

# Emergency Medicine

# Report

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Newsletter Publishers Association

Volume 19, Number 18

August 31, 1998

*The first part of this two-part series on evaluation and management of the febrile adult focused on strategies for patient evaluation and the cost-effectiveness of laboratory and radiographic evaluation. Once the historical features and laboratory data base are established, the emergency physician is still faced with the challenge of determining the precise origin of fever. (See Table 1.)*

*Frequently, the diagnosis is obvious—the elderly patient with urinary tract infection, the alcoholic with aspiration pneumonia, the acute bacterial exacerbation of COPD—but in many cases, the etiology of fever is not immediately apparent, especially when the underlying cause is non-infectious or when the patient is elderly, immunocompromised, or has a history of multiple medication use. Not only is the treatment course unclear in these cases, but the triage decision can be especially difficult.*

*To a great degree, these ambiguous cases require the physician to, first, generate a comprehensive, targeted differential diagnosis, and second, to perform a systematic exclusion or inclusion of these diagnostic possibilities based on historical, laboratory, and radiographic data. Once a likely cause for fever is ascertained, appropriate treatment measures are implemented. In the case of infectious etiologies—pneumonia, urinary tract infection, abdominal infection, prostatitis, skin and soft tissue infections, etc.—authoritative, empirical treatment protocols are available. For such non-infectious causes of fever as arthritis, vasculitis, and other inflammatory disorders, the*

*management is often less straightforward and, frequently, requires subspecialty consultation.*

*With these issues in mind, this second (and final) part of our series on the febrile adult highlights issues in the differential diagnosis of the adult febrile patient. Both infectious and non-infectious etiologies are discussed in detail, and fever in specific patient subgroups—post-partum, the diabetic, the elderly, the alcoholic individual—is analyzed. Finally, in addition to our treatment card, this issue includes a Quick Consult insert outlining some new and unusual aspects of fever management and a comprehensive antibiotic treatment table with recommendations for empiric treatment of the febrile patient with a confirmed infectious etiology.*

—The Editor

## The Febrile Adult: Part II, Differential Diagnosis and Management of Infectious and Non-Infectious Syndromes

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## Non-infectious Causes of Fever

**Drug-Related Fever.** Drug fever is defined as a temperature-elevation fever that coincides temporally with the administration of a drug and resolves after the drug is discontinued in a patient in whom other causes of fever have been excluded. Since there are no definitive diagnostic tests for drug fever, this entity remains a diagnosis of exclusion. (See Table 2.)

A large number of drugs are capable of producing fever through myriad mechanisms. These include: 1) febrile responses caused by impurities in the drug, 2) disorders in thermo-regulation, 3) induction of pyrogen release, and 4) hypersensitivity reactions.

Certain antibiotics, clot-dissolving medications such as

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streptokinase, and certain chemotherapeutic agents contain microbial products that are not completely removed during the drug manufacturing process. Vancomycin used to be a problem in this regard, but newer and cleaner preparations have essentially eliminated this problem. Other drugs may induce fever by either increasing internal heat production or interfering with external heat dissipation. Thyroxine, amphetamines, and dinitrophenol are capable of elevating body temperature by causing an increase in heat production. Epinephrine induces vasoconstriction, and atropine impairs perspiration, both of which can lead to decreased heat dissipation. Antiparkinsonian drugs, as well as other drugs with anticholinergic effects, have similar effects. In addition to their atropine-like effects, phenothiazines and butyrophenones depress hypothalamic function, which can result in hyperthermia. However, the majority of drug-induced febrile episodes are caused by drug-induced hypersensitivity reactions. These are associated with antibody production in response to the offending agents, development of drug-antibody immune complexes, and subsequent release of endogenous

Table 1. Causes of Fever

NON INFECTIOUS	INFECTIOUS
Drug fever	Viral
Thrombo-embolic disease	Bacterial
Tumor fever	Fungal
Rheumatic illness or collagen vascular diseases	Opportunistic Pathogens
Granulomatous diseases (sarcoidosis)	
Idiosyncratic reactions (Malignant hyperthermia, transfusion reaction, etc.)	
Neuroleptic malignant syndrome	
Miscellaneous (familial Mediterranean fever, profound type V hyperlipidemia, etc.)	

**Emergency Medicine Reports™** (ISSN 0746-2506) is published biweekly by American Health Consultants, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

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Periodical postage paid at Atlanta, GA. **POSTMASTER:** Send address changes to **Emergency Medicine Reports**, P.O. Box 740059, Atlanta, GA 30374.

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pyrogens. Although these reactions may be accompanied by eosinophilia, oftentimes the eosinophil count is normal.

Unfortunately, no single pattern of drug-induced fever is sufficiently specific to permit differentiation from other causes of fever. Although low-grade fevers are characteristic, patients may present with shaking rigors suggestive of bacteremia with sepsis. In fact, dramatic temperature elevations can be seen with reports of temperatures as high as 43°C.<sup>1</sup> In most cases, however, the degree of temperature elevation is more moderate; drug fever is rarely associated with hypotensive events.

Although a relative bradycardia may be associated with drug fever, it is an unusual finding. A minority of patients complain of headaches and myalgias. In one large study of drug-induced fever, leukocytosis was present in 22% of cases and eosinophilia in another 22%.<sup>1</sup> Rashes were observed in 18% of patients. In this study, although death was a rare event, in a small percentage of cases, the drug reaction appeared to contribute to the patient's demise.<sup>1</sup>

It should be stressed that drug fever may occur at any time during therapy with a particular agent. However, certain therapeutic classes have characteristic lag times prior to the onset of fever. For instance, antineoplastic agents tend to cause drug fever during the first day of therapy and then again at the point of neutrophil nadir. Antimicrobial agents frequently induce fever about one week after onset of therapy. Cardiac and antiepileptic medications have been reported to cause fever both early and after several months of therapy. It must be emphasized that, because of the marked degree of variability, timing of onset of fever cannot be reliably used to implicate any particular agent.

Malignant hyperthermia is a syndrome characterized by profound temperature elevation that occasionally follows anesthesia induction with succinylcholine and potent inhalational anesthetics, such as halothane.<sup>2</sup> It is typically associated with muscular rigidity, tachypnea, metabolic acidosis, ventricular ectopy, and circulatory instability. It may be complicated by severe rhabdomyolysis and acute renal failure. The mortality rate of malignant hyperthermia ranges from 28% to 70%.<sup>1</sup> Although the precise mechanism is unclear, it appears that, in genetically predisposed individuals, skeletal muscle inappropriately releases calcium when exposed to certain anesthetic agents. (See Table 3.)

Neuroleptic malignant syndrome (NMS) is a rare, potentially lethal disorder that occurs after use of major tranquilizers.<sup>3</sup> The most common causative agent is haloperidol, but phenothiazines and thioxanthenes have also been implicated. NMS is characterized by profound hyperthermia, muscle rigidity, autonomic dysfunction, and altered mentation. Clinicians should be aware that NMS is an idiosyncratic reaction, and is not related to the dosage or duration of the inciting agent. It appears to be caused by central dopaminergic blockade, leading to sustained muscle contraction, internal heat production, and inappropriate peripheral vasoconstriction. This cascade results in profound hyperthermia, dehydration, and physical exhaustion. Although therapy is somewhat controversial, most authorities recommend a peripheral muscle relaxant, such as dantrolene, in association with physical cooling measures.<sup>3</sup>

**Pulmonary Thromboembolism.** Approximately two-thirds of patients with angiographically proven pulmonary thromboemboli will exhibit fever.<sup>4</sup> Although the precise pathophysiology is not clearly understood, suspected contributing factors include infarction with tissue necrosis, hemorrhage with extravasation of blood, atelectasis, vascular inflammation, and occult infection. Moreover, as many as 20% of patients with pulmonary emboli have fever in the absence of pulmonary infarction.<sup>5</sup>

The fever associated with pulmonary emboli can be relatively high. In this regard, 10% of patients in one study were found to have temperatures greater than 39.5°C.<sup>6</sup> The duration of fever may be as long as a week or even longer, but a rectal temperature higher than 38.5°C persisting for more than four days or a temperature greater than 38°C lasting more than six days is unusual. Accordingly, persistent fevers beyond this time should provoke an evaluation for recurrent emboli or intercurrent infection.

**Tumor Fever.** Various malignancies are capable of generating a febrile response either as a result of the primary disease process, drug-induced temperature elevation, or infection. As with drug fever, however, this is a diagnosis of exclusion. Patients with malignancy, especially if they have undergone chemotherapy or radiation therapy, are prone to a wide variety of infections. The most common malignancies associated with fever are Hodgkin's and non-Hodgkin's lymphomas, leukemia, hypernephroma, hepatoma, and atrial myxoma. Other malignancies associated with fever include metastatic tumors to the liver, neuroblastoma, central nervous system tumors, and adenocarcinoma of the gastrointestinal tract, breast, and lung.

The cause of fever from malignancy is not completely understood. In some instances, endogenous pyrogens are produced by the tumor, leukocytes, or other cells. This mechanism has been demonstrated in Hodgkin's disease and hypernephroma. In other tumors that undergo rapid growth with subsequent necrosis, fever may be produced as a result of monocyte/macrophage recruitment, with subsequent release of endogenous pyrogens.

As a rule, evaluation of a febrile patient with a malignancy in the emergency department (ED) will require pursuit of an infectious process as the likely cause of fever.

**Rheumatic Illnesses and Connective Tissue Disorders.** Some rheumatic illnesses present with fever as their sole, initial manifestation. In particular, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), and a variety of vasculitic disorders present in this fashion. Adult-onset Still's disease is a disorder characterized by arthritis, pharyngitis, splenomegaly, lymphadenopathy, and leukocytosis. Daily temperature spikes often reach 39.6-40.0°C, and may be the only manifestation of the disease for several months.

**Table 2. Pharmacologic Agents Causing Hyperthermia**

<b>INCREASED MUSCULAR ACTIVITY</b>	
Amphetamines	
PCP	
Monoamine oxidase inhibitors	
Cocaine	
Tricyclic antidepressants	
Halothane, succinylcholine ("malignant hyperthermia")	
Antipsychotics, lithium ("neuroleptic malignant syndrome")	
<b>INCREASED METABOLIC RATE</b>	
Salicylates	
Thyroid hormone	
<b>IMPAIRED THERMOREGULATION</b>	
Phenothiazines	
Ethanol	
<b>IMPAIRED HEAT DISSIPATION</b>	
Anticholinergics	
Antihistamines	
Tricyclic antidepressants	
Phenothiazines	

**Table 3. Medical Conditions Causing Fever/Hyperthermia**

Infectious disorders	Neoplastic disease
Mechanical trauma	Vascular accidents
Crash injury	Immune disorders
	Collagen vascular disease

Rheumatoid factor is not present in these patients, and the diagnosis is frequently delayed until symptoms other than fever are apparent.

Fever is the only initial symptom of SLE in approximately 5% of patients. Serologic studies may help clarify the diagnosis. Temporal arteritis (TA) should be considered in the elderly patient who presents with prolonged, recurrent fevers in the absence of "localizing" findings. Symptoms such as headache, jaw claudication, temporal artery tenderness, and visual disturbances may help confirm the diagnosis, but these findings can be absent. Although a high sedimentation rate is typical of temporal arteritis, a normal sedimentation rate does not rule out TA. In an elderly patient at risk, with prolonged fever, temporal artery biopsy should be considered.

**Factitious and Self-Induced Fever.** Factitious fever and self-induced illness are more common than generally recognized. The patient will typically present with an "unusual" systemic illness, but appears to be clinically well. As a rule, there is no evidence of illness other than fever. The majority of patients with factitious or self-induced fever are women, many of whom have a medical background.<sup>7,8</sup> Oftentimes there is an underlying, severe personality disorder, conversion reaction, or psychosis. In some instances, there is some degree of perceived secondary gain; for example, prisoners may find hospitalization preferable to incarceration.

Recognition of self-induced fever may require checking multiple, simultaneous temperatures at different body sites (i.e., axilla, mouth, and rectum), while observing the patient. Another

**Table 4. Chronology and Manifestations of Post-operative Fever**

<b>Cause and etiology</b>	<b>Post-Operative Time Frame</b>
<b>Physiological</b>	<b>24 h</b>
Tranfusion and drug reaction hours	generally within 24 h
<b>Malignant Hyperthermia</b>	<b>Generally within 30 min of anesthesia</b>
Metabolic derangements (prolonged hypotension with poor tissue perfusion)	within 6 h
<b>Endocrine derangements (unmasking thyroid storm or pheochromocytoma)</b>	<b>within 6 h</b>
Pulmonary causes	24 h
<b>Urinary tract infection</b>	<b>2nd/3rd d</b>
Wound infection	3rd/4th d
<b>Thrombo-embolic disease</b>	<b>beyond 3-5 d</b>
Post-operative pancreatitis	3 d
<b>Post-operative suppurative parotitis</b>	<b>within 2 weeks</b>
Post-operative maxillary sinusitis	within 2 weeks

technique is to check the temperature of freshly voided urine. Patients with self-induced temperature elevations use a number of methods. Fever may be generated by injecting themselves with feces, urine, dirty water, or other noxious or infectious substances. The presence of polymicrobial bacteremia in an immunocompetent patient without underlying malignancy or GI, GU, or biliary tract pathology, should alert the clinician to this possibility. Occasionally, a patient may ingest a medication to which he or she has a known hypersensitivity. This has been reported with phenolphthalein.

**Miscellaneous Disorders.** Various noninfectious disorders not previously discussed also may present with fever. (See Table 4.) For example, disorders such as granulomatous hepatitis, sarcoidosis, and inflammatory bowel disease can present with fever. Inherited disorders such as familial Mediterranean fever and profound type V hyperlipidemia, with or without pancreatitis, can also present with isolated fever. Moreover, the central nervous system can generate a febrile response in the absence of active infection. This is observed in patients who have pathologic processes such as tumors, hemorrhage, vascular abnormalities, or degenerative disease occurring in or near the hypothalamic thermoregulatory center. Laennec's cirrhosis is commonly associated with fever, especially when laboratory and pathologic evidence of active hepatic disease is present. Although it may not be possible to confirm diagnosis of these disorders in the emergency setting, clinicians should maintain a high index of suspicion.

**Treatment of Fever**

The definitive therapy for fever generally requires treatment of the underlying cause. Infections, endocrinopathies, neoplasms, connective tissue diseases, and other causes of fever should be diagnosed and treated expeditiously. Availability of safe and effective pharmacological agents directed at fever

**Table 5. Factors Associated with Bacteriuria in Elderly Patients**

- Incontinence
- Instrumentation
- Immobility
- Indwelling catheter
- Residual urine in the bladder
- Condom catheter

**Table 6. Factors Associated with Pneumonia in Elderly Patients**

- Pharyngeal colonization with gram-negative bacilli
- Aspiration
- Poor clearance of aspirated material
- Poor systemic response to sepsis

reduction also has facilitated patient management. Although, in most cases, antipyretics do not affect the underlying illness, the patient frequently feels subjectively improved.

In patients with an asymptomatic, low-grade temperature, it is not necessary to prescribe antipyretic agents routinely. In the symptomatic patient, however, it is reasonable to prescribe fever-lowering drugs. Patients frequently feel most ill when the temperature is rising or falling. After the fever has reached a plateau, patients are frequently asymptomatic.

Agents most frequently used in adults for treatment of fever include aspirin, acetaminophen, and non-steroidal anti-inflammatory agents (NSAIDs). These agents lower the hypothalamic set point in febrile patients, while having no significant effect on the temperature of afebrile individuals. It should be stressed that these agents have little or no effect on patients suffering from hyperthermia because the elevated temperatures are not caused by an elevation of their hypothalamic set points, but by altered heat production or dissipation mechanisms.

Extremely high temperatures associated with hyperthermia require emergent application of local cooling measures. Lukewarm baths or sponge baths are effective and augment the body's ability to dissipate heat through evaporation. Cooling blankets and fans are also helpful. These measures, however, may be deleterious in the patient with "true fever" if used without central hypothalamic set point lowering agents because the body will simply expend more energy to produce more heat in order to achieve its hypothalamic goal.

**Special Patient Subgroups**

**Fever and Rash.** Patients with fever and a rash frequently are encountered in the ED. The etiology can be infectious or noninfectious, and treatment should be specific or symptomatic depending on the etiology. A thorough history should be undertaken, including a search for the site of onset of the rash, direction of spread, symptoms (pruritus, dyspnea, etc.), documentation of medications taken within the past month, possible exposure to animals, plants or other toxins, travel, immunization state, risk factors for arthropod bites, and recent exposures to ill persons, individuals with sexually transmitted disease, or known allergens. Physical examination should focus on the rash morphology as well as a search for associated signs.

**Fever in the Elderly and Nursing Home Patient.** Elderly

and debilitated patients frequently present to the ED with fever, but with minimal or no localizing signs and symptoms. Urinary tract infection is the most common cause of bacteremia and sepsis in the elderly, especially in those with indwelling urinary catheters or recent urethral manipulation (e.g., post TURP).<sup>9,10</sup> (See Table 5.) Pneumonia, which is the leading cause of death due to infection in the elderly,<sup>9,10</sup> may present with vague symptoms of malaise, weakness, anorexia, or behavioral changes; cough or sputum production may or may not be present, even if there is significant hypoxia. (See Tables 6 and 7.) Intra-abdominal infections may present without the typical localizing tenderness or signs of peritoneal irritation. The incidence of gangrene of the gallbladder and appendix is high in this age group,<sup>9,10</sup> as is diverticulitis.

Febrile patients on peritoneal dialysis with abdominal pain should have dialysate gram stain and, if indicated, culture and sensitivity should be performed. Significant peritonitis in these patients can develop without the usual rebound, guarding, and rigidity.

Soft tissue infections (e.g., pressure ulcers, wound infections, and cellulitis) are common sources of seemingly occult infections in the elderly. The possibility of tetanus must also be considered, as many of these patients are inadequately immunized. Meningitis is easily missed in the elderly, as is endocarditis, tuberculosis, and septic arthritis. Patients with recent travel history should be evaluated for infections endemic to the area in which they traveled.

The elderly demonstrate a blunted fever response to infection, as well as diminished leukocytosis. Bandemia (especially greater than 6%), even with normal leukocyte count, is suggestive of sepsis in the elderly. A low threshold for performing ancillary tests such as peripheral smear and blood count, blood culture, chest radiograph, UA, and CSF examination is prudent in this vulnerable group of patients.

**Fever of Unclear Etiology.** Patients of any age may present to the ED with fever without localizing signs or symptoms. Certain infections are well known for their paucity of localizing symptoms. These include infections of the genitourinary and biliary tracts, intra-abdominal abscess, and endocarditis. Rocky Mountain Spotted Fever, Lyme disease, Q-fever, malaria, and typhoid fever should be considered in travellers or those who live in endemic areas.

Immunocompromised patients on chemotherapy who have neutropenia should be aggressively evaluated for common infections, as well as less common entities such as coagulase-negative staphylococcal sepsis or fungemia. Special attention is paid to those with indwelling intravascular access devices. One study reported a rise from 7% to 16% between January 1993 and April 1995 in the frequency of primary bloodstream infections related to intravascular devices.<sup>11</sup> Unless there are obvious local signs of infections at the site, the diagnosis may require removal and culture of the device.

**Post Partum Fever.** Post partum fever occurs in about 2-4% of vaginal deliveries and in 5-35% of cesarean deliveries, depending on whether the C-section was planned or performed after prolonged labor and ruptured membranes. These rates almost double in indigent populations.<sup>12</sup>

In the first few hours after delivery, thyroid storm may present as a rare, non-infectious etiology of fever. In this early period, infectious etiologies include early group B streptococcal infection or chorioamnionitis. Over the next few days, pulmonary atelectasis, pneumonia, UTI, and wound infection begin to emerge as important causes of fever. Breast engorgement may produce fever in some women. By the end of the first post partum week, mastitis

**Table 7. Clinical Features of Pneumonia in Elderly Patients**

- Insidious onset
- Chest pain uncommon
- Fever may be absent
- Cough weak or absent
- Delirium common
- Sputum minimal or absent

and septic pelvic vein thrombophlebitis should be considered as possible etiologies of fever. Wound abscess, pulmonary embolism, or mastitis are late causes of puerperal fever.

Endometritis is a polymicrobial uterine infection caused by normal vaginal flora that gain access to the upper genital tract or beyond as a result of vaginal examinations during labor or surgical manipulation. The onset of fever associated with the entity typically occurs within 36 hours of delivery, and is accompanied by malaise, lower abdominal pain, uterine tenderness, and foul smelling lochia. Common pathogens include group B strep, anaerobic strep, aerobic gram-negative bacilli (*E. coli*, *K. pneumoniae*, and *Proteus* sp.), and *Bacteroides* spp. *Chlamydia* must be considered in late-presenting endometritis (after the first post partum week).

Fever from breast engorgement rarely exceeds 30°C and does not require antibiotic therapy. It begins within 2-3 days of delivery and usually lasts for less than one day. Mastitis is associated with higher fever, erythema of the breast, and usually occurs two weeks or more post partum.

Septic pelvic vein thrombophlebitis occurs in 1:2,000 pregnancies and can be associated with endometritis (approximately 1% of patients with endometritis develop septic pelvic vein thrombophlebitis).<sup>12</sup> Onset is usually within 48-96 hours of delivery and is signaled by fever, pain, and tenderness in the lower abdomen, which is usually unilateral. Nausea, vomiting, and bloating may be present. Physical examination reveals localized tenderness, guarding, and, in 50-70% of patients, a rope-like mass is palpable in the area of the cornua extending laterally and cephalad. Other considerations include: ovarian torsion, pelvic abscess, broad ligament hematoma, appendicitis, ureterolithiasis, and upper urinary tract infection. The diagnosis of septic pelvic vein thrombosis can be confirmed by CT imaging or magnetic resonance angiography. Treatment is intravenous heparin for 7-10 days in addition to appropriate antibiotic therapy.<sup>12</sup>

**Fever in the Neutropenic Cancer Patient.** Patients with cancer are at increased risk for fever both as a result of their underlying disease state and as a consequence of their cancer treatment. Infection is of greatest concern, especially in the neutropenic patient, but other causes such as drug fever (most commonly in response to antibiotics such as the penicillins, cephalosporins, and amphotericin B, cardiovascular drugs, phenytoin, and other CNS drugs, cytotoxics, and immunotherapy), tumor fever, transfusion-related fever, or fever due to thromboembolism also must be considered.

Fever in the neutropenic cancer patient represents medical emergency. Specifically, fever in neutropenia is defined as a single oral temperature greater than 38.3°C or persistent temperature greater than 38°C on at least two occasions greater than four hours apart within a 24-hour period in a patient with an absolute neutrophil count of less than 500 cells/mm.<sup>13</sup> The

**Table 8. Life-Threatening Infections Associated with Diabetes**

<b>Infection</b>	<b>Characteristics</b>
Malignant otitis externa	<i>Pseudomonas</i> infection with risk of craniofacial osteomyelitis, meningitis, subdural empyema
Rhinocerebral mucormycosis	Fungal infection of upper respiratory tract with risk if CNS and vascular thromboses
Emphysematous cholecystitis	Symptoms of cholecystitis but gas forms in and around the gall bladder. 50% are acalculus
Emphysematous pyelonephritis	Gas forming renal infection, usually <i>E. coli</i> . CT is diagnostic; IVP contraindicated
Necrotizing fasciitis	Polymicrobial infection of decubitus ulcers, perineum and lower extremities

degree and duration of neutropenia are independent risk factors for infection.<sup>13</sup> As these patients are at risk for rapidly aggressive infections with high morbidity and mortality, it is imperative that evaluation and empiric treatment be assigned high priority. A thorough history includes information about type of the cancer, details of chemotherapy, and any potential exposures to infection. Ancillary studies include at least two sets of blood cultures, urine culture, as well as cultures of any other suspected sites of infection. A leukocyte count with differential and a chest radiograph are helpful in this subset of febrile adults.

Based on knowledge of the most likely organisms involved and guided by specific risks for the individual patient, the choice of initial therapy is a broad spectrum antibiotic. Historically, gram-negative organisms were the leading cause of infection in neutropenic cancer patients, but in the last 10 years, gram-positive organisms have predominated and currently account for more than two-thirds of infections.<sup>14</sup> Fungal infections caused by such organisms as *Candida* and *Aspergillus* must also be considered.

Treatment options for neutropenic febrile patients continue to evolve in response to the changes in types of infective organisms, antibiotic development, and emerging antibiotic resistance. Treatment with single antibiotic therapy continues to be evaluated and shows promise,<sup>15,16</sup> although most experts recommend two or more agents providing broad spectrum coverage. Outpatient treatment has been shown to be acceptable in low-risk neutropenic patients.<sup>17</sup> Vancomycin, widely used in this setting, must be used judiciously because of increasing incidence of vancomycin-resistant pathogens.

**Fever in the Diabetic.** Patients with diabetes are at risk for a variety of infections secondary to compromised immune function apparently related to impaired leukocyte function. Microangiopathy and neuropathy contribute to the increased risk of infection.

Certain life threatening infections unique to the diabetic patient include: necrotizing fasciitis, malignant (necrotizing) otitis externa, rhinocerebral mucormycosis, and emphysematous cholecystitis.<sup>18</sup> (See Table 8.) Malignant otitis externa, also known as invasive or necrotizing, primarily affects the elderly diabetic patient. As is the case with common otitis externa, this infection is frequently caused by *Pseudomonas* sp., and presents with otalgia, otorrhea, and periauricular tenderness. Otolscopy

may reveal a mass of granulation tissue in the external auditory canal. While these patients may not appear to be "toxic," they are at risk for cranial and facial bone osteomyelitis; contiguous infection, including involvement of the temporomandibular joint can lead to cranial nerve palsies, meningitis, lateral and sigmoid sinus thrombosis, and subdural empyema. CT imaging can establish the degree of bony involvement, while MRI will demonstrate soft tissue and central nervous system involvement. Traditional treatment has required dual antibiotic therapy (beta-lactam plus aminoglycoside) and surgical debridement.

Rhinocerebral mucormycosis is a rare fungal infection seen in poorly controlled diabetic patients. Common soil and food fungi can infect the upper respiratory passages and invade local vasculature, causing hemorrhage, thrombosis, and tissue infarction. Infections can spread in to the brain. Rhinocerebral mucormycosis presents with abrupt onset of lethargy and headache along with fever. Facial pain and swelling occurs early, and is followed by necrosis of the palate and/or nasal turbinates. Visual impairment and proptosis are common. Black, necrotic pus may drain from the eyes. Known complications include cavernous sinus thrombosis, carotid artery thrombosis, and cranial nerve palsies (CN V and VII). Brain involvement is signaled by seizures or coma. Diagnosis is established by biopsy of any necrotic eschars that are present. CT and MR imaging are useful ancillary tests. Treatment involves normalization of blood sugars, parenteral amphotericin B, and surgical debridement.

Emphysematous cholecystitis presents with signs and symptoms typical of "infective cholecystitis," but gas develops in or around the gallbladder within 48 hours of onset of infection. Demonstration of gas by plain radiography, CT, or ultrasound establishes the diagnosis. This entity should be suspected in all diabetics with acute cholecystitis. The gallbladder is acalculus in nearly one-half of cases. Treatment is open cholecystectomy plus antibiotic coverage for clostridia and anaerobic gram-negative bacilli, usually with a penicillin, clindamycin, and an aminoglycoside.

Emphysematous pyelonephritis is a gas-forming infection in the renal collecting system most commonly caused by *E. coli*, although *K. pneumoniae*, *E. aerogenes*, *P. mirabilis*, and *P. aeruginosa* are the other offending pathogens. Rarely, fungal infections also have been implicated in emphysematous pyelonephritis. Emphysematous pyelonephritis, which can be confirmed by CT imaging, should be suspected when a diabetic with UTI fails to respond to the usual antimicrobial regimen. Failure of intensive antibiotic therapy may require nephrectomy.

Diabetics are also at risk for necrotizing fasciitis and cellulitis, which are usually polymicrobial infections involving the perineum, decubitus ulcers, or the lower extremities. These patients appear toxic with high, unremitting fevers. Lesions are typically anesthetic, draining ulcers, or bullae, with varying amounts of necrosis, although in some cases the skin may appear normal. Diagnosis is based on clinical presentation confirmed by cultures of excised tissue. Treatment is surgical debridement or amputation and antibiotics, which may include imipenem. Hyperbaric oxygen therapy has been shown to be helpful in selected cases.<sup>19</sup>

Febrile illnesses, especially respiratory or gastrointestinal illnesses, may precipitate diabetic ketoacidosis. Any evidence of infection should be sought in any patient presenting with diabetic ketoacidosis or hyperosmolar, hyperglycemic, nonketotic diabetic states.

**The Alcoholic Patient.** Alcoholics are at risk for febrile ill-

ness due to a variety of infectious and noninfectious processes. The most common cause of noninfectious fever in the alcoholic patient are alcohol withdrawal, delirium tremens, prolonged postictal state, hepatitis, pancreatitis, and, infrequently, unrecognized subarachnoid hemorrhage.<sup>19</sup> Pneumonia has been identified as the most common cause of an infection in the alcoholic patient.<sup>19</sup> *Streptococcus pneumoniae* and *Hemophilus influenza* are the most common pathogens, although tuberculosis and other atypical infections are also precipitants in the alcoholic population. These patients are also at risk for aspiration pneumonia (polymicrobial infections are common) that is often indolent and can present with minimal symptoms.

Spontaneous bacterial peritonitis should be considered in alcoholic patients with cirrhosis or ascites. These infections, which usually spread to the ascitic fluid hematogenously, are most commonly caused by pneumococci or gram-negative enteric bacteria. The diagnosis is established by paracentesis demonstrating ascitic fluid with greater than 300 leukocytes/mm<sup>3</sup>, a pH less than 7.35, and a lactate greater than 25 mg/dL. A gram stain and culture of the ascitic fluid may yield an etiologic diagnosis.

Alcoholics with liver disease are also at risk for spontaneous bacteremia, most commonly secondary to *E. coli* due to hepatic reticuloendothelial system dysfunction. A rare but aggressive cause of sepsis associated with bullae, cutaneous ecchymosis, and subcutaneous necrosis is seen in alcoholics infected with *Vibrio vulnificus* from ingestion of infected shellfish.

**Intravenous Drug Users.** Intravenous drug users (IVDUs) frequently present to the ED with fever. While the fever may be due to common or minor infections, IVDUs are at risk for specific life-threatening infections. The increased incidence of HIV and viral hepatitis among IVDUs is well established. Patients with history of IVDU who present with fever without a clear cause should be evaluated for HIV infection.

Infective endocarditis is a major cause of hospitalization of IVDUs. *Staphylococcus aureus* is the most common offending agent, although a number of other bacteria or fungi can be responsible for infective endocarditis. The diagnosis may be difficult and the course of the illness indolent.

Fever resulting from other infectious processes in an alcoholic patient include pneumonia (*S. pneumoniae* and *H. influenza*), cellulitis at injection sites, tetanus, septic pulmonary emboli, or tuberculosis. Common non infectious causes of fever in the IVDU are due to opioid withdrawal or pyogenic reactions secondary to drug adulterants.<sup>20</sup>

**HIV Infected Patients.** The differential diagnosis of a febrile, HIV-infected patient is extensive. Primary HIV infection usually presents with fever associated with lymphadenopathy, pharyngitis, rash, and myalgias. The natural history of HIV infection is an "acute retroviral syndrome" occurring 2-4 weeks after infection during which seroconversion has not occurred. During this stage, the diagnosis can be established by HIV viremia and high levels of p24 antigen. During the latent period (months to years), there is a gradual decrease in CD4 count. When the CD4 count is below 500/mm<sup>3</sup>, the patient is increasingly prone to infections with relatively virulent, community-acquired pathogens. If the CD4 counts drop below 200/mm<sup>3</sup>, infection with opportunistic organisms is more common.

Infections in HIV-infected patients with CD4 counts greater

than 500/mm<sup>3</sup> include pneumonia due to *S. pneumoniae*, *S. aureus*, and *H. influenza*, bronchitis, sinusitis, PID, pyelonephritis, cellulitis, viral respiratory infections, and tuberculosis (pulmonary and/or extra-pulmonary).

Febrile, HIV-infected patients with CD4 counts less than 200 must be evaluated for infections with opportunistic pathogens and for neoplasms such as non-Hodgkin's lymphoma and visceral Kaposi's sarcoma. Opportunistic infections include *Pneumocystis carinii* pneumonia (PCP), disseminated *Mycobacterium avium* complex (MAC), *Histoplasma capsulatum*, cryptococcal meningitis, and others. Disseminated cytomegalovirus (CMV) infection does not typically present with persistent fever although, on rare occasions, fever may be the only manifestation.<sup>21</sup>

PCP classically presents with fever, cough, dyspnea, chest discomfort, and general malaise that develops over days to weeks. The incidence of PCP has decreased significantly over the past several years.<sup>22</sup> The chest radiograph may fail to show an infiltrate in 20% or more of cases. Resting or exercise-induced oxygen desaturation and elevated serum lactate dehydrogenase support the diagnosis of PCP. Diagnosis is confirmed by presence of cysts in sputum or lavage specimens.

MAC, a complex infection associated with advanced immuno-suppression, presents with indolent fever with weight loss, anorexia, night sweats, weakness, and diarrhea. The diagnosis is usually established by isolation of the organism from blood, however, the process typically takes several weeks.

Disseminated CMV is an opportunistic infection that occurs late in HIV, typically in patients with CD4 counts less than 25/mm<sup>3</sup>. The most common form is retinitis, but it may cause other problems such as colitis, enteritis, gastritis, esophagitis, or, less commonly, encephalitis, hepatitis, or pancreatitis. The diagnosis is made by tissue stain or culture from infected organs or by identification of the characteristic fundoscopic changes.

Noninfectious causes of fever in a HIV-infected patient are common when CD 4 counts are below 200/mm<sup>3</sup>. Neoplasms such as Kaposi's sarcoma, non-Hodgkin's lymphoma, and primary CNS lymphomas can induce febrile episodes. Late stage HIV patients are unusually susceptible to drug fever, and this may be seen with drugs such as TMP-SMZ, clindamycin, dapsone, amphotericin B, antivirals, antimycobacterial agents, erythropoietin, granulocyte colony stimulating factor, and several antineoplastic agents.<sup>21</sup>

Evaluation is guided by the stage of the disease as well as the history and physical of the current illness. Laboratory evaluation includes CBC, blood culture, urinalysis, and chest radiograph. When indicated, appropriate body specimen fluids should be sent for acid fast stain and mycobacterial culture. Abdominal CT imaging can help identify intra-abdominal infections (especially involving the liver) in patients with abdominal pain and hepatosplenomegaly.

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### Physician CME Questions

33. Many drugs can produce fever through several different mechanisms. These mechanisms include:
  - A. febrile responses caused by impurities in the drug.
  - B. induction of pyrogen release.
  - C. disorders in thermo-regulation.

- D. hypersensitivity reactions.
- E. All of the above

34. What percent of patients with angiographically proven pulmonary thromboemboli will exhibit fever?
  - A. One-half
  - B. Two-thirds
  - C. 90%
  - D. 10%
  - E. 15%
35. The most common malignancies associated with fever are:
  - A. Hodgkin's and non-Hodgkin's lymphomas.
  - B. hepatoma and atrial myxoma.
  - C. leukemia and hypernephroma.
  - D. all of the above
36. Post partum fever occurs in what percent of vaginal deliveries?
  - A. 2-4%
  - B. 15-18%
  - C. About 30%
  - D. 12%
  - E. 50%
37. Septic pelvic vein thrombophlebitis is associated with what percent of patients with endometritis?
  - A. 50%
  - B. 1%
  - C. 60%
  - D. 10%
  - E. 25%
38. The most common cause of emphysematous pyelonephritis is:
  - A. *K. pneumoniae*.
  - B. *P. mirabilis*.
  - C. *P. aeruginosa*.
  - D. *E. coli*.
  - E. *E. aerogenes*.
39. What is the most common offending agent in infective endocarditis?
  - A. *E. coli*
  - B. *Klebsiella pneumoniae*
  - C. *Staphylococcus aureus*
  - D. *Mycobacterium tuberculosis*
  - E. *H. influenza*
40. Disseminated cytomegalovirus (CMV) infection typically occurs in patients with CD4 counts of:
  - A. 100/mm<sup>3</sup>.
  - B. 200/mm<sup>3</sup> or greater.
  - C. 150/mm<sup>3</sup>.
  - D. less than 25/mm<sup>3</sup>.
  - E. 500/mm<sup>3</sup>.

In Future Issues

Syncope