Advances in the Prevention and Treatment of High Altitude Illness

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KEYWORDS

• Altitude • Acute mountain sickness • High altitude pulmonary edema
• High altitude cerebral edema • Prevention • Treatment

KEY POINTS

- Acetazolamide remains the best choice for prevention of acute mountain sickness (AMS).
- The best treatment for all high altitude illness is descent or oxygen, or both.
- Dexamethasone is excellent for treating moderate to severe AMS, and for high altitude cerebral edema (HACE).
- Supplemental oxygen is first-line therapy for high altitude pulmonary edema; descent is primary therapy if oxygen is not available.
- Descent is the definitive treatment for HACE and should not be delayed. Dexamethasone and supplemental oxygen are important adjunctive treatments for HACE until descent can be facilitated.

INTRODUCTION

High altitude illness (HAI) comprises a spectrum of conditions that occur at elevation as a result of hypoxia, and includes acute mountain sickness (AMS), high altitude cerebral edema (HACE), and high altitude pulmonary edema (HAPE). Whereas AMS is self-limited, HACE and HAPE represent true emergencies that require timely intervention and stabilization. This review focuses on recent advances in the prevention and treatment of these conditions.

Background

The concentration of oxygen in air remains constant at 21% regardless of the altitude. However, the partial pressure of oxygen decreases with increasing altitude, resulting

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in alveolar hypoxia, hypoxemia and eventual tissue hypoxia. In the lower Rocky Mountain resorts of Colorado (2500 m/8000 ft), there is one-quarter less available oxygen than at sea level. At Everest Base Camp (5300 m/17,500 feet) there is one-half the available oxygen, and on the summit of Mount Everest there is only one-third. Although a given elevation primarily determines oxygen availability, barometric pressure also decreases with increasing latitude, the winter season, and with low-pressure storm fronts. Accordingly, these effects may combine to raise the effective altitude by hundreds of meters, resulting in an increased risk of HAI.

The high altitude environment is roughly organized into stages according to physiologic stress and resultant pathology.

- *Intermediate altitude* (1520–2440 m/5000–8000 ft): Increased compensatory ventilation occurs along with a decrease in exercise performance. However, blood oxygen saturation is typically preserved at greater than 90%. For most susceptible individuals, AMS will occur above 2100 m.
- *High altitude* (2440–4270 m/8000–14,000 ft): Most HAI occurs in this range owing to the easy availability of overnight tourist facilities at these elevations. In this altitude range, oxygen saturation can be less than 90%, and hypoxemia worsens during exercise and sleep.
- *Very high altitude* (4270–5490 m/14,000–18,000 ft): Abrupt ascent is dangerous. A period of acclimatization is required to prevent HAI. Rates of HAPE and HACE are increased.
- *Extreme altitude* (>5490 m/18,000 ft): Marked hypoxemia and hypocapnia are present. Hypoxic stress leads to progressive physiologic deterioration that eventually overwhelms the body's ability to acclimatize. Long-term human habitation is, therefore, impossible.

Table 1 summarizes the effect of increasing altitude on barometric pressure, blood oxygen saturation, and arterial concentration of P_{O_2} and C_{O_2}.

Acclimatization

A full discussion of high altitude acclimatization is beyond the scope of this review. Several excellent publications cover this topic in full detail.[1,2] **Table 2** provides a basic summary of the acclimatization process organized by organ system.

Table 1
Effects of increasing altitude on respiratory physiology

Altitude	Equivalent	Pb (mm Hg)	Estimated Pao_2 (mm Hg)	Estimated Sao_2 (%)	$Paco_2$ (mm Hg)
Sea level	—	760	90–100	97–99	38–42
5280 ft (1610 m)	Denver	623	65–80	93–97	32–42
8000 ft (2440 m)	Machu Pichu	564	45–70	88–95	31–36
12,000 ft (3660 m)	La Paz, Bolivia	483	42–53	80–89	24–34
17,500 ft (5330 m)	Everest Basecamp	388	38–50	65–81	22–30
29,000 ft (8840 m)	Everest Summit	253	28–32	54–62	10–14

Pressures expressed in mm Hg.

Abbreviations: Pb, barometric pressure; Sao_2%, arterial oxygen saturation.

Adapted from Roach CR, Lawley JS, Hackett PH. The physiology of high altitude. In: Auerbach PS, editor. Wilderness medicine. Philadelphia: Elsevier; 2016. p. 3.

Table 2
Acclimatization by organ system

Organ System	Effect	Onset
Pulmonary	Increased ventilation modulated by hypoxic ventilatory response and limited by respiratory alkalosis. Pulmonary vascular remodeling	Immediate onset with maximum effect 4–7 d
Renal	Bicarbonate diuresis counteracts alkalosis, increases ventilation	Onset within hours, reaching maximal effect 4–7 d
Cardiovascular	Increased sympathetic tone Systemic blood pressure Increased heart rate Decreased stroke volume Overall cardiac output	Immediate onset, peaks 5 d Response immediate but variable, may remain elevated Peak effect 3–4 d, then declines Peaks 2–3 d, remains 20% below baseline Increases 20% in 2–3 d, then returns to baseline
Hematologic	Hemoconcentration followed by increased red cell mass	First 2 d increased hematocrit from plasma volume loss; erythropoietin levels increase within hours of hypoxic exposure; increased red cell mass peaks in 4–6 wk
Brain	Increased cerebral blood flow	Immediate; lasts 3–5 d, then approximates baseline values

There are limits to an individuals ability to acclimatization to high altitude. Above 5500 m (18,000 ft), weight loss owing to catabolic loss of fat and lean body mass is inevitable. Intestinal malabsorption, impaired renal function, polycythemia leading to microcirculatory sludging, right ventricular strain from excessive pulmonary hypertension, fragmented sleep, and prolonged cerebral hypoxia all combine to limit the human body's ability to adapt to extreme altitude. Even at more modest altitudes, some individuals suboptimally acclimatize owing to genetic or acquired factors.

Pathophysiology

Hypobaric hypoxia resulting in hypoxemia is the pathogenic stressor that leads to all forms of high-altitude illness.[2] Broadly speaking, HAI is the clinical manifestation of inadequate acclimatization. One's susceptibility to illness is largely driven by degree and rate of onset of hypoxemia (altitude and rate of ascent), along with genetic factors; fitness is not protective. Therefore, susceptibility to high-altitude illness varies markedly among both individuals and populations. It is useful to distinguish the pathophysiology of cerebral forms of HAI (AMS and HACE) from the pulmonary form—HAPE.

Cerebral high altitude illness: acute mountain sickness and high altitude cerebral edema

Clinically, AMS and HACE represent a continuum of illness, because AMS usually precedes HACE, although not always. They may share an initial common pathophysiology, with HACE the extreme end result. On ascent to high altitude, cerebral vasodilation in response to hypoxemia leads to increased cerebral blood flow and increased cerebral blood volume, which causes the initial headache. Whether headache is owing to distension of pain-sensitive structures such as arteries, venous

sinuses, or meninges, or owing to activation of the trigeminal vascular system, or owing to an increase in intracranial pressure, or a combination of these factors, is unclear. See Lawley and colleagues[3] for a recent comprehensive review. With acclimatization, cerebral blood flow returns toward normal and symptoms resolve. For those who progress beyond a headache and develop AMS, cerebral blood flow and possibly intracranial pressure remain elevated longer, but eventually intracranial dynamics and blood flow are restored to baseline, with eventual resolution of AMS. Although a small amount of vasogenic brain edema is present on MRI after 8 to 12 hours of altitude hypoxia, it is now clear that this edema does not necessarily correlate with AMS.[4] Therefore, mild edema alone is unlikely to be responsible for the clinical manifestations of mild to moderate AMS.[5] In those who go on to develop severe AMS and HACE, edema is apparent on computed tomography scans and MRI. As illness progresses, intracranial pressure progressively increases, and can lead to death. Exactly how AMS progresses to HACE is unclear; possible mechanisms include disruption of the blood–brain barrier from mechanical and biochemical insults, intracellular edema (cytotoxic), and perhaps venous outflow obstruction. **Fig. 1** summarizes current hypotheses of the pathophysiology of AMS and HACE.

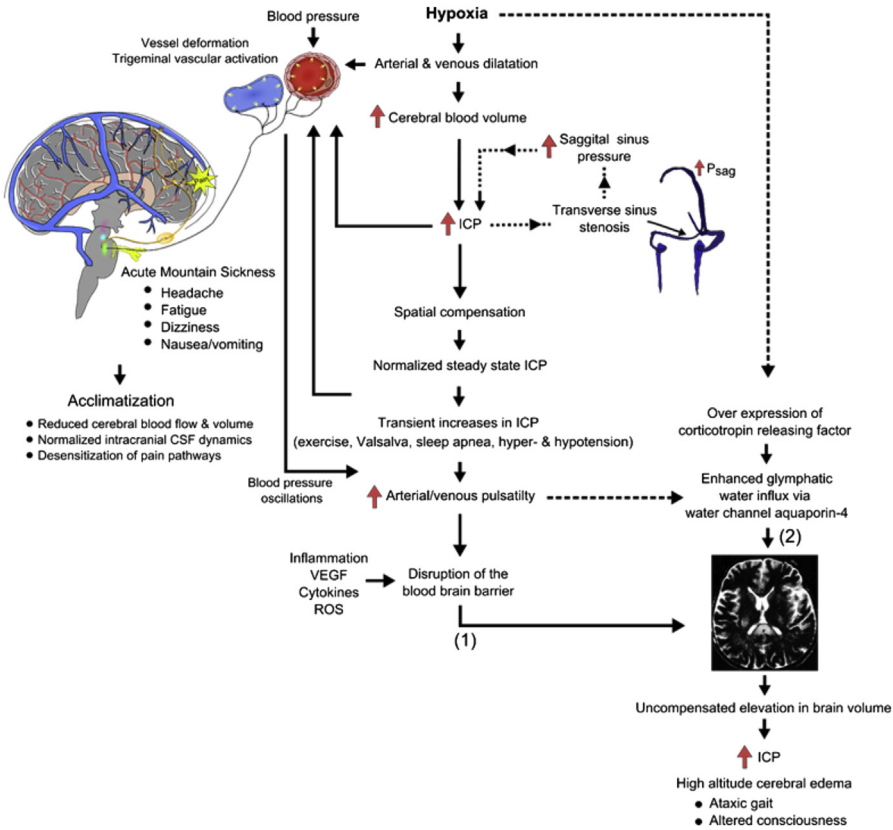

Fig. 1. Pathophysiology of acute mountain sickness and high altitude cerebral edema (HACE). ICP, intracranial pressure; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

Pulmonary high altitude illness: high altitude pulmonary edema

HAPE is a noncardiogenic edema in which a leak in the pulmonary blood–gas barrier leads to accumulation of edema fluid in the lung. Left ventricular function is preserved. Pulmonary artery pressure increases in all individuals at high altitude, owing to hypoxic pulmonary vasoconstriction. In those with HAPE, hypoxic pulmonary vasoconstriction is thought to be uneven, such that high microvascular pressure occurs in the pulmonary capillary beds that are not protected by arteriolar vasoconstriction. Capillary hypertension results in fluid shifts via Starling principles, as well as stretching or disruption of cellular junctions and pores. Other factors include inadequate ventilatory response, increased sympathetic tone, inadequate production of endothelial nitric oxide, and impaired clearance of alveolar fluid.[6–8] **Fig. 2** summarizes our current understanding of the pathophysiology of HAPE.

PATIENT EVALUATION OVERVIEW

Acute Mountain Sickness

The diagnosis of AMS is purely clinical. The symptoms are nonspecific, often described as being similar to an ethanol hangover. The setting is rapid ascent of an unacclimatized individual above 2000 m (6560 ft), or ascent to a higher altitude when already at altitude. The classic symptoms develop after several hours, but may be delayed until the next day. For research purposes, the diagnosis of AMS requires a headache in addition to at least 1 of the following symptoms: nausea,

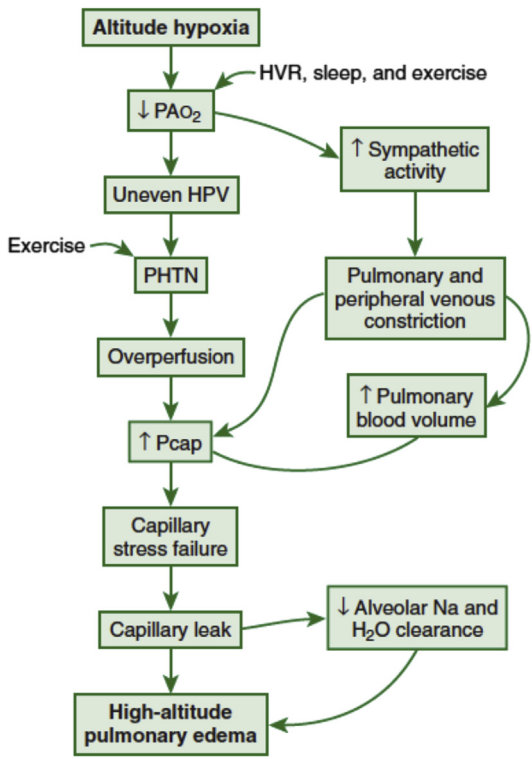

Fig. 2. Pathophysiology of high-altitude pulmonary edema. HPV, hypoxic pulmonary vasoconstriction; HVR, hypoxic ventilatory response; PHTN, pulmonary hypertension.

vomiting or anorexia, general weakness or fatigue, dizziness or lightheadedness, or difficulty sleeping. For clinical purposes, a headache is not a requirement for the diagnosis. Sleep disturbance caused by periodic breathing is common at high altitude, but is exacerbated in those with AMS. These symptoms constitute The Lake Louise Acute Mountain Sickness Scoring System.[9]

The headache of AMS ranges from mild to incapacitating. It is typically bitemporal, dull or throbbing in nature, and is made worse with exertion or with Valsalva maneuvers such as when an individual bends over to lift a backpack. Classically the headache is worst during the night or just after awakening. As the illness progresses the headache becomes more severe and gastrointestinal and constitutional symptoms also worsen. The person with AMS can be irritable and wants to be left alone. Symptoms reach maximum severity in 18 to 24 hours[10] if ascent is halted, followed by gradual resolution. Most individuals become symptom free by the second or third day without further ascent. Symptoms with onset after 3 days of acclimatization should not be attributed to AMS.

Physical findings in AMS are not helpful except to exclude other diagnoses. Heart rate and blood pressure are usually within the normal range. Oxygen saturation is typically normal or slightly low for a given altitude, but overall correlates poorly with the diagnosis of AMS.[11] Facial and peripheral edema may be observed, but are not specifically related to AMS. Central nervous system (CNS) findings indicate HACE, not AMS.

The differential diagnosis of AMS is summarized in **Box 1**. Two conditions deserve special attention. Carbon monoxide poisoning is a risk at high altitude owing to use of heaters or stoves within confined spaces. Carbon monoxide poisoning is easily misdiagnosed as AMS, given the similar symptoms.[12,13] Migraine can also be confused with AMS, and hypoxia is a known trigger for migrainous headache in those with and without a previous history of migraine.[14,15] When there is diagnostic uncertainty, an altitude headache often dissipates within 15 to 20 minutes of supplemental oxygen administration, unlike headaches from other causes. Clinicians may find an oxygen trial useful if it is available.

High Altitude Cerebral Edema

Altered mental status and ataxia are the classic findings in HACE.[16] Individuals usually suffer from preceding AMS and/or HAPE over the previous 24 to 48 hours but isolated HACE can occur. Headache is often present but is not universal. Early symptoms include drowsiness and subtle psychological and behavioral changes, including apathy and social withdrawal.[17,18] Eventually, these more subtle signs lead to overt

Box 1
Differential of acute mountain sickness

- Migraine
- Carbon monoxide poisoning
- Dehydration
- Viral syndrome
- Alcohol hangover
- Physical exhaustion
- Heat exhaustion

confusion. Ataxia has been reported in approximately 40% to 60% of cases and papilledema may be present in up to 50%.[16] Gastrointestinal symptoms including anorexia and vomiting may also occur. Visual and auditory hallucinations and seizures are rare. HACE is an encephalopathy; focal CNS findings are unusual and should be investigated thoroughly. Retinal hemorrhages are associated with HACE, but may also be present in those who are asymptomatic. An initially alert patient with HACE may deteriorate rapidly to coma, so initial mental status is a poor predictor of eventual disease severity. It is critical to maintain a broad differential diagnosis for those patients with altered mental status at high altitude, especially in patients with atypical presentations or those who are not responding to conventional therapy. **Box 2** summarizes the differential diagnosis for HACE.

HACE diagnosis is based on the setting, symptoms, and findings. Imaging studies and laboratory analysis are primarily used to rule out an alternative diagnosis. Importantly, the clinician should evaluate for concurrent HAPE. Laboratory tests including electrolytes, complete blood count, glucose, ethanol level, carboxyhemoglobin level, and toxicology screen can be used to exclude other disorders (see **Box 2**).[18] Patients with HACE may mount a mild leukocytosis, so clinical correlation is necessary to exclude infection.[16] A lumbar puncture may be performed if there is sufficient concern for encephalitis or subarachnoid hemorrhage; typical findings in HACE include normal cell counts and elevated opening pressure. Values up to 220 cm water have been reported in the literature.[19] Head computed tomography typically shows white matter signal attenuation with effacement of sulci and flattening of gyri. MRI findings include increased T2 signal observed in the splenium of the corpus callosum.[20] Alternatively, MRI using susceptibility-weighted imaging can show hemosiderin deposition owing to microhemorrhage in the corpus callosum (**Fig. 3**). This finding is detectable by MRI for years after an episode of HACE, making this imaging useful when diagnosis of HACE is historically uncertain.[21] Because imaging findings lag behind clinical recovery, imaging can be used to confirm the diagnosis of HACE even after empiric therapy and clinical improvement.

Box 2
Differential of high altitude cerebral edema

- Hypoglycemia
- Hyponatremia
- Hypothermia
- CNS infection
- Postictal state
- Complex migraine
- Psychosis
- Stroke
- CNS space-occupying lesion
- Intracranial hemorrhage
- Carbon monoxide poisoning
- Drugs, alcohol or toxins

Abbreviation: CNS, central nervous system.

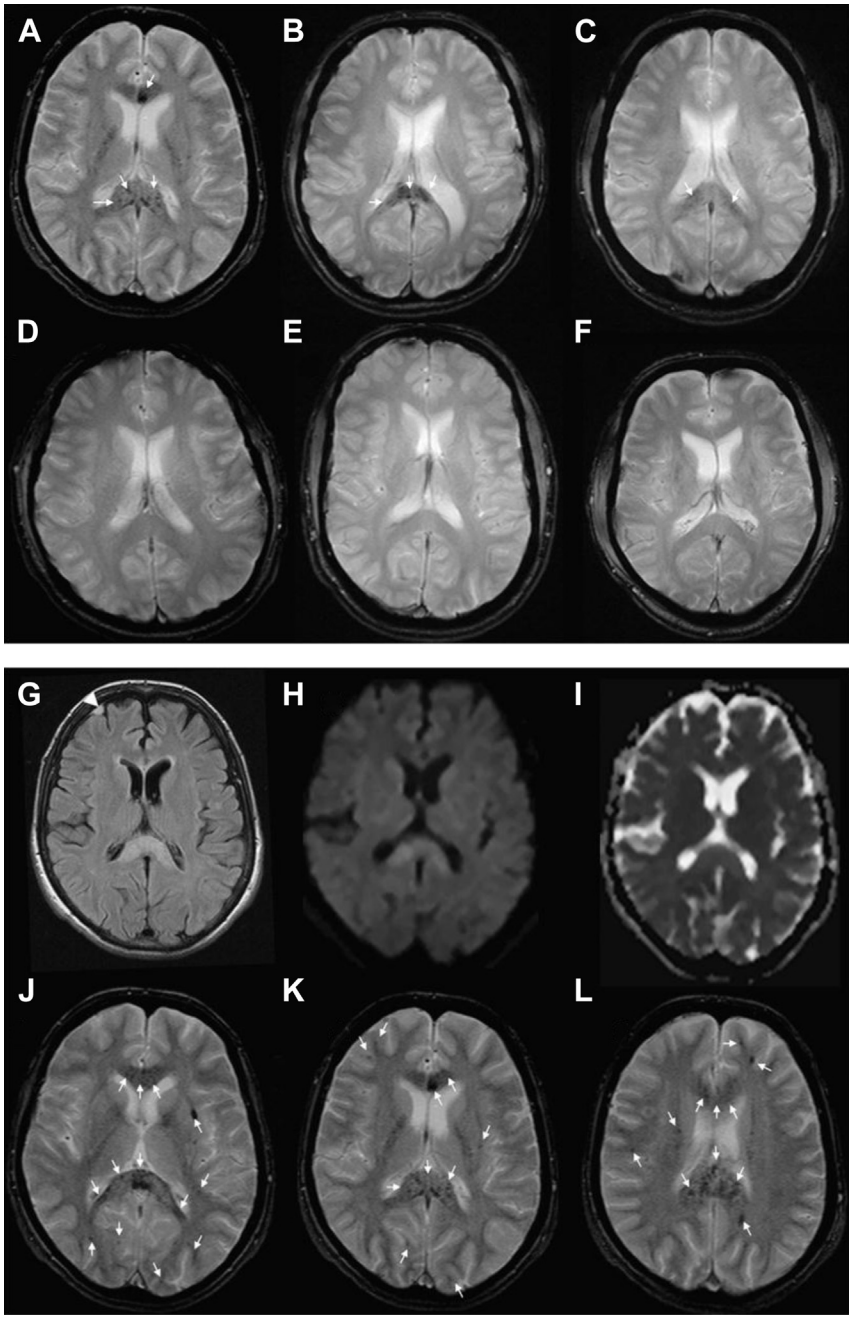

Fig. 3. MRI findings representative of HACE. Susceptibility-weighted T2* images show the differences between the normal MRI of acute mountain sickness patients (*D–F*) and HACE patients (*A–C*), with multiple lesions representing hemosiderin deposits predominantly located in the splenium of the corpus callosum (*arrows*). Fluid-attenuated inversion recovery (FLAIR) (*G*) shows edema in the corpus callosum. The right frontal meningioma (*arrowhead*) is an incidental finding. Areas of edema are confirmed by diffusion-weighted imaging (*H*), with increased values in the apparent diffusion coefficient (*I*), indicating increased water diffusivity compatible with vasogenic edema. Multiple microhemorrhages consistent with hemosiderin deposition (*arrows*) are displayed on the T2* images (*J–L*).

High Altitude Pulmonary Edema

The classic victim of HAPE is a young, healthy person, often male, who is fit enough to rapidly ascend to high altitude. Early recognition is paramount, because in this stage HAPE can be easily treated with descent or low-flow oxygen. Decreased exercise performance and dry cough are the earliest symptoms of HAPE. Whereas AMS is present in one-half of cases, it may notably be absent.[22] Symptoms typically develop on the second night of a new and higher sleeping altitude. Development of HAPE after 4 days at a given altitude is rare and should prompt the consideration of alternative diagnoses (**Box 3**). Without intervention, symptoms quickly progress from dyspnea with exertion to dyspnea at rest. Fever is common and does not preclude a diagnosis of HAPE. Oxygen saturation is often 10 to 20 points lower than asymptomatic individuals at the same altitude. As HAPE progresses, patients experience worsening tachycardia, tachypnea, lassitude, productive cough, and cyanosis. Eventually, altered mental status and coma develop, either from profound hypoxemia or concomitant HACE.

On physical examination, a prominent P_2 and right ventricular heave may be appreciated with auscultation and palpation. Râles are often first appreciated in the right mid-lung field. In a minority of patients, râles absent at rest can be elicited after brief exertion. Electrocardiographic findings of right heart strain may be observed, consistent with acute pulmonary hypertension. Chest radiographs typically show patchy lung infiltrates with normal heart size (**Fig. 4**). The absence of infiltrates on chest radiographs suggest an alternate diagnosis. Arterial blood gas analysis reveals respiratory alkalosis with severe hypoxemia. Partial pressure of arterial oxygen is typically between 30 and 40 mm Hg.[23]

PREVENTION AND TREATMENT OF HIGH ALTITUDE ILLNESS

The overall goals of prophylaxis and treatment of HAI are to optimize acclimatization to prevent illness, and to recognize and manage illness correctly. Three guiding principles hold true for the management of all HAI:

- Never proceed to a higher sleeping altitude with symptoms of HAI.
- Descend if symptoms do not improve despite expectant management or temporizing pharmacologic treatment.
- Descend and/or treat immediately in the presence of confusion, ataxia, or dyspnea at rest with relative hypoxemia.

Descent is the definitive treatment for all forms of altitude illness. However, descent may not always be possible owing to weather or logistic constraints. Nor is descent

Box 3
Differential diagnosis of high altitude pulmonary edema

- Asthma
- Bronchitis
- Heart failure
- Mucus plugging
- Myocardial infarction
- Pneumonia
- Pulmonary embolus

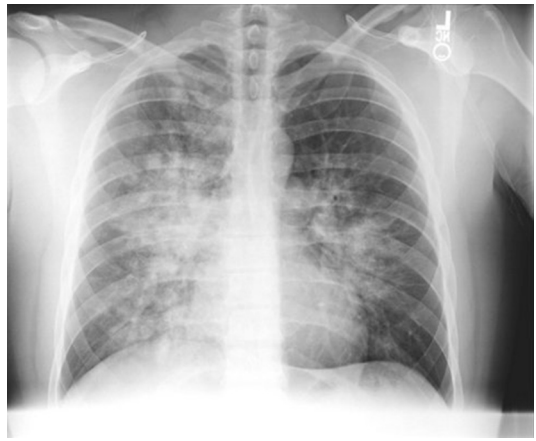

Fig. 4. Chest radiograph showing patchy lung infiltrates with normal heart size.

always necessary. Although prevention and treatment strategies are organized into pharmacologic and nonpharmacologic approaches, in clinical practice these strategies are often combined for best results. **Table 3** summarizes the pharmacologic approach for prevention and treatment of HAI, including newer strategies.

Pharmacologic Strategies

Prevention of acute mountain sickness

Acetazolamide Acetazolamide benefits those with a known history of AMS or those with rapid ascent to sleeping altitude above 2500 m.[24] By inhibiting the enzyme carbonic anhydrase, acetazolamide reduces renal reabsorption of bicarbonate, causing a bicarbonate diuresis and metabolic acidosis that increases one's respiratory rate and enhances (speeds) acclimatization. As a result, the Pa_{O_2} is higher. The recommended regimen is 125 mg orally twice daily, started 8 to 24 hours before the ascent. Using this lower dosage minimizes side effects.[25,26] The drug should be continued for the first 2 days at a stable altitude, or continued for ongoing ascent. It can be restarted safely if symptoms of AMS recur with ascent to a higher altitude. Acetazolamide reduces incidence of AMS by approximately 75% in persons ascending rapidly to sleeping altitudes of greater than 2500 m (>8200 ft).[27] Although several other pharmaceutical options are available, acetazolamide remains the mainstay for AMS prophylaxis.

Benzolamide Acetazolamide can have several side effects, including headache and nausea. It has also been linked with Stevens-Johnson syndrome.[28] More hydrophilic carbonic anhydrase inhibitors such as benzolamide may have fewer CNS side effects. Recently, benzolamide was compared with acetazolamide for the prevention and AMS.[29] In this trial, fewer side effects were noted in the benzolamide cohort. Unfortunately, benzolamide is not currently licensed for use in the United States. However, in the future, alternative carbonic anhydrase inhibitors may represent a viable alternative to acetazolamide once further validation is completed.

Dexamethasone Dexamethasone is an effective prophylactic agent for AMS.[24,30] However, because of more potential side effects, it is usually reserved for treatment. Dexamethasone is an appropriate agent for those with anaphylaxis to sulfonamides or acetazolamide intolerance. The dose for prophylaxis is either 2 mg PO every 6 hours or

Table 3
Pharmacologic strategies for high-altitude illness

Agent	Indication	Dosage	Adverse Effects	Comments
Acetazolamide	Prevention of AMS	125 mg every 12 h. Begin 24 h before ascent. Continue for at least 48 h after arrival at highest altitude.	Common: paresthesiae, polyuria, altered taste of carbonated beverages Less common: nausea, fatigue, headache Rare: Stevens-Johnson or anaphylaxis	Enhances acclimatization; pregnancy category C; avoid if breastfeeding
	Treatment of AMS	250 mg PO every 12 h.		
Dexamethasone	Treatment of AMS HACE	4 mg every 6 h PO, IM, or IV. 8 mg initially, then 4 mg every 6 h PO, IM, or IV.	Common: Mood changes, insomnia, dyspepsia Rare: Adrenal suppression, psychosis, hyperglycemia	Rapidly improves AMS symptoms, beware minor rebound symptoms; life saving in cases of HACE; pregnancy category C
Ibuprofen	Prevention of AMS?	600 mg every 8 h during ascent.	Dyspepsia; exercise-induced kidney injury	Risk of gastrointestinal bleed
Budesonisde	Prevention of AMS	200 μg every 12 h, beginning 3 d before ascent.	Sore throat, myalgias, headache, oral candidiasis	Vastly more expensive than acetazolamide or dexamethasone; optimal regimen needs validation
Tadalafil	Prevention of HAPE	10 mg PO every 12 h starting 24 h before ascent. Continue for 2–4 d at max sleeping altitude,	Common: headache, facial swelling Rare: priapism	BID dosing, compared with TID dosing with sildenafil; fewer side effects, less hypotension when compared with nifedipine; pregnancy category B
Nifedipine	Prevention of HAPE	30 mg extended release, PO every 12 h, starting 24 h before ascent.	Reflex tachycardia, hypotension (uncommon)	
	Treatment of HAPE	30 mg extended-release PO every 12 h.		Pregnancy category C; Not necessary, if oxygen available

Abbreviations: AMS, acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema; IM, intramuscularly; IV, intravenous.

4 mg PO every 12 hours, starting the day of ascent and continuing for the first 2 days at altitude, or for a rapid increase in altitude.

Budesonide In 2 recent studies, inhaled budesonide was shown to be effective in prevention of AMS.[31,32] In these experiments, 200 μg budesonide was inhaled twice daily, starting 3 days before ascent. In a study by Zheng and colleagues,[32] inhaled budesonide reduced the incidence of AMS by 36% relative to placebo, comparable with the reduction observed with oral dexamethasone in the same study. These data raise important as mechanistic question: Why is an inhaled steroid with minimal systemic absorption effective at preventing AMS? Although more study is necessary for external validation and to explore mechanism of action, these data may herald an important shift in the approach to AMS prophylaxis. Nonetheless, it is also important to consider that budesonide is far more expensive compared with acetazolamide and dexamethasone.

Ibuprofen Several recent studies have explored the efficacy of ibuprofen for prevention of AMS, but they did not compare ibuprofen with acetazolamide. In 1 trial, 86 individuals were taken from 1240 to 3810 m and were randomized to receive either ibuprofen or placebo. The ibuprofen cohort had a significantly lower rate of AMS (odds ratio, 0.3; 95% CI, 0.1–0.8).[33] During the ASCENT trial (Altitude Sickness in Climbers and Efficacy of NSAIDs Trial), trekkers in the Himalayas were randomized to placebo or ibuprofen on ascent from approximately 4200 to 4900 m. Using an intent-to-treat analysis, the investigators demonstrated that ibuprofen was somewhat effective for the prevention of AMS, but it was not in those who completed the protocol; nor did it prevent severe AMS.[34] In these studies, a regimen of 600 mg PO was given 3 times per day. More study is necessary, because it is not clear whether ibuprofen reduced headache as an analgesic or had a significant impact on AMS.

Ginkgo biloba Conflicting evidence exists on the efficacy of ginkgo biloba for AMS prophylaxis.[35,36] A lack of consistency between commercially available gingko preparations may explain these differing results. Despite the variable results, ginkgo is a safe option for those individuals who strongly prefer a more natural alternative.

Prevention of high altitude cerebral edema

Based on the pathophysiology, agents that prevent AMS and HAPE will also prevent HACE. However, adequate acclimatization is the best strategy.

Prevention of high altitude pulmonary edema

Nifedipine Nifedipine 30 mg PO every 12 hours while ascending may provide effective prophylaxis in HAPE susceptible individuals.[37] Although controlled data are scarce, nifedipine is used commonly for this purpose.

Phosphodiesterase inhibitors The phosphodiesterase inhibitors sildenafil and tadalafil have shown promise for prevention of HAPE.[38] These agents blunt hypoxic pulmonary vasoconstriction and thereby prevent the pathologic pulmonary hypertension associated with HAPE. Anecdotally, tadalafil is used more frequently than sildenafil because of its longer half-life. It is also important to note that both of these agents can cause headache. In 1 study, tadalafil 10 mg PO twice a day effectively prevented HAPE in HAPE-susceptible individuals started the day before ascent.[39]

Dexamethasone Dexamethasone was effective for preventing HAPE in HAPE-susceptible individuals in a single study.[39] Data are not available comparing efficacy of dexamethasone with nifedipine or other agents, and clinical experience is limited.

However, if an individual who is susceptible to both AMS and HAPE is required to travel to a high altitude, dexamethasone may offer a useful preventive approach.

Salmeterol Using high-dose inhaled salmeterol (125 μg twice daily), investigators were able to demonstrate a 50% reduction in the incidence of HAPE in those persons with known susceptibility, which is less than nifedipine or tadalafil.[40] Clinical experience is limited. Therefore, salmeterol is recommended as an adjunctive treatment in addition to a medication such as nifedipine.[41]

Treatment of acute mountain sickness

Acetazolamide Acetazolamide is not well-established as a treatment for AMS, unlike for prevention. A single small study found that 2 doses of 250 mg given 8 hours apart was superior to placebo and improved gas exchange.[42] Specific data regarding optimal treatment dose are lacking. Side effects are dose related and include peripheral paresthesiae, headache, and nausea. Treatment should be continued until symptoms of AMS have abated.

Dexamethasone Dexamethasone 4 mg every 6 hours is effective for treatment of AMS. Dexamethasone can be administrated PO, intramuscularly, or intravenously depending on available resources and the presence of vomiting. However, dexamethasone is best reserved for cases of moderate or severe AMS because of its side effect profile and small risk of rebound symptoms. A short taper period is not required if used for 5 days or less. In contrast with acetazolamide, dexamethasone does not aid acclimatization. Combination treatment with acetazolamide has not been studied, but acetazolamide to speed acclimatization and dexamethasone to abort illness is rational, and is used in the field.

Symptomatic care (analgesia plus antiemetic)

Symptomatic treatment of AMS is often sufficient. Acetaminophen 650 to 1000 mg or ibuprofen 600 mg are both effective for headache. Ondansetron orally disintegrating tablets dosed at 4 mg every 4 to 6 hours will effectively treat nausea and vomiting associated with AMS. Ultimately, pharmacologic treatment for AMS offers an alternative to descent or oxygen if these options are unavailable, or if symptoms are only mild to moderate in severity.

Treatment of high altitude cerebral edema

Dexamethasone The gold standard for treatment of HACE is descent whenever possible and evacuation to a medical facility (see Nonpharmacologic Approach). However, dexamethasone should also be administered and is given as an 8-mg loading dose, followed by 4 mg every 6 hours. In the patient with HACE, dexamethasone must often be given intramuscularly owing to coma or tenuous mental status.

Other adjunctive treatment There are no data to support the use of hypertonic saline, loop diuretics, or mannitol in HACE patients. Loop diuretics should be avoided because of the danger of hypotension, reduced cerebral perfusion pressure, and ischemia.

Treatment of high altitude pulmonary edema

Nifedipine Controlled studies for the treatment of HAPE are lacking and only 1 study has demonstrated the efficacy of nifedipine for HAPE.[43] Nonetheless, nifedipine has been used extensively in the field, especially when oxygen and descent are not available. The suggested regimen is nifedipine 30 mg (extended release) administered twice daily by mouth until the victim has descended and been evacuated to medical

care. However, recent data suggest that nifedipine is unnecessary if descent and oxygen therapy are available.[44]

Phosphodiesterase inhibitors There are only case reports supporting the use of phosphodiesterase inhibitors for treatment of HAPE.[45] However, their use in the field is relatively common in anecdotal reports, when oxygen and descent are not available. Tadalafil 10 mg twice daily by mouth is the accepted regimen. Importantly, tadalafil should not be used with nifedipine owing to the overlap in mechanism of action. This could result in deleterious hypotension.

Neither of these pharmaceutical regimens are as effective as oxygen or descent for the treatment of HAPE.

Nonpharmacologic Strategies

Prevention of high altitude illness

Graded ascent Graded ascent to allow time for acclimatization is the best prevention for all HAI. For those traveling from sea level to the Rocky Mountains (>2500 m), spending a night at an intermediate elevation such as Denver or Salt Lake City (1500–2000 m) lessens the risk of AMS. Although controlled studies are scare,[46] above 2500 m mountaineers and trekkers should not ascend faster than 500 m/d. Furthermore, for every 1500 m gain in sleeping elevation, an extra night should be budgeted for acclimatization.[41]

Preacclimatization Preacclimatization strategies are now being used by several commercial guiding companies in the Himalaya to reduce "time to summit day" when climbing. These strategies use intermittent exposure either to hypobaric hypoxia or normobaric hypoxia through a commercial hypoxia tent, chamber, or mask. These devices vary considerably in hypoxic "dose" (simulated altitude) and exposure time. Only a few preacclimatization programs are able to demonstrate a meaningful decrease in AMS incidence.[47–49] Intermittent, short-term exposure to hypoxia of less than 6 h/d does not seem to prevent AMS. Sleep quality may also suffer during these preacclimatization programs.[50]

Remote ischemic preconditioning Remote ischemic preconditioning is a technique in which brief, discrete episodes of ischemia–reperfusion are induced in the extremities, typically with an inflated blood pressure cuff. Data suggest that this preexposure may result in resistance to further hypoxemic insults in tissue such as the myocardium.[51] Theoretically, such an approach could have a benefit for the prevention of AMS. Unfortunately, the application of this technique for AMS prevention is not supported currently by the literature.[52]

Oxygen Low-flow oxygen (<2 L/min), delivered via nasal cannula, especially during sleep, is a reasonable strategy for HAI prevention. Oxygen relieves the physiologic stress of hypobaric hypoxia and effectively simulates sea level if below 3000 m. Oxygen concentrators are readily available in mountain resort towns of the Rocky Mountain region and oxygen supplementation may be an appropriate strategy for lowlanders, especially those with chronic medical conditions, or those with second homes at high altitude.

Treatment of acute mountain sickness

Oxygen Oxygen quickly and effectively relieves symptoms of AMS, especially headache and dizziness. Nocturnal administration of low-flow oxygen (0.5–1 L/min) is often sufficient to alleviate mild to moderate AMS.

Descent A decrease in altitude of 300 to 1000 m (980–3280 ft) will resolve AMS.

Treatment of high altitude cerebral edema

Oxygen If available, oxygen should be given for any patient with suspected HACE. Given the high rate of concomitant HAPE, oxygen supplementation becomes even more important in the treatment of critically ill patients with HAI. Oxygen saturation should be titrated to 90% or higher. Care should be given to avoid prolonged hyperoxia given the recent association of increased mortality in critically ill patients.[53] Comatose patients may require oxygen supplementation through an advanced airway.

Body position Keep the patient's head elevated to 30° in the supine position.

Descent Descent is critical for victims of HACE. At a minimum, providers should attempt to evacuate the patient to an altitude where the patient was previously asymptomatic. Descent of at least 1000 m is an alternative goal.

Portable hyperbaric chambers Portable hyperbaric chambers are effective for the treatment of severe HAI (**Fig. 5**).[54] The patient is inserted into a zippered fabric chamber. A rescuer then raises the ambient pressure within the chamber to 0.9 kg/2.5 cm^2 (2 lb/$in.^2$) with a manual or automated pump. This increase in pressures simulates a descent of up to 1500 m (4920 ft), depending on the ambient elevation. A valve system provides sufficient ventilation to avoid carbon dioxide accumulation. Patients must stay in the chamber for several hours to see meaningful effect, and rebound symptoms are possible when the patient is removed from the bag.[55] Clinical care in a chamber can be complicated by vomiting, voiding, suboptimal communication, and claustrophobia. Nonetheless, these devices can be life saving if descent is impossible owing to weather or logistics, and if oxygen is not available. More recent designs have decreased the weight of these portable chambers to less than 4 kg (8.8 lbs).

Treatment of high altitude pulmonary edema

Oxygen Oxygen supplementation immediately lowers pulmonary artery pressure in those with HAPE. Oxygen, even without descent, can resolve mild to moderate HAPE within 2 to 3 days. In resource-rich settings such as Colorado ski resorts, supplemental oxygen is a practical alternative to descent or evacuation. Oxygen flow rates should be titrated to maintain an oxygen saturation of 90% to 92%.

Descent If oxygen is unavailable, all patients with suspected HAPE should be evacuated to an altitude at least 1000 m lower.

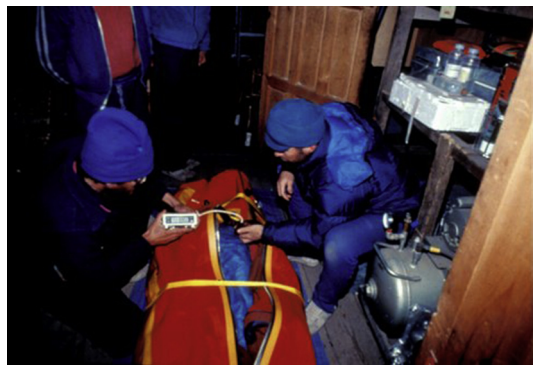

Fig. 5. Portable hyperbaric chamber.

Portable hyperbaric chambers See the description in the section on the treatment of high altitude cerebral edema.

Other management considerations Providers should attempt to mitigate any environmental factors that would lead to further pulmonary hypertension. Because cold stress increases the pulmonary artery pressure, the patient should be kept warm. Patients should also avoid exertion whenever possible.

TREATMENT COMPLICATIONS AND PITFALLS

Pharmacologic

Acetazolamide

There are decades of experience using acetazolamide for AMS. Although acetazolamide is usually a safe drug, there are several considerations worth noting. Acetazolamide does contain a sulfhydryl moiety. Some individuals who are allergic to antimicrobial sulfonamides may also be allergic to nonmicrobial sulfonamide drugs. Therefore, acetazolamide should be avoided in individuals with a history of anaphylaxis to sulfa antibiotics. In those individuals who have experienced rash or less severe reactions to sulfa antibiotics, a test dose of acetazolamide before ascent is a reasonable strategy to test tolerance. The most commonly reported side effects are increased urination, paresthesia, fatigue, and gastrointestinal upset.[56] Stevens-Johnson syndrome is rare, but documented.[28]

Dexamethasone

Dexamethasone is a remarkably effectively drug, with wide applications across the spectrum of HAI. However, its use must be weighed cautiously against the risk of adverse events such as adrenal suppression and steroid psychosis. These adverse events typically occur with use beyond 7 days. Although controlled data are lacking, there are reports of frequent use or abuse among the mountaineering population in the Himalayan Everest with disastrous consequences.[57]

Ibuprofen

Recent data suggest that mountaineers climbing above 4000 m are at risk for hemorrhagic gastritis and duodenitis based on endoscopies performed at extreme altitude.[58] Whether the use of ibuprofen for AMS places individuals at higher risk for gastrointestinal bleed, or whether the risk of altitude gastritis or duodenitis translates to lower altitudes (2000–4000 m) is worthy of further study.

Nonpharmacologic

- Critically ill patients with HACE who progress to coma require an advanced airway and bladder drainage. In these patients, avoid hyperventilation, which may result in cerebral ischemia.
- Avoid rapid depressurization of portable hyperbaric chambers, which may result in middle ear squeeze. Although barotrauma has not been reported, it is theoretically possible.
- Critically ill patients with HAPE are often volume depleted and require intravenous fluid resuscitation. Despite the presence of pulmonary edema, intravenous fluids are not contraindicated to treat dehydration because cardiac function is most often preserved.
- Monitor blood pressure carefully in patients with HACE. Hypotension may lead to a drop in cerebral perfusion pressure, leading to further cerebral ischemia.
- Infection and HAPE may coexist; when in doubt, treat for both.

SUMMARY

- Acetazolamide remains the best choice for prevention of AMS.
- The best treatment for all HAI is descent or oxygen, or both.
- Dexamethasone is excellent for treating moderate to severe AMS, and for HACE.
- Supplemental oxygen is first-line therapy for HAPE; descent is primary therapy if oxygen is not available. Oxygen and descent are more efficacious than pharmacologic therapy such as nifedipine or phosphodiesterase inhibitors.
- Descent is the definitive treatment for HACE and should not be delayed. Dexamethasone and supplemental oxygen are important adjunctive treatments for HACE until descent can be facilitated.

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