Infectious Diseases at High Altitude

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ABSTRACT  Travel to elevations above 2,500 m is an increasingly common activity undertaken by a diverse population of individuals. These may be trekkers, climbers, miners in high-altitude sites in South America, and more recently, soldiers deployed for high-altitude duty in remote areas of the world. What is also being increasingly recognized is the plight of the millions of pilgrims, many with comorbidities, who annually ascend to high-altitude sacred areas. There are also 400 million people who reside permanently in high mountain ranges, which cover one-fifth of the Earth’s surface. Many of these high-altitude areas are in developing countries, for example, the Himalayan range in South Asia. Although high-altitude areas may not harbor any specific infectious disease agents, it is important to know about the pathogens encountered in the mountains to be better able to help both the ill sojourner and the native high-altitude dweller. Often the same pathogens prevalent in the surrounding lowlands are found at high altitude, but various factors such as immunomodulation, hypoxia, poor physiological adaptation, and harsh environmental stressors at high altitude may enhance susceptibility to these pathogens. Against this background, various gastrointestinal, respiratory, dermatological, neurological, and other infections encountered at high altitude are discussed.

INTRODUCTION

High mountain ranges cover approximately one-fifth of the earth’s surface, and approximately 400 million people permanently reside in these locations. Travel to elevations above 2,500 m is an increasingly common activity undertaken by a diverse population of individuals. These may be trekkers, climbers, miners in high-altitude sites in South America, and more recently, soldiers deployed for high-altitude duty in remote areas of the world. What is also being increasingly recognized is the plight of the millions of pilgrims, many with comorbidities, who annually ascend to high-altitude sacred areas.

Some high-altitude destinations include Cuzco, Peru (11,150 ft; 3,400 m), Leh, Ladakh, India (3,500 m, 11,500 ft), La Paz, Bolivia (12,400 ft; 3,780 m), Everest Base Camp in Nepal (17,598 ft; 5,364 m), Kilimanjaro in Tanzania (19,341 ft; 5,895 m), and Kailash Mansarovar (5,000 m), a high-altitude sacred site in Tibet. Many of the high mountains are located in developing countries, and travel itineraries frequently include transit through airports and cities in lowland areas. In these lowland cities, the traveler may be exposed to infectious agents whose symptoms manifest during their ascent into the mountains. Other mountains exist in developed countries where infections may be less common, but the stress on the human physiological reserve is the same.

At high altitude, the body is exposed to a lower barometric pressure, resulting in a decreased partial pressure of oxygen (hypoxia), increased ultraviolet (UV) solar radiation, less humidity, and a higher potential for weather extremes. These harsh environmental conditions interact in a complex way to alter the host immune response, leading to a higher susceptibility to infection. Crowding, poor sanitation, decreased availability of food and potable water, inadequate facilities for hand washing and personal hygiene, poverty, and distance from medical care all contribute to the spread of disease.

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Further, prolonged moderate to heavy physical activity and limited or inadequate sleep also lower the ability of an individual to resist infection. The risk of contracting an infection varies based on the prevalence of the specific pathogens, the immunocompetence of the individual, and the length of exposure. There are few published studies on infectious diseases occurring at high altitude. The Himalayas are among the world’s tallest peaks and exist in some of the most impoverished countries of the globe (Fig. 1). This remote, less-developed mountain range is an excellent example of the complexities associated with infectious disease and high-altitude medicine (Table 1).

**IMMUNE SUPPRESSION AT HIGH ALTITUDE**

It has been observed that infections are more common at high altitude, slower to resolve, and often resistant to antibiotics. Hypoxia is a stress that affects both the innate and adaptive immune systems. Hypoxia-inducible factors are transcription factors that modulate this immune response through gene regulation. The innate immune system, comprised of neutrophils, macrophages, mast cells, dendritic cells, and natural killer cells, evolved from single-cell and early multicellular organisms found in the hypoxic environment that predated photosynthesizing plants one to two billion years ago. As a result, these cells appear to function well in hypoxia.

The adaptive immune system, also known as the acquired immune system, is triggered when a pathogen evades the innate immune system and is comprised of T and B lymphocytes. T lymphocytes comprise the cell-mediated response where helper T cells, or CD4 cells, signal immune cells including the cytotoxic T cells, or CD8 cells, to destroy pathogens by apoptosis of infected cells. The B lymphocytes generate antibodies against specific antigens and play a large role in the humoral immune response. Hypoxia alters the normal immune hemostasis. The function of T lymphocytes is impaired, their overall numbers are decreased, and there is an alteration in their subset ratios; the CD4 cell subset is decreased, while the CD8 cell counts remain the same. In contrast, B lymphocytes do not appear to be impaired.

Overall, these finding suggest that the innate immune system functions well in hypoxic environments, and the ability to resist viral infections therefore may remain intact. Conversely, while B lymphocyte functions are preserved, T lymphocyte functions are impaired, leading to an increased susceptibility to bacterial infection as...
compared to a normoxic environment. A suppurative hand wound, for example, may not respond with only antibiotics until descent to a lower altitude is carried out. In a practical sense impaired immunity at high altitude must be anticipated when dealing with burns, trauma, and bacterial infections. Important limitations of studying immune status at high altitude are the many confounding factors (cold, poverty, UV radiation) which may influence the outcome of diseases.

### RESPIRATORY INFECTIONS

Respiratory symptoms are common at high altitude and may predispose a traveler to develop acute mountain sickness. Hypoxia stimulates pulmonary vasoconstriction, leading to an increased pulmonary permeability and pulmonary congestion. Pulmonary defense mechanisms are further reduced by bronchospasm, nasal obstruction, and impaired ciliary activity. Cold, low humidity, crowded conditions, and air pollution from traditional stoves support the general consensus that most infections are worse at high altitude.

Respiratory infections can mimic high-altitude pulmonary edema (HAPE), and a low threshold for descent should be considered in a patient with presumed bacterial pneumonia, in addition to administering antibiotics (Fig. 2). Additionally, it is theorized that respiratory infections may increase hypoxemia secondary to an impaired diffusion capacity and may induce HAPE.

In general, the virulence and transmissibility of *Mycobacterium tuberculosis* is lowered with hypoxia, UV radiation, and lower humidity, explaining why alpine sanatoriums were popular before the advent of antituberculosis drugs. However, current conditions of overcrowding and poverty now contribute to an increased prevalence of tuberculosis in high-altitude populations such as in the Himalayas. Cough and hemoptysis in a local high-altitude resident in South Asia should prompt investigation for tuberculosis among other diseases such as mitral stenosis due to rheumatic heart disease.

### TABLE 1 Infectious risks at high altitude<sup>a</sup>

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Infection(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Enteropathogenic bacteria (<em>Escherichia coli, Salmonella, Shigella, Campylobacter</em>), viruses, protozoa (<em>Giardia, Cryptosporidium, Entamoeba, Cyclospora</em>), typhoid fever, hepatitis, abdominal tuberculosis in local people</td>
</tr>
<tr>
<td>Neurological</td>
<td>Rabies, Japanese encephalitis, bacterial meningitis</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Sinusitis, upper respiratory tract infection, bronchitis, pneumonitis, influenza, tuberculosis</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Pyoderma, furuncle, carbuncle, persistent wound infections, cellulitis, lymphangitis, herpes simplex, trauma and frostbite infections, scabies, lice, varicella</td>
</tr>
<tr>
<td>Urological and gynecological</td>
<td>Sexually transmitted diseases, genital candidiasis, urinary tract infections</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Malaria, dengue, typhoid fever, typhus, leptospirosis, dental caries, bone infections</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adapted from Basnyat B et al. (2001), with permission.

### FIGURE 2A,B

High-altitude evacuation of a Nepalese porter in the Himalayas by the Himalayan Rescue Association in Pheriche, Nepal. This patient was diagnosed with pneumonia complicated by HAPE. He was febrile, tachycardic to 149, and his oxygen saturation was 67% without supplemental oxygen. Photos by Jennifer M. Starling. doi:10.1128/microbiolspec.IOL5-0006-2015.f2
GASTROINTESTINAL INFECTIONS
Diarrheal infections are the leading cause of illness in travelers. One study in the Himalayas found that 14% of a cohort of trekkers developed gastroenteritis, and another study reported that severe diarrheal diseases contribute to 10% of all helicopter evacuations in the Nepal Himalayas. While no systematic surveys have examined the prevalence and epidemiology of enteric pathogens encountered at high altitude, the most common causes of diarrhea are presumed to be enteropathogenic bacteria, *Giardia lamblia*, *Entamoeba histolytica*, and *Cyclospora cayetanensis*. The five most common enteropathogenic bacteria are *Campylobacter*, enterotoxigenic *Escherichia coli*, *Shigella*, enteropathogenic *E. coli*, and *Salmonella*. Ciprofloxacin is effective against most causes of traveler’s diarrhea with the exception of that caused by *Campylobacter*. *Campylobacter* isolates cause as much as 20% of bacterial diarrhea in South Asia, and is up to 71% resistant to fluoroquinolones. Azithromycin is recommended for treatment of diarrhea that does not respond to ciprofloxacin. Oral fluid intake should be encouraged, and attention should be directed toward potential electrolyte loss. Metronidazole or tinidazole can be used to treat *G. lamblia* and symptomatic *E. histolytica*. The only effective treatment for cyclosporiasis is trimethoprim-sulfamethoxazole.

While travelers rarely acquire a sufficient inoculum to develop systemic disease, local populations are frequently diagnosed with parasitic worm infections. These infections include the giant human roundworm, *Ascaris lumbricoides*, the whipworm, *Trichuris trichiura*, the hookworms *Ancylostoma duodenale* and *Necator americanus*, and the tapeworms *Taenia solium* and *Echinococcus*. In communities in Bolivia, at 3,800 to 4,200 m, *A. lumbricoides* and *T. trichiura* were detected with prevalence rates up to 28 and 24%, respectively. School-age children are at highest risk and may suffer from nutritional deficits and cognitive impairments. Because stool analysis is not always available in resource-constrained mountainous settings, empiric treatment for abdominal bloating or pain with albendazole or mebendazole is acceptable. Additionally, in Peru, one study found the prevalence and severity of gastritis and *Helicobacter pylori*-associated gastric lesions to be greater in patients living at high altitude compared to coastal or jungle communities.

HEPATOBILIARY INFECTIONS
Hepatitis A, B, C, and E virus infections are common in developing countries. In local populations hepatitis A infections and subsequent immunity are usually acquired in early childhood. Many Himalayan trekkers acquired hepatitis A before the introduction of the vaccine, which is 97 to 99% effective in preventing infection. Hepatitis E, on the other hand, currently has no commercial vaccine available outside of China. It remains one of the most common causes of jaundice in the adult population of the Indian subcontinent, including the mountainous areas, and several cases are diagnosed each year in tourists and expatriates in this region. Women who contract hepatitis E while pregnant experience high mortality rates from liver failure, and miscarriage is commonly seen. Tourists who are pregnant should be counseled about this risk prior to travel.

Ingestion of *Echinococcus granulosus* eggs can cause cystic echinococcosis, also known as hydatid disease. *E. granulosus*, a dog tapeworm, is endemic in the mountains of Tibet, where there are stray dogs and the majority of families keep guard dogs. Dogs become infected from eating infected sheep, goat, and yak carcasses, and poor sanitation and hygiene lead to local human infection. Symptoms depend on the location of the cysts in the body. A patient who has cysts in the liver may suffer abdominal tenderness, hepatomegaly, and a palpable abdominal mass. Most patients go into anaphylactic shock if their cysts rupture either from trauma or during surgery. Amoebic liver abscesses, which can be seen in both locals and visitors, can also present as hepatomegaly and right upper quadrant abdominal pain. Abdominal tuberculosis, also on the differential, may present with ascites, wasting, and other nonspecific abdominal signs and symptoms.

DERMATOLOGIC INFECTIONS
Pyoderma, carbuncles, furuncles, and infected wounds are common problems encountered in the mountains of the developing world. Because *Clostridium tetani* may contaminate traumatized skin, pretravel tetanus boosters should be obtained as indicated. UV radiation increases by about 10% with every 300 m increase in altitude and influences the reactivation of herpes simplex virus. Acyclovir prevents this reactivation, whereas application of sunscreen with a sun protection factor (SPF) of 15 failed to influence the reactivation rate.

Lice and scabies are also common given close living quarters and potential contact with contaminated bedding, clothing, and towels. Permethrin cream is considered to be the drug of choice for scabies, although ivermectin is reported to be an effective oral medication, though it is not FDA-approved. Varicella infection...
is common in children, and visitors unsure of their immune status should consider antibody testing or varicella vaccination prior to travel to developing countries.

Podocniosis, also known as “mossy foot disease” or “endemic nonfilarial elephantitis,” is a noninfectious neglected tropical disease that affects four million people in low-income countries. This disease is caused by living and walking barefoot in high alkaline volcanic clay soils found in regions located at altitudes greater than 1,000 m, particularly in Ethiopia. Mineral particles penetrate the skin and cause an inflammatory reaction, leading to fibrosis and lymphedema with asymmetrical swelling of the feet and lower limbs. This condition can be confused with *Wuchereria bancrofti* filarial elephantiasis, although it is generally bilateral, rarely involves the upper leg or groin, and importantly, occurs at altitudes where infectious filariasis is not transmitted. There is a familial clustering of the disease, and the heritability is estimated to be 63%. This disease is mentioned here because it is a neglected disease that occurs at high altitude in local populations, where it creates significant social stigma, loss of income, and morbidity. Further, it is entirely preventable through education, footwear, and foot hygiene.

**NEUROLOGICAL INFECTIONS**

Rabies, a universally fatal progressive encephalomyelitis, is highly endemic and transmitted through the saliva of dogs, bats, and other mammals in Latin America, Africa, and Asia. Travelers to high altitudes are at an increased risk because their remote high-altitude location may delay expedient postexposure prophylaxis. Complete postexposure prophylaxis includes rabies vaccination and human rabies immunoglobulin; a three-dose pre-exposure rabies vaccination simplifies postexposure prophylaxis by eliminating the need for immunoglobulin, which is frequently unavailable in lower-income countries. Further, one critical field intervention that should be performed is emergent wound irrigation with a virucidal agent (i.e., povidone-iodine or chlorine dioxide).

While Japanese encephalitis, a mosquito-transmitted flavivirus infection, exists in rural areas of Southeast Asia and parts of the Indian subcontinent, no tourists to high-altitude regions have been diagnosed with Japanese encephalitis. This is most likely due to the inability of the *Culex* mosquito vector to survive at higher elevations. However, visitors may contract this illness while traveling through an endemic area, and an effective vaccine is available for those who are at risk.

**FEBRILE ILLNESSES**

Arthropod-borne febrile illnesses are extremely common in travel to developing countries. Malaria is an ever-present risk in most of the tropical world, and the *Anopheles* mosquito vector’s distribution is slowly climbing to higher elevations with global warming. *Plasmodium* species are not typically transmitted in higher-altitude locations, but exceptions have been reported. For example, in high-altitude villages of northwest Ethiopia, people who traveled to malaria-endemic areas for work developed *Plasmodium falciparum* malaria, and then their infection was transmitted to nontravelers in their home villages. Tourists who develop a febrile illness and whose trip itineraries included African safaris or other travel in endemic malarial areas should be considered to have a presumptive diagnosis of malaria and undergo a supervised evacuation to lower altitude.

Dengue virus and, increasingly, Chikungunya virus are endemic to the tropics and subtropics. Like malaria, these are mosquito-borne diseases that present with fevers, myalgia, joint pains, headaches, and other neurologic symptoms. There are no vaccines or chemoprophylaxis, and the care is supportive. As with malaria, the diagnosis is presumptive, and descent is imperative.

Typhoid fever, also known as enteric fever, is one of the most common causes of undifferentiated febrile illness in the Indian subcontinent. Patients with headache, fatigue, and fever at high altitude have been mistakenly diagnosed as having high altitude cerebral edema and later found to have typhoid fever. Typhoid fever vaccinations are only 50 to 80% effective against *Salmonella enterica* serotype *Typhi* and offer no protection against *S. enterica* serotype *Paratyphi* infection. A high suspicion for this entity should remain, and travelers should be reminded to take food and water precautions despite vaccination. Typhus, as well as other rickettsial diseases, may also be an under-diagnosed cause of fever in mountain travelers who have traveled through endemic areas.

Carrion’s disease is a febrile condition endemic to arid, high-altitude (approximately 600 to 3,200 m) valleys in the Andes Mountains of Peru, Colombia, and Ecuador. The disease has two distinct phases: oroya fever (acute phase) and verruga Peruana (eruptive phase). It is caused by the bacteria *Bartonella bacilliformis* and transmitted between humans by the *Phlebotomus* sand fly. The acute symptoms of fever, myalgia, headache, and jaundice occur approximately 60 days following the bite, and this acute phase is fatal in up to 88% of patients without antibacterial intervention. The eruptive phase manifests
as blood-filled nodular skin lesions that provide a reservoir for infecting additional sand flies and maintaining the bacteria in nature. Treatment options include tetracycline and chloramphenicol.

OTHER ILLNESSES
Leptospirosis is an infection characterized by a range of symptoms from mild headache, muscle pains, and fevers to Weil’s disease with jaundice, kidney failure, and bleeding. It is usually spread through contaminated water with transmission of *Leptospira*, a spirochete, through abraded skin, conjunctiva, or other mucous membranes. Floods and heavy rains can wash hillside *Leptospira*-contaminated urinary waste into mountain lakes and streams. Treatment involves doxycycline or ampicillin depending on the severity of infection. Another illness, tularemia is caused by *Francisella tularenis* and has been reported in the Southeastern Swiss Alps at 1,700 m.

Fungal vaginitis and urinary tract infections are common and present in their typical fashion at high altitude. Recent antibiotic use and inadequate personal hygiene may increase susceptibility. Sexually transmitted diseases (STDs) are also possible, particularly in individuals engaging with new sexual partners or taking increased risks while traveling.

OTHER DISEASES AT HIGH ALTITUDE
The differential diagnosis of illness at high altitude includes other conditions that may mimic an infection. Examples of conditions that may be misdiagnosed include high altitude cerebral edema, HAPE, subarachnoid hemorrhage, transient ischemic attack, cerebral neoplasm, migraine, Guillain-Barré syndrome, pulmonary embolism, asthma exacerbation, myocardial infarction, hypothermia, dehydration, carbon monoxide poisoning, chemical or plant toxin exposure, and acute psychiatric illness.

CONCLUSIONS
Travelers to high altitudes should consult their local travel clinic 6 to 8 weeks prior to departure for a pretravel health consultation, immunizations, and malaria chemoprophylaxis, as indicated. They should also be prescribed altitude medications, antibiotics for traveler’s diarrhea, and a small quantity of narcotic pain medication for personal use in the event of serious injury in a remote location. Physicians who are responsible for treating travelers at high altitude should carry a well-stocked group medical kit. Antibiotic suggestions include dicloxacillin, trimethoprim-sulfamethoxazole, metronidazole, doxycycline, a macrolide, and a fluoroquinolone. They should also carry altitude sickness medications including acetazolamide, dexamethasone, nifedipine, and ibuprofen. Other medications that should be included are hydrocortisone cream, an antifungal, antiemetics, antihistamines, antidiarrheals, epinephrine, and analgesics. Extra sunscreen, hand sanitizer, water purification tablets, a pulse oximeter, and protective medical gloves and CPR mask should also be included. Additionally, we find it helpful to carry urine pregnancy test kits and urine dipsticks to help modify therapy in the field.

In summary, infections at high altitude often parallel those in adjacent lowland environments. Hypoxemia, hypobaria, harsh environmental stressors, exposure to foreign agents, and reckless behavior can all enhance the traveler’s susceptibility to pathogens. Wound healing and response to antibiotics may be slower than anticipated, and infections at high altitude may trigger or worsen altitude illnesses. The ultimate treatment of many medical problems requires descent to a lower altitude. Prevention is crucial; both pretravel counseling and immunizations are essential. Additional research on infections occurring at high altitude is needed to better understand the impairment of the immune system and the epidemiology of specific diseases to improve their recognition, prevention, and treatment.

PRACTICAL TIPS
- Descend to a lower altitude, especially if infections do not improve with antibiotics alone.
- Wash hands with soap and/or liquid cleanser.
- Use insect repellents with DEET (diethyltoluamide) to help avoid mosquito and tick bites. Cover exposed skin, especially when trekking.
- Use pyrethrin-treated clothes and bed nets if necessary.
- Sterilize water.
- Avoid salads, ice, and other foods that can become easily contaminated.
- Use a silk scarf to breathe through at high altitude to help humidify the cold air.
- Use sunscreen on all exposed skin, including lips and ears.
- Maintain adequate hydration.
Obtain appropriate immunizations including seasonal influenza vaccine.

Review medical history, medication use, allergies, and pregnancy status prior to ascent.

Visit the dentist prior to the trip.

Purchase evacuation insurance, register at the local embassy, and become familiar with evacuation procedures.

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RECOMMENDED READINGS


