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High Altitude Illness: Diagnosis, Prevention, and Treatment

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Altitude sickness may occur in a variety of settings and for a variety of reasons. Multiple risk factors may predispose an individual to altitude sickness, such as a previous history of altitude illness, congenital heart disease, and prior surgery to the carotid bodies. Physical fitness does not protect against altitude sickness and vigorous activity may be initially detrimental to acclimatization. Physicians need to understand the pathophysiology, preventative strategies, and acute management of patients with altitude sickness. This article presents an overview of the spectrum of altitude illness, diagnosis, and current management strategies, as well as preventative strategies.

— The Editor

Introduction

One-fifth of the earth's surface is composed of mountains and high plateaus. Many people visit high altitudes for recreation, work, religious, military, and personal reasons. With the increasing popularity and ease of travel to high altitudes, more people are exposed to the dangers of altitude illness than ever before. Emergency physicians who practice in or near high altitude areas or who visit there themselves should have a general knowledge of acclimatization to altitude and know how to diagnose and manage high altitude illness, especially acute mountain sickness (AMS), high altitude cerebral edema (HACE), and high altitude pulmonary edema (HAPE). Serious high altitude illness is completely preventable and deaths should be rare with proper treatment.

Definitions

There are no standard definitions for terms such as high altitude or extreme altitude. Physiologic effects of decreased inspired oxygen begin at an elevation of about 1500 m (5000 ft),

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and can be divided into the following three levels based on physiologic response.[1]

• *High Altitude:* Elevations about 1500 to 3500 m (5000-11,500 ft). At these altitudes, there is minor impairment of arterial oxygen transport and oxygen saturation (SaO_2) is maintained above 90%. AMS is common with rapid ascent above 2500 meters (8200 feet).

• *Very High Altitude:* Elevations of 3500 to 5500 m (11,500-18,000 ft). At this altitude range, maximum SaO_2 is less than 90%. This is the most common range for serious altitude illness.

• *Extreme Altitude:* Elevations of 5500 to 8850 m (18,000-29,000 ft). Exposure to altitudes above 5500 m results in marked hypoxemia and hypocapnia. During prolonged stays at these heights, deterioration eventually outstrips acclimatization.

High altitude illness refers to cerebral and pulmonary syndromes that develop in non-acclimatized persons upon acute exposure to altitude (over hours to days). The main syndromes are AMS, HACE, and HAPE. *(See Table 1.)*

Epidemiology

Most cases of altitude illness are not reported. The number of persons at risk also is unknown except in a few well-defined geographic areas. These factors make the incidence difficult to determine. Reported incidence ranges from less than 10% to more than 90% for AMS and 0.01% to 31% for HACE and HAPE,[2] depending on the activity being studied and the rates of ascent. AMS affects up to one in four visitors to Colorado ski resorts,[3] and almost half of those who fly to the Everest region in Nepal.[4]

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Etiology

Hypoxia of altitude is referred to as hypobaric hypoxia, noting the decrease in barometric pressure at increasing altitudes. The partial pressure of oxygen remains constant at 21% of barometric pressure. Barometric pressure decreases as altitude increases, which causes hypoxia at an elevated altitude. In addition to elevation gain, weather changes and latitude also affect barometric pressure.[5,6] Storm fronts and winter seasons lower the barometric pressure. The atmosphere is thicker in lower latitudes and thinner nearer the poles. At higher latitudes there is less atmospheric mass and, therefore, lower atmospheric pressure at a given altitude compared to more equatorial regions.

Acclimatization is the process of physiologic adaptation to hypobaric hypoxia at altitude. Most people can acclimatize up to about 5500 m (18,000 ft) if ascent is gradual. Altitude illness represents failure of acclimatization.

There are multiple risk factors for developing high altitude illness. Susceptibility varies greatly among individuals. The incidence and severity of high altitude illness increase with altitude and with rate of ascent. A slow ascent rate and residence above 900 m (3000 ft) are associated with a lower incidence of altitude illness.[7,8] Individuals with a previous history of high altitude illness have a high rate of recurrent illness.[9] Older people tend to have a slightly lower incidence than younger people.[10] Although some studies have suggested that females[3] and obese persons[11] have a slightly higher incidence, these are not usually considered predisposing factors.[1] Certain pre-existing conditions, such as congenital absence of one pulmonary artery and primary pulmonary hypertension, greatly increase the risk of HAPE.[12] Surgery affecting the carotid bodies also can increase the risk of altitude illness.[13] Some individuals are especially susceptible to HAPE in the absence of obvious risk factors, and are referred to as HAPE-S.

Physical fitness neither improves acclimatization nor protects against high altitude illness, although it is certainly advisable for other reasons. Vigorous activity is initially detrimental to acclimatization and can exacerbate hypoxemia at altitude.[14] Smoking, heart disease, and hypertension have not been shown to be risk factors for altitude illness.[1]

Physiology and Pathophysiology

The initial response to altitude is increased ventilation. At altitudes above 1500 m (5000 ft), ventilation increases in response to hypoxemia detected by peripheral chemoreceptors located in the carotid bodies. This is referred to as the hypoxic ventilatory response (HVR), and is responsible for a rapid drop in the partial pressure of alveolar CO_2 ($PACO_2$). Lowering of $PACO_2$ allows for an increase in the partial pressure of alveolar O_2 (PAO_2) because the total pressure of gases in the alveoli must be equal to barometric pressure and because the partial pressures of the other gases (mostly nitrogen and water vapor) is constant. This effect is most important at very high and especially at extreme altitudes. The resulting respiratory alkalosis inhibits the medullary respiratory center. A compensatory metabolic acidosis occurs by increased renal excretion of bicarbonate, allowing for continued

Table 1. High Altitude Illness

SYNDROME	TYPICAL ONSET	SYMPTOMS AND SIGNS
Acute Mountain Sickness (AMS)	12-36 hrs >2500 m (8200 ft)	Headache, GI Symptoms (anorexia, nausea, vomiting), sleep disturbance, fatigue, weakness, dizziness, lightheadedness
High-Altitude Cerebral Edema (HACE)	2-5 days >3000 m (9800 ft)	Mental status changes and/or ataxia, usually as progression of AMS
High-Altitude Pulmonary Edema (HAPE)	2-5 days >2500 m (8200 ft)	Dyspnea at rest, cough, decreased exercise tolerance, fatigue, chest congestion

hyperventilation. Over a period of hours to days, the degree of hyperventilation decreases, but ventilation still remains higher than it is at sea level.

Initially, cardiac output and pulmonary perfusion increase. Decreased arterial oxygen (PaO_2) results in catecholamine secretion, with increased levels of epinephrine and norepinephrine.

Alveolar hypoxia causes an increase in PaP due to hypoxic pulmonary vasoconstriction (HPVC). This may improve ventilation-perfusion (V/Q) matching by redistributing blood flow to areas of the lung that are not usually well-perfused. An exaggerated HPVC causes pulmonary hypertension, which plays a role in the pathogenesis of HAPE, especially in HAPE-S individuals.

The brain is critically sensitive to hypoxemia and augments cerebral blood flow in response to lower oxygen levels. Cerebral vasodilation is opposed by cerebral vasoconstriction induced by hypocapnia. The net response is a mild increase in global cerebral blood flow. This may play a role in the pathogenesis of AMS in susceptible individuals by increasing the volume of the brain.[9]

Total hemoglobin and hemoglobin concentration increase at high altitude. In the first day or two, there is a relative increase in hematocrit due to hemoconcentration from diuresis and fluid shifts into the extravascular space.[15] Increased erythropoietin secretion begins hours after ascent to stimulate an increase in red blood cell production. Red cell mass increases over the next several weeks. Hemoglobin mass and hematocrit eventually reach a plateau.[16] In some cases, there is an inappropriate increase to very high levels over a period of many years. This is found in Chronic Mountain Sickness.[17] Chronic Mountain Sickness affects only long-term residents of high altitudes and is beyond the scope of this article.

Oxygen delivery to body tissue is influenced by the oxyhemoglobin dissociation curve. At high altitude, an increase in 2,3-DPG theoretically shifts the curve to the right, toward unloading oxygen from hemoglobin. This is balanced by respiratory alkalosis, which pushes the curve to the left. At very high and extreme altitudes, respiratory alkalosis predominates, causing a left shift. While a right shift of the curve would theoretically increase oxygen delivery to tissues, this would come at the detriment of oxygen loading in the lungs and would decrease the oxygen content of the blood.[18] In fact, due to higher hematocrit, the oxygen content of the blood generally is higher at high altitude than it is at sea level.[19] Blood in working tissues is more acidotic, which facilitates local unloading of oxygen.[20]

The final steps of oxygen transport and utilization involve tissue adaptations to improve the delivery of oxygen to cells and to mitochondria, which are the engines of oxidative metabolism within cells. These adaptations are not well understood. In some animal studies, there is an increased density of blood vessels, an increased concentration of myoglobin, and more mitochondria in acclimatized individuals and in high-altitude natives.[21]

Acute Mountain Sickness (AMS) and High Altitude Cerebral Edema (HACE)

Failure to acclimatize may result in AMS, the cerebral form of altitude illness. AMS is associated with relative hypoventilation and fluid retention,[22] but the pathophysiology is not well understood. AMS and HACE represent a clinical continuum of cerebral dysfunction. Mild AMS is usually self-limited and disappears after acclimatization. HACE is the severe form of AMS. It rarely occurs below 2500 m (8200 ft) and is most common above 3000 m (9800 ft).[23] Brain swelling *(see Figure 1)* alone does not account for AMS. A small study of nine subjects who ascended to a simulated altitude of 4570 m (15,000 ft) in a chamber all developed brain swelling on MRI, regardless of whether they developed AMS.[24] It is unclear why brain swelling at altitude does not always result in AMS. One hypothesis is that those with limited cranial capacity — "tight brains" — who cannot accommodate swelling are more likely to develop AMS.[9] This may be why there is a lower incidence of AMS in the elderly, who have lower brain volumes. The permeability of the blood-brain barrier increases in HACE, possibly due to increased levels of vascular endothelial growth factor (VEGF) and nitric oxide (NO). The result is increased vascular leakage.[25] If HACE is not effectively treated, death ultimately results from brain herniation.

High Altitude Pulmonary Edema (HAPE)

HAPE is associated with a large rise in pulmonary artery pressure (PaP). HAPE-S individuals have an exaggerated rise in PaP when exposed to hypoxia and when they exercise in normoxic and hypoxic environments.[26] The exaggerated rise is thought to result in non-homogenous vasoconstriction leading to

Figure 1. Cerebral Edema

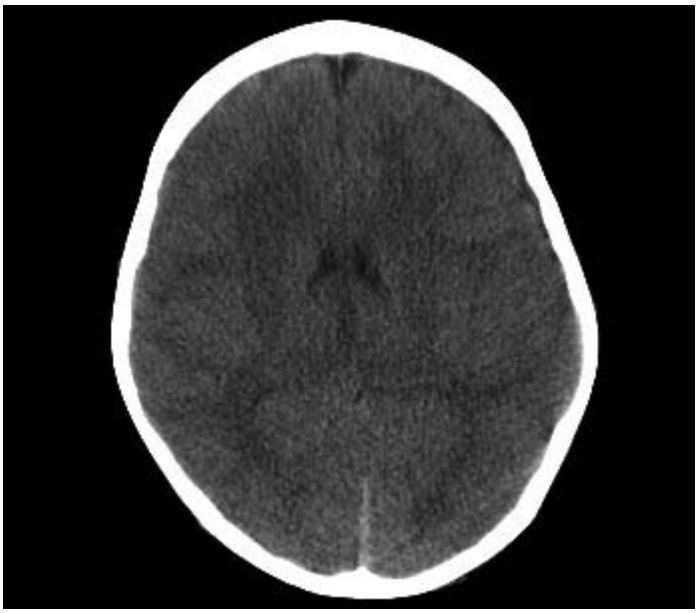


Table 2. Lake Louise Consensus Committee Definition of AMS*

REQUIRES THAT THE PATIENT HAVE A HEADACHE AND ONE OR MORE OF THE FOLLOWING SYMPTOMS:
❑ Gastrointestinal (nausea, vomiting, anorexia),
❑ Sleep disturbance (insomnia, difficulty sleeping),
❑ Fatigue or weakness, dizziness, or lightheadedness.

From: Roach RC Bärtsch P, Oelz O, et al. The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and Mountain Medicine.* Burlington, VT: Queen City Printers; 1992:266-273.

regional overperfusion, stress-induced failure and the patchy pulmonary infiltrates on chest x-ray. Mechanical mechanisms alone do not seem to be sufficient to cause HAPE. There also is an increase in pulmonary vascular endothelial permeability.[27] There is significant individual variability in the capacity to remove lung edema. Defects in the sodium-dependent transepithelial transport mechanisms of type II alveolar cells may predispose individuals to edema accumulation.[28]

Clinical Features and Diagnosis

In general, illnesses occurring after recent ascent to altitude should be considered to be altitude illnesses until proven otherwise. Descent to a lower altitude is usually therapeutic as well as diagnostic; many altitude-related symptoms resolve with descent.

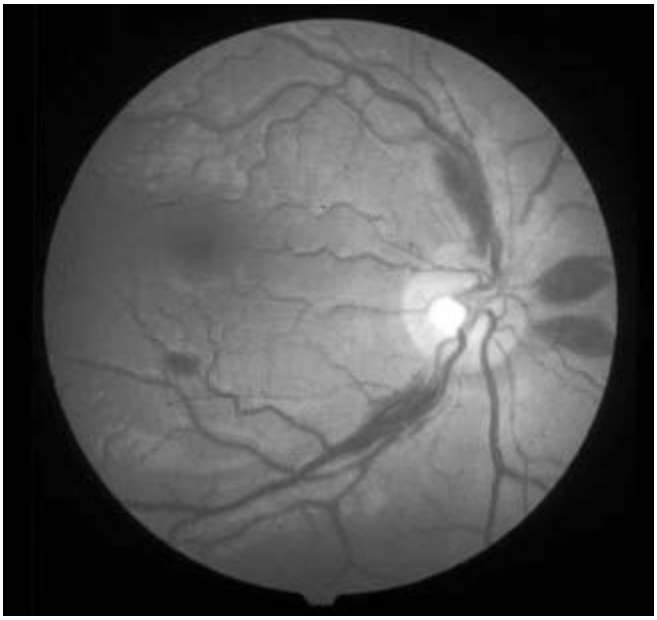
AMS. The diagnosis of AMS is made purely on clinical grounds. There is no confirmatory diagnostic test. Symptoms are typically self-limiting. The main concern is the risk of developing HACE. The Lake Louise Consensus Committee definition of AMS requires that the patient have a headache and one or more of the following symptoms: gastrointestinal (nausea, vomiting, anorexia), sleep disturbance (insomnia, difficulty sleeping), fatigue or weakness, dizziness, or lightheadedness.[29] *(See Table 2.)* The headache tends to be frontal or bitemporal and worse at night or on awakening, as well as with exertion.[4] Symptoms typically develop 12-24 hours after ascent, but can develop as late as 96 hours. Most symptoms resolve in 2-5 days.[30,31] Persistent symptoms after several days at a new altitude should suggest another diagnosis, but there are people who fail to acclimatize over periods of weeks and a few who seem never to acclimatize.

HACE. HACE is the severe form of AMS and is life-threatening.[32,33] It is distinguished from AMS by the presence of changes in mental status and/or ataxia. HACE usually occurs as a worsening of AMS, but HACE can be diagnosed on the basis of altered mental status with ataxia, even in the absence of antecedent AMS. The diagnosis is generally easily made. Mental status changes are most likely to consist of lethargy and eventually coma. Truncal ataxia is a diagnostic physical sign, which is best elicited early in the course by testing tandem gait. Cranial nerve palsies and other focal neurologic deficits also have been described, but suggest another diagnosis, such as migraine equivalent or CVA (cerebrovascular accident). Retinal hemorrhages may be an incidental finding, but are not useful for diagnosis; they also are common in well-acclimatized people above 5000 meters (16,400 feet). *(See Figure 2.)*

Imaging studies rarely are necessary for the diagnosis. Most places in which HACE occurs are unlikely to have any imaging capability. Imaging is most helpful if a patient who has been diagnosed with HACE fails to improve as expected after descent to a lower altitude. CT scan may show low attenuation diffusely or in the white matter, with flattening of the gyri and compression of the sulci. T2-weighted MRI may show increased signal in the white matter, especially in the splenium of the corpus callosum.[34] MRI findings will lag behind clinical recovery. A lumbar puncture is rarely necessary to exclude other causes, such as subarachnoid hemorrhage or infection. Imaging and lumbar puncture usually are reserved for cases in which symptoms are not resolving with descent or when the clinical picture is confusing. Opening pressures are typically high in HACE, with values from 44 to 220 mm H_2O; CSF analysis is normal.[33,35] MRI techniques for estimating intracranial pressures are currently only a research tool. Ultrasound of the optic nerve has the potential to measure ICP (intracranial pressure), but currently has no role in the diagnosis of HACE.

HAPE. HAPE is a noncardiogenic form of pulmonary edema. The earliest symptoms of HAPE are usually decreased exercise tolerance and prolonged exercise recovery time. Symptoms generally begin within 1-3 days at a high altitude. The most common presentation is awakening with apparent sudden onset after the second night at an altitude, but earlier and later presentations are common.[1] Symptoms of HAPE are dyspnea at

Figure 2. Retinal Hemorrhages



Courtesy of Peter Hackett, MD, Institute for Altitude Medicine.

Table 3. Differential Diagnosis of Altitude Illness

AMS
Viral syndrome
Hangover
Dehydration/volume depletion
Exhaustion
CO poisoning
Migraine headache
HACE
Cerebellar stroke
Sedative-hypnotic drugs, including alcohol
Migraine headache
Cerebral venous thrombosis
All other causes of altered mental status
HAPE
Bronchitis
Pneumonia
Congestive heart failure

rest, cough, chest tightness or congestion, and weakness or easy fatigue. Signs include wheezing, central cyanosis, tachypnea, and tachycardia. In practice, the diagnosis is usually clinically apparent. A low-grade fever usually is present.[36] Crackles usually are heard first in the right middle lobe, so it is important to auscultate the lungs in the right axilla — also known as the right auscultatory area — especially in early cases. The reason for this is not known, but probably relates to relatively higher pulmonary artery pressures in this area. A cough with frothy pink sputum is a late and ominous sign. In patients with HAPE, room air SaO_2 at rest is decreased below the expected normal value for a given altitude.

Chest x-ray is not necessary for diagnosis. Early on, the x-ray will show patchy infiltrates, sometimes only in one area, usually the right middle lobe, but sometimes the left middle lobe. This may cause confusion with pneumonia. In more advanced stages of HAPE, bilateral and more confluent infiltrates are seen; this is referred to as a butterfly distribution.[37] Cardiomegaly is absent. Radiologic changes, as in most diseases, may lag behind the clinical findings, although x-ray may show changes of HAPE in patients without clinical symptoms. Radiographic changes typically appear 18 hours after a rapid ascent and resolve within 24-72 hours after descent or treatment. Laboratory studies are seldom useful. Cardiac echo has been proposed to help differentiate other causes, but should be reserved for cases not improving after descent.

Differential Diagnosis

Differential diagnosis is generally straightforward. *(See Table 3.)* AMS does not cause fever or myalgias. These symptoms suggest a viral syndrome. The diagnosis of a hangover, which may coexist with AMS, is made by history. Dehydration usually resolves promptly with the administration of fluid, unlike AMS. Exhaustion may be difficult to distinguish from AMS if headache is present. The effects of carbon monoxide are very similar to those of AMS and may add to existing altitude illness. Carbon monoxide poisoning is common in high altitude settings, especially those involving cooking in a closed space, such as a tent.

Hypothermia can cause mental slowing and ataxia, mimicking HACE, but should be easily diagnosed by taking the patient's temperature. Sedative-hypnotic medications also may cause ataxia and mental status changes. A cerebellar stroke or peripheral vertigo can cause ataxia, but HACE does not cause vertigo. All other causes of altered mental status, including toxic causes (CO poisoning) or infectious causes potentially can be confused with HACE.

Respiratory illnesses may mimic HAPE. The cough in HAPE is nonproductive until its late stages when the sputum tends to be blood-tinged rather than purulent. A high fever with or without a productive cough suggests a respiratory infection. Since respiratory infections predispose to high altitude illness, clinicians should bear in mind that AMS, HACE, and HAPE may be superimposed on a pre-existing viral syndrome. Congestive heart failure may occur at an elevated altitude, but is rare.

Severe headaches at high altitudes have the same differential diagnosis as at sea level. Migraine headaches may be precipitated by high altitude. Intracranial masses may become symptomatic at altitude.[38] Lack of response to oxygen or descent suggests a diagnosis other than AMS as the cause of a headache.[39]

Prevention of Altitude Illness

The primary means of preventing high altitude illness is by a graded ascent. The most important parameter is sleeping altitude, probably because oxygen desaturation occurs during sleep. How

Table 4. The Golden Rules of Altitude Illness*

GOLDEN RULE #1
If you are sick at an altitude, you have altitude illness until proven otherwise.
GOLDEN RULE #2
Don't ascend further if you have symptoms of altitude illness.
GOLDEN RULE #3
Descend immediately if your symptoms are severe or if you can't walk a straight line.
GOLDEN RULE #4
Never send someone with altitude illness down alone.
GOLDEN RULE #5
It's okay to have mild altitude illness, but not to die from altitude illness.
GOLDEN RULE #6
Even doctors can die of altitude illness.

* Adapted from the Himalayan Rescue Association. Zafren K, Honigman B. High-altitude medicine. *Emerg Med Clin North Am* 1997;15:191-222.

high one goes during the day is of little consequence compared to the altitude at which one sleeps.

Residents of altitudes below 1500 m (5000 ft) should try to avoid rapid ascent to a sleeping altitude above 3000 m (9800 ft). A night at an intermediate altitude of about 2500 m (8200 ft) will further decrease the risk of altitude illness, although susceptible individuals may suffer AMS and rarely HAPE even with this very conservative ascent profile. Non-acclimatized individuals should avoid an increase in sleeping altitude of more than 300 m (1000 ft) per night and should plan on spending 2 nights after every total gain of 1000 meters or if larger elevation gains are unavoidable. This suggested ascent profile has been advocated by the Himalayan Rescue Association (HRA), with more than 30 years experience in Nepal.[1] Some individuals will have mild AMS, especially on the initial night at about 3000 meters, (9800 feet) but only highly susceptible individuals will have significant altitude illness with this ascent profile. Nepal is subtropical (low latitude), which means that the barometric pressure at a given altitude is higher than at corresponding altitudes in higher latitudes. Use of a more conservative ascent profile is prudent in middle and high latitude locations.

The HRA also has developed a set of guidelines for prevention of serious altitude illness, which is applicable to laypersons as well as to physicians. These have been termed the Golden Rules of Altitude Illness.[1] By following these rules, it would be almost impossible to die of altitude illness, although some susceptible individuals will still have AMS. *(See Table 4.)*

Golden Rule #1: If you are sick at an altitude, you have altitude illness until proven otherwise. Symptoms of altitude illness in the setting of recent ascent are most likely to due to altitude.

Golden Rule #2: Don't ascend further if you have symptoms of altitude illness. This emphasizes the danger of further ascent with altitude illness. If symptoms are relieved by simple medications such as acetaminophen or prochlorperazine, it is permissible to ascend at a conservative rate.

Golden Rule #3: Descend immediately if your symptoms are severe or if you can't walk a straight line. This refers to severe AMS, HACE, and HAPE. In remote settings, especially, descent is mandatory unless there is considerable medical expertise and suitable equipment available. In some cases, oxygen or simulated descent in a portable hyperbaric chamber, with monitoring of oxygen saturation, may be sufficient. Helicopter rescue has become possible in many remote areas, like Nepal, but remains unavailable in most of the world outside developed countries. Even in areas where helicopters are an option, they can often not fly at night or in bad weather. Under most circumstances, descent should not be delayed while waiting for helicopter rescue. If descent is impossible, the use of a portable hyperbaric chamber may be a useful temporizing measure.

Golden Rule #4: Never send someone with altitude illness down alone. Patients with HACE or HAPE may become incapacitated while descending and should be accompanied by someone who can assure that they can continue to descend, even if their condition temporarily worsens.

Golden Rule #5: It's okay to have mild altitude illness, but not to die from altitude illness. Mild AMS is not life threatening. There is great individual variation in susceptibility to AMS; some individuals will require an even more gradual ascent profile than the one recommended by the HRA if they are to avoid altitude illness completely.

Golden Rule #6: Even doctors can die of altitude illness. Doctors are not immune from altitude illness and should follow the rules they set down for their patients.

Pharmacologic Prevention of Altitude Illness

AMS. Acetazolamide is the only medication approved by the FDA for prevention of altitude illness. Use of acetazolamide is reasonable in individuals who are known to be very susceptible to altitude illness, who will not be able to adhere to a conservative ascent profile and who have no contraindications to its use. Acetazolamide also is helpful in cases in which it is not possible to follow a gradual ascent profile, such as flying to a high altitude destination from sea level. Examples would include flying to La Paz, Bolivia (sleeping altitude about 3500 m or 11,500 ft) or to Lhasa, Tibet (3800 m or 12,500 ft).

Acetazolamide speeds acclimatization rather than masking symptoms,[9] making it the safest drug for prevention of altitude illness. Contraindications include rare cross-reactions in individuals who are allergic to sulfa drugs, photosensitivity reactions and the other potential risks of sulfa-like drugs. The most frequent side effects, which are dose dependent, are paresthe-

sias of the lips, fingers and toes, which may be quite severe, and polyuria. Because it is a carbonic anhydrase inhibitor, it makes carbonated beverages, including beer, taste flat.

In situations in which AMS is less likely, there is little advantage in taking acetazolamide unless symptoms occur. It acts rapidly to increase ventilation and to alleviate the symptoms of AMS.

The lowest effective dosage of acetazolamide that prevents AMS while minimizing side effects is not known, but some evidence suggests it is probably about 5mg/kg/day in 2-3 divided doses.[40] For most people, 125 mg orally twice a day is adequate.[41] Clinicians might consider 250 mg orally twice a day for heavier persons. A meta-analysis[42] that claimed to show that 750 mg was the lowest effective daily dose suffered from serious methodologic flaws. Had the authors not misclassified a single, crucial study, they would have drawn the conclusion that lower doses were effective. This conclusion has been validated by several subsequent large studies.[41,43] Since side effects increase with increasing dosage, the optimum dose is the lowest dose that is effective.

Acetazolamide should be started the day before ascent and should be continued during ascent and for 2 days at the maximum altitude. It can be discontinued as soon as one starts descending. If there are pauses during ascent of more than 2 days, acetazolamide can be stopped until further ascent.

Dexamethasone also can be used to prevent AMS. A dose of 4 mg orally twice a day is effective, started 24-48 hours prior to ascent and continued for several days at the maximum altitude. It can be discontinued after descent below 3000 meters (9800 feet).[44] Dexamethasone should be used with caution, partly because of potential psychiatric side effects. Unlike acetazolamide it does not speed acclimatization. Rebound is common when it is discontinued.

HAPE. As with AMS/HACE, the primary means of preventing HAPE is graded ascent, with gradual increase in sleeping altitude. For patients who are known to be susceptible to HAPE (HAPE-S), pharmacologic prevention with nifedipine 20 mg orally three times a day beginning the day prior to ascent and continued for 3 days after ascent has been shown to be effective with rapid ascent to 4560 m (15,000 ft).[45]

Other agents have shown promise in preventing HAPE with rapid ascent in HAPE-S patients. Salmeterol, an inhaled beta-agonist, decreased the incidence of HAPE by 50% in one small study of HAPE-S patients.[46] In another small study, both tadalafil, which is known to reduce pulmonary artery pressure, and dexamethasone reduced the incidence of HAPE in HAPE-S patients.[47] Dexamethasone had the added benefit of helping to prevent AMS, but must be used with caution.

Treatment of Altitude Illness

AMS. Anyone with AMS should not ascend further until symptoms abate completely. Most cases resolve over 2-5 days without descent. Headaches can be treated with any of the usual analgesic medications, such as acetaminophen.[48] Although some have advocated the use of ibuprofen or aspirin, the incidence of gastrointestinal hemorrhage is increased at higher altitudes,[49] so it seems prudent to limit the use of NSAIDs. Any antiemetic is acceptable, but prochlorperazine has been shown to be a respiratory stimulant,[50] while others cause potentially detrimental respiratory depression. Sleep disturbances should be treated with acetazolamide (see subsequent section on "Sleep Disturbances") unless there are contraindications.

Oxygen or treatment in a portable hyperbaric chamber is often therapeutic as well as diagnostic.[51] AMS headaches often resolve within about 10 minutes.

In treating AMS without descent, the patient should limit exertion. Acetazolamide is the only FDA approved medication for the treatment of AMS. The most effective dose has been debated in the literature, but most experts use 250 mg orally twice a day for treatment of AMS. Once symptoms have resolved, treatment can be discontinued, because acetazolamide speeds acclimatization rather than masking symptoms. However, symptoms may reoccur with further ascent.

Dexamethasone also is effective in treating AMS, but its use should be reserved for those who have contraindications to taking acetazolamide.[52] It only treats the symptoms of AMS rather than speeding acclimatization.[53] Caution is necessary when using dexamethasone to treat AMS, partly because of the potential for psychiatric disturbances at higher altitude. If it is discontinued prematurely, symptoms may return. This is sometimes termed "rebound." For treatment of AMS, the recommended dose is 4 mg orally every 6 hours. For treating HACE, the first dose is usually doubled to 8 mg. The first and subsequent doses can be given IM or IV if the patient is unable to take medications orally. Dexamethasone should be continued for several days when treating AMS and should be discontinued for a day or two prior to further ascent.

Patients whose AMS is severe and whose symptoms are not relieved by symptomatic treatment with or without acetazolamide should descend, for their own comfort and well-being until they are feeling better. Descent to the last altitude at which they felt well is usually sufficient. Even small amounts of elevation loss, on the order of 300-500 m (1000-1600 ft), may alleviate or completely cure symptoms.

HACE. For patients with HACE, definitive treatment is descent. Patients should be taken down as rapidly as possible until their mental status is normal. Ataxia and cognitive impairment may persist. Ataxia in particular often takes days or months to resolve.[32,33] Patients with HACE should not reascend until all symptoms have resolved. Some experts believe that they should not reascend for weeks to months after HACE has resolved, but this has not been studied.

Oxygen (to maintain $SaO_2 > 90\%$) and dexamethasone (8-10 mg PO/IM/IV followed by 4 mg every 6 hours) are useful adjuncts if available.[23] If immediate descent is not possible, hyperbaric therapy can be a temporizing measure. Patients in a coma require emergent airway management and other usual coma care. Hyperventilation is not recommended since these patients already have a respiratory alkalosis and further hyperventilation could worsen cerebral ischemia. There are no data

Table 5. High-Altitude Illness Management

	WILDERNESS TREATMENT	HIGH-ALTITUDE CLINIC/HOSPITAL
AMS: headache, nausea, decreased appetite, fatigue, poor sleep	Hold further ascent for 1-2 days until acclimatized or descend generally > 500 m (1600 ft). Descend if symptoms are severe or worsening. Consider acetazolamide 250 mg PO BID. Symptomatic treatment with analgesics and antiemetics.	Same treatment as in field. Can add oxygen 1-2 L/min until symptoms are resolving.
HACE: Mental status changes and ataxia	Immediate descent, generally > 1000 m (3300 ft). Oxygen to maintain SaO_2 > 90%. Dexamethasone 8 mg once, then 4 mg every 6 hrs. Hyperbaric treatment if unable to descend immediately.	Treatment same as in field. Coma care as needed. Hyperventilation not recommended. Consider MRI if available and diagnosis is uncertain.
HAPE: Dyspnea at rest, cough, severe exercise limitation, chest tightness/ congestion. Crackles, wheezing, tachypnea, tachycardia, low SaO_2	Descend generally > 1000 m (3300 ft). Portable hyperbaric chamber and/or oxygen if available to maintain SaO_2 > 90%. Keep patient warm, minimize exertion. Nifedipine, inhaled beta-agonists, 5-HT blockers (sildenafil or tadalafil) are used by some as an alternative to nifedipine. Treat HACE if present.	Bed rest and oxygen or portable hyperbaric chamber for mild cases below 3500 m (11,500 ft). Descent for severe cases. Admit those with associated HACE, O_2 requirement > 4 L/min, co-morbidities. Nifedipine is a proven adjunct. Sildenafil and tadalafil also are used.

supporting the use of furosemide, mannitol, or glycerol for HACE.

HAPE. Many cases of isolated HAPE at altitudes below 3500 m (11,500 ft) respond to rest and supplementary oxygen without descent.[36] Oxygen treatment reduces PaP and increases arterial oxygenation. Hyperbaric therapy in a portable hyperbaric chamber such as the Gamow bag is a reasonable substitute for actual descent in settings in which descent is difficult.[1] Patients treated at altitudes above 3500 m (11,500 ft) should generally descend to a lower altitude for a few days before reascending.

The patient should be kept warm and at bed rest, because cold stress and exertion elevate PaP. It the patient must descend on foot in a wilderness setting, someone else should carry the patient's pack.

Pharmacologic therapy is a useful adjunct in the treatment of HAPE, but does not replace the need for supplemental oxygen. Nifedipine 10 mg orally followed by 20 mg sustained release every 6 hours has been shown to be effective in treating HAPE,[54] and remains the first-line drug for many experts. Mild hypotension does occur, but is seldom a problem in practice. The PDE-5 inhibitors, particularly sildenafil and tadalafil, are increasingly being used in clinical settings. Advocates point to the fact that they rarely cause systemic hypotension.

Disposition

Patients with AMS need not be admitted to a medical facility and can continue ascent after their symptoms have resolved. Patients with HACE must descend. They should be admitted to a medical facility if they still have altered mental status or marked ataxia after descent. Occasional HACE patients with severe symptoms at altitude may need help with activities of daily living for days to weeks at sea level.

Patients with HAPE generally improve rapidly after descent. HAPE patients below 3500 m (11,500 feet) who have mild symptoms and who can maintain oxygen saturation at or above 90% on supplementary oxygen at 2-4 L/min can be treated as outpatients with an oxygen concentrator and are usually seen in follow-up at 24 hours. They can resume normal activities at altitude after 1-2 days. HAPE patients who do not meet these criteria should be treated by descent. If feasible, they should be evaluated at a medical facility located at a much lower altitude, and should be admitted if they still have severe symptoms or are unable to maintain SaO_2 at or above 90% on room air or on oxygen at 2-4 L/min. *(See Tables 5 and 6.)*

Other Conditions at High Altitude

Although Golden Rule #1 of altitude illness emphasizes that most illnesses after recent ascent to altitude are due to the altitude, any acute medical problem can and does occur at increased altitudes. Basnyat and colleagues have summarized this in a review article.[55] There are conditions other than AMS, HACE, and HAPE, described in subsequent sections, that are related to altitude.

Sleep Disturbances. Poor sleep is not necessarily associated with AMS. Sleep stages are disrupted at altitude, even after acclimatization.[56] Sleep disturbance is commonly due to periodic breathing of altitude, which is characterized by periods of apnea during which oxyhemoglobin desaturation occurs. This is sometimes mistakenly labeled as Cheyne-Stokes breathing, but the pattern of respiration is different. Periodic breathing of alti-

Table 6. Pharmacologic Prophylaxis and Treatment

ACETAZOLAMIDE: FIRST LINE FOR PREVENTION/TREATMENT OF AMS

Dose: *Prevention of AMS:* 125-250 mg PO BID or 5 mg/kg/day in 2-3 divided doses starting the day before ascent and continued for 2 days at maximum altitude.
Treatment of AMS: 250 mg PO BID until symptoms resolve. Prevention or treatment of insomnia/poor sleep: 62-125 mg po before bed time.

Mechanism: Carbonic anhydrase inhibitor which causes a metabolic acidosis and increases ventilation and oxygenation. Also may act by decreasing CSF volume and pressure.

Side Effects: Polyuria, paresthesias, nausea, alters taste of carbonated beverages.

Other: Give with caution in patients who are allergic to sulfa drugs.

DEXAMETHASONE: FIRST LINE FOR TREATMENT OF HACE

Dose: *Prevention of AMS in patients who cannot take acetazolamide:* 4mg PO BID starting 24-48 hrs prior to ascent.[30]
Treatment of AMS: 4 mg PO (IM or IV if necessary) q6h.
For treatment of HACE: 8 mg PO/IV/IM initially then 4 mg PO/IV/IM q6h. Also may be effective for prevention of HAPE.[47]

Mechanism: Unknown. Probably central effect for prevention of AMS/HACE. Blunts rise in PaP to prevent HAPE.

Side Effects: Rebound likely when stopped. Does not speed acclimatization. May cause hyperglycemia or gastric irritation.

NIFEDIPINE: FIRST LINE FOR PREVENTION/TREATMENT OF HAPE

Dose: 20 mg PO TID or 30-60 mg daily of sustained release for prevention of HAPE when started on the day of ascent and continued for 72 hrs at elevated altitude[31,45] 10 mg PO once then 20 mg sustained release QID for treatment of HAPE.[54]

Mechanism: Calcium channel blocker, smooth muscle relaxant. Reduces PaP.

Side Effects: Hypotension and reflex tachycardia, dizziness, nausea can occur, but cardiovascular effects are not usually a problem in prevention or treatment of HAPE.

SALMETEROL

Dose: 125 micrograms inhaled BID for HAPE prevention and possibly treatment, starting the day prior to ascent and continued for 2 days at maximum altitude.

Mechanism: Upregulates pulmonary transepithelial sodium transport to increase alveolar fluid clearance.

Side Effects: Mild tachycardia.

SILDENAFIL/TADALAFIL

Dose: Tadalafil 10 mg po BID for prevention of HAPE. Sildenafil 50 mg TID or tadalafil 10 mg po BID for treatment of HAPE

Mechanism: PDE-5 inhibition increases NO in pulmonary vasculature.

Side Effects: Visual disturbances (which may be permanent), possibly fatal interaction with nitrates.

tude responds well to low-dose acetazolamide (62.5-125 mg at dinner time),[1] which eliminates the periods of apnea. Low dose benzodiazepines are probably safe.[57] Sedative/hypnotic medications such as zolpidem are probably even safer, since they do not depress respiration.[58] These can, however, cause erratic behavior, possibly mimicking the altered mental status of HACE. A trial at sea level is probably warranted, prior to use at high altitude. Others in the group should be made aware of this potential side effect.

Neurologic. Any neurologic condition that occurs at sea level can occur at high altitude. Apparent transient ischemic attacks are common at extreme altitudes even in young, apparently healthy climbers.[59] Most of these events are probably migraine equivalents. Cerebral venous thrombosis may mimic HACE, but does not improve with descent.[60] Treatment of focal neurologic events at altitude is essentially the same as at sea level with the addition of oxygen, descent and the use of steroids if the patient has HACE.

Syncope. High altitude syncope has been described.[61] It is benign, tends to occur after the use of alcohol or a large meal, and is common at night. It is questionable whether it is a distinct entity related to altitude.

Peripheral Edema. Swelling of the face and extremities is common at an elevated altitude, especially in women. It is annoying and often disfiguring, but resolves completely after descent. In the absence of other conditions, such as AMS, HAPE, or HACE, it can be treated with low doses of furosemide.[62]

High Altitude Retinopathy. Retinal hemorrhages are very common above 5000 meters (16,400 ft).[63] Most are asymptomatic and resolve with descent. Retinal hemorrhages that overly the macula may cause blindness. This usually resolves with descent, but central scotomata may persist for years or be permanent. Asymptomatic retinal hemorrhages do not require descent.

High Altitude Pharyngitis and Bronchitis. Sore throat and cough are common at high altitude and universal after two weeks above 5500 m (18,000 ft). High altitude cough may be dry or purulent and can be severe enough to break ribs. Antibiotics are not helpful. Cough drops and measures to reduce the dryness of inspired air, such as breathing through a face mask are helpful.[64]

Immune Suppression. Resistance to bacterial infections is decreased at altitude. Infections, such as wound infections not responding to the usual antibiotics often respond promptly after descent. Resistance to viral infections and active immunizations are not affected.[65]

Conclusion

The most common conditions associated with ascent to high altitude — AMS, HACE and HAPE — are largely preventable by gradual ascent. These conditions can be treated effectively if recognized early. While AMS is largely an annoyance, its severe form — HACE — is life threatening, as is HAPE. Treatment for HACE and HAPE consists of descent, with or without drug therapy. Emergency physicians also should be aware of other altitude-related conditions and should keep in mind that virtual-

ly any condition found at sea level also can occur at an elevated altitude.

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CME Questions

1. Initial physiologic changes on ascent to high altitude include which one of the following:
   A. Increased red blood cell mass
   B. Decreased hematocrit
   C. Increased ventilation
   D. Decreased pulmonary artery pressure

2. The best way to prevent altitude illness is
   A. Gradually increase the altitude reached during each day
   B. Gradually increase sleeping altitude
   C. Acetazolamide 250 mg po BID
   D. Dexamethasone 4 mg po BID

3. Which of the following drugs acts by speeding acclimatization:
   A. Acetazolamide
   B. Dexamethasone

CNE/CME Objectives

Upon completing this program, the participants will be able to:

a.) discuss conditions that should increase suspicion for traumatic injuries;
b.) describe the various modalities used to identify different traumatic conditions;
c.) cite methods of quickly stabilizing and managing patients; and
d.) identify possible complications that may occur with traumatic injuries.

CNE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. **After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided in order to receive a letter of credit.** When your evaluation is received, a letter of credit will be mailed to you.

C. Nifedipine
D. Sildenafil

4. The lowest effective dose of acetazolamide to prevent AMS in a 70 kg person is:
   A. 125-250 mg po BID
   B. 250 mg po TID
   C. 250 mg po QID
   D. 500 mg po BID

5. Which of the following distinguishes HACE, from AMS
   A. Headache
   B. Nausea
   C. Ataxia
   D. Fatigue

6. Which of the following drugs have shown efficacy in preventing HAPE?
   A. Dexamethasone
   B. Nifedipine
   C. Tadalafil
   D. All of the above

7. A 50 year old male skier has flown from sea level to Denver 1600 m (5300 ft) and then to a ski area at 2900 m (9500 ft), where he slept in a condominium. He awakens the next morning with a headache and nausea. Which one of the following would be the best treatment?
   A. Immediate descent back to Denver
   B. Acetaminophen and rest, with acetazolamide
   C. Acetaminophen and rest with nifedipine
   D. Ski off the symptoms

8. A 30-year old man is one of a group of friends climbing Chimborazo, a 6000 m (20,000 ft) peak in Ecuador. After 2 nights at Quito, Ecuador at 2800 m (9200 ft), the group slept one night in base camp at 5000 m (16,400 ft) before moving to high camp at 5800 m (19,000 ft). He awakens the next morning, complains of a headache, then immediately becomes unresponsive. Which one of the following would be the best treatment?
   A. Nifedipine
   B. Acetazolamide
   C. Dexamethasone
   D. Immediate descent

9. A 35-year-old skier has flown from sea level to Denver 1600 m (5300 ft) and then driven to a ski resort at 2900 m (9500 ft), where he slept in a condominium with friends. He skied hard the next day and on the second morning woke up short of breath. His friends brought him to a nearby clinic. On oxygen at 4 L/min his oxygen saturation is 91%. He has crackles on auscultation of his right middle lobe. He can be treated safely with bed rest, nifedipine, and oxygen at 4L/min from an oxygen concentrator in his condominium if one of his friends stays with him and he returns to the clinic for 24-hour follow-up or immediately if he is more short of breath.
   A. True
   B. False

10. A 25-year old trekker is helped from the lodge where she has been staying to the nearby Himalayan Rescue Association aid post at Pheriche, Nepal, located at 4270 m(14,000 feet). She has dyspnea at rest and a dry cough after her second night at that altitude. Her SaO2 on oxygen at 4 L is 78% (normal at 4270 m is 86%). You hear crackles when you listen to her lungs. There are no roads in the area and only very rough trails, so that carrying a patient down is very difficult. What is the best course of action?
    A. Continue ascent at a slower rate
    B. Continue ascent at a slower rate and administer nifedipine
    C. Rest at the same altitude for a day, breathing oxygen at 4 L/min
    D. Treatment in a hyperbaric chamber, administer nifedipine, and descend after she is no longer dyspneic at rest.

Answers: 1. C; 2. B; 3. A; 4. A; 5. C; 6. D; 7. B; 8. D; 9. A; 10. D

In Future Issues:

Pediatric Concussion