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Fever is a nonspecific body response to a variety of environmental and internal factors. It is among the most frequent reasons for patients to present to the ED, accounting for 6% of adult and 20-40% of pediatric visits.

Unlike the pediatric patient, in whom fever most frequently reflects an infectious etiology, fever in an adult can be due to non-infectious conditions such as collagen vascular diseases, malignancy, embolic disease, and other conditions. Fever at the extremes of age or in an immunocompromised patient remains a diagnostic challenge. An ill appearing elderly or immunocompromised patient suspected of harboring an infection who presents without fever can be difficult to assess, since the "septic elderly" may not mount the expected febrile response. Symptoms of infection may be masked in adults with chronic diseases or altered sensorium. Moreover, recent expansion in the use of "medical hardware" increases the risk of "occult" infection in the elderly.

This issue reviews definitions of fever, clinical evaluation, and differential diagnosis of the febrile adult patient. In part II of this two-part series, 10 clinical conditions associated with fever are discussed in detail.

—The Editor

The Febrile Adult: Part I, A Systemic Approach to Diagnosis and Evaluation

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Fever: Clinical Considerations

Normal body temperature is controlled within a narrow "physiologic" range through a variety of behavioral and physiologic mechanisms. The preoptic area of the hypothalamus is the body's thermoregulatory center. It consists of thermosensitive neurons whose rate of discharge is affected by the temperature of the local blood supply, and has neural connections with temperature sensors distributed in skin and muscle. These neurons are also affected by a variety of hormones, cytokines, and neurotransmitters. In response to these signals, the hypothalamus directs efferent nerve pathways, resulting in actions that lead to heat generation or loss; for example, peripheral vasoconstriction and shivering cause heat generation, and peripheral vasodilatation causes heat loss.

Generally, fever represents a controlled elevation of "normal" body temperature and is associated with a reset of the hypothalamic set point. In humans, the normal set point ranges between 36°C and 37.8°C. The daily variation of body temperature of approximately 1°C is referred to as the circadian rhythm. Typical body temperatures are lowest in the early morning and highest in the late afternoon.

Hyperthermia is defined as an elevation of normal body temperature that occurs when peripheral heat-dissipating mechanisms become overwhelmed, as with vigorous exercise, environmental exposure, hyperthyroidism, or the use of anticholinergic or phenothiazine medications. In almost all cases, a temperature higher than 41.5°C reflects "hyperthermia" rather than true fever. Behavioral mechanisms are also important, as is exemplified by the use of blankets or warmer

clothing during a chill in the early phase of infection.[1] *(See Table 1.)*

Whether temperature elevation represents a significant defense mechanism in humans has been debated. Temperature elevation results in increased oxygen and caloric demands, and poses potential damage to neural tissue. Fever also is associated with excessive protein breakdown and with increased gluconeogenesis,[2] perhaps, in part, mediated by interleukin-1.[3] A patient's basal metabolic rate may be increased as much as 15% for each degree Celsius rise in temperature. This "response" to temperature elevation can drain metabolic reserves in a critically ill or an elderly patient.

Neurological damage is the most important complication of significant elevations in temperature. This complication is most often encountered with hyperthermia. Alteration of mental status is common at temperatures above 41°C. Temperatures greater than 42°C may produce loss of consciousness, and neurological damage may occur if these temperatures are sustained for a prolonged period of time.

Moderate elevations in temperatures are usually well tolerated by the patient and may aid to some degree in "host defense." In this regard, increases in body temperature directly inhibit replication of such viruses as Coxsackie and polio. The only infections in which fever has clearly been shown to inhibit microbial growth, however, are neurosyphilis and a disseminated gonococcemia.[1]

The genesis and maintenance of fever represents a complex interaction between various biochemical predicters that elevate the hypothalamic set point. Pyrogens, which are capable of inducing fever, can either be endogenous or exogenous. Endogenous pyrogens are produced within the body, whereas exogenous pyrogens are introduced by infecting microrganisms. Exogenous pyrogens may be either the microorganisms themselves, or they may represent metabolic products or toxins produced by the offending agent. They generally cause fever by inducing the host to produce endogenous pyrogens.

Endogenous pyrogens are a heterogeneous collection of cytokines that include interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), interferon-a and -b, and others. In response to infectious, inflammatory, or immunological stimuli, monocytes and macrophages produce endogenous pyrogens, which travel via the blood to the thermoregulatory center of the hypothalamus. There, arachidonic acid is released, which is associated with production of prostaglandin E2 (PGE2). When the hypothalamic set point is raised, efferent signals lead to peripheral vasoconstriction, increased internal heat production, and behavioral changes that conserve heat. Ultimately, the new thermostatic set point is reached, and a new equilibrium for body temperature prevails. Fever is maintained as long as the levels of endogenous pyrogen remain steady and the effects of pyrogens are not inhibited. If the levels of endogenous pyrogen fall, the thermostat is reset at a lower level. Cyclo-oxygenase inhibitors, such as aspirin, decrease temperature by blocking production of PGE2.

Clinical Evaluation of the Febrile Adult

A detailed history, when available, can generate a useful differential diagnosis in most febrile patients presenting to the emergency department (ED). The history will suggest specific aspects of the physical examination. The majority of febrile illnesses are infectious, and, therefore, clinical findings indicating involvement of a specific organ system may suggest a diagnosis. Overall, the diagnosis of 70-85% of adult febrile illnesses can be made on the basis of a history and a physical examination.[4,5]

The origin and duration of the current illness should be considered, including an inquiry into the time and the magnitude of fever. A history of associated symptoms, if any, should be elicited. Consider infectious (e.g., amoebiasis, malaria) and noninfectious conditions (e.g., pulmonary embolus) in patients with a recent history of travel. A history of chronic illness, recent and past surgeries, presence of "medical hardware," and medication use (prescription and nonprescription) is important; immunization status also should be considered. A recent hospitalization should prompt consideration of a nosocomial infection, whereas a history of exposure to animals, toxic fumes, raw or poorly

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Table 1. Ranges of Fever and Associated Neurological Symptoms

- Normal: between 36°C and 37.8°C
- Circadian rhythm: daily variation of approximately 1°C
- Hyperthermia: > 41°5 C
- Alteration of mental status: > 41°C
- Loss of consciousness: > 42°C (neurological damage may occurif these temperatures are sustained for a prolonged period of time)

cooked meats, or unpasturized dairy products can provide important clues to fever in an adult without an obvious source of infection. The patient should be questioned about sexual activity and the use of protective measures.

Vital Signs. Blood pressure, temperature, heart rate, and respiratory rate are noted. Pulse oximetry is useful in selected patients who are severely ill. Temperature is measured either orally or rectally. Axillary and tympanic temperatures are unreliable, as are oral temperatures measured after recent intake of hot or cold beverages, smoking, or hyperventilation.[6] Rectal temperatures are approximately 17.2°C higher than the oral temperature.[6] Serial temperatures measured via the same route provide additional information. The heart rate can be expected to increase by approximately ten beats per minute per 17.2°C of temperature elevation. Relative bradycardia or temperature-pulse dissociation is seen in such conditions as typhoid fever, brucellosis, leptospirosis, drug-associated fevers, and factitious fever.[6] The physician should consider rheumatic fever, Lyme disease, viral myocarditis, bacterial endocarditis, presence of underlying cardiac conduction disease, or concurrent use of medications such as beta-blockers in a febrile patient with frank bradycardia. Tachypnea, a sign of dyspnea, suggests pulmonary disease. In the absence of dyspnea, tachypnea can be a nonspecific sign of sepsis.[7]

Sensorium. Mental status changes, especially in the elderly and the chronically ill patient, require evaluation for infection. Altered mental status can present as decreased level of consciousness, confusion, lethargy, agitation, anorexia, weakness, lightheadedness, vertigo, falls, incontinence, or memory loss. Severe agitation or coma in a febrile patient on neuroleptic medications raises the possibility of neuroleptic malignant syndrome. Rigors, which generally suggest bacteremia, can occur in noninfectious diseases such as lymphoma. Rigors are absent in more than half of bacteremic patients.[8]

Physical Examination

Skin. The skin should be examined for exanthema. Viral exanthema is frequently maculopapular. Purpuric lesions are characteristic of meningococcemia, and petechial lesions are characteristic of vasculitis or thrombocytopenia. Decubitus ulcers can be a portal of entry for systemic infection. The characteristic hot red lesions of cellulitis can be missed if not specifically sought. Specific rashes associated with fever are reviewed later.

Head and Neck. Palpebral conjunctivitis is characteristic of several viral infections, while bulbar conjunctivitis can be associated with leptospirosis. Scleral icterus may suggest hepatitis, biliary tract obstruction, or hemolysis. Funduscopic abnormalities associated with fever include fluffy, white exudates associated with disseminated candidiasis; retinal hemorrhage associated with leukemia; emboli associated with endocarditis; or yellow nodules associated with miliary tuberculosis.[9] Erythema of the tympanic membrane or air fluid levels on otoscopic examination suggest otitis media. Bullae on the tympanic membrane are characteristic of *Mycoplasma* infection. The presence of erythema, epithelial debris, and exudate along with pain on auricular manipulation are characteristic of otitis externa, whereas tenderness on palpation of the mastoid process may indicate mastoiditis.

Stridor is a late finding associated with supraglottitis or epiglottitis in adults.[10,11] The presence of an enlarged erythematous uvula is seen in uvulitis, which has been associated with epiglottitis. Poor dentition and oral hygiene is associated with gingival infection, periodontal abscess, and aspiration pneumonia. Tonsils and peritonsillar tissues should be examined for swelling, erythema, injection, soft palate petechiae, and exudates. Severe tonsillitis can present with stridor. Unilateral tonsillar swelling with unilateral soft palate edema and erythema and uvular deviation suggest peritonsillar abscess. Tonsillar exudates are seen with a number of infectious agents and are not pathognomonic of Group A beta hemolytic strep infection.

The neck should be examined for lymphadenopathy, masses, and thyroid enlargement. Nuchal rigidity is suggestive of meningitis, but this sign is frequently absent in the elderly or chronically debilitated individual. Soft tissue infections in the neck, such as parapharyngeal or retropharyngeal abscess can present with sore throat with or without stridor, drooling, and muffled or "hot potato" speech.

The differential diagnosis of fever associated with lymphadenopathy includes autoimmune disorders, malignancy, drug-related side effects and a variety of infections. Lymphadenopathy caused by infections is usually tender, whereas malignant lymphadenopathy is usually painless, rubbery, hard, and firm. Infectious agents usually cause bilateral cervical lymphadenopathy. Unilateral cervical lymphadenopathy is more often malignant. Supraclavicular nodes can be felt in association with fungal infections such as cocciodomycosis and histoplasmosis, but are more common with malignancies of lung, abdominal, or pelvic organs.

Epitrochlear nodes may be encountered in hand infections as well as in non-Hodgkin's lymphoma and secondary syphilis. Axillary and inguinal lymphadenopathies are commonly associated with infection, although malignancies (specifically breast and melanoma) can also present in this manner. Infections that cause generalized lymphadenopathy include acute viral infections, brucellosis, leptospirosis, and AIDS. Non-infectious etiologies of generalized lymphadenopathy associated with fever include: lymphoma, sarcoidosis, collagen vascular disorders, immune globulin disorders, myeloproliferative and lymphoproliferative diseases, and side effects of such drugs as phenytoin, methyldopa, and procainamide.

Chest. Auscultation of the chest may yield findings associated with pneumonia or congestive heart failure; ronchi and wheezes may reflect bronchospasm caused by bronchitis, reactive airway disease, or exacerbation of chronic obstructive pulmonary disease.The presence of a pericardial rub on auscultation

Table 2. Laboratory and Radiological Studies in the Febrile Patient

- Leukocyte counts
- Acute phase reactants
- Strep screen and throat culture
- Sputum gram stain
- Urine analysis and culture
- Blood cultures
- Cerebrospinal fluid examination
- Stool evaluation

can indicate pericarditis. A new murmur in an IV drug user or elderly patient should suggest the possibility of endocarditis. New onset of congestive heart failure can be seen with myocarditis.

Abdomen. The abdomen should be examined for distention, the presence of atypical "tinkles and rushes" associated with evolving obstruction, areas of tenderness, signs of peritoneal irritation, intraperitoneal fluid, and organ enlargement. Rectal examination may demonstrate perianal or perirectal abscesses. Prostatic tenderness indicates prostatitis, which can be a source of recurrent infections. Intra-abdominal infections such as cholecysitis, diverticulitis, appendicitis, and abscesses of the liver, spleen, or pancreas are a common cause of fever that may be difficult to diagnose.

Noninfectious causes of fever with abdominal pain include inflammatory bowel disease and pancreatitis. Elderly patients, as well as patients with diabetes or those on chronic corticoidsteroid therapy, may lack typical physical findings. The clinician should note the low sensitivity and specificity of "classic" predictors (temperature > 37°C, white blood cell count > 14,000, rebound, and vomiting) of appendicitis in patients 60 years and older.[12]

Genitourinary. External genitalia should be examined for ulcerations, swelling, discharge, and nodules. The foreskin, if present, should be examined and retracted. Urethral discharge suggests urethritis that is caused by a sexually transmissible disease. An enlarged, tender testicle requires evaluation for orchitis or torsion. The epididymis is palpated for enlargement and tenderness, findings that suggest epididymitis.

Suprapubic tenderness associated with dysuria and/or urinary frequency should prompt a urinalysis to evaluate for urinary tract infection, a common cause of fever in the elderly and debilitated patient. A pelvic examination is performed routinely to evaluate for the cervical motion tenderness and cervical discharge of pelvic inflammatory disease, as well as adenexal tenderness or mass associated with tubo-ovarian abscess or ovarian cyst.

Musculoskeletal and Extremities. Examination of the extremities and axial skeleton is often overlooked in the evaluation of the febrile patient. Palpation of the spine may reveal tenderness that can indicate spinal osteomyelitis, discitis, or epidural abscess. The latter is common in intravenous drug abusers and alcoholics. Palpation and inspection of the extremities can reveal osteomyelitis, cellulitis, deep venous thrombosis, ruptured Baker's cyst, diabetic ulcers, or acute septic arthritis.

Differential Diagnosis of Fever

The differential diagnosis in patients presenting to the ED with fever is broad. Age and underlying medical conditions are the most important considerations in generating a list of differential diagnosis in an adult febrile patient. For example, a young healthy patient is more likely to have a benign viral illness, whereas an elderly diabetic is more likely to have a serious bacterial infection. Since infections are responsible for most fever-related visits to the ED, an initial evaluation directed toward infectious etiologies is most likely to be rewarding.

In general, the goal of ED evaluation of a febrile adult is to detect either a "treatable infection" (which in most cases is a bacterial illness) or a serious, life-threatening noninfectious cause of fever (such as pulmonary embolus). The ED investigation is a time-restricted process that includes a history, physical examination, and limited ancillary tests. In the majority of cases, safe discharge from the ED or the decision to hospitalize an adult febrile patient is made on the basis of clinical information and physical examination rather than on ancillary tests.

Laboratory and Radiological Studies

Judicious use of laboratory and radiologic tests guided by a careful history and physical examination—and a well developed differential diagnosis—can provide high quality, yet cost efficient, patient care. *(See Table 2.)*

Leukocyte Counts. The leukocyte (WBC) count frequently is used to evaluate the febrile patient in order to distinguish bacterial from viral etiologies of fever, and to gauge the severity of infection. Although a leukocytosis suggests a higher likelihood of occult bacterial infection, even with a left shift, viral illness is still possible. As a result, the usefulness of the absolute leukocyte count, with or without an increase in immature cell forms, is limited.[13-18] Leukocyte count is neither sensitive nor specific for the type or severity of infection. Demargination of neutrophils in response to strenuous exercise can account for a leukocytosis as high as 35,000/mm.[6,17] Neutrophilia with a "left shift" can be a nonspecific reaction to acute emotional stress, acute or chronic inflammation, benign or malignant tumors, other non infectious states, or medications such as steroids, lithium, and epinephrine.[17] Although relatively inexpensive to perform, the true cost of a leukocyte count includes the cost of over treatment in response to abnormal, but clinically irrelevant, leukocytosis.[18] In one study, only two out of 860 leukocyte counts with differentials had a clearly beneficial effect on patient care.[16]

However, the leukocyte count is useful in the assessment in *selected* febrile patients. It should be interpreted and correlated with the entire clinical picture and used as one of several tools to aid in the decision making process. The leukocyte count can be used to increase the suspicion of a bacterial illness in the following selective clinical conditions: 1) febrile elderly patients, 2) febrile adults without a definite source of infection, and 3) immunocompromised febrile adults.

Acute Phase Reactants. In the febrile patient, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are sometimes used to screen for an inflammatory or infectious processes. As with the leukocyte count, these tests can be misleading if they are not interpreted cautiously.

ESR, a simple and an inexpensive test, is an index of the suspension stability of red blood cells in citrated blood. ESR measures the distance in millimeters that erythrocytes fall in one hour. In clinical practice, the ESR is used to monitor progression or improvement of a documented disease and response to therapy. In the ED, ESR is primarily used to identify the presence or absence of a disease such as temporal arteritis in an older patient with headache and fever. Numerous studies have reported the inconsistent sensitivity and poor specificity of the ESR. However, the ESR does not help discriminate between those patients who have serious bacterial infection and those who do not.[19-26]

Although less than ideal, CRP is both more sensitive and more specific than ESR.[23,24] With serial measurements, CRP is more useful in monitoring response to therapy.[26] CRP rises faster in infectious states than does ESR,[24,25] which enhances its usefulness in emergency medicine. In a cohort study of elderly patients, neither ESR nor CRP satisfactorily discriminated between patients with and without ongoing active or chronic disease.[27] In addition, the same study reported elevation of ESR and CRP with infection, although neither had an advantage over the other.[27] In some chronic illnesses, such as diabetes and chronic renal failure, a rise in CRP is considered to be more specific for infection.[20,28]

Strep Screen and Throat Culture. Viral and bacterial pharyngitis are self-limited illnesses in most immunocompetent patients. However, a variety of symptoms accompanying bacterial-mediated "sore throat" resolve more quickly with prompt (early) initiation of antibiotic therapy. In addition, the association of Group A beta hemolytic strep (GAS) with rheumatic heart disease is well documented.

Throat cultures have been the "gold standard" for diagnosis of bacterial, and, specifically, streptococcal pharyngitis. However, throat cultures can be falsely positive and indicate a carrier state or they may be falsely negative. Multiple commercial rapid strep screens are available, with sensitivities ranging from 55% to 96% and specificities ranging from 50% to 98%.[29-33] A newer technique, optical immunoassay, has a reported sensitivity of 97.4-98.9% and a specificity of 95.6-98.0%, which is more sensitive than bacterial culture.[33]

These screening tests only detect GAS, while other organisms commonly implicated in pharyngitis, such as *Chlamydia trachomatis, Mycoplasma pneumonia,* and gonococcus, are not detected by a screening test.

The most outcome-effective treatment protocol for acute pharyngitis is controversial. Some experts recommend antibiotic treatment on the basis of a history and physical examination, while others advocate treating only those with positive cultures or rapid assays.[32] As a rule, a strep screen is not indicated when the clinical suspicion for GAS is high and antibiotics will be prescribed based on clinical presentation alone. The prudent use of antibiotics in the treatment of acute pharyngitis is based on the results of a strep screen in patients with sore throat and recent exposure to GAS; those with a history of rheumatic fever, diabetes, or fever higher than 38.8°C; and those with the presence of a scarlatiniform rash or sore throat that persists for longer than six days.[34]

Sputum Gram Stain. In the febrile patient with a productive cough, a sputum gram stain is sometimes helpful. An appropriate sample of sputum has more than 25 neutrophils and less than 10 epithelial cells/HPF on gram stain. Sputum cultures are often not as helpful due to the presence of fastidious anaerobes that fail to grow or to the overgrowth of oral flora. In cases of pneumococcal pneumonia, bacteria fail to grow in approximately one-half of cases in which it was demonstrated on gram stain.[35,36]

Urine Analysis and Culture. Dysuria, urgency, and frequency of urination accompanied by suprapubic tenderness and a urinalysis demonstrating pyuria and bacteruria confirm the diagnosis of urinary tract infection. As a rule, young adult females with no prior episodes of cystitis do not require further microbiological evaluation other than consideration of a curvical culture to rule out *Chlamydia* infection. Males with urinary infection require urine *culture* and sensitivity, as well as rectal examination to evaluate prostatic pathology. Examination of the urine after prostatic massage may reveal increased leukocytes suggesting prostatitis.

Despite a few studies challenging the usefulness of its ability to screen for infection, dipstick urine analysis is widely used and relatively accurate.[37] A positive leukocyte esterase test, in conjunction with positive urine tests for nitrite and blood on dipstick test, suggest the presence of urinary infection. The dipstick test has been reported to have a sensitivity and specificity of greater than 88%.[37] The sensitivity is lower when there are less than 10 WBC/HPF. However, a positive dipstick test does not always indicate a urinary infection. Non-infectious causes such as interstitial nephritis, nephrolithiasis, or vaginal discharge also can produce pyuria. As false-negative tests for infection are common with dipstick urine testing, a microscopic urinalysis is recommended when urine dip stick testing is negative in a patient with a strong clinical suspicion of urinary infection.

The presence or absence of a "true" urinary tract infection is difficult to confirm in light of controversy regarding the precise criteria indicating urinary infection. Colony forming unit (CFU) count or "colony count" higher than 100,000 CFUs/mL of urine has been traditionally used as a marker for urinary tract infection. However, infections can be documented with much lower CFUs. Bacteremia, too, can occur with lower concentrations of bacteria in the urine.[37] Not suprisingly, in the literature, the presence of urine infection has been characterized according to many different criteria: 10,000-100,000 CFUs/mL of a *single* urinary pathogen; 1000 CFUs/mL of a single urinary pathogen from a catheterized specimen; or 100 CFUs/mL of a single urinary pathogen in a "symptomatic" female patient.

In the absence of any risk factors, a urine culture usually is *not* necessary in most cases of uncomplicated urinary tract infection when symptoms suggest only "lower urinary tract" infection. However, in the presence of normal microscopic and dipstick urine tests and a *high* clinical suspicion of urinary tract infection, urine culture is recommended. Urine culture also is indicated in the patient with recurrent urinary tract infections or when urinary symptoms persist for more than seven days, and in those patients with a history of recent hospitalization, catheterization, pregnancy, or diabetes.[38] Urine culture is mandatory in the febrile, toxic-appearing adult and in the chronically debilitated patient

Table 3. Patient Subgroup and/or Clinical Conditions Benefitting from Blood Culture Studies

- Signs of sepsis, which may include fever, chills, tachycardia, and/or hypertension
- Acute alteration of mental status, especially in the elderly
- Identifying the causative organism in established cases of pneumonia, meningitis, osteomyelitis
- Unexplained leukocytosis in an ill-appearing patient
- Ill-appearing immunocompromised patient
- New onset of organ failure such as renal failure, liver failure, etc.

with a fever who has an indwelling urinary catheter or surgically altered urinary tract.

In the absence of a uniform definition of a urine culture that indicates a urine infection, the results of urine analysis and urine culture must be interpreted in association with clinical findings. This is particularly relevant when evaluating a female with acute dysuria. Since the results of a urine analysis can be misleading, the cause of acute dysuria in women (cystitis, urethritis and vaginitis) should be made clinically.

Blood Cultures. Blood cultures are performed to recover organisms that may be responsible for infection. Blood cultures are expensive, with a cost ranging from $25-$60 per set. False positive and false-negative results are common. Studies have reported that of *all* blood cultures drawn, true-positive results are obtained in less than 5% of samples.[39-41] Interestingly, the incidence of contamination is also approximately 5%.[39,41]

Although spiking fever and chills are typical signs of a bacteremic episode, well-defined clinical criteria that predictabaly identify bacteremia are lacking. When a bacteremic episode is suspected, two or three sets of blood cultures should be drawn by separate venipuncture for each set of blood cultures. Femoral vessels and vessels underlying skin the with dermatological disease should be avoided. The site is prepared with 70% isopropyl alcohol in a concentric fashion starting at the center. After allowing time for drying, the site is then prepared a second time with providine-iodine 10% solution in the same fashion and allowed to dry. Improvement in blood culture accuracy by using "a dedicated blood culture team" of phlebotomists has been reported.[39] A minimum of 10 mL and a maximum of 30 mL of blood is required for appropriate blood culture.[41]

Selected patient subgroups and/or clinical conditions that can benefit from blood culture studies *(See Table 3)* include:

- Signs of sepsis, which may include fever, chills, tachycardia and/or hypotension;
- Acute alteration of mental status, especially in the elderly;
- Identifying the causative organism in established cases of pneumonia, meningitis, osteomyelitis, etc.;
- Unexplained leukocytosis in an ill-appearing patient;
- Ill-appearing immunocompromised patient; and
- New onset of organ failure such as renal failure, liver failure etc.;

Cerebrospinal fluid examination. Lumbar puncture for collection of cerebrospinal fluid (CSF) is indicated whenever the diagnosis of central nervous system (CNS) infection, a CNS inflammatory process such as lupus cerebritis or a CNS neoplastic process, is suspected. Cardinal signs and symptoms of adult meningitis include fever, headache, and signs of meningeal irritation such as nuchal rigidity, Kernig's sign and Brudzinski's sign.

The diagnosis of CNS infection in the elderly and the chronically ill can be difficult inasmuch as the classic signs of meningeal irritation are frequently absent. Accordingly, a low threshold for the examination of CSF in these patients is prudent.

Cerebrospinal fluid is analyzed for cell count and differential, gram stain, culture and sensitivity testing, glucose, protein, and testing for bacterial antigens. The opening pressure is elevated in most cases of meningitis. The CSF may be clear, cloudy, or frankly purulent. The leukocyte count is frequently elevated with neutrophilic predominance. Low cell counts in *bacterial* meningitis are associated with poor prognosis. CSF pleocytosis with predominant polymorphonuclear leukocytes does not always indicate a "bacterial" infection. The CSF may or may not show pleocytosis in viral infections. Protein levels are elevated in bacterial meningitis. CSF glucose falls to less than 40 mm/dL in approximately 60% of cases, and a CSF-to-serum glucose ratio of less than 0.31 is seen in 70% of cases.[42] Reports of xanthochromia or even frank blood in CSF in cases of meningitis have been reported.[42]

The CSF gram stain demonstrates the offending bacteria with an overall sensitivity of 75%. The CSF culture is positive in 70-85% of patients with cofirmed bacterial meningitis.[42] Prior antibiotic therapy decreases the sensitivity of the CSF gram stain and the culture. A variety of immunologic tests are available for identifying bacterial antigens in the CSF; some have a sensitivity and specificity in the 95% range.[42] However, a negative antigen test *does not* rule out bacterial meningitis.

Stool Evaluation. Most cases of diarrheal illness are mild and self-limited and, therefore, stool evaluation is not helpful. Laboratory evaluation of the stool is helpful in the following conditions: chronic or subacute diarrhea, a cluster of diarrheal illness, severe diarrhea, or a diarrhea accompanied by abdominal pain, tenesmus, or hematochezia.

A Wright's (or leukocyte) stain is used to evaluate leukocytosis in the stool. Stool examination for the presence of fecal leukocytes is the most useful diagnostic study in patients with acute diarrhea. When correlated with stool cultures, the fecal leukocyte test is 82% sensitive and 83% specific for detecting a bacterial pathogen.[43] Diarrhea caused by invasive pathogens, such as enteroinvasive *E. coli*, *Salmonella* sp., *Shigella* sp., *Campylobacter* sp., *Yersinia* sp., *Vibrio* sp., *E. histolytica*, and *C. difficile*, are associated with presence of fecal leukocytes. Diarrheal illness caused by *Vibrio cholera*, enteropathic, enterotoxic *E. coli*, rotavirus, Norwalk agent, adenovirus, Giardia, Cryptosporidium, Strongyloides, and *Staphylococcus aureus*, *Bacillus cereus*, and *Clostridium* sp., are not associated with fecal leukocytes in the absence of mixed infection. It should be stressed that routine stool culture does not provide much help in detecting the offending pathogen in the absence of fecal leukocytes on stool gram stain. The false-negative incidence of a fecal leukocyte test is approximately 15%.[44]

C. difficile-induced diarrhea should be considered when a

Table 4. Liver Enzyme Elevation in the Febrile Patient

MEASUREMENT OF HEPATIC ENZYMES CAN BE HELPFUL IN THE EVALUATION OF:

- Suspected infectious or inflammatory hepatitis
- Sepsis
- Lower lobe pneumonia
- Legionnaires disease

Table 5. Clinical Findings Associated with Abnormal Chest X-ray in the Febrile Patient

- Fever
- Cough
- Chills/rigors
- Tachypnea
- Abnormal breath sounds
- Tachycardia
- Chest pain
- Dyspnea
- Wheezing
- Occupational exposure of toxins
- Weight loss
- Old age
- Alteration of mental status
- History of tobacco use
- Substance abuse (particularly intravenous drug use)
- Stroke
- COPD
- AIDS

diarrheal illness occurs following a recent course of antibiotic therapy. Diagnosis is made by detecting *C. difficile* toxin in the stool.

Parasite-induced diarrheal illness is diagnosed by identification of parasites in the stool or, occasionally, in the small bowel aspirates.

Other Laboratory Tests. Measurement of hepatic enzymes can be helpful in evaluation of suspected infectious or inflammatory hepatitis. Hepatic enzymes may also be elevated in sepsis, lower lobe pneumonia, and Legionnaires disease. *(See Table 4.)* Serum glucose determination can reveal occult diabetes and should be considered in patients with infected leg ulcers and soft tissue infections such as lower extremity cellulitis. Genital cultures are useful for diagnosis of gonorrhea and chlamydial infections; however, nuclear acid hybridization (DNA probe) technology is rapidly replacing genital and urethral cultures due to its high specificity, rapidity, and ease of performance. Routine cultures of eye, ear, nose, and sinus drainage are discouraged since these are almost universally contaminated by normal flora. Cultures of skin, soft tissue wounds, and decubitus ulcers are also likely to be contaminated with skin flora. The offending agents are more reliably found with culture of surgically obtained biopsy material. Aspiration of infected intact vesicles or bullae following meticulous skin preparation can isolate causative organisms. Fluid accumulation may occur in a variety of body organs, cavities, or spaces in response to infection or inflammation that may be amenable to aspiration (arthrocentesis, paracentesis, thoracentesis, etc.) and subsequent culture.

Table 6. Intra-abdominal Findings Suggesting Pathology in the Febrile Patient

- Obstructive pattern
- Air fluid levels and ileus (bowel obstruction)
- Local ileus (appendicitis)
- Free air (bowel perforation)
- Appendicolith (appendicitis)
- Psoas shadow obliteration and haziness over the sacroiliac joint (appendicitis)
- "Thumbprinting" or gas in the bowel wall and portal system (Mesenteric ischemia)
- Gall stones and kidney stones

Microscopic detection of infective organisms with stains other than Gram's stain, such as acid fast stain, methylene blue stain, KOH prep, and malaria smears should be performed as indicated. Specialized immune microscopy techniques include fluorescent antibody tests—either direct (DFA) or indirect (IFA)—that detect antigens or antibodies for such organisms as *S. pyogenes, B. pertussis, C. parvum, Brucella* Spp., *Francisella tularensis, Y. pestis, Legionella, C. trachomatis, P. carinii,* and selected viruses (herpes, rabies, influenza, parainfluenza, and RSV). Enzyme-linked immunosorbant assay (ELISA or EIA) is used for detection of antibodies to HIV, hepatitis A, B, or C, parasitic agents, fungi, *C. difficile* toxin, and Group A strep, among others. Latex agglutination is useful for determining streptococcal groups.

Radiologic Studies. Selected diagnostic imaging studies can help determine the etiology of fever. The chest radiograph, which is the the most frequently performed diagnostic radiological study, provides a wealth of information at relatively low cost. In a febrile patient, chest radiography should be performed as a "diagnostic test" rather than a "screening test." Numerous studies have reported the difficulty of using clinical findings for predicting bacterial pneumonia. In this regard, lack of auscultatory findings are reported in 6-25% patients with proven radiological presence of lung infiltrates.[45,46] In contrast, in patients with "normal" chest radiographs, abnormal auscultatory findings are reported to be present in 20-62% of patients in some studies.[47-49]

One study attempted to validate low-yield criteria for chest radiography, but was unable to derive or validate parameters that were any more useful than a "seasoned clinician's probability estimate of pneumonia."[47] Clinical findings associated with a positive finding on a chest radiograph include: fever, cough, chills/rigors, tachypnea, abnormal breath sounds, tachycardia, chest pain, dyspnea, wheezing, occupational exposure of toxins, weight loss, old age, alteration of mental status, a history of tobacco use, substance abuse (particularly intravenous drug use), stroke, COPD, or AIDS. *(See Table 5.)*

Abdominal radiographs rarely provide additional information beyond that available from a clinical examination of an adult febrile patient. Selected findings on plain abdominal radiographs that may suggest an intra-abdominal pathology include: obstructive pattern, air fluid levels and ileus (bowel obstruction), local ileus (appendicitis), free air (bowel perfora-

tion), appendicolith (appendicitis), psoas shadow obliteration and haziness over the sacroiliac joint (appendicitis), "thumbprinting" or gas in the bowel wall and portal system (Mesenteric ischemia), and gall stones and kidney stones. *(See Table 6.)* Although plain radiography is rarely useful in the diagnosis of acute cholecystitis, ultrasonographic examination *is* useful. Helical (or spiral) CT imaging can help in high-risk cases of suspected appendicitis. Helical CT imaging is now the imaging modality of choice in many cases of suspected pulmonary embolus. Pelvic ultrasound is helpful in evaluation of tubo-ovarian abscess or free fluid secondary to pelvic inflammatory disease. Intra-abdominal abscesses are frequently occult, presenting with spiking fever and vague abdominal complaints; they are best assessed with CT imaging.

Plain radiographs of the extremities may show gas formation in soft tissue infections, suggesting infection with gas forming, anaerobic organisms. Advanced osteomyelitis can be apparent on plain radiographs, although triple phase bone scan is more sensitive and becomes positive much earlier.

Sinus radiography is not recommended for the routine diagnosis of community-acquired sinusitis because of a lack of specificity.[50] Viral rhinosinusitis associated with the common cold is the most common form of sinusitis. Bacterial conversion is reported to be estimated at 0.5% to 2% of cases. Complete unilateral opacification of the adult sinus represents disease in approximately 75% of cases; an air fluid level also correlates with bacterial infection in 75% of cases. Mucosal thickening, in contrast, correlates with sinus pathology in fewer than 50% of cases.[50] Mastoid films can establish the diagnosis of mastoiditis, which is quite rare, however CT is more sensitive and specific.

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Physician CME Questions

25. In most cases, a temperature higher than 41.5°C reflects which of the following?
    A. Hyperthermia
    B. True fever
    C. Sepsis
    D. none of the above

26. For each degree Celsius rise in temperature, a patient's basal metabolic rate may increase as much as:
    A. 5%.
    B. 25%.
    C. 15%.
    D. 30%.
    E. 35%.

27. The diagnosis of what percent of febrile illnesses can be made on the basis of a history and physical examination?
    A. 50%
    B. 70-85%
    C. 10-20%
    D. 100%
    E. 25%

28. In a febrile patient with frank bradycardia, a physician should consider:
    A. viral myocarditis and bacterial endocarditis.
    B. rheumatic fever and Lyme disease.

C. concurrent use of medications such as beta-blockers.
D. the presence of underlying cardiac conduction disease.
E. all of the above

29. Purpuric lesions are characteristic of:
A. vasculitis.
B. meningococcemia.
C. thrombocytopenia.
D. cellulitis.
E. none of the above

30. In the literature, the presence of urine infection has been characterized according to which criteria?
A. 10,000-100,000 CFUs/mL of a single urinary pathogen.
B. 100 CFUs/mL of a single urinary pathogen in a "symptomatic" female patient.
C. 1000 CFUs/mL of a single urinary pathogen from a catheterized specimen.
D. all of the above

31. The false-negative incidence of a fecal leukocyte test is approximately:
A. 15%.
B. 5%.
C. 50%.
D. 75%.
E. 22%.

32. Cardinal signs and symptoms of adult meningitis include:
A. Kernig's sign.
B. fever.
C. Brudzinski's sign.
D. headache.
E. all of the above

Correction

In the August 3, 1998, issue of Emergency Medicine Reports, "The Implantable Cardioverter Defibrillator: Technology, Complications, and Emergency Management," the physician CME questions should have been numbered 17-24. We apologize for any confusion this may have caused.

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The Febrile Adult
Part II