Fever in Children

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FOCUS QUESTIONS

1. What is the mechanism of action of the antipyretic drugs most useful for treating children?
2. What nonpharmacologic measures are helpful in the treatment of fever in children?
3. What is the epidemiology of occult bacteremia?
4. What is the differential diagnosis of fever of unknown origin in infants, children, and adolescents?

Fever is the most common presenting complaints in pediatric practice, accounting for 10% to 20% of office and emergency room visits.

Pathophysiology of Fever

Three pathophysiologic bases exist for fever. The first involves the raising of the hypothalamic set point in the central nervous system. Infection, collagen vascular disease, and malignancies are most commonly responsible. This type of fever is lowered by antipyretics and physical removal of heat. A second type of fever is a result of heat production exceeding heat loss as, for example, in salicylate overdose, hyperthryroidism, excessive environmental temperature, and malignant hyperthermia. The third type of fever is caused by defective heat loss, as seen with ectodermal dysplasia, heat stroke, and poisoning via anticholinergic drugs. Antipyretics are ineffective for the second and third types of fever.

Biologic Process of Fever Reduction

Fever occurs as a result of a number of complex biologic interactions. Exogenous pyrogens, including viruses, bacteria, fungi, antigen-antibody complexes, and drugs, are engulfed by phagocytic leukocytes, leading to the production of an endogenous pyrogen called interleukin-1 (Fig. 1). This compound (also known as lymphocyte-activating factor), in conjunction with interleukin-2, is responsible for increasing the number of helper T cells and initiating the production of prostaglandins in the hypothalamus. Helper T cells are instrumental in fighting infections; prostaglandins are responsible for producing fever.

Phagocytic leukocytes, when activated by leukotrienes, prostaglandins, and calcium, phagocytose the exogenous pyrogen and synthesize the endogenous pyrogen interleukin-1 (Fig. 2). Monocytes and macrophages are particularly productive of interleukin-1, leukocytes and eosinophils less so, and lymphocytes not at all.

Interleukin-1 acts on the arachidonic acid pathway, stimulating the production of prostaglandins in the vascular endothelial cells of the hypothalamus. Prostaglandins form as a result of the catabolism of phospholipids in endothelial cells of the central nervous system to arachidonic acid, then by the enzyme cyclo-oxygenase through endoperoxides, and ultimately to prostacyclins, prostaglandins, and thromboxanes (Fig. 3).

Treatment

The febrile child may be treated with antipyretic drugs or by nonpharmacologic adjunctive measures. The use of antibiotics in the management of patients who have suspected infectious etiologies is discussed separately in the sections on acute fever and fever of unknown origin.

ANTIPYRETICS

How do prostaglandins and antipyretics affect body mechanisms so as to raise and lower body temperature? Current evidence suggests that microinjections of prostaglandins in-

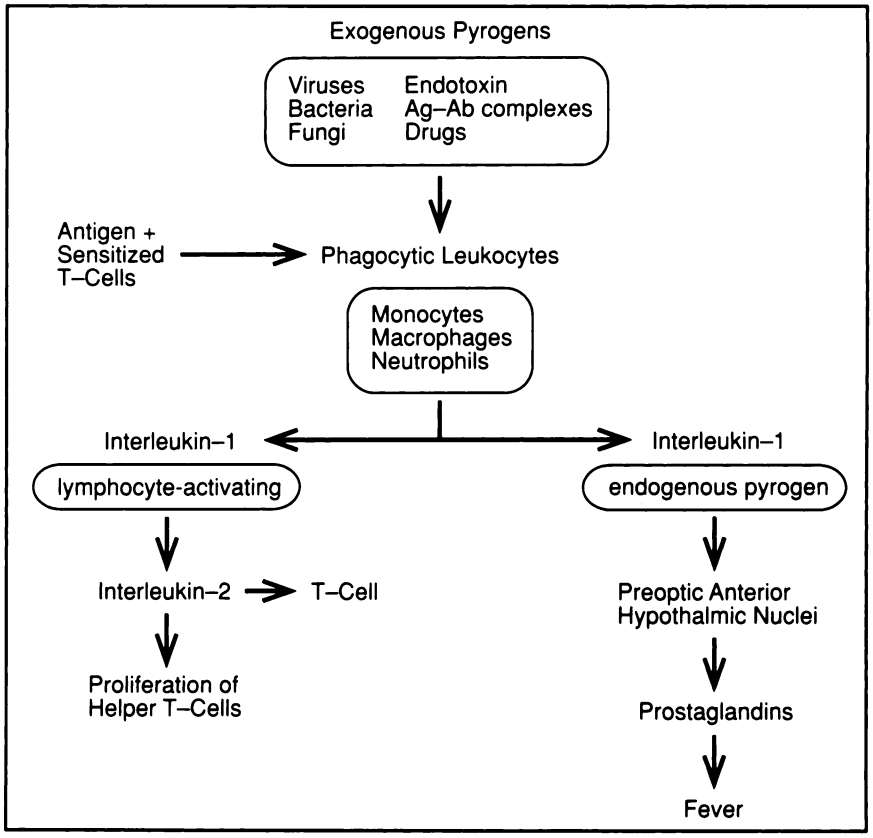

FIGURE 1: Mechanisms of fever production.

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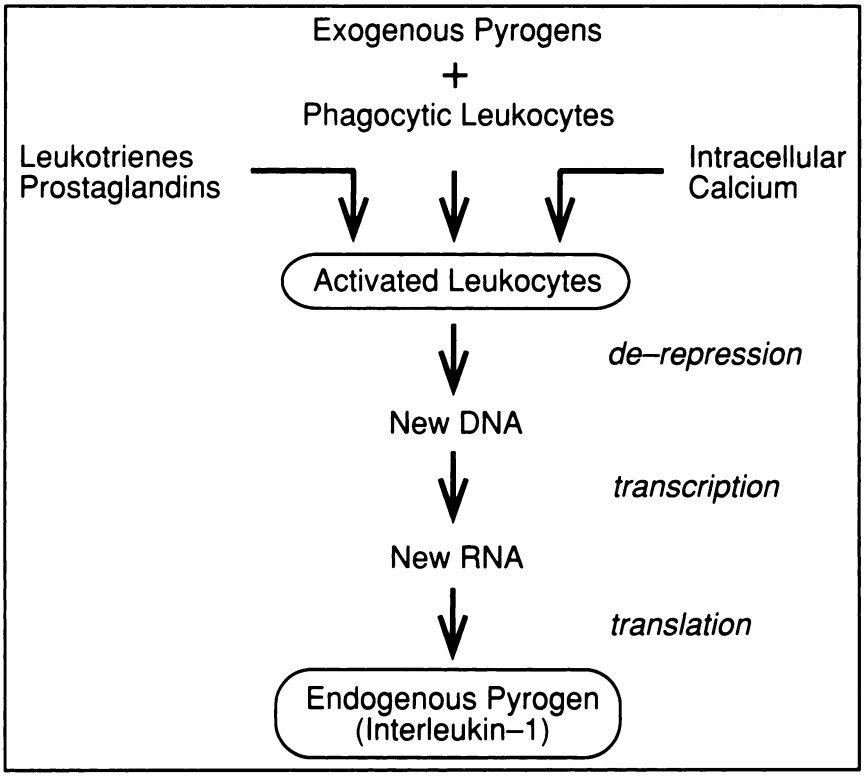

FIGURE 2: Mechanisms for the production of endogenous pyrogen.

crease the firing rate of cold-sensitive cells in the preoptic anterior nuclei and decrease the activity of warm-sensitive cells, resulting in shifting of the set point to a higher temperature setting. The body responds to a colder peripheral skin temperature by vasoconstriction, which decreases heat loss, and through increased shivering, which increases heat generation. Antipyretics lower the central set point, resulting in the periphery feeling hot at the skin surface. The body lowers its temperature by vasodilation, which increases heat loss, and lying quietly, which minimizes heat generation.

Arguments exist both for and against lowering fever. Arguments for include: 1) decreasing the discomfort associated with fever and, often, settling an apprehensive home environment; 2) keeping extreme temperature elevations (>41°C to 41.6°C [106°F to 107°F]) from causing permanent damage to the central nervous system; and 3) decreasing, in theory, the likelihood of a febrile seizure in those who have such seizures, although no study has demonstrated that treatment of fever decreases the incidence of febrile seizures. Arguments against lowering fever include: 1) situations where adverse effects associated with the use of antipyretics outweigh the benefits of fever reduction; 2) situations where reducing fever may obscure diagnostic or prognostic signs; 3) the generally recognized view that most fever is short-lived and benign; and 4) an increasing body of information suggesting that fever may protect the host.

It now is clear that aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs exert their antipyretic effect through inhibition of the cyclo-oxygenase enzyme, thereby preventing synthesis of prostaglandins from arachidonic acid (Fig. 3). Because they do not suppress interleukin-1, they do not diminish proliferation of helper T cells and, thus, do not adversely affect the body's ability to fight infection. Corticosteroids in vitro and in vivo, on the other hand, decrease interleukin-1 release from monocytes and macrophages quantitatively. This activity is, in fact, detrimental to the body's ability to fight infection.

Aspirin, acetaminophen, and nonsteroidal anti-inflammatory agents all have excellent antipyretic and analgesic activity. Only aspirin and nonsteroidal agents have anti-inflammatory activity.

NONPHARMACOLOGIC ADJUNCTIVE MEASURES

In addition to the pharmacologic means of lowering elevated body temperature, adjunctive approaches may be taken. Since the rate of fluid loss may be increased as a result of an elevated temperature, it is important for the febrile child to receive adequate hydration. In addition, maintenance of adequate intravascular volume allows for better heat dissipation. The child, however, should not be overhydrated, which can occur when large volumes of water or non-electrolyte-containing solutions are administered, because this runs the risk of hyponatremia. Sponging with tepid water has been shown to be effective in lowering fever. When this measure is used by itself, however, body temperature quickly returns to its previous level as a result of shivering, which attempts to bring the body temperature back up to the untreated elevated set point. For these reasons, sponging is considered useful only as an adjunct to antipyretic therapy; the combination of tepid water sponging and an antipyretic may result in more rapid and effective temperature lowering than antipyretic therapy alone, often decreasing patient discomfort and allaying parental concern. Parents should be advised to use tepid water because cold water will increase discomfort. Finally, although alcohol baths or sponging have been recommended in the past, this measure has fallen out of favor because the alcohol can be absorbed through inhalation and through the skin surface, potentially leading to alcohol-induced hypoglycemia and even coma.

Fever may occur as an acute event or as a prolonged symptom in the pediatric patient. The following two sections will review the approach to the child whose fever is acute as well as the child whose fever is of unknown origin (FUO).

Acute Fever and Bacteremia

The most vexing clinical question to be answered in any febrile child is: Is this fever a marker for occult bacteremia? As opposed to the term

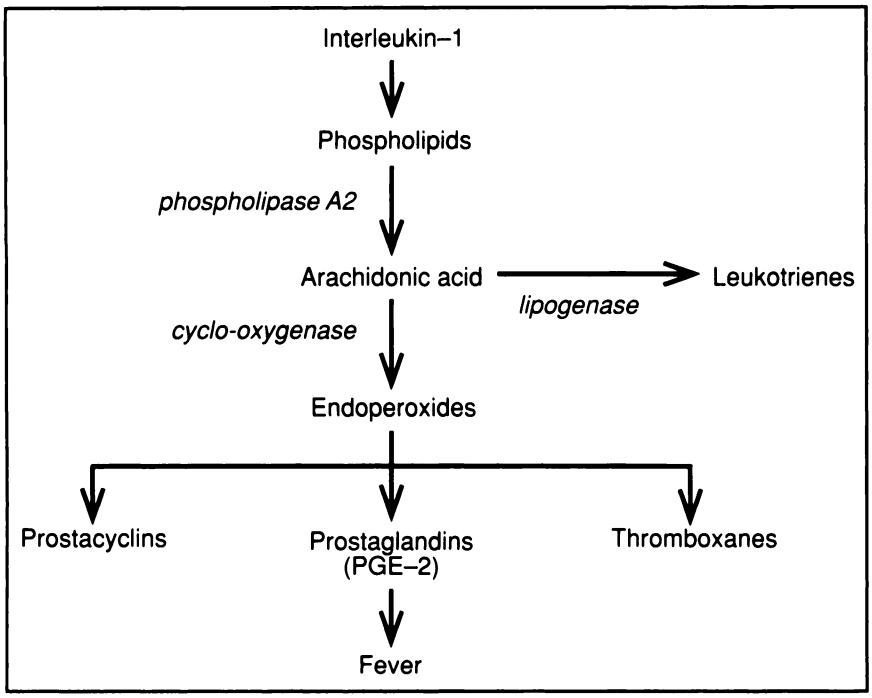

FIGURE 3: Catabolic pathway of arachidonic acid.

"sepsis," which should be used only to describe the ill-appearing febrile child, occult bacteremia refers to the relatively well-appearing child whose blood culture is positive for a pathogenic organism. The primary clinical concern in children who have occult bacteremia is the small but important percentage of those who develop secondary complications from invasive bacterial disease—most notably, meningitis, septic arthritis, and bacterial sepsis. Therefore, the approach to the febrile child requires management strategies that can identify the child at risk for bacteremia and use of treatment options that diminish the risk of secondary complications.

EPIDEMIOLOGY

Numerous epidemiologic studies have delineated the causative organisms of occult bacteremia. Early reports of pneumococcal bacteremia in pediatric patients in the ambulatory setting appeared in the medical literature in the early 1970s. Subsequently, Klein and colleagues reported their finding that occult bacteremia occurred in 3.2% of 600 consecutive febrile children from the "walk-in" clinic at Boston City Hospital. A more recent multicenter study involving 6794 febrile children (temperature >39.0°C and ages 3 to 36 months) found a 2.9% incidence of occult bacteremia in children who were managed in the ambulatory setting (Table 1). Most studies have confirmed a 3% to 5% incidence of bacteremia in this age group. Occult bacteremia occurs most commonly in the child 3 to 36 months of age because of both immunologic and epidemiologic factors. These include the normal decline of protective maternal antibodies, bacterial colonization of the nasopharynx, increased contact with other ill children, and the virulence and invasive nature of the organisms usually responsible for bacteremia.

Although *Streptococcus pneumoniae* is the most common organism that produces occult bacteremia, other bacterial pathogens remain important, including *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Salmonella* sp, group A *Streptococcus*, and on rare occasions, enteric pathogens. Although the incidence of bacteremia has remained essentially constant, the relative importance of various organisms has changed considerably. Previously, *H influenzae* type b was reported as the responsible organism in 25% of bacteremic children. Two recent studies have described an incidence of *H influenzae* bacteremia of 2 of 27 (7.4%) and 9 of 192 (4.7%).

Because infections due to *H influenzae* often are more severe than those due to other organisms, children who have *H influenzae* disease often require hospitalization at the initial visit. Other reasons for the decline of *H influenzae* disease include the effectiveness of the *H influenzae* conjugate vaccine and a decline in the presence of the organism in the community. The decline in *H influenzae* disease may be more significant epidemiologically because the rate of complications was higher with *H influenzae* type b than with other bacteria.

EVALUATION

The differential diagnosis of the acutely febrile child includes benign conditions such as viral upper respiratory tract infections and serious infections such as bacteremia and meningitis (Table 2). Distinguishing between these entities requires the expertise of an experienced clinician who is well-versed in the subtle presentations of the diseases that underlie the fever.

The history of any febrile child should focus on the duration and height of the fever as well as on associated symptoms such as vomiting and diarrhea, respiratory symptoms, and a history of rash (especially pete-

Table 1. Etiology of Occult Bacteremia* in Children who Have Bacteremia (N = 192)

ETIOLOGIC AGENT	NUMBER OF CASES
Streptococcus pneumoniae	167
Haemophilus influenzae type b	9
Salmonella	4
Neisseria meningitidis	2
Other	10

**Multicenter Occult Bacteremia Study Group*

Table 2. Differential Diagnosis of the Child Who Has Acute Fever

Upper Respiratory Tract Disease
Viral respiratory tract disease
Otitis media
Sinusitis
Lower Respiratory Tract Disease
Bronchiolitis
Pneumonia
Gastrointestinal Disorders
Bacterial gastroenteritis
Viral gastroenteritis
Musculoskeletal Infections
Cellulitis
Septic arthritis
Osteomyelitis
Urinary Tract Infections
Bacteremia
Meningitis

chiae). Additionally, assessment of neurologic functioning should include behavioral changes such as irritability and lethargy as well as parental estimate of the degree of illness and the child's level of interaction. A careful review of any known exposures should include family illnesses and ill contacts with other children, especially in settings such as child care centers. The child's immunization status and travel history may provide valuable information. A history of previous serious infections, such as bacteremia and meningitis; recurrent bacterial infections; loss of splenic function; or the presence of immunologic disorders, such as human immunodeficiency virus (HIV) infection, sickle cell disease, and hypogammaglobulinemia and other immunodeficiency disorders, indicates an increased risk for bacterial disease. Finally, the use of antibiotics and antipyretics may have implications for the evaluation of febrile children; the former may alter the utility of diagnostic cultures and the latter may affect the clinical evaluation of the patient. Recent studies have suggested that clinicians are more likely to differentiate children who have serious bacterial infections prior to the defervescence produced by the use of antipyretics.

PHYSICAL EXAMINATION

The first step in the physical examination of a febrile child should be a careful consideration of his or her general appearance. In the hands of an experienced clinician, this assessment remains the most important aspect of the physical examination. Observation scales such as the Acute Illness Observational Scale may help to focus assessment of the ill child and predict the risk of significant illness. Using this scale, McCarthy and colleagues found that children who had scores greater than 10 were more likely to have serious bacterial infections compared with children whose scores were less than 10. While there is no evidence of an improved outcome in children who are evaluated via such observation scales, they remain helpful as a mechanism to focus the examiner on the behavioral and interactive state of the child. Careful observation and analysis of vital signs, state of hydration, and peripheral perfusion are required to assess the acuity of the illness as well as the need for hospitalization. The height of the fever, especially in children who have temperatures >40°C, appears to be a marker for an increased risk of occult bacteremia.

A careful examination may localize a bacterial focus of infection such as otitis media. Tachypnea out of proportion to the degree of fever, even in the absence of focal pulmonary findings, suggests pneumonia. Sinusitis is supported by a history of chronic nasal discharge, especially if mucopurulent. The presence of suprapubic or costal vertebral angle tenderness suggests an acute urinary tract infection. A detailed musculoskeletal examination, including a careful examination of the child's gait, may help uncover the sometimes elusive diagnoses of septic arthritis or osteomyelitis.

Finally, a detailed neurologic examination, including mental status changes, is required to diagnose the child who may have a central nervous system (CNS) infection.

Despite a careful assessment, the clinician frequently is faced with the dilemma of the febrile child who has no discernible focus of infection. In such a case, it may prove helpful to augment the clinical examination with laboratory data.

LABORATORY EVALUATION

The laboratory evaluation can be used to identify the child who is at increased risk for bacteremia as well as to diagnose infections that may not be apparent on clinical examination. Most studies seeking to identify the "child at risk" have focused on the utility of the peripheral white blood cell count. Because of an association of peripheral white blood cell counts >15 000/mm^3 with the presence of occult bacteremia, decision analysis studies have attempted to refine the approach to the febrile child. A recent study by Jaffe et al, for example, suggested that a white blood cell count >15 000/mm^3 is an insensitive marker for occult bacteremia and suggested instead that a value of >10 000/mm^3 be used when making decisions regarding presumptive antimicrobial therapy. Other markers of acute inflammation, including the absolute band count, increased sedimentation rate, and elevated C-reactive protein, also have not helped identify the bacteremic patient. Currently, no single laboratory test can predict the likelihood of bacteremia in febrile children with certainty.

An important consideration in the employment of laboratory studies is the search for other "clinically silent" infections, especially pneumonia and urinary tract infections. The child who has significant respiratory symptoms or any focal pulmonary abnormality on examination warrants a chest radiograph. Because of the inability of the child to localize complaints specific to the urinary tract and the nonspecific nature of the symptoms of urinary tract infections, a careful examination of freshly obtained urine is necessary in the evaluation of the febrile child. Urinary tract infections occur in 1% to 4% of febrile children and are suggested by the presence of a positive reaction of assays for leukocyte esterase or urinary nitrites or the presence of pyuria, bacteriuria, or both on wet mount examination of the urine. Although more time-consuming, a urine Gram stain demonstrating bacteria under oil immersion microscopy has been shown to correlate with positive urine culture results.

Examination of the stool for the presence of white blood cells may offer evidence of invasive bacterial gastroenteritis. A lumbar puncture certainly is not required in all febrile children, but should be reserved for those in whom there is any clinical suspicion of CNS involvement. This becomes critically important in children less than 12 months of age, as even an experienced clinician may have difficulty localizing the signs of CNS infections in this age group.

TREATMENT

The presence of a focal bacterial infection on examination warrants antimicrobial treatment aimed at the most common bacterial etiologies. However, controversy continues to surround the question of the utility of antimicrobial therapy in the febrile child who has no source of infection. Early studies suggesting an improved outcome for bacteremic patients who received oral antimicrobial therapy at their initial visit prior to obtaining the results of blood cultures have not been corroborated by more recent randomized clinical trials. The results of a recent multicenter trial suggest that treatment with intramuscular ceftriaxone (50 mg/kg) is more likely to decrease the incidence of focal bacterial infections and to eradicate bacterial pathogens from the blood of bacteremic children compared with children receiving oral amoxicillin.

Other factors that need to be considered when contemplating antibiotic therapy include the overall assessment of the child, the status of the child's immunologic functioning, the ability of the parents or caretakers to observe for the subtle manifestations of bacterial sepsis, and the ease of obtaining follow-up within the first 24 hours after initial presentation. Clinicians will need to individualize their approach to the febrile child: No single parameter can be used to determine the most appropriate therapy.

COMPLICATIONS

Complications from occult bacteremia have been reported to occur in 4% to 20% of patients. These usually are due to the development of a secondary focus, in particular, meningitis, pneumonia, septic arthritis, pneumonia, or persistent bacteremia. The incidence of complications currently is organism-specific and has been reported to occur in 2% to 4% of children who have *S pneumoniae* bacteremia, 7% of children who have *H influenzae* bacteremia, and 25% of those who have *N meningitidis* bacteremia.

THE CHILD WHO HAS BACTEREMIA

Because 3% of children will have positive blood cultures for a true bacterial pathogen, clinicians will be faced with other management decisions once the results of blood cultures are known. All children who have a positive blood culture require a repeat clinical examination to determine the presence of any focal complication. This is especially true if infection with the organism is associated with a high rate of complications, such as in *H influenzae* type b and *N meningitidis*, or if the organism is an unusual pathogen, such as *Escherichia coli* or any of the pathogens associated with urinary tract disease. If the follow-up clinical assessment finds the child to be afebrile and clinically improved, outpatient antimicrobial therapy should be initiated for 5 to 7 days. Sensitivity patterns of the organism can be used to guide the selection of antibiotics, although amoxicillin (40 mg/kg per day) or penicillin VR (25 000 to 50 000 U/kg per day) generally is sufficient for the treatment of pneumococcal infections, and third-generation cephalosporins or combination therapy with amoxicillin/clavulanic acid will maximize the coverage for beta-lactamase-producing organisms such as *H influenzae* type b. If on repeat examination the child is febrile or exhibits other manifestations of focal bacterial infection, he or she requires a complete evaluation, including lumbar puncture and hospitalization for intravenous antibiotic therapy and assessment for any focal complications (Table 3).

PROGNOSIS

The prognosis for most children who have bacteremia remains excellent.

Table 3. Algorithm for Child Who Has Known Bacteremia

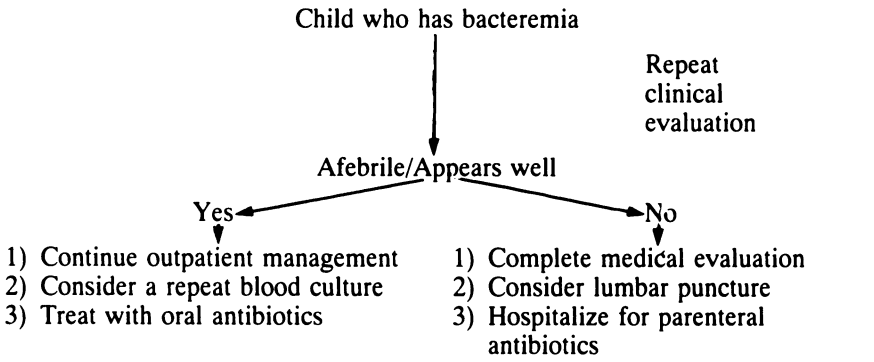

Table 4. Causes of Fever of Unknown Origin (FUO) in Childhood

Infectious Diseases (localized)
Endocarditis
Mastoiditis
Meningitis
Occult abscesses
  Hepatic
  Pelvic
  Perinephric
  Subdiaphragmatic
Osteomyelitis
Pneumonia/empyema
Pyelonephritis/urinary tract infection
Septicemia
Sinusitis
Tonsillitis/peritonsillar abscess

Infectious Diseases (systemic)
Viral: Cytomegalovirus
Ebstein-Barr virus
Hepatitis viruses
HIV
Bacterial: Brucellosis
Cat-scratch disease
Leptospirosis
Lyme disease
Salmonellosis
Tuberculosis
Tularemia
Other: Histoplasmosis
Malaria
Rickettsial infections
Toxoplasmosis

Collagen-Inflammatory Diseases
Henoch-Schoenlein purpura
Juvenile rheumatoid arthritis
Rheumatic fever
Systemic lupus erythematosis

Neoplastic diseases
Histiocytosis
Leukemia/lymphoma
Neuroblastoma
Solid tumors (eg, hepatoma)

Miscellaneous disorders
CNS dysfunction
Drug fever
Factitious fever
Immunodeficiency
Inflammatory bowel disease
Kawasaki syndrome
Sarcoidosis
Subdural hematoma/effusion
Thyroiditis

For many, occult bacteremia will be a transient phenomenon requiring outpatient antibiotic treatment. However, clinicians should be aware of the risks of focal infections, especially life-threatening events such as meningitis and bacterial sepsis, even in the well-appearing febrile child. Although studies designed to decrease the risk of bacterial complications do not, as of yet, support routine antimicrobial treatment of the febrile child, other factors, including the clinical assessment of an experienced physician, the ability and ease of obtaining follow-up, and the observational abilities of the parent or caretaker, remain important considerations in management.

Fever of Unknown Origin (FUO)

Although precise definitions vary, when a child has a significant fever (>38.5°C) lasting more than 2 weeks and the diagnosis remains uncertain despite a careful history and physical examination, it is appropriate to consider the patient to have fever of unknown origin (FUO). Because fever is a primary manifestation of many diseases (Table 4), including benign, self-limited infections, chronic multisystem inflammatory processes, and life-threatening malignancies, the pediatrician is faced with an important and challenging diagnostic dilemma. An organized framework for the evaluation of children who have FUO is essential: 1) to facilitate early diagnosis, 2) to ensure that thorough attention is given to excluding serious disease, and 3) to avoid a "fishing expedition" involving expensive or invasive tests of low diagnostic yield.

EPIDEMIOLOGY

Although published series of FUO in children differ substantially in their inclusion criteria, certain important considerations emerge. First, infections are the most common identified source of FUO in children (approximately 50% of cases), followed in order by collagen-inflammatory disorders (more common in females and children greater than 6 years of age) and neoplastic diseases. Second, the vast majority of patients have a disease process seen commonly in general pediatrics. Thus, rather than an exhaustive search for rare or exotic diagnoses, attention should be focused on recognizing subtle or atypical presentations of common disorders. Finally, although roughly 20% of cases (presumed viral infections) will resolve spontaneously, a larger percentage will have infections requiring specific therapy. Up to 40% of patients will have a serious disorder or lasting sequelae; mortality rates of 6% to 17% have been reported in studies of pediatric FUO. Therefore, prolonged fever in childhood cannot be approached casually.

Perhaps the most important lesson to be learned from the pediatric FUO literature is that there is no substitute for a complete and detailed history and careful, repeated physical examination. The final diagnosis in the majority of patients was indicated or suggested by history or physical findings rather than by specific laboratory investigations or imaging studies.

EVALUATION

When a child presents having FUO, the history should include a meticulous review of any relevant symptoms. Significant weight loss or linear growth impairment suggests long-standing chronic conditions such as inflammatory bowel disease. The first appearance of symptoms such as fatigue, malaise, and diminished appetite (which commonly accompany acute fever in children) should be documented because these may predate the onset of fever. Other symptoms, such as abdominal pain, cough, headache, or dysuria, may be a clue to localized infection. Joint pain and rashes are characteristic of collagen-inflammatory diseases and of infections such as hepatitis B virus and Lyme disease. A medical history of recurrent fevers or infections may indicate an immune defect such as cyclic neutropenia or IgG subclass deficiency. Recent surgical procedures could provide a nidus for occult infection, while transfusion of blood products carries a small risk of hepatitis virus or HIV transmission. Drug fevers may occur as a reaction to a medication the child has been

prescribed. Family history should be screened for autoimmune disease, inflammatory bowel disease, and tuberculosis.

Any contact with infected or otherwise ill individuals should be investigated thoroughly. Child care centers can be a source of exposure to communicable diseases, such as Ebstein-Barr Virus (EBV), cytomegalovirus (CMV), hepatitis, or salmonellosis. Animal exposure may result in transmission of leptospirosis (dogs), toxoplasmosis (cats), rat-bite fever (rats), psittacosis (birds), or salmonellosis (turtles). A detailed history could raise the possibility of endemic disease such as malaria, hepatitis, enteric fever, tuberculosis, histoplasmosis, or coccidiomycosis. One should inquire about visits to wooded areas, tick bites (Lyme disease, Rocky Mountain spotted fever, relapsing fever), and mosquito bites (arboviruses). The dietary history should focus on consumption of raw meat (brucellosis, toxoplasmosis), game meat (tularemia), raw fish (hepatitis, salmonellosis), and unpasteurized milk (brucellosis, salmonellosis). Children who have pica may expose themselves to infectious diseases such as visceral larva migrans or toxoplasmosis.

High spiking fevers suggest transient bacteremia associated with pyogenic infections. This pattern also is seen in juvenile rheumatoid arthritis (JRA). Typhoid fever classically is sustained. Relapsing fevers are seen in malaria, *Borrelia* infections, rat-bite fever, and lymphomas. Recurrent fevers separated by several afebrile days may represent a series of different infections (''pseudo-FUO''), perhaps as a result of an underlying immunodeficiency state. The height or pattern of fever itself has not been shown to predict the ultimate diagnosis or prognosis in the larger pediatric FUO series.

PHYSICAL EXAMINATION

The physical examination of a child who has FUO must be both thorough and repeated, for studies suggest that 25% of patients develop key findings at some point after their initial presentation.

A careful dermatologic examination may demonstrate the evanescent rash of JRA, which recurs at the time of fever spikes. A perineal rash may aid in the diagnosis of Kawasaki syndrome, a seborrheic rash in histiocytosis, and petechiae or purpura in bacterial endocarditis or a systemic vasculitis.

Generalized adenopathy or hepatosplenomegaly suggests viral infections (eg, infectious mononucleosis) and collagen vascular disease (eg, JRA, drug reactions, leukemia, or HIV-related immunodeficiency). Regional adenopathy indicates a localized bacterial infection, cat-scratch disease, or malignancy.

Conjunctivitis is found with Kawasaki syndrome, leptospirosis, tularemia, and systemic lupus erythematosis. Fundoscopic examination may reveal papilledema (brain tumor, subdural hematoma, meningoencephalitis), Roth spots (infective endocarditis), or granulomatous changes (tuberculosis, sarcoidosis). A slit lamp examination is useful in identifying uveitis (JRA, Crohn disease, toxoplasmosis).

Joints, including the hips, should be examined for arthropathy associated with collagen inflammatory disorders, toxic synovitis, or septic arthritis. Reactive arthritis is seen with brucellosis, bacterial enteric infections such as shigellosis, and hepatitis virus infection. Bony tenderness could indicate osteomyelitis or neoplastic marrow invasion. The sinuses and mastoid area should be palpated carefully and transilluminated. Muscle soreness is seen with underlying abscesses.

Every patient who has FUO should receive a rectal examination to look for tenderness or adenopathy indicative of abdominal or pelvic abscesses or tumors.

Stools should be examined for occult blood loss (guaiac test), characteristic of inflammatory bowel disease. A pelvic examination is indicated in adolescent females to rule out inflammatory disease or abscess.

LABORATORY EVALUATION

All patients who have FUO should have a complete blood count with differential taken. Anemia is seen in inflammatory bowel disease, JRA, malaria, and parvovirus B19 infection. Low platelet counts are associated with EBV infection, toxoplasmosis, tuberculosis, and spirochetal infections. Thrombocytosis is common in Kawasaki syndrome. Leukocytosis with a ''left shift'' increases the likelihood of bacterial infection, whereas atypical lymphocytes are characteristic of systemic viral infections. Immature leukocyte forms or pancytopenia suggest leukemia.

Aerobic and anaerobic blood cultures, urinalysis, tuberculin skin test (with controls), liver chemistries, serum protein analysis, and chest and sinus radiographs are appropriate initial ''screens'' for children who have FUO. In older children, a heterophil antibody test and antinuclear antibody titer could be added to the list. Erythrocyte sedimentation rate or C-reactive protein level are of little diagnostic value, but as indicators of significant illness (bacterial infection, tumor, collagen vascular disease), they can be useful to follow disease activity and guide the need for further evaluation.

DIAGNOSTIC APPROACH

A schematic approach to the evaluation of the child who has FUO is shown in Figure 4. The algorithm emphasizes an essential feature in the evaluation: the painstaking pursuit of every diagnostic lead uncovered, no matter how insignificant it may appear at first.

History or physical findings provide the clue to the final diagnosis in the majority of patients. Potential exposure to infectious agents via sick contacts, travel to endemic areas, or dietary intake should guide serologic studies and special cultures. A history of repeated infections may signal the need for a more elaborate immunologic evaluation or HIV serology. Abdominal symptoms or linear growth impairment indicate barium studies to rule out inflammatory bowel disease. Unusual cutaneous findings or enlarged lymph nodes may yield a diagnosis on biopsy.

Failure to use existing laboratory data appropriately also has been shown to contribute significantly to delayed diagnosis of FUO. Abnormal findings in the peripheral blood may be an indication for bone marrow examination. Eosinophilia is seen in parasitic infections, drug reactions, and malignancy. Sterile pyuria is a common overlooked diagnostic clue

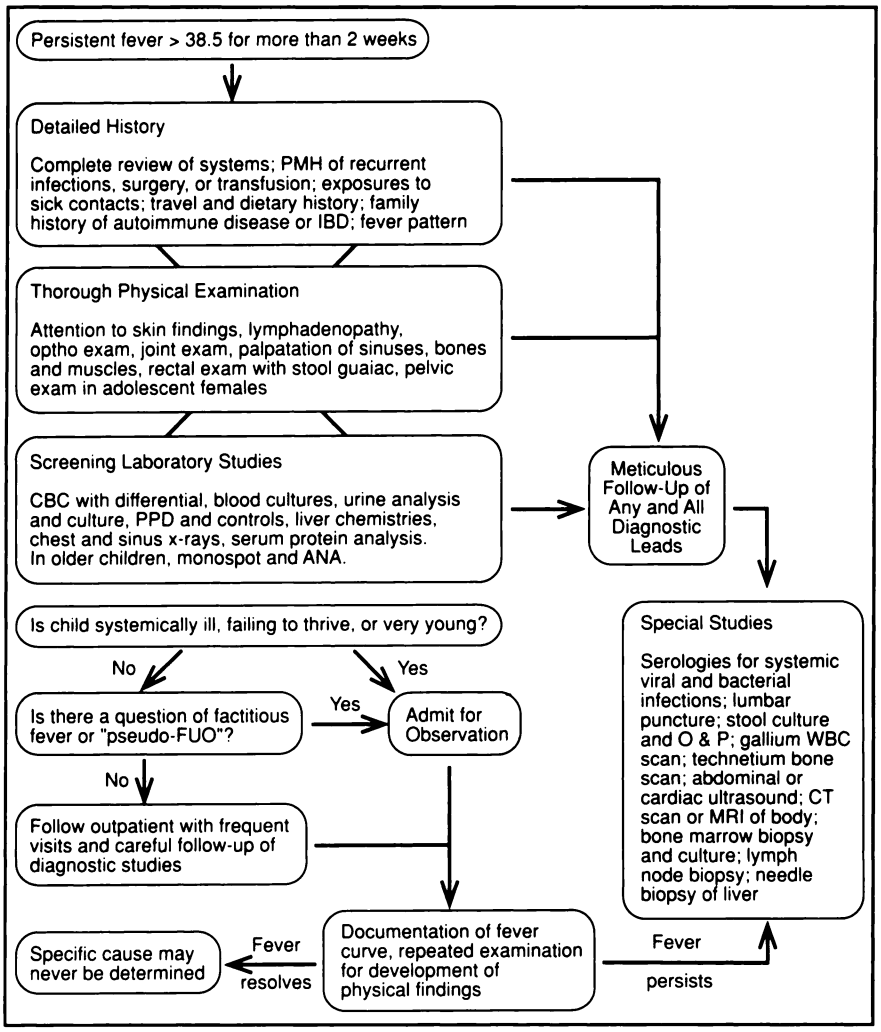

FIGURE 4: Diagnostic approach to the child who has FUO.

to Kawasaki syndrome or tuberculosis. Evidence of liver inflammation, biochemical dysfunction, or cholestasis should be pursued with appropriate serologies (hepatitis screen, EBV/CMV, leptospirosis) and ultrasonographic imaging.

IS HOSPITAL ADMISSION NECESSARY?

If a child who has FUO is not systemically ill, if thorough history taking, physical examination, and screening laboratory studies have been performed, and if all diagnostic leads have been pursued, it is appropriate to follow the patient over time in the outpatient setting. Studies suggest that up to 20% of fevers will resolve spontaneously, with the specific cause never determined. Important physical findings or laboratory abnormalities may develop later.

Hospital admission, however, is indicated for very young children or for those who have severe systemic symptoms. An advantage to admitting children who have FUO is the opportunity for careful, repeated history-taking and physical examination. Constant observation may unveil subtle clinical features (eg, the rash of JRA). A parent's misinterpretation of several unrelated febrile illnesses as persistent fever (pseudo-FUO) and factitious fevers (eg, Munchausen syndrome by proxy) sometimes is clarified only by hospital admission.

MORE ELABORATE TESTING

If fever persists beyond a month or if the child is systemically ill or failing to thrive, more elaborate testing is justified. A gallium white blood cell scan may help to localize abscesses, granulomatous foci (eg, tuberculosis, sarcoidosis), and certain malignancies (lymphomas, many solid tumors). A technetium bone scan may reveal an occult osteomyelitis. Spinal fluid analysis should be considered in patients who have headache or neurologic symptoms. Bone marrow examination is indicated to rule out hematologic malignancies or neuroblastoma; the marrow also should be cultured for mycobacteria and salmonella. Abdominal ultrasonography, body computed tomography, or magnetic resonance imaging may identify masses, deep lymph nodes, or abscesses. Studies suggest that exploratory laparotomy is not useful unless indicated by imaging studies.

TREATMENT

A child in whom JRA is suspected should receive a trial of nonsteroidal anti-inflammatory agents. Empiric trials of broad-spectrum antibiotics generally are without diagnostic or therapeutic benefit and may mask or delay the diagnosis of infections such as endocarditis, meningitis, or osteomyelitis. The high incidence of infectious processes emphasizes the need for bacterial cultures before antibiotics are started.

Conclusion

The wise evaluation and treatment of fever in children tests the skills of the best pediatrician. This article offers an approach that we hope simplifies that process and will result in a higher degree of accuracy in diagnosis and treatment.

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PIR QUIZ

1. Antipyretic therapy is *most* likely to be effective in the treatment of fever caused by:
   A. Collagen-vascular disease.
   B. Ectodermal dysplasias.
   C. Heat stroke.
   D. Hyperthyroidism.
   E. Salicylism.

2. Among the following, the *least* acceptable argument against lowering fever with antipyretics is that:
   A. Adverse effects of treatment outweigh benefits.
   B. Fever may be protective to the host.
   C. Interleukin-1 is suppressed.
   D. Lowering can obscure diagnostic signs.
   E. Most fever is short-lived.

3. Among the following, the organism that *most* commonly causes occult bacteremia in small children is:
   A. Group A *Streptococcus*.
   B. *Haemophilus influenzae* type b.
   C. *Neisseria meningitidis*.
   D. *Salmonella* sp.
   E. *Streptococcus pneumoniae*.

4. The incidence of complications from occult bacteremia is *highest* in children infected with:
   A. Group A *Streptococcus*.
   B. *Haemophilus influenzae* type b.
   C. *Neisseria meningitidis*.
   D. *Salmonella* sp.
   E. *Streptococcus pneumoniae*.

5. A *true* statement regarding fever of unknown origin is:
   A. An infectious etiology is unlikely.
   B. A specific diagnosis ultimately can be made in all cases.
   C. Rectal examination should be reserved for patients who have bowel symptoms.
   D. Serial physical examinations can be helpful to diagnosis.
   E. The majority of patients ultimately are found to have a rare disease.

6. Among the following causes of fever of unknown origin, which might be *best* diagnosed by admission to the hospital?
   A. Drug reaction.
   B. Factitious fever.
   C. Juvenile rheumatoid arthritis.
   D. Leptospirosis.
   E. Sarcoidosis.

Fever in Children

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