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Contributor Disclosures

In accordance with ACCME Standards and ACEP policy, contributors to Critical Decisions in Emergency Medicine must disclose the existence of significant financial interests in or relationships with manufacturers of commercial products that might have a direct interest in the subject matter. Authors and editors of these Critical Decisions lessons reported no such interests or relationships.

Method of Participation

This educational activity consists of two lessons with a posttest and should take approximately 5 hours to complete. To complete this educational activity as designed, the participant should, in order, review the learning objectives, read the lessons, and complete the online posttest. Release date December 1, 2009. Expiration date November 30, 2012

Accreditation Statement

The American College of Emergency Physicians (ACEP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. ACEP designates this educational activity for a maximum of 5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity. Approved by ACEP for 5 Category I credits. Approved by the American Osteopathic Association for 5 hours of AOA Category 2-B credit (requires passing grade of 70% or better).

Target Audience

This educational activity has been developed for emergency physicians.
Objectives

On completion of this lesson, you should be able to:

1. Outline a basic clinical approach to evaluating febrile travelers.
2. Describe the epidemiological and public health implications of important causes of fever in returning travelers.
3. Discuss the pathophysiology and the diagnostic and treatment approach to important causes of fever in returning travelers.

From the EM Model

1.0 Signs, Symptoms, and Presentations
   1.1 General (Fever)

Fever in Returning Travelers

Boris Garber, DO, and Svetlana Reznikova-Steinway, MD

Widespread international and domestic travel brings some unique challenges to an emergency physician evaluating a febrile patient. Various maladies, infectious and noninfectious, mundane and rare, local and widespread, are associated with travel. A number of urgent questions, both patient-centered and public health-related, must be answered in these cases.

Case Presentations

Case One

A 30-year-old man comes to the emergency department with a 4-day history of fevers to 39.5°C (103.1°F), rigors, occasional vomiting, and generalized myalgias. The patient returned from the southeastern Ukraine 12 days ago; he had been visiting his relatives in a small town. He describes swimming in the local river, fishing, and eating home-prepared meals. On the day of admission, the patient developed epistaxis, global headache, and cough productive of brown sputum. The patient looks sick, has mild active epistaxis, icteric sclera, suffused conjunctiva, and bilateral rhonchi on lung examination.

Case Two

A 56-year-old man with a history of high blood pressure is brought to an emergency department by his son. The patient is complaining of progressively worsening shortness of breath for the past 24 hours associated with nonproductive cough, diarrhea, and confusion. He has just returned from Detroit 3 days previously, where he had attended a conference and stayed in a hotel. He flew there and back with each flight taking 1 hour. The patient appears sick and dyspneic, he is oriented to name only. He is hypotensive, hypoxic, and febrile to 39.8°C (103.6°F). A portable chest radiograph shows a right lower-lobe infiltrate. His sodium is measured at 127 mmol/L.

Fever is a common and challenging problem for emergency physicians. Although it should be carefully evaluated in any patient, a few populations demand special attention because they are at increased risk for serious disease. Certain travel patterns also put patients at risk for serious illness, both infectious and noninfectious in etiology. Some of the associations are well appreciated such as the risk of malaria with travel into the tropics or the risk of deep venous thrombosis after a transpacific flight. Others may be underappreciated, such as the prevalence of Lyme disease in Wisconsin or endemic tick-borne viral encephalitis in Siberia. The time it takes for a traveler to become sick after exposure to a pathogen is typically brief, and symptoms can appear while the traveler is still traveling. There are, however, several important exceptions to this general rule—namely malaria, other than falciparum malaria, and tuberculosis; these infections can take weeks or even months to manifest symptoms.
Critical Decisions

- When is isolation necessary?
- Is a history of fever sufficient to prompt a workup?
- Are “cold symptoms” reassuring in a returning traveler?
- What information elicited from the history is helpful in identifying the source of fever in a returning traveler?
- Do all febrile travelers suffer from exotic infections?
- What initial diagnostic steps are helpful in making a diagnosis?
- When should empiric antibiotics be given? What antibiotics should be considered?
- What role do supportive measures have in early management of febrile travelers?
- When should public health officials be notified?

**CRITICAL DECISION**

**When is isolation necessary?**

The necessity of isolation should be addressed on patient presentation and initial evaluation. The combination of fever with hemoptysis, rash, mental status changes, or abnormal bleeding should prompt initial isolation. Similarly, when there is concern for an outbreak of a respiratory illness (eg, severe acute respiratory syndrome [SARS], influenza) or a communicable disease (eg, tuberculosis), fever and cough should prompt both isolation and appropriate barrier precautions.

Remember to initiate appropriate antibiotic prophylaxis for contacts when necessary (examples include plague, meningococcal meningitis, anthrax). Suspected cases of tuberculosis and SARS require that the patient be placed in a negative-pressure room; patients with diphtheria or pertussis only need droplet precaution (Table 1).

**CRITICAL DECISION**

**Is a history of fever sufficient to prompt a workup?**

A reliable history of a recent fever given either by the patient or a caretaker should be treated the same as fever documented in the emergency department. Many diseases characteristically produce fevers only at certain times of day; in others, antipyretics taken prior to the emergency department visit could produce normothermia when the patient’s temperature is measured in the emergency department. A history of fever may be the only early symptom in some life-threatening diseases (eg, falciparum malaria, Rocky Mountain spotted fever, plague).

**CRITICAL DECISION**

**Are “cold symptoms” reassuring in a returning traveler?**

Do not be falsely reassured by nonspecific symptoms or a mundane presentation. Myalgias, sore throat, and mild diarrhea, when present in a febrile patient, are easily ascribed to a “cold,” but these symptoms have been described in diseases as varied and serious as malaria, dengue, and leptospirosis. Falciparum malaria and Rocky Mountain spotted fever patients sometimes initially appear well but can rapidly deteriorate even with appropriate antibiotic treatment. Be sure to frequently reevaluate the patient, repeating vital signs and assessing mental status as necessary.

<table>
<thead>
<tr>
<th>Table 1. Infection control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard precautions</strong> (avoidance of exposure to bodily fluids and secretions)—Always appropriate.</td>
</tr>
<tr>
<td><strong>Contact precautions</strong> (private room or cohorted, gloves and masks for providers)—Appropriate for methicillin-resistant <em>Staphylococcus aureus</em>, vancomycin-resistant enterococci, <em>Clostridium difficile</em>, herpes simplex, cholera, typhoid fever, rotavirus, norovirus, <em>Escherichia coli</em> O157:H7. Travelers with draining abscesses or severe diarrhea would be included here initially in the emergency department.</td>
</tr>
<tr>
<td><strong>Droplet precautions</strong> (for particles of respiratory secretions transmitted up to 6 feet from the source; patients should be in private rooms or cohorted)—Appropriate for <em>Neisseria meningitidis</em>, <em>Bordetella pertussis</em>, mycoplasma, streptococcus group A (except localized skin infections), diphtheria, pneumatic plague, influenza, rubella, mumps, adenovirus, respiratory syncytial virus, viral hemorrhagic fevers caused by Ebola, Lassa, Marburg, Crimean Congo viruses. Travelers with altered mental status and fever, hemorrhagic manifestations, or severe pharyngitis are included here. Travelers with severe pneumonia should be placed in airborne precautions until tuberculosis can be ruled out.</td>
</tr>
<tr>
<td><strong>Airborne Precautions</strong> (for infectious agents that can be transmitted over long distances when suspended in the air; negative-pressure room is needed and providers should wear a HEPA-certified respirator)—Appropriate for measles, SARS, smallpox, tuberculosis, and varicella; especially when any suspicion for tuberculosis exists, ie, respiratory symptoms and hemoptysis, travel to an endemic area, personal history or belongs to a high-risk group, destructive or cavitary pneumonitis; disseminated vesicular rash; in the context of a specific outbreak.</td>
</tr>
</tbody>
</table>
CRITICAL DECISION
What information elicited from the history is helpful in identifying the source of fever in a returning traveler?

Numerous papers have been published over the years addressing the optimal approach to a returned febrile traveler. The history of the present illness is the absolute key to the diagnosis. The associated symptoms can help clarify the differential diagnosis (Table 2). Neurologic symptoms such as headache or altered mental status can be a clue to meningitis or other infections in which neurologic symptoms predominate. When the patient has respiratory difficulties, pneumonia or other infections predominately involving the lungs should be considered likely. Those patients with abnormal bleeding can have hemorrhagic viral fevers or other serious dangerous infections that damage the coagulation system. The physician’s examination of the skin can offer a valuable clue that the patient has an infection or illness involving the liver (presence of jaundice) or a characteristic rash that limits the differential diagnosis to certain serious diseases.

The specific region visited (not just the country—endemic diseases can vary widely from one locale to another, even in a small country), modes of transportation, activities undertaken (eg, swimming in fresh water in much of the tropics can result in Katayama fever, contact with farm animals can lead to Q fever, contact with rodents in Arizona could cause infection with plague), and prophylaxis or treatment already instituted are especially important. Missionary workers, military personnel, adventure travelers, and refugees present specific challenges, because they are often exposed to relatively unsanitary living conditions. For example, the vectors for epidemic typhus, relapsing fever, and trench fever are body lice, which are often found in the unsanitary and overcrowded conditions in some refugee camps. Poor sanitation also harbors diseases with a fecal-oral mode of transmission such as typhoid fever. Former residents of a region who return as visitors after being away for a long time are also at special risk. Immunity to certain pathogens (most notably malaria) resulting from the continuous exposure that occurs in endemic regions lapses when people move away. These patients also often come into closer contact with local populations than most casual travelers (Table 3, Table 4).

CRITICAL DECISION
Do all febrile travelers with fever suffer from exotic infections?

Be sure to consider noninfectious causes of fever, both travel-related (deep venous thrombosis and pulmonary embolism) and general (drug fever, evolving myocardial infarction, connective tissue disorder, malignancy), in the appropriate setting. Mundane infections such as urinary tract infection and community-acquired pneumonia are no less common in travelers than in age-matched controls who did not travel.

CRITICAL DECISION
What initial diagnostic steps are helpful in making the diagnosis?

The history and physical examination are pivotal to correct diagnosis in most febrile patients, but laboratory and radiographic tests may also be necessary although results are often nonspecific. In unclear cases a CBC and differential, chemistries, blood glucose, thick and thin smears, blood cultures, urinalysis, stool studies if there is diarrhea, and a chest film should be obtained early. Special precautions can be required in handling specimens (ie, if tularemia is suspected).

CRITICAL DECISION
When should empiric antibiotics be given? What antibiotics should be considered?

Timely and appropriate antimicrobial therapy can make a real difference in outcome in certain infectious diseases. Specifically, in cases of falciparum malaria, central nervous system infections, and sepsis of any cause, early antibiotic therapy has been shown to reduce mortality. Patients with rickettsial infections must be treated expeditiously with tetracyclines or chloramphenicol. Immunoologic compromise from any cause also demands extra vigilance, because in such patients the clinical manifestation of a given infection could be atypical but the disease progression rapid. Early on, it can be impossible to discern a specific etiology in a sick febrile patient, and broad-spectrum antibiotics are necessary along with an aggressive diagnostic workup. Appropriate initial antibiotics for a patient thought to be at risk of a serious bacterial infection are an extended-spectrum β-lactam or a fluoroquinolone combined with an aminoglycoside, and a tetracycline combined with an anti-falciparum regimen—either chloroquine or quinine with either tetracycline or clindamycin.

CRITICAL DECISION
What role do supportive measures have in early management of febrile travelers?

Supportive measures are integral to the management of febrile patients and range from life-saving (airway management, intravenous fluids, and pressors) to comfort measures (antipyretics, antiemetics, and analgesics). In the early stages of the disease, many tropical fevers, including falciparum malaria, rickettsial infections, particularly epidemic typhus, plague, and typhoid fever, present as sepsis. It is prudent to ask about travel history of every patient presenting with an infectious disease.
Table 2.
Differential diagnosis in febrile travelers based on predominant associated symptoms

<table>
<thead>
<tr>
<th>Fever and Headache&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Fever and Abnormal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Dengue hemorrhagic fever</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Fulminant infectious hepatitis</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>Hemorrhagic viral fevers—Ebola, Lassa, Marburg, Machu, Junin, Sabia, Guanarito, Rift Valley fever, Crimean-Congo hemorrhagic fever, Omsk hemorrhagic fever, Whitewater Arroyo hemorrhagic fever, Kyasanur Forest disease, Argentine hemorrhagic fever, Bolivian hemorrhagic fever, hantavirus hemorrhagic fever with renal syndrome</td>
</tr>
<tr>
<td>Acute sinusitis</td>
<td>Meningococcemia</td>
</tr>
<tr>
<td>Falciparum malaria</td>
<td>Sepsis with disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Rickettsial infections</td>
<td>Typhoid fever—late: lower gastrointestinal bleeding</td>
</tr>
<tr>
<td>Weil disease</td>
<td>Weil disease</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Yellow fever</td>
</tr>
<tr>
<td>Q fever</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
</tr>
<tr>
<td>Viral hemorrhagic fevers&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fever and Altered Mental Status&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Fever and Jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Viral hepatitis</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Viral hemorrhagic fevers&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>Malaria</td>
</tr>
<tr>
<td>Falciparum malaria</td>
<td>Yellow fever</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Leptospirosis</td>
</tr>
<tr>
<td>Rickettsial infections, especially epidemic typhus, murine typhus, and scrub typhus</td>
<td>Acute cholangitis</td>
</tr>
<tr>
<td>Rabies</td>
<td>Liver abscess</td>
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<tr>
<td>Legionella pneumonia</td>
<td></td>
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<tr>
<td>Sleeping sickness</td>
<td></td>
</tr>
<tr>
<td>Fulminate hepatitis</td>
<td></td>
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<tr>
<td>Plague</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Fever and Respiratory Difficulties&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Fever and Rash&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community acquired pneumonia including Legionella</td>
<td>Eschar—anthrax, tularemia, community-acquired methicillin resistant Staphylococcus aureus (associated with abscess formation), many rickettsial infections—eschars can be multiple (eschars are absent in Rocky Mountain spotted fever, murine and epidemic typhus, Q fever, Bartonella infections).</td>
</tr>
<tr>
<td>Hantavirus pulmonary syndrome</td>
<td>Petechia/purpura—anemococcemia, Rocky Mountain spotted fever and other rickettsial spotted fever group infections, erythema arthriticum epidemicum, Colorado tick fever, Weil disease, epidemic typhus, viral hemorrhagic fevers&lt;sup&gt;&lt;sup&gt;b&lt;/sup&gt;&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Non-specific (eg, macular, papular, urticarial)—many viral diseases (coxsackie, parvovirus, certain members of Herpesviridae, acute HIV infection), dengue, Katayama fever, typhoid and paratyphoid fever, measles, scarlatina, erythema migrans—Lime disease</td>
</tr>
<tr>
<td>Epiglottitis</td>
<td>Cellulitic—pyoderma, septicompexia, erysipelas, necrotizing fasciitis</td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
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<tr>
<td>Well disease</td>
<td></td>
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<tr>
<td>Pneumonic plague</td>
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<tr>
<td>Tuberculosis</td>
<td></td>
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<tr>
<td>SARS</td>
<td></td>
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</tbody>
</table>

<sup>a</sup> High fever commonly triggers a headache regardless of cause.

<sup>b</sup> See the list in Fever and abnormal bleeding section.

<sup>c</sup> Especially in the elderly and the very young common infections can present with altered mental status.

<sup>d</sup> Significant metabolic acidosis and air hunger are common in severe sepsis of any cause; significant RBC loss from bleeding or hemolysis (remember malaria) routinely presents with dyspnea.

<sup>e</sup> Drug rash, including Stevens-Johnson syndrome, should always be considered.

<sup>f</sup> Macular, papular, and urticarial rash can be present early on or concurrently.
### Causes of Fever in Recent Travelers by Geographic Region

<table>
<thead>
<tr>
<th>Causes of Fever in Recent Travelers</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>from the Americas</strong></td>
<td><strong>from Africa</strong></td>
<td><strong>from Europe</strong></td>
</tr>
<tr>
<td>Acute coccidiomycosis</td>
<td>Acute HIV infection</td>
<td>Acute HIV infection</td>
</tr>
<tr>
<td>Acute histoplasmosis</td>
<td>Arboviral encephalitis</td>
<td>Arboviral encephalitis</td>
</tr>
<tr>
<td>Acute HIV infection</td>
<td>Chikungunya fever</td>
<td>Borreliosis</td>
</tr>
<tr>
<td>Arboviral encephalitis</td>
<td>Crimean–Congo fever</td>
<td>Crimean–Congo fever</td>
</tr>
<tr>
<td>Babesiosis</td>
<td>Dengue</td>
<td>Dengue</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>Diptheria</td>
<td>Diphtheria</td>
</tr>
<tr>
<td>Dengue</td>
<td>Ebola</td>
<td>Ebola</td>
</tr>
<tr>
<td>Diptheria</td>
<td>Hepatitis A and E</td>
<td>Hepatitis A</td>
</tr>
<tr>
<td>Ehrlichiosis</td>
<td>Infectious colitis</td>
<td>Infectious colitis</td>
</tr>
<tr>
<td>Hantavirus</td>
<td>Katayama fever</td>
<td>Katayama fever</td>
</tr>
<tr>
<td>Hepatitis A and E</td>
<td>Lassa fever</td>
<td>Lassa fever</td>
</tr>
<tr>
<td>Infectious colitis</td>
<td>Leptospirosis</td>
<td>Leptospirosis</td>
</tr>
<tr>
<td>Legionnaires’ disease</td>
<td>Malaria</td>
<td>Malaria</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>Marburg virus fever</td>
<td>Marburg virus fever</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Meningococcal infections</td>
<td>Meningococcal infections</td>
</tr>
<tr>
<td>Malaria</td>
<td>Plague</td>
<td>Plague</td>
</tr>
<tr>
<td>Plague</td>
<td>Polio</td>
<td>Polio</td>
</tr>
<tr>
<td>Rabies</td>
<td>Relapsing fever</td>
<td>Relapsing fever</td>
</tr>
<tr>
<td>Relapsing fever</td>
<td>Rickettsial infections</td>
<td>Rickettsial infections</td>
</tr>
<tr>
<td>Rickettsial infections</td>
<td>Rift Valley fever</td>
<td>Rift Valley fever</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Sleeping sickness</td>
<td>Sleeping sickness</td>
</tr>
<tr>
<td>Tularemia</td>
<td>Tuberculosis</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Typhoid and paratyphoid fever</td>
<td>Typhoid and paratyphoid fever</td>
<td>Typhoid and paratyphoid fever</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Yellow fever</td>
<td>Yellow fever</td>
</tr>
</tbody>
</table>

* Travelers to urban areas in developed countries face few unique infectious disease challenges with Legionnaires’ disease being a notable exception.

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### Table 3.
Causes of fever in recent travelers by geographic region

- **from the Americas**
- **from Africa**
- **from Europe**
- **from Asia**
- **from Australasia**
in your state or practice area. State health departments maintain online lists of diseases requiring notification; an internet search should bring up the information. An annually updated list of nationally reportable diseases can be found on the Centers for Disease Control and Prevention (CDC) Web site: http://www.cdc.gov/ncphi/diss/ndss/phs/infdis.htm.

Serious Travel-Associated Illnesses

Febrile travelers can be suffering from more than one ailment, and more than one tropical disease can be present. In particular, malaria should always be considered in febrile patients returning from endemic regions even when another cause of fever is apparent.

Malaria

This parasitic mosquito-borne febrile illness is the most common and important “tropical” fever encountered in returning travelers. It is spread via bites of the Anopheles mosquito, a mosquito that is active primarily after dusk. A detailed travel history should be obtained because the risk of acquiring malaria, specific parasites, and patterns of antiplasmodial resistance vary greatly from region to region even within a country. The CDC offers an excellent Web resource: www.CDC.gov/Malaria/clinician.htm. Acute fever or history of such, especially when associated with anemia, combined with any history of travel to endemic areas should always suggest malaria.

Dengue Fever

This flavivirus infection is endemic to many tropical regions and is transmitted via bites of the Aedes aegypti mosquito, a species that is active by day (in contrast to Anopheles mosquitoes that transmit malaria and are mostly active after dusk). Dengue is very common, and its vector is encountered in many urban areas (again unlike malaria which is primarily a rural malady). There are four serotypes of dengue virus. After an incubation period ranging from 3 to 14 days, patients typically have a sudden onset of high fevers, headaches, and severe body aches (hence the name “break-bone fever”).

Rickettsial Infections

Rickettsiae are a unique group of intracellular bacteria that retain independent metabolic activity and have a predilection for endothelial cells (http://www.cdc.gov/travel/yellowbook/2010/chapter-5/rickettsial-and-related-infections.aspx). All rickettsial infections are transmitted via arthropods; they have the potential for serious morbidity and mortality, and their initial presentations are nonspecific. Specific rickettsioses are endemic in many portions of the world. Anywhere that ticks coexist with wild mammals, specific rickettsiae circulate, and humans can be infected. Louse-borne typhus is encountered in impoverished areas and refugee camps. Murine typhus is transmitted from rats via fleas and is similar to louse-borne typhus, although milder. Scrub typhus caused by Orientia tsutsugamushi begins with a bite from an infected chigger. Local changes (primary lesion) develops at the site of the arthropod bite and can be associated with anemia, combined with any history of travel to endemic areas should always suggest malaria.

Leptospirosis

Leptospira are spirochetes. A bacterial zoonosis primarily contracted via infected water contact with broken skin or mucous membranes, leptospirosis has worldwide distribution. Carrier animals develop chronic renal infection and shed bacteria in their urine. It is commonly contracted in the tropics but has been described in travelers in Hawaii and Eastern Europe. After a variable incubation period, most patients develop a self-limited febrile illness. Some patients, however, will have a severe course, developing hepatorenal involvement, pneumonia (hemorrhagic in

<table>
<thead>
<tr>
<th>Table 4. Special patient groups with regards to tropical disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent immigrants and refugees</td>
</tr>
<tr>
<td>Adventure travelers (including those traveling to developed</td>
</tr>
<tr>
<td>countries)</td>
</tr>
<tr>
<td>Missionary workers</td>
</tr>
<tr>
<td>Scientists on field trips</td>
</tr>
<tr>
<td>Military personnel</td>
</tr>
<tr>
<td>Former residents of a region returning</td>
</tr>
</tbody>
</table>
severe cases, with hemoptysis), and hemorrhagic complications. Ophthalmologic (uveitis, iridocyclitis) and neurologic complications (notably meningitis) occur in the severe form called Weil disease. Fever, muscle pains and tenderness, and conjunctival suffusion are notable early signs. Definite diagnosis is based on serology or culturing leptospira. Testing is inevitably delayed, and an infectious disease specialist or state health department should be contacted for assistance. Importantly, a range of endemic viral hemorrhagic fevers overlap with leptospirosis in their epidemiology and initial presentation. Leptospirosis is treated with penicillin G (preferred), ceftriaxone, or ampicillin; doxycycline may be used but is not recommended for severe infection. Reasonable clinical suspicion of leptospirosis should prompt at least oral antibiotic therapy. Supportive care is essential in Weil disease, with attention to bleeding, vascular, and eye complications. A Herxheimer reaction can develop after initiation of intravenous antibiotics.

Katayama Fever

Early clinical manifestations of schistosomiasis (infection with schistosomes, parasitic trematode worms) related to migrating schistosomula and egg deposition are termed Katayama fever (or syndrome). Schistosomiasis results from any skin contact with infested fresh water in endemic regions (salt water is safe). The symptoms of Katayama fever are rather nonspecific—fever, abdominal pain, hematuria, cough, body aches, and headache—and are thought to reflect an allergic reaction to migrating larvae and deposited eggs. As in other disorders caused by migrating worms, a chest radiograph could show patchy infiltrates in association with eosinophilia (Loeffler syndrome). Importantly, Katayama fever usually resolves whether the infestation is treated or not; although occasionally it causes severe sequelae, and death has been reported. Unrecognized and untreated schistosomiasis can induce fibrotic changes around affected organs, potentially with serious morbidity and a potential for malignant transformation. Once the disease is suspected based on history, the diagnosis is based on egg detection and serology. These tests should be repeated if they are negative the first time. Praziquantel and artemisinin are used in treatment, and steroids can be added for acute anti-inflammatory effect. No treatment regimen is 100% effective, and referral to an infectious disease specialist for re-screening is important.

Plague

This ancient bacterial zoonosis is maintained in nature in many species of wild rodents in all continents except Australia. It is caused by Yersinia pestis and transmitted via flea bites from infected rodents or from close contacts with the rodents. There are several forms, with bubonic being the most common and septicemic and pneumonic the most deadly. Untreated bubonic plague commonly progresses to secondary pneumonic plague, sepsis, or meningitis. Human-to-human transmission is possible, and any suspicion of plague mandates strict respiratory isolation. The incubation period ranges from 2 to 8 days. Fever and lymphadenopathy characterize bubonic plague initially, with sepsis and coagulopathy being the main complications. The disease can progress rapidly, and timely antibiotics are essential. Streptomycin and gentamicin are first-line agents; doxycycline and ciprofloxacin may also be used. Insecticide agents should be administered to both the patients and their contacts, who also should be given antibiotic prophylaxis and observed.


Tularemia

Tularemia is a bacterial zoonosis caused by Francisella tularensis. Several subspecies of the bacterium exist with different geographical distributions. The organism infects many species of vertebrates, both wild and domestic, and a range of invertebrates including ticks, mosquitoes, horse flies, fleas, and lice. It is widely distributed in the Northern hemisphere, and cases have been reported from every state except Hawaii and from most European countries except Iceland, Portugal, and the British Isles. Handling of infected animals, sleeping in rodent-infested dwellings, ingestion of inadequately cooked meat, drinking contaminated water, animal scratches or bites, and arthropod bites (especially ticks but also mosquitoes) can cause infection. An outbreak of primary pneumonic tularemia in 2000 in Martha's Vineyard, Massachusetts, was linked to lawn mowing and cutting brush, leading to the aerosolization of this extremely hardy bacterium. It is not transmitted from person to person. The incubation period is usually 3 to 6 days although wide variation is reported. Clinical presentation depends on the way tularemia is acquired and the subspecies, with F. tularensis subspecies causing an especially severe disease. Sudden onset of fevers, chills, and malaise is typical. Depending on the route of entry, primary pneumonitis

Critical Decisions in Emergency Medicine
(respiratory tularemia—primary or secondary), the ulceroglandular (consisting of eschar and regional lymphadenopathy), oropharyngeal (ulcerative pharyngitis or tonsillitis), or ocuologlandular (primary lesion on conjunctiva) form develops. Typhoid form is rare and consists of systemic manifestations without primary lesion development. Meningitis, endocarditis, and gastrointestinal involvement are primary complications. The diagnosis is primarily a clinical one. If tularemia is suspected and culture is attempted, the laboratory should be specifically notified, because special procedures are necessary both for protection of personnel and for optimizing culture growth. Culturing of tularemia is only available in few places. Suspicious ulcers, sputum, and blood can all be cultured. Serologic evidence of tularemia can be established, but the equipment is only available in select research laboratories. Prompt antibiotic administration is essential, because untreated disease has a high mortality rate; streptomycin is the first choice followed by gentamicin. Fluoroquinolones are also appropriate. β-Lactams are ineffective. β-Lactams are ineffective. For information on the distribution of tularemia cases in the United States see: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5109a1.htm

**Sleeping Sickness**

This parasitic infection is endemic to sub-Saharan Africa. There are two forms: a more acute form caused by Trypanosoma brucei rhodesiense occurring in the east and south, and an indolent form caused by Trypanosoma brucei gambiense occurring in the west. Although travelers on safari and those visiting remote areas are at risk, this remains a very rare cause of fever in returning travelers. The disease is transmitted by biting tsetse flies and has an incubation period ranging from 1 to 4 weeks. An eschar forms at the bite site followed by fever, malaise, arthralgias, lymphadenopathy, and headache. The central nervous system infection that follows manifests with altered mental state and sleep-cycle disturbances. If left untreated, the disease progresses to frank coma and death. Diagnosis rests on identifying parasites in a thick smear of blood or, in late stages, cerebrospinal fluid. Treatment is difficult, and the drugs used are highly toxic and best administered by an infectious disease specialist.

**Hantaviruses**

These zoonotic viral infections are endemic in many parts of the world and are contracted from various rodents. Infection occurs when infected rodent droppings are aerosolized. Of note is Hantavirus pulmonary syndrome endemic to the rural southwestern United States as well as other places in Canada and South America. The natural reservoir of the causative Sin Nombre virus is the deer mouse. After an incubation period of variable duration that can be weeks long, patients present with a nonspecific flu-like illness progressing to noncardiogenic pulmonary edema and respiratory failure with a high mortality rate. The disease is not transmitted person to person. The definitive diagnosis is based on serology, while early therapy rests on suspicion and is supportive and symptomatic. Any suspicion of Hantavirus pulmonary syndrome mandates admission, preferably to an ICU. Another important hantavirus disease is hemorrhagic fever with renal syndrome endemic to the Russian Far East and Northern China, manifested by fever, thrombocytopenia, and renal failure that can necessitate hemodialysis. The diagnosis is bacteriological, with Salmonella isolated from blood, stool, or urine. Fluoroquinolones, third-generation cephalosporins, and azithromycin are used for treatment. Multi-drug resistance has been reported. A carrier state can develop.

**Case Resolutions**

### Case One

This patient’s physical examination also showed normal mental status and no nuchal rigidity. His pulse oximetry was 89% on room air, improving to 96% on 4 liters of oxygen. His abdominal examination revealed right upper-quadrant tenderness. The skin examination revealed scattered petechiae. His laboratory tests showed a WBC count of 16,000, with 80% neutrophiles, 11% monocytes, 8% lymphocytes, and 1% eosinophiles; elevated AST and ALT to four times normal; and serum bilirubin of 26 mg/dL. Hemoglobin was 11.9, and the platelet count was 130,000. Serum chemistries were significant for sodium of 130 and potassium of 3. His urine dipstick showed large leukocytes but no bacteria. A hepatitis panel showed no evidence of hepatitis A, B, C, or E. A chest radiograph showed bilateral patchy infiltrates, and abdominal ultrasonography revealed moderate hepatomegaly without liver abscess or gallbladder disease. The differential diagnosis initially included tuberculosis, community-acquired pneumonia, fulminant hepatitis, leptospirosis, and hemorrhagic
Pitfalls

- Common things are common; pneumonia, urinary tract infection, and common viral infections happen to returning travelers.
- Do not rely on patients to volunteer their travel history; ask specific questions.
- Consider and investigate noninfectious causes of fever when appropriate.
- Consider a reliable history of fever the same as if it had been documented in the emergency department.
- A detailed travel history is the key to the right diagnosis.
- Involve infectious disease specialists early, especially when caring for a pregnant, pediatric, or seriously sick patient.

Pearls

- Not treating a fever in a returning traveler as a medical emergency.
- Relying on a single negative thick smear to rule out malaria.
- Failure to hospitalize a patient with suspected falciparum pneumonia.
- Failure to initiate appropriate antibiotics early on in suspected rickettsial infections, plague, and tularemia—remember doxycycline.
- Over-reliance on normal or nonspecific laboratory parameters or on nonspecific symptoms such as cough, myalgias, and sore throat when deciding whether there is a serious cause for a patient’s fever.

Viral fever. Blood cultures were drawn, and the pathologist was specifically notified of the concern for leptospirosis. Leptospira were eventually demonstrated in one of the tubes. Acid fast bacilli were not found in his sputum. The patient was initially placed in a negative-pressure room, and intravenous ceftriaxone and azithromycin were given. The patient’s bilirubin peaked at 40 mg/dL and then declined to normal. His headache worsened after admission despite analgesics, and a lumbar puncture demonstrated 110 WBCs with 99% lymphocytic predominance, 2 RBCs, protein of 50 mg/dL, and normal glucose; no organisms were seen on Gram stain. His symptoms slowly improved, and he was discharged home in good condition after 8 days in the hospital.

Case Two

The patient’s blood pressure was initially 78/40, heart rate 110, and oxygen saturation 88% on a nonrebreathing mask. He was given an intravenous bolus of isotonic saline and orally intubated via an intravenous bolus of isotonic saline and orally intubated via nonrebreathing mask. He was given an intravenous bolus of isotonic saline and orally intubated via nonrebreathing mask. He was initially placed in a negative-pressure room, and intravenous ceftriaxone and azithromycin were given. The patient’s bilirubin peaked at 40 mg/dL and then declined to normal. His headache worsened after admission despite analgesics, and a lumbar puncture demonstrated 110 WBCs with 99% lymphocytic predominance, 2 RBCs, protein of 50 mg/dL, and normal glucose; no organisms were seen on Gram stain. His symptoms slowly improved, and he was discharged home in good condition after 8 days in the hospital.

Summary

Fever in a returning traveler is a complex diagnostic and therapeutic challenge. Obtaining a detailed travel history allows development of an appropriate differential diagnosis. A high degree of suspicion and early aggressive antibacterial and supportive therapy are required when a serious infection is suspected. In the emergency department most early interventions must be based on the clinical picture without awaiting confirmatory tests.

References

The LLSA Literature Review

“The LLSA Literature Review” summarizes articles from ABEM’s “2010 Lifelong Learning and Self-Assessment Reading List.”

Many of these articles are available online in the ACEP LLSA Resource Center (www.acep.org/llsa) and on the ABEM web site.

Article 11

Care of the HIV-Positive Patient in the Emergency Department in the Era of Highly Active Antiretroviral Therapy

Reviewed by Deborah L. Ensler, MD, and J. Stephen Bohan, MD, MS, FACEP, Harvard Affiliated Emergency Medicine Residency; Brigham and Women’s Hospital


Highly active antiretroviral therapy (HAART) initiation for HIV-positive patients is considered when the CD4 count is less than 350 or in those with an AIDS-defining illness, HIV-associated neuropathy, or coinfection with hepatitis B. Usual HAART regimens include two nucleoside-analog reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor.

All antiretroviral medications carry a risk for hepatotoxicity ranging from an asymptomatic increase in transaminase levels to fulminant hepatic failure. Patients who are co-infected with hepatitis B and C are at two to three times the risk of developing chronic liver disease compared with non-HIV infected individuals. Neutropenia and thrombocytopenia are usually due to HIV itself and will improve with HAART. HIV-induced nephropathy is a cause of significant morbidity and mortality and is an indication for initiation of HAART.

Antiretrovirals carry a risk for hematotoxicity, ranging from an asymptomatic increase in transaminase levels to fulminant hepatic failure. Patients who are co-infected with hepatitis B and C are at two to three times the risk of developing chronic liver disease compared with non-HIV infected patients with hepatitis B or C. Coinfection with hepatitis C is also associated with a worse response to HAART. Of note, atazanavir and indinavir are associated with a benign increase in unconjugated bilirubin; this represents an expected and harmless effect and no further evaluation is needed. Renal disease is becoming increasingly common in patients with HIV. Tenofovir has been associated in case reports with renal toxicity, and indinavir has been associated with urolithiasis.

There is an increased risk of cardiovascular disease in HIV-infected patients particularly at a younger age. Protease inhibitor use is associated with hyperlipidemia and truncal obesity as well as an increased risk of insulin resistance without development of frank diabetes mellitus. The risk of dilated cardiomyopathy is generally decreased with the initiation of HAART (except for zidovudine which might predispose individuals to this). Patients on a protease inhibitor and HMG-CoA reductase inhibitor can present with rhabdomyolysis.

Pneumocystis jiroveci (formerly Pneumocystis carinii) is still the most common opportunistic infection in AIDS patients but the incidence has decreased in the post-HAART era. Streptococcus pneumoniae is the most commonly identified cause of pneumonia currently; treatment is the same as for non-HIV infected individuals. HIV is a risk factor for the development of chronic obstructive pulmonary disease, and there is a 0.5% risk for pulmonary hypertension in those on HAART.

A particular complication of HAART seen in the first 8 weeks after its initiation is the immune reconstitution inflammatory syndrome. This syndrome can result in an exacerbation of opportunistic disease or the aggravation of autoimmune illness. These patients can also develop a self-limited rheumatic ailment that causes them to develop sarcoidosis or autoimmune thyroiditis. Treatment is generally supportive including anti-inflammatory medications and corticosteroids; rarely does HAART need to be discontinued.

Post-HAART, CNS opportunistic infections (Toxoplasma gondii and Cryptococcus neoformans) and CNS lymphoma have markedly decreased but progressive multifocal leukoencephalopathy (PML) continues to occur in 1% to 2% of AIDS patients and is treated with HAART. Sensory neuropathies are due to HIV or nucleoside-analog reverse transcriptase inhibitors (didanosine and stavudine); these drugs should be discontinued in the face of this diagnosis.

Anemia is seen in more than 50% of HIV-infected patients; hemolytic anemia can be seen in those taking ribavirin and zidovudine together. Neutropenia and thrombocytopenia are usually due to HIV itself and will improve with HAART. HIV also has a clear association with thrombotic thrombocytopenic purpura. Warfarin interacts with most protease inhibitors, and delavirdine and must be initiated with caution. There is an increased risk of malignancies in HIV-infected patients, particularly Hodgkin lymphoma, anal cancers, and lung cancers.

Up to 5% of patients on abacavir develop a severe hypersensitivity reaction occurring 9 days after initiation of therapy. Treatment is supportive, but abacavir must be discontinued and reintroduction can be fatal.

Highlights

• Hepatotoxicity due to HAART or hepatitis B or C is a significant cause of morbidity in HIV-positive patients.
• HIV-induced nephropathy is a cause of significant morbidity and mortality and is an indication for initiation of HAART.
• The immune reconstitution syndrome is a particular complication of HAART and can result in aggravation of opportunistic infections.
• HAART carries a risk of lactic acidosis, which manifests with nonspecific symptoms and can be life threatening.
• Hematologic/oncologic manifestations of HIV include anemia, neutropenia, thrombocytopenia, Hodgkin lymphoma, anal cancer, and lung cancer.
The Critical Image

A 44-year-old Spanish-speaking man presenting with 5 months of right lower quadrant abdominal pain, worsening in the past 4 days. He is afebrile but is noted to have right lower quadrant tenderness. His WBC count and differential, including neutrophils, lymphocytes, and eosinophils, are normal. A CT scan is obtained to evaluate for appendicitis and urinary calculi.

Images A – D. Sequential axial CT images showing the patient’s small bowel.

- Worldwide, cases of *Ascaris lumbricoides* infection are common, with an estimated prevalence of 1.25 billion cases. In the United States, infection rates are much lower but might still be as high as 4 million cases, concentrated in the southern states. The parasite is endemic in tropical regions worldwide and should be considered as a cause of abdominal pain in immigrants and returning travelers.\(^1\)\(^3\)
- *Ascaris* infections can be complicated by small bowel obstruction, appendicitis, and biliary ductal obstruction.
- Traditionally, intestinal ascariasis is diagnosed with small bowel series, on which worms appear as tubular filling defects within the column of intestinal contrast.
- CT findings of small bowel ascariasis are similar, with tubular filling defects noted when oral contrast is administered. Depending on the orientation of the worm relative to the axial slices, the filling defect can appear circular, elliptical, or linear.\(^4\)\(^5\)
- Unlike appendicitis, for which oral contrast is not essential to CT diagnosis, *Ascaris* infection likely requires enteric contrast to reveal filling defects, although no studies have compared CT without contrast.

The patient was treated with oral anthelmintic agents.

Objectives

On completion of this lesson, you should be able to:

1. Describe the signs and symptoms of high-altitude illnesses.
2. Explain high-altitude physiology and pathophysiology.
3. Discuss the management concepts of high-altitude illnesses.
4. Discuss the medications used for treatment of high-altitude illnesses.
5. Identify factors that increase an individual's risk of developing high-altitude illness.

From the EM Model

6.0 Environmental Disorders
6.4 High-altitude Illness

Critical Decisions in Emergency Medicine

High-Altitude Illness

David S. Bullard, MD, MEd, FACEP, and Jessica E. Sotelo, MD

Lesson 8

Increased interest in and ease of travel to remote areas brings more visitors to areas of high elevation. High-altitude illnesses are not only seen in mountaineers attempting an Everest summit (8,840 m), but also in individuals traveling to comparatively lower altitudes (2,500 m) for recreational, economic, or military purposes. The incidence of acute mountain sickness depends on both the altitude reached and the rate of ascent. In a study of Colorado skiers, the incidence of acute mountain sickness was found to be 25% at altitudes of 1,920 to 2,950 meters (6,300 to 9,700 ft). This incidence increases to 42% when the altitude attained increases only slightly to nearly 3,500 meters (10,000 ft). Although altitude illnesses can prove fatal to mountain climbers and trekkers traveling to extreme altitudes, these illnesses affect millions of tourists traveling to relatively moderate altitudes of less than 10,000 feet.

Case Presentations

Case One

A 45-year-old man presents to an emergency department in the mountains of Colorado with complaints of a headache, fatigue, and nausea. He is a healthy nonsmoker with no medical problems. He arrived at the nearby ski resort yesterday for a family vacation. He notes that he feels a little short of breath and had difficulty sleeping last night. He describes his headache as a mild throbbing tightness over his forehead and temples. He describes some intermittent nausea, but he has not vomited. Vital signs are blood pressure 144/84, pulse rate 96, respiratory rate 24, and oral temperature 37.2°C (99°F). His pulse oximetry is 97% on room air. Breath sounds are clear. There is no jugular venous distention. Heart sounds are normal, without murmur, rub, or gallop. His abdomen is soft, with normal bowel sounds.

Case Two

A 34-year-old woman is with a group attempting a summit on Denali (6,194 m or 20,320 ft). During her trek to High Camp (17,200 ft) she develops a cough and some increased work of breathing. The following morning, she is short of breath, has frothy pink sputum, and is very fatigued. She has no significant past medical history and was in excellent health at the start of the expedition. Vital signs are blood pressure 108/68, pulse rate 122, respiratory rate 32, and oral temperature 37.4°C (99.3°F). Her pulse oximetry is 82%. There is no jugular venous distention. Her lungs have course rales halfway up both lung fields. The heart rate is tachycardic but is without murmurs or rubs.

Case Three

A 36-year-old man climbing Mt. Everest is noted by his climbing party to be behaving abnormally while he is making his way to Everest High Camp at 21,500 ft (6,550 m). In the
morning, he seemed to be quieter than usual and was complaining of a headache. After a couple of hours, he was slurring his speech and having difficulty walking. Vital signs are blood pressure 144/88, pulse rate 116, respiratory rate 24, and an oral temperature 36.8°C (98.2°F). Breath sounds are clear. There is no jugular venous distention. Heart sounds are tachycardic but normal, without murmur, rub, or gallop. His abdomen is soft, with normal bowel sounds. He is slow to answer questions, is oriented to person only, can move all extremities spontaneously, but is uncoordinated in his movement and speech. His pupils are symmetric, midrange, and sluggishly reactive.

Altitude Physiology and Pathophysiology

Although the concentration of oxygen in air remains constant, the degree of hypoxia experienced at a given altitude is proportional to the decreased barometric pressure present at that altitude. A reduced partial pressure of oxygen of ambient air results in a decreased inspired partial pressure of oxygen, decreased alveolar \( P_{O_2} \) and decreased arterial blood oxygen. For example, at the summit of Mount Everest (8,850 m), the partial pressure of oxygen is about one third of the pressure at sea level.\(^3\) Oxygen saturations measured in individuals at this altitude range between 58% and 75%.\(^7\) As individuals ascend to higher altitudes, the body begins to experience the challenge of hypoxia. Weather patterns that decrease the barometric pressure, respiratory depressants, exertion, basal temperature, and certain medical problems can exaggerate the hypoxic effects of altitude. These variables should be considered when examining the acute syndromes of high altitude: acute mountain sickness, high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE).\(^3\)

The driving force of the physiologic derangements seen in altitude illnesses is hypoxia. Hypoxia elicits neurohumoral and hemodynamic responses that result in overperfusion of microvascular beds, elevated hydrostatic capillary pressure, capillary leakage, and consequent edema.\(^5\) These responses are the direct causes of acute mountain sickness, HAPE, and HACE.

Cerebral Syndromes

Acute Mountain Sickness

Hypoxia is the initiating cause for altitude illnesses. This hypoxic effect on the brain results in a continuum of disease ranging from mild acute mountain sickness to HACE. The Lake Louise score was developed as a research tool to assess the severity of altitude illnesses.\(^9\)

Acute mountain sickness is defined by the presence of a headache in the setting of a recent gain in altitude and at least one of the following symptoms: anorexia, nausea, vomiting, fatigue, weakness, dizziness, lightheadedness, and difficulty sleeping. These vague symptoms of acute mountain sickness are often described as resembling a hangover. In the early stages of acute mountain sickness physical findings are often absent, symptoms are vague, and practitioners should maintain a broad differential before diagnosing a patient with an altitude sickness. The differential diagnosis includes exhaustion, carbon monoxide poisoning, migraines, transient ischemic events, hypothermia, drugs, psychiatric problems, dehydration, viral syndromes, meningitis, encephalitis, and pneumonia.

CRITICAL DECISION

What therapies are effective in treating acute mountain sickness?

As with much of modern medicine, the best treatment of illness is prevention (Table 1). Altitude illnesses are no exception, and acclimatizing individuals to participate in activities at altitude is a good start for the prevention of acute mountain sickness, HAPE, and HACE. Gradual ascent is the first axiom for acclimatization and prevention of altitude illnesses. The guidelines recommend that once above 2,500 meters, a climber’s sleeping altitude should not increase by more than 600 meters in 24 hours. It is also advised that climbers add an additional day of acclimatization for every 600 to 1,200 meters gained in altitude above 2,500 meters. Avoiding alcohol and over-exertion, staying hydrated, minimizing cold stress, and consuming a carbohydrate-rich diet further aid in the acclimatization to altitude. Early symptoms of altitude illness must be recognized and treated with descent to lower elevations whenever possible.

<table>
<thead>
<tr>
<th>Critical Decisions</th>
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<tr>
<td>• What therapies are effective in treating acute mountain sickness?</td>
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<tr>
<td>• What factors influence the incidence of HAPE?</td>
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<td>• What therapies are effective in treating HAPE?</td>
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<table>
<thead>
<tr>
<th>TABLE 1. Treatment of acute mountain sickness</th>
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<tr>
<td>Prevention of illness</td>
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<tr>
<td>Acclimatize to altitude</td>
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<tr>
<td>Avoid alcohol</td>
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<tr>
<td>Hydrate well</td>
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<tr>
<td>Avoid cold</td>
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<tr>
<td>Take in high carbohydrate diet</td>
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<tr>
<td>Descent to lower altitude</td>
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<tr>
<td>Oxygen</td>
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<tr>
<td>Symptomatic treatment (NSAIDs, antiemetics, etc.)</td>
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<tr>
<td>Acetazolamide</td>
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<td>Dexamethasone</td>
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December 2009 • Volume 24 • Number 4
Because hypoxia is the primary cause of high-altitude illnesses, oxygen is the logical first-line treatment of these illnesses. If a victim is able to be evacuated, then descent to lower altitudes with increased oxygen concentration is always recommended. Often a descent of only 500 to 1,000 meters is all that is necessary for patient improvement. Environmental conditions, other injuries, victim incapacitation, or other logistical issues may, however, prevent or delay descent. If medical oxygen is available, administering it to the patient is helpful. Larger expeditions to altitude often include a portable hyperbaric chamber as part of their medical kit. These lightweight, fabric-coated bags are large enough to hold an adult patient. When pressurized with a foot-pump, these chambers are capable of being inflated to 200 mm Hg above ambient atmospheric pressure; this simulates a descent of about 1,500 meters.

Mild acute mountain sickness may be treated symptomatically. Headaches can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs); for patients with contraindications, allergies to these drugs, or severe gastrointestinal upset from acute mountain sickness, acetaminophen may be used instead. The anorexia, nausea, and vomiting caused by acute mountain sickness may be managed with antiemetics. Newer drugs such as ondansetron offer fewer side effects and come in easier-to-ingest forms such as oral disintegrating tablets. Older drugs such as prochlorperazine and promethazine are likely to be more accessible on overseas treks and to be less expensive. Prochlorperazine might have additional utility in acute mountain sickness treatment because it acts as a respiratory stimulant, augmenting the hypoxic ventilatory response at high altitude.

Acetazolamide expedites acclimatization and has become the mainstay of drug therapy for both treatment and prophylaxis of acute mountain sickness. By inhibiting carbonic anhydrase, this drug causes the kidneys to excrete bicarbonate. Physiologically, this decreases the systemic pH and thus stimulates ventilation. By acting as a respiratory stimulant, $P_aO_2$ is increased. Additionally, this medication may decrease cerebral edema by stimulating diuresis and decrease intracranial pressures by slowing cerebrospinal fluid production. The recommended dose is controversial; in the literature, dosages vary from 750 mg daily (250 mg, 3 times a day),7 to 500 mg daily (as a sustained release product),9 to smaller doses of 250 mg daily (125 mg, twice a day).9 The side effects of acetazolamide are generally mild; a change in the taste of carbonated beverages and paresthesias in fingers and toes are the most common. Acetazolamide contains a sulfa moiety, so caution is needed when giving this drug to patients with sulfa allergies.

Dexamethasone has been shown to treat and prevent acute mountain sickness. It is thought to act primarily by stopping the capillary leak across the blood-brain barrier, thus reducing cerebral edema. Unlike acetazolamide, dexamethasone does not promote acclimatization and should be continued for several days once started. Because of this, dexamethasone should be reserved for treatment of acute mountain sickness rather than prophylaxis. Suggested treatment doses vary in the literature, but a loading dose of 8 mg followed by 4 mg every 6 hours is generally accepted.5,10 The medication may be given orally, intramuscularly, or intravenously. Using dexamethasone as preventive therapy for acute mountain sickness may be considered as preventive therapy for acute mountain sickness. If a descent to lower altitudes with increased oxygen concentration is not possible, acetazolamide and acetazolamide can help. There are no prospective, randomized studies on the treatment of HACE. Dexamethasone is often used as the mainstay of treatment for patients every 8 hours12 or 4 mg twice a day or 2 mg 4 times a day.5

**High-Altitude Cerebral Edema**

Acute mountain sickness is a continuum of disease with progression from mild to severe symptoms. The endpoint of these neurologic sequelae is HACE. HACE is diagnosed in patients with symptoms of acute mountain sickness or HAPE that progress to ataxia and a change in consciousness. The incidence of HACE depends on the altitude reached and the time given to acclimatize. Cases of HACE among climbers of Denali, in Alaska, are 2% to 3%, with climbers sleeping at altitudes ranging from 9,800 to 17,400 feet. (3,000 to 5,300 m).13 A study of soldiers rapidly transported to altitudes of 3,350 to 5,000 meters reported an incidence of HACE of 1.2%.14

In the field, HACE remains a clinical diagnosis. Patients with symptoms of acute mountain sickness progress to have ataxia and a change in consciousness. In the clinical setting, imaging studies can be helpful as well. Although computed tomography scanning of the brain does not confirm the diagnosis of HACE, it can be helpful in excluding other HACE mimics such as subdural hematoma, subarachnoid hemorrhage, and occult intracranial neoplasm. Magnetic resonance imaging (MRI) of the brain can show specific changes from HACE. These patients may show an increase in T2 signal in brain white matter on MRI.

**CRITICAL DECISION**

**What therapies can be used to treat HACE?**

The cornerstone of the treatment of HACE is descent to lower elevation as soon as possible. Additionally, supportive care with oxygen, analgesics, antiemetics, and acetazolamide can help. There are no prospective, randomized studies on the treatment of HACE. Dexamethasone is often used as the mainstay of treatment for patients...
with HACE. The drug acts by reducing brain edema. The general consensus on the recommended dose of dexamethasone for HACE is an 8-mg loading dose followed by 4 mg every 6 hours. For patients in extremis with HACE, therapy with mannitol, glycerol, and furosemide have been used, but there are no well-designed studies to evaluate the usefulness of these agents.

**Pulmonary Syndrome**

**High-Altitude Pulmonary Edema**

HAPE typically occurs at altitudes above 2,400 meters and accounts for most of the mortality related to high-altitude illness. The Lake Louise consensus definition of HAPE requires at least two of the following symptoms and two signs. Symptoms are dyspnea at rest, cough, congestion, weakness, decreased exertion performance, and chest tightness; signs are crackles or wheezing, central cyanosis, tachypnea, and tachycardia. Early diagnosis of HAPE is critical, because the condition has a high mortality rate.

HAPE usually progresses in hours to days, but usually manifests by 4 days after arriving at high altitude. Individuals with HAPE can have a cough with blood-tinged fluid, audible gurgling with respirations, or obvious respiratory distress. Low readings on a portable pulse oximeter can also be a clue to diagnosing HAPE in the field.

A chest radiograph, if available, can be useful in making the diagnosis. The appearance of patchy infiltrates on chest radiograph is typical of HAPE. Because the development of HAPE is secondary to nonuniform pulmonary vasoconstriction, distribution of the infiltrates is irregular. However, infiltrates seem to develop most reliably in the right middle lobe, and rales in this distribution and low arterial oxygen saturation by pulse oximeter are suggestive of HAPE. As pathology worsens, infiltrates become bilateral in the midlunng fields.

If an individual is developing symptoms consistent with HAPE beyond 4 days after arrival at altitude, alternative diagnoses such as pulmonary embolism, pneumothorax, congestive heart failure, and pneumonia should be considered. The presence of an S3 on cardiac examination should direct the examiner to cardiogenic causes of pulmonary edema, because an S3 will not be heard in HAPE.

**CRITICAL DECISION**

**What factors influence the incidence of HAPE?**

The incidence of HAPE is generally higher in the winter months because of ski tourism. The likelihood of these travelers and vacationers developing acute mountain sickness and HAPE is affected by many variables: rate of ascent, maximum altitude attained, duration at high altitude, preexisting illness or medications, the sleeping altitude, the barometric pressure, physical effort, and preacclimatization.

The inciting event in the pathogenesis of HAPE is thought to be nonuniform pulmonary vasoconstriction in response to hypoxia. This event results in increased pulmonary capillary stress and failure in the context of a normal left atrial pressure. Pulmonary capillary failure leads to the interstitial edema and the alveolar congestion that commonly characterize altitude illness. Edema increases the arterial-alveolar oxygen difference and worsens hypoxia.

In the clinical setting, perhaps the most reliable predictor that an individual will develop HAPE is a history of having HAPE or acute mountain sickness in the past. HAPE-susceptible individuals have an exaggerated increase in pulmonary artery pressure with alveolar hypoxia. At altitude, a HAPE-susceptible individual would have increased pulmonary artery pressure and more fluid extravasation and develop pulmonary edema more rapidly than a non-susceptible counterpart. More specifically, data suggest that an individual’s predilection for developing HAPE is affected by many factors including increased sympathetic activity and lower endogenous nitric oxide production. Additionally, specific genotypes of the angiotensin converting enzyme appear to be involved in the efficiency of oxygen utilization and confer improved performance at altitude. Impaired sodium transport in the alveolar epithelial cells is also thought to contribute to development of alveolar congestion characteristic of HAPE. Therefore individuals with defects in sodium-dependent transepithelial transport mechanisms of type II alveolar cells could be predisposed to alveolar congestion and the development of HAPE.

Researchers continue to investigate and identify various genotypes that increase an individual’s susceptibility to HAPE. For the clinician, it is simply important to know that an individual can have a genetic predilection to the development of HAPE or, more generally, high-altitude illness. Eliciting a history of high-altitude illness from a patient who is preparing to travel to altitude could prompt a clinician to develop a more aggressive prophylactic treatment plan for acute mountain sickness and HAPE.

**CRITICAL DECISION**

**What therapies are effective in treating high-altitude pulmonary edema?**

Most cases of HAPE respond promptly to increased pressure of inspired oxygen through descent to lower altitude. Increasing $P_{O_2}$ reduces pulmonary artery pressures and improves hypoxia. Descent to a lower altitude increases the $P_{O_2}$ and is, thus, the most definitive treatment for high-altitude illness. However, if descent is not possible, it can be simulated with supplemental oxygen (4 to 6 L/min) delivered through nasal cannula...
or expiratory positive airway pressure or hyperbaric therapy via a portable hyperbaric chamber until descent is possible.

In the field, patients should be kept warm and allowed to rest, because exertion and cold stress contribute to high pulmonary artery pressures. Patients who wish to remain at altitude or are physically unable to descend usually improve with 2 to 3 days of rest and supplemental oxygen. In the setting of isolated HAPE, patients may reattempt ascent 2 to 3 days after complete resolution of symptoms. Gradual ascent, no more than 600 meters per day, will allow for acclimatization and reduce the patient’s likelihood of developing HAPE.

When descent or supplemental oxygen is not an option, medical therapy becomes essential. Medical therapies in the management of HAPE target the underlying pathophysiology in the development of HAPE—namely pulmonary vasoconstriction and alveolar congestion.

Multiple selective pulmonary vasodilating agents are used in the treatment of HAPE. Nifedipine, 10 mg initially and then 30 mg of extended-release formulation every 12 to 24 hours, is a recommended dose for the prevention of HAPE. Twenty to thirty milligrams of extended-release formulation every 12 hours are recommended for prevention of HAPE in individuals with repeated HAPE episodes.

Sildenafil, a selective phosphodiesterase-5 inhibitor, has been shown to reduce pulmonary vascular resistance and act as a selective pulmonary artery vasodilator while maintaining systemic arterial pressure. Faoro showed that one potential advantage of sildenafil over nifedipine is that sildenafil maintains systemic arterial pressure and may provide an additional benefit when the goal is to maximize oxygenation.

Other agents that induce pulmonary capillary vasodilation such as nitric oxide and endothelin-1 are also being considered in the treatment of pulmonary hypertension associated with HAPE; however no recommendations for their routine use in the treatment of HAPE have been made.

Maintaining sodium transport within the alveolar epithelial cell is another target of drug therapies in the treatment of HAPE. Inhaled β-agonists might be beneficial in the treatment of HAPE by stimulating alveolar sodium transport out of the alveoli. A recommended dose of salmeterol is 125 micrograms every 12 hours. Other inhaled β-agonists may be used, but the long duration of action and worldwide availability of salmeterol are advantageous to climbers.

Furosemide and dexamethasone, choice agents in the treatment of HACE, have generally not been recommended by experts to treat HAPE, unless HACE is also present. However, a small randomized controlled trial suggested that dexamethasone decreased the incidence of HAPE in subjects with a history of HAPE when taken prophylactically. The authors proposed that the effectiveness of the drug in reducing incidence of HAPE when used prophylactically may be secondary to effects requiring alterations in genetic expression. The proposed mechanism by which dexamethasone slows the development of HAPE is by stimulating production of vasodilatory substances such as nitric oxide within the alveolar epithelial cells. Additionally, dexamethasone stimulates alveolar sodium and water resorption from the alveoli thereby decreasing alveolar congestion.

Like dexamethasone, acetazolamide is widely used in the treatment of acute mountain sickness and HACE and may also help in the treatment of HAPE, because it stimulates diuresis. However, it also stimulates ventilation and could worsen dyspnea.

**Pearls**
- Ascend to altitude slowly to allow acclimatization.
- Maintain a broad differential diagnosis.
- A history of high-altitude illness is the best predictor of developing high-altitude illness in the future.
- The first-line treatment for altitude illnesses is descent to lower altitude.

**Pitfalls**
- Continuing ascent to altitude when symptoms of altitude sickness are present.
- Failing to recognize subtle symptoms as acute mountain sickness, HAPE, or HACE.
- Failing to maintain a broad differential diagnosis early with patients presenting with symptoms suggestive of altitude illnesses.

**Case Resolutions**

**Case One**

This patient was diagnosed with acute mountain sickness. He received an antiemetic, a liter of normal saline, and acetaminophen in the emergency department and had resolution of his nausea and improvement in his headache. He was discharged and instructed to stay hydrated, take over-the-counter NSAIDs for his headache, avoid alcohol, and to get regular sleep for the next couple of days. Two days later, his symptoms completely resolved, and he enjoyed the remainder of his vacation.

**Case Two**

This patient’s climbing party administered supplemental oxygen, nifedipine, and sildenafil. They were able to descend with the patient about 1,500 meters with some improvement in her respiration. The party radioed for a helicopter evacuation, but
darkness and a storm made this too dangerous. The following morning, the patient felt better but still had difficulty breathing. With help, she was able to descend another 1,200 meters to a more suitable landing site and was evacuated by Army helicopter to an emergency department. Her chest radiograph was consistent with a diagnosis of HAPE. She recovered uneventfully 2 days after her descent.

**Case Three**

Recognizing the emergency as probable HACE, the medic in the party administered supplemental oxygen and dexamethasone to the patient. The party turned around and was able to help this climber down to the medical tent at Everest Base Camp at 17,500 feet (5,300 m). Over the next 24 hours, he clinically improved, and his neurologic function returned to baseline. He was unable to summit this season, but he was able to walk out under his own power and return home.

**Summary**

As the access to high-altitude destinations and the popularity of visiting them increases, clinicians must become familiar with the physiologic challenges of high altitude and the treatment and prevention of high-altitude illness in order to effectively manage affected travelers and adventurers. These conditions often require a clinical diagnosis and early field management for successful outcomes. The mainstays of treatment are descent to lower elevation, supportive care, and a few medications to manage the altered physiology present in patients venturing to altitude.

**References**

Altitude illness, acute mountain sickness, high-altitude cerebral edema, and high altitude pulmonary edema are related disorders associated with rapid ascent to elevations over 10,000 feet in non-acclimatized patients. Symptoms include headache, sleep disturbance, fatigue, nausea and vomiting, lightheadedness, ataxia, and, in more severe cases, stupor, coma, and death. Acetazolamide is used to facilitate acclimatization and reduce the symptoms related to altitude illness. Its use as prophylaxis to prevent altitude illness is typically reserved for those individuals with a history of severe altitude illness or those ascending at a rate greater than 600 meters per day. It is not otherwise recommended as routine prophylaxis.

### Acetazolamide

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Carbonic anhydrase inhibitor causing diuresis and excretion of bicarbonate in the urine, lowering pH and stimulating respiratory drive, reducing cerebral edema and pulmonary edema altitude sickness.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Prevention and reduction of symptoms related to pulmonary edema and cerebral edema altitude sickness.</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>125 mg orally twice daily beginning 24 hours before ascent and continuing until 48 hours after peak altitude or descent or up to 500 mg orally twice daily for rapid or extreme ascents</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>Dehydration, hypokalemia, paresthesias, dysgeusia, and metabolic acidosis</td>
</tr>
<tr>
<td><strong>Approximate cost</strong></td>
<td>$1.64 per dose</td>
</tr>
<tr>
<td><strong>Contraindication/Precautions</strong></td>
<td>Renal disease</td>
</tr>
<tr>
<td></td>
<td>Pregnancy category C</td>
</tr>
</tbody>
</table>

*Cost data provided by Summa Health System Pharmacy*

**Feature Editor:** Michael S. Beeson, MD, MBA, FACEP, and Amy K. Niertit, MD
CME Questions

Qualified, paid subscribers to Critical Decisions in Emergency Medicine may receive CME certificates for up to 5 ACEP Category I credits, 5 AMA PRA Category I Credits™, and 5 AOA Category 2-B credits for answering the following questions. To receive your certificate, go to www.acep.org/criticaldecisionstesting and submit your answers online. You will immediately receive your score and printable CME certificate. You may submit the answers to these questions at any time within 3 years of the publication date. You will be given appropriate credit for all tests you complete and submit within this time. Answers to this month’s questions will be published in next month’s issue.

1. Which of the following clinical presentations should prompt initial respiratory isolation?
   A. 22-year-old febrile traveler returning from Oklahoma with macular rash to his wrists
   B. 30-year-old adventure traveler with fever and hemoptysis
   C. 40-year-old missionary returning from Africa with fever, pallor, and mild jaundice
   D. 60-year-old traveler with fever and urinary frequency
   E. 70-year-old traveler returning from a Mexican sea resort with fever and a nonproductive cough

2. Which of the following is true?
   A. antibiotics should always be withheld when a sick febrile traveler is evaluated until a definite bacterial causative agent is isolated
   B. a febrile traveler returning from Africa with sore throat and mild diarrhea can be safely discharged without any workup
   C. normothermia at admission to the emergency department rules out serious febrile illness
   D. patients presenting with fever and hemoptysis should initially be isolated
   E. tropical disease does not present as or mimic sepsis

3. Which of the following statements is true?
   A. ceftriaxone and ciprofloxacin are antibiotics of choice in suspected rickettsial infections
   B. patients with Rocky Mountain spotted fever commonly report an eschar and lymphadenopathy preceding fever
   C. prompt administration of appropriate antibiotics drastically reduces mortality in rickettsial infections
   D. rickettsial infections share the fecal-oral mode of transmission
   E. there is no rickettsial infection endemic to the United States

4. Which of the following statements is true?
   A. antibiotics are not indicated in the treatment of leptospirosis
   B. doxycycline is the first-line choice for treatment of severe leptospirosis
   C. leptospirosis affects humans only, there is no animal reservoir
   D. leptospirosis does not occur in the United States
   E. severe pulmonary complications can occur in Weil disease

5. Which of the following is correct?
   A. only the pulmonic form of plague is life-threatening
   B. patients with suspected rickettsial infections should be isolated
   C. streptomycin is recommended for the treatment of tularemia
   D. tularemia is uncommon in the northern hemisphere
   E. tularemia is very contagious

6. Which of the following is correct?
   A. absence of skin lesions rules out tularemia
   B. plague can be spread via mosquito bites
   C. plague is endemic in Australian mammals
   D. streptomycin and gentamicin are the first-line agents in treatment of plague
   E. tularemia affects humans only

7. Which of the following is correct?
   A. dengue fever is not a consideration if one did not go to a rural area while traveling
   B. fever in a returning traveler means infection
   C. most rickettsial infections are spread by ticks
   D. patients with sleeping sickness should be isolated
   E. patients with suspected dengue fever should be given broad-spectrum antibiotics

8. Which of the following is correct?
   A. sleeping sickness is common among travelers returning from African game parks
   B. sleeping sickness is common in the Amazon
   C. sleeping sickness is spread by mosquito bites
   D. sleeping sickness is spread via contaminated food
   E. sleeping sickness treatment is difficult and available antibiotics may be toxic

9. Which of the following is correct?
   A. Hantavirus infections are only described in the southwestern United States
   B. Hantavirus pulmonary syndrome’s incubation period is always less than 1 week
   C. Sin Nombre infection starts with a nonspecific rash
   D. Sin Nombre virus causes noncardiogenic pulmonary edema
   E. Sin Nombre virus is primarily spread by ticks

10. Which of the following is correct?
    A. the fever in typhoid fever is persistent and might not peak until several weeks into the illness
    B. intestinal perforation is a common, early complication in typhoid fever
    C. presence of rash in a febrile patient virtually rules out typhoid fever
    D. typhoid fever is spread by fleas
    E. typhoid fever presents with severe diarrhea
11. Which of the following factors is most strongly associated with the development of high-altitude pulmonary edema (HAPE)?
   A. age under 35
   B. comorbidities
   C. diet
   D. prior episode of high-altitude illness
   E. sex

12. Which of the following best explains the mechanism of action of acetazolamide in improving acute mountain sickness symptoms?
   A. decreases vasoconstriction of pulmonary vasculature
   B. expedites acclimatization
   C. increases urination
   D. prevents free radical accumulation with symptoms of acute mountain sickness
   E. worsens dyspnea

13. Which of the following medications used for high-altitude illness should be avoided in patients with a history of severe allergic reactions to sulfonamides?
   A. acetazolamide
   B. dexamethasone
   C. nifedipine
   D. salmeterol
   E. sildenafil

14. Which measure is useful in the prevention of high-altitude illness?
   A. drinking alcohol
   B. minimizing cold stress
   C. ondansetron
   D. pre-ascent physical training
   E. rapid ascent of 1,000 meters per day

15. High-altitude cerebral edema (HACE) is characterized by:
   A. ataxia or altered mental status in an individual with acute mountain sickness or HAPE
   B. cerebral infarction
   C. hyperpyrexia
   D. proptosis
   E. retinal detachment

16. Which of the following is true regarding HAPE?
   A. early diagnosis is critical to a good outcome
   B. it always has a low mortality rate
   C. onset of illness is usually 5 to 7 days after arrival at maximum altitude
   D. pulmonary vasoconstriction is uniform throughout the pulmonary tree
   E. typically occurs at elevations between 1,800 and 2,000 meters

17. What is the mechanism of action of sildenafil in the treatment of HAPE?
   A. binds to free radicals
   B. decreases pulmonary vascular resistance
   C. elevates blood pressure
   D. improves alveolar clearance
   E. reduces formation of inflammatory cytokines

18. Six days after his arrival in Flagstaff, AZ (~7,000 ft), a patient presents with dyspnea at rest and cough and has bibasilar crackles and tachycardia on examination. What is the least likely diagnosis?
   A. congestive heart failure
   B. HAPE
   C. pneumonia
   D. pneumothorax
   E. pulmonary embolism

19. What is the driving force behind the physiological derangements seen in altitude illness?
   A. alveolar congestion
   B. failure of chemoprophylaxis
   C. hypoxia
   D. increased pulmonary capillary vasoconstriction
   E. lack of physical conditioning

20. The presence of which physical finding makes a diagnosis of HAPE unlikely?
   A. basilar rales
   B. cough
   C. fever
   D. hypoxia
   E. S3 heart sound
Sinus tachycardia with atrioventricular (AV) dissociation and third-degree AV block, AV junctional rhythm, rate 41, left bundle-branch block (LBBB), nonspecific T-wave abnormality. Independent atrial (sinus rate 130) and ventricular activity exist, indicating AV dissociation. There do not appear to be any P waves conducted to the ventricle, indicating third-degree (complete) heart block. The wide QRS complexes can suggest a ventricular rhythm originating from within the ventricle itself, or they could represent an AV junctional rhythm conducted to the ventricles with an LBBB. The rate of 41 is consistent with either a ventricular rhythm or an AV junctional rhythm. The distinction is difficult, but a previous ECG was obtained in this case and showed evidence of a prior LBBB with similar QRS morphology.

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