highest risk. Because of the potential for morbidity and mortality from the organisms that cause invasive disease, identification of patients at high risk is essential. Although there is no single, timely series of tests that correctly categorizes all patients, the combination of careful clinical evaluation and appropriate laboratory screening criteria can help identify a level of risk in children of different ages. The reduction of bacteremia due to vaccine-serotype pneumococcus has led to a careful reduction in diagnostic testing, especially in the 3-36 month old child with FWS. Red flags include a history of immunodeficiency or other chronic medical illness, no prior immunizations, toxic appearance, signs of shock, petechiae or purpura, poor responsiveness, and other signs of altered mental status.

Some children, who are initially thought to have FWS, develop into patients with FUO. Definitions of FUO in children vary. A practical definition balancing different recommendations is FUO is a temperature higher than 38°C (100.4°F) daily for at least 8-14 days and no diagnosis after an initial evaluation. Work-up of the patient with FUO should proceed in a stepwise manner. It should be kept in mind that many patients with FUO have unusual, atypical, or complicated manifestations of common childhood illness, mainly infections. Red flags include weight loss, night sweats, signs of organ system dysfunction or failure, or unstable vital signs suggestive of sepsis. Only in this last category should a rapid diagnostic approach be performed and empirical antibiotic therapy initiated.

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