

## FEVER - QUESTIONS

A 35-year-old man with a history of abrasion of the right hand presents with acute pain in the right shoulder. His physical examination reveals a temperature of 39.5°C (103°F) and rigor, and he appears to be quite ill. There is dusky erythema and edema of the right shoulder and right upper extremity with marked tenderness. Within a few hours the patient is unresponsive and is found to be hypotensive. Laboratory evaluation reveals an elevated serum, creatinine, thrombocytopenia, and elevated hepatic transaminases. The soft tissues in the right upper extremity have begun to necrose. Blood culture obtained at the time of initial presentation has already turned positive. **(Questions 1 and 2)**

1. The organism that is most likely to be responsible for this clinical syndrome is:
  - a. group A streptococci
  - b. group D streptococci
  - c. *Staphylococcus aureus*
  - d. *Bacteroides fragilis*
  - e. *Clostridium septicum*
  
2. The most appropriate therapy for this patient is:
  - a. penicillin G
  - b. penicillin G/clavulanic acid
  - c. erythromycin
  - d. vancomycin
  - e. surgery
  
3. Typhoid fever is characterized by which of the following statements?
  - a. The illness is usually acquired from inhalation.
  - b. Leukocytosis occurs in acutely ill persons.
  - c. Rose spots are usually present at the time when the fever begins.
  - d. Chloramphenicol is effective in preventing relapse.
  - e. Fluoroquinolone antibiotics eradicate the organism even in the presence of gallstones.
  
4. A previously healthy 28-year-old man describes several episodes of fever, myalgia, and headache that have been followed by abdominal pain and diarrhea. He has experienced up to 10 bowel movements per day. Physical examination is unremarkable. Laboratory findings are notable only for a slightly elevated leukocyte count and an elevated erythrocyte sedimentation rate. Wright's stain of a fecal sample reveals the presence of neutrophils. Colonoscopy reveals an inflamed mucosa. Biopsy of an affected area discloses mucosal infiltration with neutrophils, monocytes, and eosinophils; epithelial damage, including loss of mucus; glandular degeneration; and crypt abscesses. The patient notes that several months ago he was at a church barbecue where several people contracted a diarrheal illness. While this patient could have inflammatory bowel disease, which of the following pathogens is most likely to be responsible for his illness?

- a. *Campylobacter*
  - b. *S. aureus*
  - c. *E. coli*
  - d. *Salmonella*
  - e. Norwalk agent
5. Four days after he and his friends were killing muskrats along a rural creek, a boy becomes ill with headache, fever, and a macular rash. On examination axillary adenopathy is noted, but otherwise the examination is normal. Which of the following tests would be most helpful in proving that this boy has tularemia?
- a. Blood culture
  - b. Aspiration and culture of an axillary lymph node
  - c. Determination of serum agglutinins for *Francisella tularensis*
  - d. Bone marrow culture
  - e. Examination of his friends
6. A 10-year-old boy is seen in a rural Arizona clinic because of prostration, fever of 40°C (104°F), and severe headache. Examination is negative for rash, stiff neck, joint tenderness, and chest and abdominal abnormalities. However, several tender, enlarged lymph nodes are palpated in the left axilla, which is very edematous. The test most likely to be of greatest help in the immediate management of this boy would be:
- a. Blood culture
  - b. Examination of a blood smear
  - c. Biopsy of an axillary lymph node
  - d. Aspiration and Gram stains of an axillary lymph node
  - e. Surgical excision of an axillary node
7. A 22-year-old gay man from New Orleans presents with a 2-week history of fever, anorexia, and progressive diffuse lymphadenopathy. Physical findings reveal an emaciated young man who has several tongue ulcers. Hepatomegaly is noted. Laboratory examination reveals pancytopenia, an elevated alkaline phosphatase, and hyperkalemia. A chest radiograph reveals a miliary pattern of diffuse infiltration. A tongue biopsy reveals the presence of hyphae that bear both large and small spores. The correct diagnosis:
- a. Histoplasmosis
  - b. Coccidioidomycosis
  - c. Cryptococcosis
  - d. Blastomycosis
  - e. Aspergillosis
8. An 18-year-old sexually active woman from the inner city presents with fever, pleuritic pain of the right upper quadrant, and lower abdominal pain. Pelvic examination reveals mucopurulent cervicitis and tenderness after the production of cervical motion. The right upper quadrant, uterine fundus, and adnexa are slightly tender. The white blood cell count and erythrocyte sedimentation rate are elevated, but the results of the remainder of the laboratory examination, including liver function tests, are normal. Which of the following agents is the most likely cause of this clinical syndrome?

- a. Herpes simplex virus
- b. *Treponema pallidum*
- c. *Neisseria gonorrhoeae*
- d. *Chlamydia trachomatis*
- e. *Mycoplasma hominis*

A 35-year-old man calls your office stating he has developed a minimally productive cough that has kept him up most of the evening. He has no other past medical history and is currently taking no medications. He complains of a fever to 38.3°C (101°F) with an occasional chill but no rigor. The patient denies chest pain but does admit to mild rhinorrhea. He also complains of abdominal pain, nausea, and vomiting. **(Questions 9 and 10)**

9. You decide to do which of the following:
- a. No intervention except recommend fluid intake
  - b. Prescribe dexbrompheniramine plus pseudoephedrine
  - c. Recommend a nonsedating antihistamine
  - d. Start systemic glucocorticoids
  - e. Prescribe ampicillin with clavulanic acid
10. The same patient arrives in your office 72 hours later with progressive symptoms. He is still complaining of continued low-grade fevers to 38.3°C (101°F). His cough is now productive of yellow greenish thick phlegm and is protracted, often resulting in vomiting. He denies any headache, sinus tenderness, or maxillary tooth pain. You prescribe which of the following:
- a. Dexbrompheniramine plus pseudoephedrine
  - b. Nonsedating antihistamine
  - c. Erythromycin
  - d. Ampicillin with clavulanic acid
  - e. Glucocorticoids

# FEVER

## Basic Science

Fever has been recognized as a cardinal manifestation of disease since ancient time and was recorded in the Sumarian cuneiform 4000 years ago. Fever was mentioned by Hippocrates, Galileo described it in the 17th century; and in the 17th century, a physician named Santorio Santorio constructed devices to measure body temperature. Gabriel Daniell Fahrenheit, an instrument maker, developed the first effective thermometer. In 1868 Reinhold August Wunderlich measured the temperature of 25,000 individuals by performing over a million temperature readings and determined that 98.6°F or 37°C was the mean temperature in healthy adults. In 1992 Philip Mackowiak re-evaluated Wunderlich's finding using modern Diatac 500 electronic thermometers, positioned in the sublingual pocket, until a final display tone was heard, to record 700 temperatures in 148 subjects. He established that the normal body temperature ranges from 35.6°C or 96.0°F to 38.3°C or 100.8°F with a median of 36.8°C and a mode of 36.7°C or 98°F and no particular significance to 37°C or 98.6°F. He found that temperatures varied diurnally with a 6:00 AM nadir and a 4:00-6:00 PM zenith.

Humans have a thermoregulatory setpoint which, if elevated, causes an average increase in heart rate of 4.4 beats/min for each one degree centigrade of temperature. The involved person will shiver thereby increasing heat production and will be peripherally vasoconstricted and will crawl under the covers and wear heavier clothing as a behavior response to decreased heat loss. When fever breaks it is thought that the thermoregulatory setpoint is returned towards normal. At this time the individual is hyperthermic. That's why a person feels warmer and will sweat during defervescence. Bacterial toxins and other stimuli cause release of endogenous pyrogen, a small molecular weight protein cleaved from macrophages which travels to the brain and the anterior hypothalamus and causes a rise in the setpoint causing release of prostaglandin E2. The endogenous pyrogen probably involves IL1-beta, and the other cytokines have been involved. Of all the cytokines involved, the concentration of IL6 is felt to correlate best with the element of fever. Alpha-TNF may actually lower the febrile temperatures, and the anterior hypothalamus is the area most critically involved in the development of fever.

Fever is your friend. Poikilothermic lizards demonstrate that fever is associated with increase in survival in infected animals. Various components of specific and nonspecific immunity are enhanced by febrile temperatures.

## Etiology of Fever

Patients presenting with fever are easily diagnosed when the fever is localized by symptoms or other clues from the history and physical examination and basic laboratory tests. The clinician must assess the height and duration of fever as well as its pattern and relationship to the pulse. Extreme hyperpyrexia is rarely associated with infectious disease. Conversely, hypothermia is a bad prognostic sign in an infectious process. Fever may cause an inability to concentrate or confusion or delirium or stupor in an elderly patient. People with heart disease may respond with high output angina or even heart failure. A shaking chill or rigor suggests bacteremia, respiratory distress, pneumonia, or sepsis and hypotension. Any relative bradycardia or pulse-temperature deficit is important in suggesting drug fever, typhoid fever, epidemic typhus, malaria, leptospirosis, yellow fever, Legionnaire's disease, dengue fever, psittacosis, lymphomas, or obscure CNS lesions. Fever curves usually have no diagnostic significance except in uncommon conditions. Hectic, septic fever in hospitalized patients is mostly seen due

to peritonitis; intra-abdominal, pelvic, or renal abscesses; or over zealous use of antipyretics. Double-quotidian fevers or two fever spikes in a 24-hr period not related to antipyretics are uncommon, but may be the only clue pointing to adult Still's disease, juvenile rheumatoid arthritis, or culture-negative gonococcal endocarditis. A single temperature spike less than 102°F is most always of no diagnostic significance unless it occurs in compromised hosts. Single temperature spikes above 102°F are usually due to manipulative or invasive procedures that induce transient bacteremias or maybe the infusion of blood products. Sustained temperature elevations over time below 102°F should be evaluated for malignancy, cirrhosis, viral hepatitis, tuberculosis, Legionnaire's disease, or one of the zoonoses. Temperatures above 102°F are somewhat easier to diagnose and should be evaluated for an abscess in the abdomen, GI tract, or pelvis. Malignancies do not cause high-grade fever unless there are metastases to the liver or CNS with the exception of hypernephromas and lymphomas. Usually with pancreatitis a temperature of 102°F is more likely to have pancreatic abscess or infected pancreatic pseudocyst.

### **Physical Examination**

Your general observations should include: inspection of the skin for petechia, which is seen with meningococemia or Rocky Mountain spotted fever; pustules seen with gonococemia and staphylococcal disease; conjunctival petechia, splinter hemorrhages, and ulcerlar and Janeway lesions seen with endocarditis; ecthyma gangrenosum seen with Pseudomonas aeruginosa; extensive bullae over the extremities may be seen with Vibrio vulnificus; and erythema chronicum migrans as seen with Lyme disease. The paranasal sinuses should be percussed, and the ostia of the nose examined for pus and the retropharynx for sinusitis. The optic fundi should be examined for Roth spots. Tympanic membranes should be inspected. Breasts, chest, and heart should be examined. A musculoskeletal exam should include a careful joint exam. The neurologic exam should include a check for meningismus or changes in mentation.

### **Fever of Unknown Origin**

In 1961 Beeson and Petersdorf authored a paper describing 100 cases gathered between 1952-57 establishing a definition of fever of unknown origin (FUO) - temperature higher than 101°F or 38.3°C on several occasions in which the diagnosis is uncertain after one week of study in the hospital. FUOs are influenced by geographic factors, referral patterns, state of the art at the time of study, experience of the investigators, and the age of the patients studied. In ambulatory patients fevers are most always due to respiratory tract infections, urinary tract infections, or chronic viral infections, i.e., HIV, Epstein-Barr, herpes, hepatitis B and C. Splenic abscesses occur and may manifest in a patient with clinically silent bacteremias.

Cytomegalovirus infections may cause nonspecific constitutional symptoms with generalized lymphadenopathy, mild hepatosplenomegaly, and fevers. Osteomyelitis of the spine with tuberculosis or Pott's disease or other bacteria may cause low-grade fever with a constellation of fever, weakness, and back pain. Lymphatic malignancy may cause fever. Hypernephroma is a frequently mentioned tumor that causes fever. In the collagen vascular diseases, Still's disease is often represented and granulomatous diseases such as Crohn's disease and non-infections such as cardiac myxoma. Recent studies encourage rapid use of non-invasive testing such as ultrasound, MRI, or CT, therefore making it unlikely that intra-abdominal abscesses would present after a week of study without diagnosis. Ultrasound and CT have more than a 90% sensitivity for hepatobiliary disease, abdominal abscesses, or kidney tumors. The role of nuclear imaging is to localize a pathologic focus of fever. A prospective French study

noted that 50% of all diagnoses of FOU would have been established earlier if CT had been performed in all patients. The yield of percutaneous CT-guided procedures is higher for infection than for tumors, 77% vs 23%. Tahara, et al, demonstrated high resolution fluro-deoxyglucose positron emission tomography (FDG-PET) uptake in human abdominal abscesses that can accurately localize a focus of fever. Yesterday's FOU is today's instantaneous diagnosis. The patient with an intravenous catheter or any patient with a catheter and fever should be considered to have a catheter-related infection until proven otherwise. The presence of two major criteria (cough and purulent nasal discharge) or one major and two minor criteria (peri-orbital edema, headache, facial pain, tooth pain, earache, sore throat, foul breath, wheezing, or fever) for greater than 7 days suggests the presence of acute bacterial sinusitis.

## **Diagnostic Categories of Fever of Undetermined Origin**

### **“The Big Three”**

#### I. Infections

##### A. Systemic

1. Tuberculosis (miliary)
2. Infective endocarditis (subacute)
3. Miscellaneous rare infections: cytomegalovirus infection, toxoplasmosis, brucellosis, psittacosis, gonococemia, chronic meningococemia, disseminated mycoses

##### B. Localized

1. Hepatic infections
  - a. Liver abscess, cholangitis
2. Other visceral infections
  - a. Pancreatic, tubo-ovarian abscesses, empyema of gallbladder, pericholecystic abscess
3. Intrapertitoneal infections
  - a. Subhepatic, subphrenic, paracolic, appendiceal, pelvic & other abscesses
4. Urinary tract
  - a. Pyelonephritis, renal carbuncle, perinephric abscess
  - b. Prostatic abscess

#### II. Neoplasms

#### III. Collagen-vascular disease

### **Less Common Causes**

#### I. Granulomatous disease (other than that due to known infectious agents)

#### II. Inflammatory bowel disease

#### III. Pulmonary embolization

#### IV. Drug fever

#### V. Factitious fever

#### VI. Hepatic cirrhosis with active hepatocellular necrosis

#### VII. Miscellaneous uncommon diseases (familial Mediterranean fever, Whipple’s disease, etc.)

#### VIII. Undiagnosed

From: Jacoby GA, Swartz MN. Fever of undetermined origin. *New Engl J Med* 289:1407-1410, 1973

## References

Mackowiak PA, Wasserman S, Levine MM. A critical appraisal of 98.6°F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *JAMA* 268:1578-1580, 1992.

Simon HB. Evaluation of fever. In: Goroll AH, Mulley AG, eds., *Primary Care Medicine: Office Evaluation and Management of the Adult Patient*, 4th ed. 2000, Lippincott, Williams & Wilkins, Philadelphia.

Jacoby GA, Swartz MN. Fever of undetermined origin. *New Engl J Med* 289:1407-1410, 1973.

Esposito AL, Gleckman RA. A diagnostic approach to the adult with fever of unknown origin. *Arch Intern Med* 139:575-579, 1979.

Gordin F, Stamler C, Mills J. Pyogenic psoas abscesses: noninvasive diagnostic techniques and review of the literature. *Rev Infect Dis* 5:1003-1011, 1983.

Hirschmann JV. Fever of unknown origin in adults. *Clin Infect Dis* 24:291-302, 1997.

Tahara T, Echiya Y, Kuwabana Y, et al. High 18F-fluro-deoxyglucose uptake in abdominal abscesses: a PET study. *J Comput Assist Tomogr* 13:829-831, 1989.

## FEVER - ANSWERS

1. **The answer is A.** This patient presents with the classic findings of necrotizing fasciitis, including systemic toxicity associated with minimal to marked skin changes. The site of inoculation, often resulting from simple trauma, is usually somewhat distant from the area of clinical involvement and may be due to simple trauma. Group A streptococci released during abdominal surgery may also cause this type of illness. While staphylococci, *Bacteroides* spp., or anaerobic streptococci can also cause a similar syndrome, group A streptococci account for about 60% of these cases.
2. **The answer is E.** As group A streptococcal necrotizing fasciitis progresses, the marked tenderness of involved skin may progress into anesthesia as a result of infarction of cutaneous nerves. Surgery is required for both diagnosis and therapy. The process usually extends beyond the area of clinical involvement; and therefore, extensive debridement is required. Antibiotics are adjunctive therapy. Penicillin G 2 to 4 million units IV every 4 hours is recommended; although erythromycin, 250 mg four times a day, may be substituted in case of allergy. This patient also has group A streptococcal toxic shock-like syndrome which, in contrast to *S. aureus*-associated toxic shock syndrome, is associated with bacteremia. The mortality rate of this syndrome, which results from a pyrogenic exotoxin A produced by the bacteria, is ~30%. (Working Group on Severe Streptococcal Infection, JAMA 269:390-391, 1993; Bisno, Stevens, N Engl J Med 334:240-245, 1996)
3. **The answer is E.** *Salmonella typhi* survives well in food and water and generally causes infection by penetrating the intestinal mucosa and entering the bloodstream. Usually at the time when affected persons present with fever and other signs of an acute illness, the white blood cell count is depressed. In contrast, rose spots usually do not occur until the second week of illness. Therapy with chloramphenicol does not prevent relapses but does alter the course of the acute illness. A chronic carrier state can develop, in large part because of the propensity of *S. typhi* to seed and inhabit the gallbladder, especially in adults with gallstones. The fluoroquinolones are becoming the treatment of choice to eradicate the chronic carrier state. (Cherubin, Rev Infect Dis 13:343-344, 1991)
4. **The answer is A.** Campylobacters are motile, curved, gram-negative rods. The principal diarrheal pathogen is *C. jejuni*. The organism is found within the gastrointestinal tract of many animals used for food production and is usually transmitted to humans in raw or undercooked food products or through direct contact with infected animals. Over half the cases are due to insufficiently cooked contaminated poultry. *Campylobacter* is a common cause of diarrheal disease in the U.S. The illness usually occurs within 2 to 4 days after exposure to the organism in food or water. Biopsy of an affected patient's jejunum, ileum, or colon reveals findings indistinguishable from those of Crohn's disease and ulcerative colitis. While the diarrheal illness is usually self-limited, it may be associated with constitutional symptoms, lasts more than one week, and recurs in 5 to 10% of untreated patients. Complications include pancreatitis, cystitis, arthritis, meningitis, and Guillain-Barre syndrome. The symptoms of *Campylobacter* enteritis are similar to those resulting from infection with *Salmonella*, *Shigella*, and *Yersinia*; all these agents cause fever and the presence of fecal leukocytes. The diagnosis is made by isolating *Campylobacter* from the stool, which requires selective media. *E. coli* (enterotoxigenic) is not generally associated with the finding of fecal leukocytes nor is the Norwalk agent. *Campylobacter* is a far more common cause of a recurrent relapsing diarrheal illness that could be pathologically

confused with inflammatory bowel disease than are *Yersinia*, *Salmonella*, *Shigella*, and enteropathogenic *E. coli*.

5. **The answer is B.** Aspiration and culture of an enlarged axillary lymph node would be most helpful in yielding a diagnosis of tularemia in the case described in the question; however, culture is positive in only 10% of cases. Agglutinin reactions ordinarily are not positive for at least one week after infection but are specific. A wide variety of animals and insects can transmit tularemia to humans.
6. **The answer is D.** In the case presented, the diagnosis of plague (*Yersinia pestis* infection) must be considered. To make this diagnosis, affected lymph nodes should be aspirated and the contents should be Gram-stained. In most cases of bubonic plague, lymph node aspirates teem with pleomorphic gram-negative bacilli, which can be definitively identified by immunofluorescent staining of the specimen. Blood culture, bone marrow examination, and lymph node biopsy may be used to diagnose plague but with unacceptable delay. In this situation, great care should be exercised in handling the infected materials, as there is a significant risk of infection for the laboratory workers.
7. **The answer is A.** The patient in question is presumably an HIV-infected man with acute disseminated histoplasmosis, often mistaken for miliary tuberculosis because of its similar pattern of constitutional findings and diffuse chest X-ray abnormalities. Indurated ulcers of the mouth, tongue, nose, or larynx also occur in about 25% of patients with acute disseminated histoplasmosis. Addison's disease, granulomatous hepatitis, gastrointestinal ulcerations, endocarditis, and chronic meningitis may also be seen. Since patients with HIV infection may present with febrile syndromes on the basis of multiple organisms and since serologic tests for histoplasmosis are plagued by frequent false-negative and false-positive results, a definitive diagnosis requires demonstration of the organism by culture or histology. The classic morphology of hyphae that bear large and small spores in this clinical setting is diagnostic. Treatment requires initial administration of amphotericin B followed by prolonged administration of itraconazole. (Wheats, Am J Med 98:336-342, 1995)
8. **The answer is C.** The findings on pelvic examination, coupled with the elevated sedimentation rate in this setting, strongly suggest acute pelvic inflammatory disease (PID). About 5% of women with PID have associated perihepatitis, termed the Fitz-Hugh-Curtis syndrome, manifested by pleuritic pain of the right upper quadrant and tenderness on palpation, along with normal liver function tests and ultrasound of the right upper quadrant. *N. gonorrhoeae* is the primary pathogen in this condition, but chlamydial salpingitis is increasing in incidence, particularly in higher socioeconomic groups. Organisms typically found in the vagina, such as peptostreptococci, *E. coli*, and group B streptococci may also play a primary or secondary role in PID.
9. **The answer is B.** The differential diagnosis of acute cough in an adult patient includes viral rhinitis or rhinosinusitis, bacterial sinusitis, allergic rhinitis, exacerbation of chronic obstructive pulmonary disease, asthma, and bacterial infection. The patient denies any rigors but has a minimally productive cough with mild rhinorrhea, suggestive of a viral rhinitis. Occasionally it can be difficult to differentiate between viral rhinosinusitis and bacterial sinusitis; but the absence of sinus discomfort, maxillary toothache, and purulent nasal secretions makes the latter diagnosis less likely. The treatment would be supportive with a common over-the-counter antihistamine with a decongestant; intranasal ipratropium has also shown relief of rhinorrhea and sneezing secondary to the common cold. The use of

a sedating antihistamine and nonsedating antihistamine without symptoms of allergic rhinitis is not indicated, and nonsedating antihistamines seem to be less effective. In addition there is no convincing evidence that intranasal or systemic glucocorticoids are beneficial or that zinc lozenges are consistently beneficial. (Irwin, Madison, N Engl J Med 343:1715-1721, 2000)

10. **The answer is C.** The patient now has progressive symptoms, and the presence of a productive cough with vomiting is suggestive of a *Bordetella pertussis* infection. The treatment of choice for patients with *B. pertussis* infection is erythromycin, 500 mg 4 times daily for 14 days, or if allergic, trimethoprim/sulfamethoxazole, 160/800 mg twice daily for 14 days. Given their in vitro activity, other macrolides are also likely to be effective. Systemic glucocorticoids have been beneficial in severely affected children, but their efficacy has not been established in adults. There is often a history of contact with a patient who has a known case of pertussis. Patients often present with the infrequently heard but characteristic whoop, and coughing with vomiting is pathognomonic. Laboratory diagnosis of pertussis is difficult to establish because there is usually a delay between the onset of cough and the suspicion of the disease. In addition, there are no reliable serologic tests for *B. pertussis* infection. Cultures on nasopharyngeal secretions are usually negative after two weeks. Serologic confirmation of the recent *B. pertussis* infection requires evidence of an elevated level of antibodies against one of the various virulence factors of the organism. This can be provided by an enzyme-linked immunosorbent assay (ELISA). (Irwin, Madison, N Engl J Med 343:1715-1721, 2000)