Acute mountain sickness and high-altitude cerebral edema

Authors: Scott A Gallagher, MD, Peter Hackett, MD
Section Editor: Daniel F Danzl, MD
Deputy Editor: Michael Ganetsky, MD

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INTRODUCTION

Anyone who travels to high altitude, whether a recreational hiker, skier, mountain climber, military personnel, or rescue worker, is at risk of developing high-altitude illness. Acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) represent a continuum of the cerebral form of such illness.

The pathophysiology, clinical presentation, treatment, and prevention of AMS and HACE are reviewed here. Other forms of high-altitude illness are discussed separately. (See "High-altitude pulmonary edema" and "High-altitude illness: Physiology, risk factors, and general prevention".)

PATHOPHYSIOLOGY

AMS and HACE are generally considered to share an underlying pathophysiology. Although several aspects of this pathophysiology remain unclear, the concept that AMS/HACE represents a continuum, and that AMS can progress to fatal HACE, fits with clinical experience and is helpful for management. A full discussion of the pathophysiology of AMS and HACE is beyond the scope of this review but can be found in the attached references [1,2].

Cerebral edema is consistently found in neuroimaging and at autopsy in patients with HACE and sometimes on magnetic resonance imaging (MRI) in patients with severe AMS [1,3,4]. In those with HACE, MRI studies reveal reversible cytotoxic and vasogenic brain edema, with characteristic increases in T2 and fluid-attenuated inversion recovery (FLAIR) signal in the splenium of the corpus callosum and subcortical white matter, transient restricted diffusion, and micro-hemorrhages on susceptibility-weighted imaging (SWI). These findings indicate increased blood-brain barrier (BBB) permeability.

Brain herniation from severely increased intracranial pressure (ICP) is the cause of death in HACE. Fatal cases demonstrate not only gross cerebral edema, but small petechial hemorrhages and sometimes venous sinus or other thromboses [5,6].

The relationship between cerebral edema and mild to moderate AMS is less clear. The initiating event for AMS is cerebral vasodilation in response to hypoxemia, which occurs in all persons exposed to hypoxic environments, but is exaggerated in those who develop AMS [7,8]. This may trigger activation of the trigeminal vascular system in a manner similar to migraine, causing headache and nausea [9]. In addition, vasodilation causes an increase in brain volume, diminished compliance, and transient increases in ICP [10]. According to the "tight fit" hypothesis, persons with a larger brain-to-cranial vault ratio (ie, less room for the swollen brain) become more symptomatic than individuals with a smaller ratio (ie, more room).

AMS resolves in most persons as arterial oxygen content increases and cerebral blood flow decreases towards normal over four days of acclimatization. However, in those who go on to develop HACE, there is evidence of a cascade of edema formation, starting with cytotoxic (intracellular) edema, leading to extravascular ionic edema, then vasogenic edema with protein extravasation, and ultimately loss of integrity of the BBB with extravasation of red cells and micro-hemorrhages, as seen on MRI [11].

EPIDEMIOLOGY

AMS epidemiology — AMS is by far the most common high-altitude illness. As with all high-altitude illnesses, the risk of AMS depends upon individual susceptibility, the elevation reached, and the rate of ascent. Thus, while AMS is uncommon below 2000 m (6500 ft), it is quite common (approximately 25 percent incidence) at sleeping elevations between 2000 and 3000 m, where many ski resorts are located (table 1 and table 2). Recreational skiers traveling to such resorts generally complete their transition to high altitude quickly

(within two days), further increasing their risk of AMS. A meta-analysis of 91 studies involving just under 67,000 participants found that above 2500 m (8200 ft), for every 1000-m (3300-ft) increase in altitude, there was a 13 percent increase (95% CI, 9.5-17) in the prevalence of AMS [12]. The prevalence at 2500 m was 19 percent.

AMS is nearly universal (85 percent incidence) among those flying directly to Syangboche, Nepal (elevation 3800 m) [13]. It occurs in 67 percent of climbers taking one to two days to reach the summit of Mount Rainier (4392 m) but affects only 30 percent of climbers taking approximately one week to reach the summit of Denali (6194 m). Conversely, the incidence of AMS is negligible among individuals who remain at altitude only an hour or two after driving to Pikes Peak (elevation 4300 m) [14].

AMS occurs in both sexes and at all ages, although it is unclear if older age is a protective factor as some authorities have suggested [15-18]. Females may be at slightly higher risk than males [19], but children and adults are both susceptible [15,20,21]. High-altitude illness in children is discussed in detail separately. (See "High-altitude disease: Unique pediatric considerations".)

Neither youth nor physical fitness confers protection against AMS. Obesity, heavy exertion upon arrival at altitude, and residence at low altitude (<1500 m) prior to ascent all appear to increase risk [22]. However, smoking, oral contraceptives, and menstruation do not appear to increase risk [15]. A more detailed discussion of the risk factors for high-altitude illness generally is provided separately. (See "High-altitude illness: Physiology, risk factors, and general prevention".)

HACE epidemiology — The incidence of HACE is reported to be 0.1 to 2 percent at elevations in excess of 3000 to 4000 m (9800 to 13,000 ft), although HACE has been reported at altitudes as low as 2100 m [22,23]. HACE is often associated with high-altitude pulmonary edema (HAPE), especially at relatively lower altitude. In fact, pure cerebral edema without pulmonary edema appears to be uncommon below 5000 m [15,24].

HACE appears to occur in all ages and both sexes in a fashion similar to AMS [25]. Younger males may be at greater risk for behavioral reasons, such as continuing to climb in the presence of AMS symptoms.

As with AMS, there are no physiologic, anatomic, or genetic characteristics that reliably predict susceptibility to HACE. Persons with pre-existing elevated intracranial pressure (ICP), hydrocephalus, space-occupying lesions, and other neurologic conditions are at increased risk for HACE [26]. Individuals with a history of AMS or HAPE are at greater risk of recurrence

and of developing HACE [15].

PRESENTATION AND DIAGNOSIS

AMS diagnosis — AMS is diagnosed clinically based upon the appearance of typical symptoms in a person who lives at low altitude but has recently ascended to high altitude (generally over 2000 m) [27,28].

The onset of AMS is usually delayed for 6 to 12 hours following arrival at high altitude but can occur as rapidly as within one to two hours or as late as 24 hours. Symptoms are often most severe after the first night, generally resolve in one to two days if there is no further ascent, and do not recur at the same altitude.

Symptoms in adults resemble those of an alcohol hangover: primarily headache (which is often associated with fatigue), lightheadedness, anorexia, nausea and vomiting, and disturbed sleep with frequent awakening. Symptoms may be mild or severely debilitating.

Symptoms of AMS in infants and young children are nonspecific and can include fussiness, crying, decreased playfulness, poor feeding, disrupted sleep, and vomiting. AMS alone does not cause an elevation in body temperature, and an appropriate evaluation for fever based upon age and immunization status is warranted in febrile children at altitude. AMS is often a diagnosis of exclusion in this group. The clinician should pay close attention to the child's signs and response to oxygen, and when in doubt should err on the side of a longer observation period before attributing symptoms to a benign cause. (See "High-altitude disease: Unique pediatric considerations", section on 'Clinical manifestations'.)

AMS may reappear upon ascent to higher altitudes. On occasion, symptoms of AMS may persist for a week or more despite no further ascent. In such cases, descent is required if there is no improvement with standard treatment. (See 'AMS treatment' below.)

There are no reliable objective measures for the diagnosis of AMS. Physical examination, laboratory values, vital signs, and pulse oximetry typically fall within the normal range for a given altitude, although oxygen saturation (SpO_2) is generally in the low to mid-range of normal values. Diagnosis may be straightforward in a young, otherwise healthy individual who has recently ascended to high altitude. However, the diagnosis may be difficult in older adults, young children, and those with confounding illness.

Supplemental oxygen may be used to support the clinical diagnosis. Providing 2 to 4 L per

minute of oxygen by nasal cannula for 15 to 20 minutes prior to other interventions should markedly improve headache and other symptoms in cases of AMS.

The onset of symptoms more than two days after arrival at a given altitude, absence of headache, dyspnea at rest, and failure to improve rapidly with supplemental oxygen should prompt the clinician to search for an alternative diagnosis. No radiographic or laboratory testing is warranted unless the diagnosis is unclear. Differential diagnoses to consider include carbon monoxide poisoning, migraine, dehydration, exhaustion, hyponatremia, viral syndrome, alcohol hangover, bacterial infection, and subarachnoid hemorrhage.

Research studies often employ a scoring system, such as the Lake Louise AMS Score, for diagnosis (table 3). Other instruments to diagnose AMS have been reported (eg, Acute Mountain Sickness-Cerebral Score, Visual Analog Scale for the Overall Feeling of Mountain Sickness, Clinical Functional Score [CFS]). Using the Lake Louise AMS Score as the standard, all appear to have similar diagnostic accuracy [12]. Most experts do **not** routinely use such scoring systems to diagnose AMS. For high-altitude clinics and research purposes, the CFS is easy to administer relative to the other scores and may be a reasonable screening tool to identify potential patients with AMS (table 4) [29]. Although the specificity of the CFS is low (67 percent), sensitivity is high and allows for the capture of patients whose AMS syndrome is not primarily headache [12].

HACE diagnosis

Clinical presentation — HACE generally occurs in individuals with AMS and/or high-altitude pulmonary edema (HAPE) at elevations over 3000 to 3500 m [15]. The hallmarks of HACE are encephalopathic symptoms and signs, including ataxic gait, severe lassitude, and progressive decline of mental function and consciousness (irritability, confusion, impaired mentation, drowsiness, stupor, and finally coma).

Signs of abnormal coordination, such as impaired performance of finger-to-nose and heel-to-toe walking tests, may be present. Focal neurologic findings, such as hemiparesis, slurred speech, or a discrete visual deficit, may rarely develop but are not typical and should raise concern for an alternative diagnosis such as ischemic stroke, intracranial hemorrhage, or hypoglycemia.

The onset of general neurological signs (ie, encephalopathy and ataxia) signifies the transition from AMS to HACE. This transition can occur unpredictably and may require as long as three days or as little as 12 hours. HACE develops faster in patients with HAPE, most likely as a result of severe hypoxemia [15]. Patients with HAPE manifest pulmonary findings,

such as crackles. (See "High-altitude pulmonary edema".)

Early symptoms of HACE may be missed or mistaken for exhaustion. Lethargy and irritability may manifest initially as diminished exercise performance, lack of participation in group activities, and the desire to be left alone. Even ataxia, the earliest physical sign of HACE, may be missed if the patient is lying in bed, insisting that he is well and simply wants to be left alone. The clinician may observe papilledema.

A working diagnosis of HACE can be made presumptively and treatment started in any patient with a history of recent ascent (especially above 3500 m) and signs of encephalopathy. After treatment, the clinician can reconsider the differential diagnosis [14]. (See 'HACE treatment' below.)

Diagnostic testing — With the exception of brain magnetic resonance imaging (MRI), ancillary testing is only useful for excluding other diagnoses.

In HACE, the white blood cell count may be elevated. Lumbar puncture may reveal an increased opening pressure, but evaluation of the cerebral spinal fluid reveals normal findings [14]. Pulse oximetry consistently shows hypoxemia in HACE, but according to several observational studies, it is not a reliable means for detecting AMS [30-33]. Arterial blood gas often reveals exaggerated hypoxemia and respiratory alkalosis.

A chest radiograph may reveal pulmonary edema. Computed tomography (CT) of the brain may show cerebral edema and attenuation of signal more in the white matter than gray matter.

MRI is more revealing, showing characteristic intense T2 and fluid-attenuated inversion recovery (FLAIR) signal in the white matter, especially the splenium of the corpus callosum, with no gray-matter lesions (image 1) [15]. There is no correlation between the severity of edema and subsequent clinical outcome [3]. Since MRI may remain abnormal for days to weeks, it can be useful to establish the diagnosis of HACE even after recovery. Hemosiderin deposits may be present on MRI years after HACE [24].

TREATMENT

AMS treatment

General approach — Treatment of AMS is based upon symptom severity, available resources, and, in mild cases, patient preference [27,28,34]. Mild illness can be treated

conservatively (avoid further ascent, limit activity) with symptomatic treatment (eg, analgesic, antiemetic) offered as needed. Patients with moderate to severe symptoms may require medication (eg, acetazolamide or dexamethasone), supplemental oxygen, or descent if medical resources are limited or absent. In the field, portable hyperbaric therapy may be available when supplemental oxygen is in short supply or unavailable. The same general treatment approach is used for both children and adults.

The authors' approach to patients with more severe symptoms is to offer descent, oxygen if available, or dexamethasone. Those who recover and wish to continue to travel at altitude should be offered acetazolamide to aid with acclimatization. (See 'Medications' below.)

It is important that group members and the afflicted individual remain alert for any symptoms or signs of worsening disease, particularly at elevations where AMS may rapidly progress to HACE (above 4000 m). Individuals with symptoms of AMS must be discouraged from ascending to higher elevations until symptoms have subsided. This may be difficult in the face of implicit or explicit pressures from members of the patient's climbing or hiking group, who do not wish to disrupt their schedule, or the patient's own desire to continue.

Conservative treatment — Patients with AMS should avoid further ascent, limit physical activity, and seek further care if any symptoms worsen. They should avoid alcohol and other respiratory depressants because of the danger of exacerbating hypoxemia during sleep. Symptomatic treatment, such as basic analgesics for headache and antiemetics, is often helpful. With conservative treatment, most patients successfully acclimatize over 24 to 48 hours, and symptoms resolve [35].

Symptomatic therapy — Symptomatic therapy for headache may include aspirin, acetaminophen, and ibuprofen or other nonsteroidal antiinflammatory drugs (NSAIDs). Promethazine and particularly ondansetron may be useful for nausea and vomiting. We avoid sleeping medications; treatment with acetazolamide is preferable.

Descent — Descent is always effective treatment for AMS, but it is not mandatory or necessary except in the setting of intractable symptoms or suspicion that illness is progressing. Descent to an altitude lower than that where symptoms started effectively reverses AMS. Although the person should descend as far as necessary for improvement, descending 500 to 1000 m (1600 to 3300 ft) is usually sufficient [15].

Individuals with AMS symptoms must **not** ascend to higher altitudes for sleeping. Doing so is a common reason for developing severe high-altitude illness, including HACE and high-altitude pulmonary edema (HAPE).

AMS patients must be carefully monitored for any sign that illness is progressing and should descend immediately if symptoms worsen despite rest or treatment. Absolute indications for immediate descent include neurologic findings (ataxia or change in consciousness) and signs of pulmonary edema. Subtle changes such as irritability, lethargy, diminished performance, and dyspnea at rest should also alert team members that the patient may be progressing toward HACE or HAPE.

Oxygen — Supplemental oxygen effectively relieves the symptoms of AMS and can serve as an alternative to descent [36]. Low-flow oxygen (1 to 3 L per minute) can be given by nasal cannula using a home oxygen concentrator or stored oxygen, if available. In the field, oxygen supplies are limited, and oxygen therapy provided at 0.5 to 1 L per minute may both relieve symptoms and help conserve supplies. Supplemental oxygen can also be used intermittently or as perceived necessary by the patient based upon the severity of symptoms.

Oxygen therapy is generally prescribed for 12 to 48 hours or during sleep only, if symptoms are not severe. Some patients will respond to short-term treatment of an hour or so and remain improved. The small oxygen canisters that are widely available contain only 2 to 10 L of oxygen (depending on size), enough for only minutes of breathing, and are therefore inadequate for treating or preventing high-altitude illness.

Hyperbaric therapy — Portable, lightweight (less than 5 kg), manually inflated hyperbaric chambers are common in remote mountain clinics and on expeditions, where supplemental oxygen supplies are limited. By increasing barometric pressure, hyperbaric bags are capable of simulating a descent of 2500 m or more, depending upon the altitude where they are used. They are effective without supplemental oxygen or may be used with an oxygen cylinder in the chamber to augment effectiveness.

One hour of treatment in a pressurized chamber relieves symptoms, although they return within 12 hours [37]. Nevertheless, hyperbaric bags can be an effective temporizing measure while awaiting descent or the benefits of medical therapy. With more severe illness, long-term (12 hours or more) treatment may be necessary to resolve AMS completely.

Although effective, hyperbaric chambers are generally unnecessary for the treatment of AMS in the hospital setting and at lower elevations where supplemental oxygen alone is usually sufficient to alleviate symptoms.

Medications — A summary of medications used to treat high-altitude illness is provided (table 5). The agents used to treat AMS are discussed in greater detail below.

Acetazolamide — Treatment with acetazolamide accelerates acclimatization to high altitude [38]. Acetazolamide, 125 to 250 mg taken orally twice daily, may be prescribed until acclimatization improves and symptoms resolve, which usually requires one to three days while the patient remains at the same altitude. Return to activity and further ascent are **not** advised until symptoms have resolved. The dose of acetazolamide is debated and ranges up to 750 mg daily, but generally, 125 to 250 mg twice daily is sufficient to alleviate symptoms while minimizing side effects [39].

Few studies have rigorously assessed the effectiveness of acetazolamide in the treatment (rather than prophylaxis) of AMS. Our approach is based upon clinical experience and extrapolation from prevention trials.

Dexamethasone — Treatment with dexamethasone alleviates the symptoms of AMS but does **not** improve acclimatization [40,41]. Dexamethasone 4 mg taken orally or intramuscularly, up to every six hours, for one to two days can be prescribed alone, in lieu of acetazolamide, or in combination with acetazolamide. Most experts recommend dexamethasone only for moderate to severe AMS and advise against further ascent while taking dexamethasone alone because of the risk of symptoms recurring or worsening when the drug is stopped.

Some providers prescribe both dexamethasone (to relieve AMS symptoms) and acetazolamide (to augment acclimatization). While side effects are generally minimal with one to two days of dexamethasone, hyperglycemia may occur. Use is generally limited to a duration of 48 to 72 hours, so tapered dosing is unnecessary.

HACE treatment

General approach — Unlike AMS, HACE requires immediate intervention [34]. Descent is the definitive treatment. Dexamethasone, supplemental oxygen, and hyperbaric therapy all play important roles in facilitating descent or temporizing illness until evacuation is possible.

HACE most often occurs in remote locations at altitudes over 3000 to 4000 m, from which immediate descent may not be feasible. Therefore, early recognition and treatment are critical. The most important action is to evacuate the patient to lower altitude before their condition renders them unable to care for themselves or assist with descent. If immediate descent is not possible, portable hyperbaric therapy and oxygen may be lifesaving [14,15].

Descent — Immediate descent at the first suspicion of HACE, while the victim is still ambulatory, is crucial to a favorable outcome. Evacuation becomes far more onerous, and

potentially impossible, once the patient is nonambulatory, comatose, or requiring airway management. Based upon clinical experience, a descent of approximately 1000 m is usually lifesaving [42]. Persons remaining symptomatic should proceed to a hospital. Persons with rapid recovery and complete resolution of symptoms should consult a medical provider on whether further descent is necessary and if or when reascent is advisable. A telemedicine consultation, if available, is acceptable and practical given the circumstances.

Dexamethasone — Dexamethasone is a critical rescue medication for all extended excursions above 3000 to 4000 m where medical care is not available. It should be administered immediately upon the first suspicion of HACE (usually ataxia or change in consciousness) at an initial dose of 8 to 10 mg orally, intramuscularly, or intravenously (IV), followed by 4 mg every six hours until descent is achieved. Dexamethasone works well when provided early in the course of HACE and may markedly improve the patient's condition and ability to assist with evacuation [43].

Dexamethasone is **not** a substitute for immediate descent. Unlike acetazolamide, dexamethasone does not facilitate acclimatization and may give a false sense of security when symptoms diminish [44]. Symptoms can recur once the drug is stopped if descent has not been accomplished [40].

No clinical studies have rigorously assessed dexamethasone for the treatment (rather than prophylaxis) of HACE. The use of dexamethasone described here is based primarily upon broad clinical experience. Treatment with other glucocorticoids may also be effective, but this has not been studied. A summary of medications used to treat high-altitude illness is provided (table 5).

Oxygen — Sufficient oxygen should be given to maintain the oxygen saturation (SpO_2) above 90 percent (if oximetry is available) [14,15]. Flow of 2 to 4 L per minute by facemask or nasal cannula is generally adequate. However, high-flow oxygen should be given if HAPE coexists. (See "High-altitude pulmonary edema".)

Hyperbaric therapy — Although formal studies are lacking, treatment in a portable, manually inflated hyperbaric chamber may be lifesaving when circumstances conspire to prevent immediate descent [45,46]. For HACE, hyperbaric treatment should be combined with dexamethasone and supplemental oxygen, if available.

Comatose patient — Comatose patients may be treated in a portable hyperbaric chamber, but with appropriate precautions to protect the airway. Systemic hypotension will cause cerebral ischemia and must be avoided. Therefore, judicious IV hydration with isotonic

crystalloid may be necessary. If resources are available, comatose patients should have bladder catheterization to help assess fluid status, in addition to usual care.

The management of patients with HACE who require mechanical ventilation can be difficult. Attempting to reduce intracranial pressure (ICP) by intubation and hyperventilation may be reasonable, but these patients have a respiratory alkalosis, and overventilation could cause cerebral ischemia. Oxygen alone markedly decreases cerebral blood flow and ICP at high altitude. Therefore, these patients should not be hyperventilated if they are well oxygenated. The fraction of inspired oxygen (FiO_2) should be increased if oxygenation is inadequate, rather than attempting alternative maneuvers that may increase airway pressures, thereby potentially raising ICP.

Once transferred to a hospital where monitoring is possible, other measures to reduce ICP may be attempted, if it remains elevated [14]. Emergency consultation with neurology and neurosurgery should be obtained. Although ICP may normalize with oxygen and descent, prolonged unconsciousness may result from the metabolic consequences of hypoxia. (See "Evaluation and management of elevated intracranial pressure in adults".)

In less severe cases, recovery is often rapid upon descent. Others may remain comatose for days and not fully recover for weeks [3]. In such prolonged cases, other causes for coma must be thoroughly assessed. (See "Stupor and coma in adults".)

HACE may reach an irreversible stage before descent, in which case the patient will die regardless of evacuation, medication, or other treatment. In survivors, HACE can cause long-term sequelae and even permanent impairment [3,47].

PHARMACOLOGIC PREVENTION OF AMS/HACE

General approach — In general, clinicians should reserve prophylactic medications for high- to moderate-risk situations, particularly individuals with a history of altitude intolerance who must ascend at a similar rate and those making a rapid ascent to high altitude. Even in individuals with a history of high-altitude illness, gradual ascent should be emphasized over pharmacologic prophylaxis. Often, ascending at a slower rate than the previous offending ascent allows individuals to avoid illness. Nonpharmacologic measures to prevent high-altitude illness are discussed separately. (See "High-altitude illness: Physiology, risk factors, and general prevention".)

For those at high to moderate risk, prophylaxis with acetazolamide or dexamethasone may

be beneficial. Acetazolamide is the drug of choice; dexamethasone is used when acetazolamide is not tolerated or in special circumstances discussed below. A summary of medications used for treatment and prophylaxis against high-altitude illness is provided (table 5). The agents used for prophylaxis against AMS and HACE are discussed in greater detail below.

Prophylactic acetazolamide should be offered to individuals with a history of high-altitude illness who ascend to altitudes above 2500 m. It is also reasonable to give acetazolamide to individuals without such a history who travel directly (in one day) from low altitude (near sea level) to altitudes above 2800 m, at which the incidence of AMS rises substantially. (See 'AMS epidemiology' above.)

An example of a special circumstance in which dexamethasone is given would be a rescue team required to ascend rapidly above 3500 m on short notice. For such a scenario, we suggest prophylaxis with dexamethasone 2 to 4 mg four times daily, beginning before the ascent if possible and continued until descent. In this circumstance where acclimatization is not possible, dexamethasone is a better choice for prophylaxis because it is relatively rapid acting, is highly effective, and does not depend upon acclimatization for effect.

Acetazolamide — Acetazolamide is the drug of choice for the prevention of AMS when rapid ascent cannot be avoided, particularly in individuals with a history of AMS. Multiple randomized trials have found that acetazolamide reduces symptoms of AMS by approximately 75 percent when used as a single agent for this purpose [23,48-53]. Systematic reviews of these studies confirm the drug's effectiveness [54-57].

The ideal dose of acetazolamide for AMS prophylaxis is debated. A clinically effective preventive dose that also minimizes side effects is 125 mg every 12 hours (250 mg daily), although most clinical trials have been performed with higher doses [15,38,39,55,58,59]. Some experts suggest that the dose at which renal carbonic anhydrase is blocked (5 mg/kg per day) is ideal, but no clinical trial has demonstrated superior results using a weight-based regimen in adults [15]. For prevention, higher doses are unlikely to provide added benefit but do increase the incidence of side effects.

The most notable side effect of acetazolamide is peripheral paresthesia. Others include polyuria, flattened taste of carbonated beverages, and less commonly, nausea, drowsiness, impotence, and myopia. Acetazolamide can induce hypersensitivity, allergic reactions, and, rarely, anaphylaxis or Stevens-Johnson syndrome.

Acetazolamide is a sulfonamide drug, although it belongs to the group of sulfonamide **non**-

antimicrobials, which are believed to have minimal cross-reactivity with sulfonamide antimicrobials, such as trimethoprim-sulfamethoxazole. Despite this, most product inserts list allergy to any sulfonamide as a possible contraindication to the use of acetazolamide. Therefore, patients with a history of significant allergic reactions to other sulfonamide drugs should be evaluated before travel to determine if acetazolamide is tolerated. This evaluation is discussed in detail separately. (See "Sulfonamide allergy in HIV-uninfected patients", section on 'Cross-reactivity'.)

Duration of treatment depends upon the ascent profile. Individuals ascending to a fixed sleeping altitude (eg, recreational skiers) may start acetazolamide the day before ascent and continue for 48 hours. If further ascent is planned, acetazolamide can be continued until maximum elevation is attained. Acetazolamide can also be taken episodically to speed acclimatization at any point while gaining altitude or to treat mild AMS. Symptoms do not recur when the drug is discontinued. Although the danger of AMS passes after a few days of acclimatization, acetazolamide may still be useful for sleep.

Acetazolamide is a carbonic anhydrase inhibitor affecting multiple organ systems, including red blood cells, brain, lungs, and kidneys. It works by a number of mechanisms to accelerate acclimatization and ameliorate hypoxemia [60,61]. Inhibition of renal carbonic anhydrase slows the hydration of carbon dioxide, reduces reabsorption of bicarbonate and sodium, and causes a bicarbonate diuresis with resultant metabolic acidosis starting within one hour of ingestion.

By disinhibiting the central chemoreceptors, acetazolamide stimulates ventilation, which rapidly improves oxygenation. Importantly, acetazolamide maintains oxygenation during sleep and prevents periods of extreme hypoxemia [62]. Acetazolamide's diuretic action helps to counteract fluid retention associated with high-altitude illness. It also diminishes nocturnal antidiuretic hormone secretion and cerebrospinal fluid production and volume, and possibly lowers intracranial pressure (ICP) [15,63].

Dexamethasone — Dexamethasone is effective for prevention of AMS/HACE but does not aid acclimatization. There is a risk of a sudden onset or worsening of symptoms if the traveler discontinues the drug while ascending. For this reason, and because of potential side effects, experts recommend acetazolamide for AMS prevention and reserve dexamethasone for treatment. Dexamethasone should not be taken for more than seven days in order to avoid hyperglycemia, hypercalciuria, protein catabolism, immune suppression, adrenal suppression, and psychiatric effects.

Nevertheless, dexamethasone can be an important adjunctive therapy for individuals ascending rapidly to altitudes higher than 3000 m, or for use in patients who are allergic to acetazolamide. A dose of 2 mg every six hours or 4 mg every 12 hours is sufficient for sedentary subjects. For exercising subjects at or above 4000 m, this dose is insufficient, and 4 mg every six hours may be necessary to prevent AMS [64].

The effectiveness of prophylactic dexamethasone has been demonstrated in several small randomized trials [40,65-68]. In one such trial, 13 climbers acclimatized for two days at 3698 m and then ascended to 5334 m over a two-day period [66]. No evidence of AMS was found in those given prophylactic treatment with both acetazolamide and dexamethasone, while AMS developed in those treated with acetazolamide and placebo.

Euphoria and mental disorientation are complications feared by some, but several studies have failed to demonstrate such symptoms. Other studies have found improvements in reaction times and mood among those using dexamethasone prophylaxis, with no ill effects identified by cognitive and psychomotor tests [69,70].

Prophylaxis with other glucocorticoids may also be effective, but this has not been well studied clinically [71].

Nonsteroidal antiinflammatory drugs and acetaminophen — Both aspirin and ibuprofen have been shown to prevent headache on ascent to high altitude in controlled studies [72-74]. Acetaminophen (1000 mg every 8 hours) may be useful, but the one published study did not include a placebo group [75].

Since headache is the cardinal symptom of AMS, and required for the research definition of the disease, it follows that these agents "prevent" AMS. For those going to moderate altitude (ie, below 3500 m), aspirin or ibuprofen may be useful for preventing the headache associated with AMS. However, it remains unclear whether these medications would be useful as prophylaxis (or treatment) in high-risk situations (ie, rapid ascent to very high or extreme altitude) or for more severe disease. The limitations of trials involving nonsteroidal anti-inflammatory drugs (NSAIDs) make such determinations difficult.

As an example, a randomized trial reported that fewer climbers given ibuprofen for prophylaxis developed AMS (19 of 44, 43 percent) compared with those given placebo (29 of 42, 69 percent) [76]. However, the study used less stringent criteria to define AMS (Lake Louise Score ≥3, rather than ≥5), involved small numbers, and did not compare ibuprofen versus established prophylaxis treatments for either AMS or headache. In a similar trial with 232 participants, ibuprofen was not compared with established treatments, and the

incidence of severe AMS (Lake Louise Score ≥5) did not differ significantly regardless of whether analysis was performed using an intent-to-treat (13 in placebo group versus 11 in treatment group) or treatment-completed approach (seven in placebo group versus nine in treatment group) [77].

Ginkgo biloba — Ginkgo biloba is a complex herbal extract preparation with many active ingredients. While some small studies suggest that ginkgo biloba is effective at reducing the symptoms of AMS in adults, larger trials have failed to demonstrate benefit [54,78]. The use of ginkgo biloba is discussed separately. (See "Clinical use of ginkgo biloba".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Management of environmental emergencies".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient education: Altitude sickness (including mountain sickness) (The Basics)")
- Beyond the Basics topic (see "Patient education: High-altitude illness (including mountain sickness) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology and risk factors** – Acute mountain sickness (AMS) is the most common high-altitude illness. As with all high-altitude illnesses, incidence depends upon individual susceptibility, the elevation reached, and the rate of ascent. The epidemiology of AMS and high-altitude cerebral edema (HACE) are reviewed further in the text; general risk factors for high-altitude illness are discussed separately. (See 'Epidemiology' above and "High-altitude illness: Physiology, risk factors, and general prevention".)

- **Clinical presentation of AMS** – AMS is diagnosed clinically in a person who lives at low altitude but has recently ascended (<24 hours) to high altitude (generally over 2000 m). Symptoms resemble those of an alcohol hangover: primarily headache often associated with fatigue, lightheadedness, anorexia, nausea and vomiting, and disturbed sleep. Onset of AMS is usually delayed for 6 to 12 hours following arrival at high altitude and is often worse after the first night, but it can occur as rapidly as within one to two hours or as late as 24 hours. (See 'AMS diagnosis' above.)

- **Clinical presentation of HACE** – HACE is a life-threatening condition. It generally occurs in individuals with AMS and/or high-altitude pulmonary edema (HAPE) at elevations over 3000 to 3500 m. The hallmarks of HACE are encephalopathic symptoms and signs, including ataxic gait, severe lassitude, and progressive decline of mental function and consciousness (irritability, confusion, impaired mentation, drowsiness, stupor, and, finally, coma). The onset of encephalopathy and ataxia signifies the transition from AMS to HACE and occurs unpredictably, requiring as long as three days or as little as 12 hours. (See 'HACE diagnosis' above.)

- **Treatment of AMS** – Treatment of AMS is based upon symptom severity. Mild illness can be managed conservatively (avoid ascent, limit activity) with symptomatic treatment (eg, analgesic, antiemetic) given as needed; moderate to severe symptoms may require medication (eg, dexamethasone), supplemental oxygen if available, and occasionally descent. Portable hyperbaric therapy may helpful. It is important that group members and the afflicted individual remain alert for any symptoms or signs of worsening disease, particularly at elevations where AMS may rapidly progress to HACE (above 4000 m). The same general treatment approach is used for children and adults. (See 'AMS treatment' above.)

- **Treatment of HACE** – Early recognition and treatment are critical. Descent is the

definitive treatment and should begin immediately at the first suspicion of HACE. Dexamethasone and supplemental oxygen play important roles in facilitating descent or temporizing illness until evacuation can be performed. The most important action is to evacuate the patient to lower altitude before their condition renders them unable to assist with descent. If immediate descent is not possible, portable hyperbaric therapy and oxygen may be lifesaving. (See 'HACE treatment' above.)

We recommend immediate treatment with dexamethasone upon the first suspicion of HACE (**Grade 1C**). Other medications are ineffective for facilitating descent. The initial dose is 8 to 10 mg given orally, intramuscularly, or intravenously (IV), followed by 4 mg every six hours until complete descent is achieved. Dexamethasone is **not** a substitute for immediate descent. (See 'HACE treatment' above and 'Dexamethasone' above.)

- **Prophylaxis** – Clinicians should reserve prophylactic medications for high- to moderate-risk situations, particularly individuals with a history of altitude intolerance. Even in individuals with a previous history of high-altitude illness, gradual ascent should be emphasized over pharmacologic prophylaxis. (See 'General approach' above.)

  Prophylactic acetazolamide should be given to individuals with a history of high-altitude illness who ascend rapidly to altitudes above 2500 m. It is also reasonable to give acetazolamide to individuals without such a history who travel directly from low altitude (near sea level) to sleeping altitudes above 2800 m in one day. (See 'Acetazolamide' above.)

  General nonpharmacologic measures to prevent high-altitude illness are discussed separately. (See 'Pharmacologic prevention of AMS/HACE' above and "High-altitude illness: Physiology, risk factors, and general prevention".)

REFERENCES

1. Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitudes. Lancet Neurol 2009; 8:175.
2. Bailey DM, Bärtsch P, Knauth M, Baumgartner RW. Emerging concepts in acute mountain sickness and high-altitude cerebral edema: from the molecular to the morphological. Cell Mol Life Sci 2009; 66:3583.
3. Hackett PH, Yarnell PR, Hill R, et al. High-altitude cerebral edema evaluated with magnetic resonance imaging: clinical correlation and pathophysiology. JAMA 1998; 280:1920.
4. Stokum JA, Gerzanich V, Simard JM. Molecular pathophysiology of cerebral edema. J

Cereb Blood Flow Metab 2016; 36:513.

5. Dickinson J, Heath D, Gosney J, Williams D. Altitude-related deaths in seven trekkers in the Himalayas. Thorax 1983; 38:646.
6. Song SY, Asaji T, Tanizaki Y, et al. Cerebral thrombosis at altitude: its pathogenesis and the problems of prevention and treatment. Aviat Space Environ Med 1986; 57:71.
7. Burtscher M, Wille M, Menz V, et al. Symptom progression in acute mountain sickness during a 12-hour exposure to normobaric hypoxia equivalent to 4500 m. High Alt Med Biol 2014; 15:446.
8. Imray C, Chan C, Stubbings A, et al. Time course variations in the mechanisms by which cerebral oxygen delivery is maintained on exposure to hypoxia/altitude. High Alt Med Biol 2014; 15:21.
9. Sanchez del Rio M, Moskowitz MA. High altitude headache. Lessons from headaches at sea level. Adv Exp Med Biol 1999; 474:145.
10. Lawley JS, Levine BD, Williams MA, et al. Cerebral spinal fluid dynamics: effect of hypoxia and implications for high-altitude illness. J Appl Physiol (1985) 2016; 120:251.
11. Turner REF, Gatterer H, Falla M, Lawley JS. High-altitude cerebral edema: its own entity or end-stage acute mountain sickness? J Appl Physiol (1985) 2021; 131:313.
12. Meier D, Collet TH, Locatelli I, et al. Does This Patient Have Acute Mountain Sickness?: The Rational Clinical Examination Systematic Review. JAMA 2017; 318:1810.
13. Murdoch DR. Altitude Illness Among Tourists Flying to 3740 Meters Elevation in the Nepal Himalayas. J Travel Med 1995; 2:255.
14. Ward, Milledge and West's High Altitude Medicine and Physiology, Luks A, Ainslie, PN, La wley JS, Roach RC, Simonson TS (Eds), CRC Press, Boca Raton 2020.
15. Hackett P, Luks AM, Lawley JS, Roach RC. High Altitude Medicine and Pathophysiology. I n: Wilderness Medicine, 7th ed, Auerbach PA (Ed), Elsevier, Philadelphia 2017. p.8-28.
16. Schneider M, Bernasch D, Weymann J, et al. Acute mountain sickness: influence of susceptibility, preexposure, and ascent rate. Med Sci Sports Exerc 2002; 34:1886.
17. Silber E, Sonnenberg P, Collier DJ, et al. Clinical features of headache at altitude: a prospective study. Neurology 2003; 60:1167.
18. Small E, Phillips C, Marvel J, Lipman G. Older Age as a Predictive Risk Factor for Acute Mountain Sickness. Am J Med 2022; 135:386.
19. Shen Y, Yang YQ, Liu C, et al. Association between physiological responses after exercise at low altitude and acute mountain sickness upon ascent is sex-dependent. Mil Med Res

2020; 7:53.

20. Theis MK, Honigman B, Yip R, et al. Acute mountain sickness in children at 2835 meters. Am J Dis Child 1993; 147:143.
21. Yaron M, Waldman N, Niermeyer S, et al. The diagnosis of acute mountain sickness in preverbal children. Arch Pediatr Adolesc Med 1998; 152:683.
22. Wu TY, Ding SQ, Liu JL, et al. Who should not go high: chronic disease and work at altitude during construction of the Qinghai-Tibet railroad. High Alt Med Biol 2007; 8:88.
23. Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. Lancet 1976; 2:1149.
24. Hackett PH, Yarnell PR, Weiland DA, Reynard KB. Acute and Evolving MRI of High-Altitude Cerebral Edema: Microbleeds, Edema, and Pathophysiology. AJNR Am J Neuroradiol 2019; 40:464.
25. Church BJ, Basnyat B, Mattingly B, Zafren K. Pediatric High Altitude Cerebral Edema in the Nepal Himalayas. Wilderness Environ Med 2019; 30:306.
26. Baumgartner RW, Siegel AM, Hackett PH. Going high with preexisting neurological conditions. High Alt Med Biol 2007; 8:108.
27. Bärtsch P, Swenson ER. Clinical practice: Acute high-altitude illnesses. N Engl J Med 2013; 368:2294.
28. Luks AM, Swenson ER, Bärtsch P. Acute high-altitude sickness. Eur Respir Rev 2017; 26.
29. Roach RC, Hackett PH, Oelz O, et al. The 2018 Lake Louise Acute Mountain Sickness Score. High Alt Med Biol 2018; 19:4.
30. Chen HC, Lin WL, Wu JY, et al. Change in oxygen saturation does not predict acute mountain sickness on Jade Mountain. Wilderness Environ Med 2012; 23:122.
31. O'Connor T, Dubowitz G, Bickler PE. Pulse oximetry in the diagnosis of acute mountain sickness. High Alt Med Biol 2004; 5:341.
32. Wagner DR, Knott JR, Fry JP. Oximetry fails to predict acute mountain sickness or summit success during a rapid ascent to 5640 meters. Wilderness Environ Med 2012; 23:114.
33. Karinen HM, Peltonen JE, Kähönen M, Tikkanen HO. Prediction of acute mountain sickness by monitoring arterial oxygen saturation during ascent. High Alt Med Biol 2010; 11:325.
34. Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med 2019; 30:S3.

35. Hackett PH, Roach RC. High-altitude illness. N Engl J Med 2001; 345:107.
36. Bärtsch P, Baumgartner RW, Waber U, et al. Comparison of carbon-dioxide-enriched, oxygen-enriched, and normal air in treatment of acute mountain sickness. Lancet 1990; 336:772.
37. Bärtsch P, Merki B, Hofstetter D, et al. Treatment of acute mountain sickness by simulated descent: a randomised controlled trial. BMJ 1993; 306:1098.
38. Grissom CK, Roach RC, Sarnquist FH, Hackett PH. Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange. Ann Intern Med 1992; 116:461.
39. Lipman GS, Jurkiewicz C, Burnier A, et al. A Randomized Controlled Trial of the Lowest Effective Dose of Acetazolamide for Acute Mountain Sickness Prevention. Am J Med 2020; 133:e706.
40. Hackett PH, Roach RC, Wood RA, et al. Dexamethasone for prevention and treatment of acute mountain sickness. Aviat Space Environ Med 1988; 59:950.
41. Keller HR, Maggiorini M, Bärtsch P, Oelz O. Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. BMJ 1995; 310:1232.
42. Hackett PH, Roach RC. High altitude cerebral edema. High Alt Med Biol 2004; 5:136.
43. Ferrazzini G, Maggiorini M, Kriemler S, et al. Successful treatment of acute mountain sickness with dexamethasone. Br Med J (Clin Res Ed) 1987; 294:1380.
44. Levine BD, Yoshimura K, Kobayashi T, et al. Dexamethasone in the treatment of acute mountain sickness. N Engl J Med 1989; 321:1707.
45. Freeman K, Shalit M, Stroh G. Use of the Gamow Bag by EMT-basic park rangers for treatment of high-altitude pulmonary edema and high-altitude cerebral edema. Wilderness Environ Med 2004; 15:198.
46. Zafren K. Gamow bag for high-altitude cerebral oedema. Lancet 1998; 352:325.
47. Houston CS, Dickinson J. Cerebral form of high-altitude illness. Lancet 1975; 2:758.
48. Forwand SA, Landowne M, Follansbee JN, Hansen JE. Effect of acetazolamide on acute mountain sickness. N Engl J Med 1968; 279:839.
49. Basnyat B, Gertsch JH, Holck PS, et al. Acetazolamide 125 mg BD is not significantly different from 375 mg BD in the prevention of acute mountain sickness: the prophylactic acetazolamide dosage comparison for efficacy (PACE) trial. High Alt Med Biol 2006; 7:17.
50. van Patot MC, Leadbetter G 3rd, Keyes LE, et al. Prophylactic low-dose acetazolamide reduces the incidence and severity of acute mountain sickness. High Alt Med Biol 2008;

9:289.

51. Pollard AJ, Niermeyer S, Barry P, et al. Children at high altitude: an international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, March 12, 2001. High Alt Med Biol 2001; 2:389.
52. Ellsworth AJ, Larson EB, Strickland D. A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. Am J Med 1987; 83:1024.
53. Furian M et. Acetazolamide to Prevent Adverse Altitude Effects in COPD and Healthy Adults. NEJM Evidence 2021; 1.
54. Seupaul RA, Welch JL, Malka ST, Emmett TW. Pharmacologic prophylaxis for acute mountain sickness: a systematic shortcut review. Ann Emerg Med 2012; 59:307.
55. Low EV, Avery AJ, Gupta V, et al. Identifying the lowest effective dose of acetazolamide for the prophylaxis of acute mountain sickness: systematic review and meta-analysis. BMJ 2012; 345:e6779.
56. Kayser B, Dumont L, Lysakowski C, et al. Reappraisal of acetazolamide for the prevention of acute mountain sickness: a systematic review and meta-analysis. High Alt Med Biol 2012; 13:82.
57. Nieto Estrada VH, Molano Franco D, Medina RD, et al. Interventions for preventing high altitude illness: Part 1. Commonly-used classes of drugs. Cochrane Database Syst Rev 2017; 6:CD009761.
58. Carlsten C, Swenson ER, Ruoss S. A dose-response study of acetazolamide for acute mountain sickness prophylaxis in vacationing tourists at 12,000 feet (3630 m). High Alt Med Biol 2004; 5:33.
59. Basnyat B, Gertsch JH, Johnson EW, et al. Efficacy of low-dose acetazolamide (125 mg BID) for the prophylaxis of acute mountain sickness: a prospective, double-blind, randomized, placebo-controlled trial. High Alt Med Biol 2003; 4:45.
60. Swenson ER. Carbonic anhydrase inhibitors and hypoxic pulmonary vasoconstriction. Respir Physiol Neurobiol 2006; 151:209.
61. Teppema LJ, Balanos GM, Steinback CD, et al. Effects of acetazolamide on ventilatory, cerebrovascular, and pulmonary vascular responses to hypoxia. Am J Respir Crit Care Med 2007; 175:277.
62. Sutton JR, Houston CS, Mansell AL, et al. Effect of acetazolamide on hypoxemia during sleep at high altitude. N Engl J Med 1979; 301:1329.
63. Senay LC Jr, Tolbert DL. Effect of arginine vasopressin, acetazolamide, and angiotensin II

on CSF pressure at simulated altitude. Aviat Space Environ Med 1984; 55:370.

64. Rock PB, Johnson TS, Larsen RF, et al. Dexamethasone as prophylaxis for acute mountain sickness. Effect of dose level. Chest 1989; 95:568.
65. Ellsworth AJ, Meyer EF, Larson EB. Acetazolamide or dexamethasone use versus placebo to prevent acute mountain sickness on Mount Rainier. West J Med 1991; 154:289.
66. Bernhard WN, Schalick LM, Delaney PA, et al. Acetazolamide plus low-dose dexamethasone is better than acetazolamide alone to ameliorate symptoms of acute mountain sickness. Aviat Space Environ Med 1998; 69:883.
67. Rock PB, Johnson TS, Cymerman A, et al. Effect of dexamethasone on symptoms of acute mountain sickness at Pikes Peak, Colorado (4,300 m). Aviat Space Environ Med 1987; 58:668.
68. Tang E, Chen Y, Luo Y. Dexamethasone for the prevention of acute mountain sickness: systematic review and meta-analysis. Int J Cardiol 2014; 173:133.
69. Lafleur J, Giron M, Demarco M, et al. Cognitive effects of dexamethasone at high altitude. Wilderness Environ Med 2003; 14:20.
70. Jobe JB, Shukitt-Hale B, Banderet LE, Rock PB. Effects of dexamethasone and high terrestrial altitude on cognitive performance and affect. Aviat Space Environ Med 1991; 62:727.
71. Basu M, Sawhney RC, Kumar S, et al. Glucocorticoids as prophylaxis against acute mountain sickness. Clin Endocrinol (Oxf) 2002; 57:761.
72. Burtscher M, Likar R, Nachbauer W, Philadelphy M. Aspirin for prophylaxis against headache at high altitudes: randomised, double blind, placebo controlled trial. BMJ 1998; 316:1057.
73. Burtscher M, Likar R, Nachbauer W, et al. Effects of aspirin during exercise on the incidence of high-altitude headache: a randomized, double-blind, placebo-controlled trial. Headache 2001; 41:542.
74. Broome JR, Stoneham MD, Beeley JM, et al. High altitude headache: treatment with ibuprofen. Aviat Space Environ Med 1994; 65:19.
75. Kanaan NC, Peterson AL, Pun M, et al. Prophylactic Acetaminophen or Ibuprofen Results in Equivalent Acute Mountain Sickness Incidence at High Altitude: A Prospective Randomized Trial. Wilderness Environ Med 2017; 28:72.
76. Lipman GS, Kanaan NC, Holck PS, et al. Ibuprofen prevents altitude illness: a randomized controlled trial for prevention of altitude illness with nonsteroidal anti-inflammatories.

Ann Emerg Med 2012; 59:484.

77. Gertsch JH, Corbett B, Holck PS, et al. Altitude Sickness in Climbers and Efficacy of NSAIDs Trial (ASCENT): randomized, controlled trial of ibuprofen versus placebo for prevention of altitude illness. Wilderness Environ Med 2012; 23:307.
78. Gertsch JH, Basnyat B, Johnson EW, et al. Randomised, double blind, placebo controlled comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT). BMJ 2004; 328:797.

Topic 182 Version 35.0

GRAPHICS

Physiologic effects of high altitude

High altitude: 1500 to 3500 m (4921-11,483 ft)
High-altitude illness common with abrupt ascent to above 2500 m (8202 ft)
Decreased exercise performance and increased ventilation
Minor impairment in SpO_2, usually at least 90 percent; PaO_2 significantly diminished 55 to 75 mmHg
Very high altitude: 3500 to 5500 m (11,483-18,045 ft)
Most common range for severe high-altitude illness
Abrupt ascent may be dangerous; requires a period of acclimatization
SpO_2 75 to 85 percent; PaO_2 40 to 60 mmHg
Extreme hypoxia may occur during sleep, exercise and high-altitude illness
Extreme altitude: 5500 to 8850 m (18,045-29,035 ft)
Progressive deterioration of physiologic function eventually outstrips acclimatization
Above the highest permanent human habitation
Abrupt ascent almost always precipitates severe high-altitude illness
A period of acclimatization necessary to ascend to extreme altitude
Severe hypoxia and hypocapnia; SpO_2 58 to 75 percent, PaO_2 28 to 40 mmHg

SaO_2: arterial oxygen saturation; PaO_2: arterial PO_2; PO_2: partial pressure of oxygen.

Data from: Hackett, PH, Roach, RC. High-Altitude Medicine. In: Wilderness Medicine, 5th ed, Auerbach, PS (Ed), Mosby, Philadelphia 2007.

Graphic 63999 Version 3.0

Elevations for high altitude cities, peaks, and resorts

Location	Altitude
Cities	
The 10 highest cities in the world	
1. Lhasa, Tibet, China	12,002 ft/3658 m
2. La Paz, Bolivia	11,910 ft/3630 m
3. Cuzco, Peru	11,152 ft/3399 m
4. Sucre, Bolivia	9331 ft/2844 m
5. Quito, Ecuador	9249 ft/2819 m
6. Toluca, Mexico	8793 ft/2680 m
7. Bogotá, Colombia	8675 ft/2644 m
8. Cochabamba, Bolivia	8390 ft/2557 m
9. Addis Ababa, Ethiopia	7900 ft/2408 m
10. Asmara, Eritrea	7789 ft/2374 m
Some large cities at high altitude	
Mexico City	7350 ft/2240 m
Johannesburg	5740 ft/1750 m
Nairobi	5446 ft/1660 m
Denver	5280 ft/1610 m
Guatemala City	5020 ft/1530 m
Some ski resorts at high altitude (lodging >8000 ft/2400 m)*	
Asia	
Lijiang, Yunnan, China	14,816 ft/4516 m
Gulmarg, Kashmir, India	8500 ft/2600 m
Other resorts in Yunnan and Sichuan, China; Iran; Kyrgyzstan	
North America	
Breckenridge, Colorado	9600 ft/2926 m

Crested Butte, Colorado	9375 ft/2858 m
Telluride, Colorado	8750 ft/2668 m
Vail, Colorado	8120 ft/ 2476 m
Aspen, Colorado	8000 ft/2439 m
South America	
Valle Nevado, Chile	9383 ft/2860 m
Portillo, Chile	8360 ft/2548 m
Europe and Japan	
None	
Peaks	
The Seven Summits	
Mount Everest, Asia	29,035 ft/8850 m
Aconcagua, South America	22,841 ft/6962 m
Denali, North America	20,320 ft/6194 m
Mount Kilimanjaro, Africa	19,563 ft/5963 m
Mount Elbrus, Europe	18,510 ft/5642 m
Vinson Massif, Antarctica	16,066 ft/4897 m
Puncak Jaya, Australia/Oceania	16,023 ft/4884 m
8000 m peaks	
Mount Everest, Nepal	29,035 ft/8850 m
K2, Pakistan	28,253 ft/8612 m
Kangchenjunga, Nepal	28,169 ft/8586 m
Lhotse, Nepal	27,940 ft/8516 m
Makalu, Nepal	27,765 ft/8462 m
Cho Oyu, Nepal	26,906 ft/8201 m
Dhaulagiri, Nepal	26,794 ft/8167 m
Manaslu, Nepal	26,758 ft/8156 m
Nanga Parbat, Pakistan	26,658 ft/8125 m
Annapurna, Nepal	26,545 ft/8091 m
Gasherbrum, Pakistan	26,470 ft/8068 m
Broad Peak, Pakistan	26,400 ft/8047 m

Gasherbrum II, Pakistan	26,360 ft/8035 m
Shisha Pangma, Tibet	26,289 ft/8013 m

ft: feet; m: meters.

* Elevations given are for lodging locations, not for ski trails or summits.

Graphic 50199 Version 6.0

Lake Louise score for AMS

Symptom	Score
Headache	
None at all	0
A mild headache	1
Moderate headache	2
Severe headache, incapacitating	3
Gastrointestinal symptoms	
Good appetite	0
Poor appetite or nausea	1
Moderate nausea or vomiting	2
Severe nausea and vomiting, incapacitating	3
Fatigue and/or weakness	
Not tired or weak	0
Mild fatigue/weakness	1
Moderate fatigue/weakness	2
Severe fatigue/weakness, incapacitating	3
Dizziness/light-headedness	
No dizziness/light-headedness	0
Mild dizziness/light-headedness	1
Moderate dizziness/light-headedness	2
Severe dizziness/light-headedness, incapacitating	3
AMS clinical functional score	
Overall, if you had AMS symptoms, how did they affect your activities?	
Not at all	0
Symptoms present, but did not force any change in activity or itinerary	1
My symptoms forced me to stop the ascent or to go down on my own power	2
Had to be evacuated to a lower altitude	3
Total	

In order to meet definition of AMS, must include at least 1 point from the "Headache" category and be in the setting of a recent ascent or gain in altitude.

3 to 5 points: Mild AMS

6 to 9 points: Moderate AMS

10 to 12 points: Severe AMS

AMS: acute mountain sickness.

Graphic 74655 Version 3.0

Screening for acute mountain sickness (AMS)

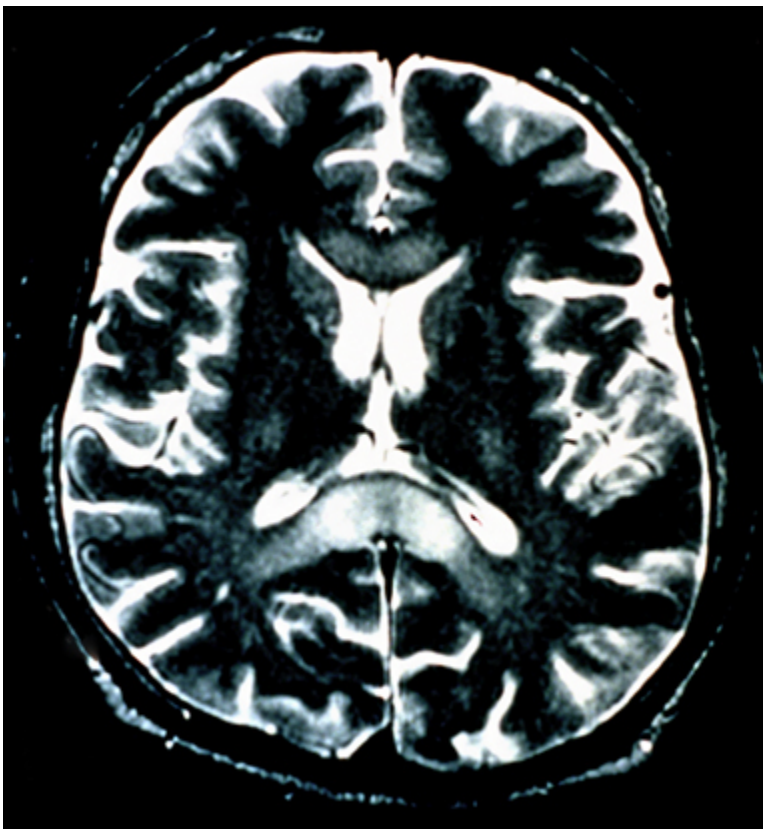
Useful questions for diagnosis of AMS, in the proper setting and after considering the differential diagnosis:	
Do you feel sick?	
Do you feel hungover?	
Overall severity of AMS symptoms and associated points:	
No reduction of daily activity:	0
Mild reduction:	1
Moderate reduction:	2
Severe reduction (bed rest):	3
Answering yes to one or both of the first questions combined with an overall severity of >2 correlates closely with AMS.	

Reference:

1. *Meier D, Collet TH, Locatelli I, et al. Does This Patient Have Acute Mountain Sickness?: The Rational Clinical Examination Systematic Review. JAMA. 2017;318(18):1810.*

Graphic 132368 Version 1.0

HACE MRI



With HACE, MRI reveals characteristic intense T2 signal in the white matter, especially the splenium of the corpus callosum, with no grey matter lesions. The MRI may remain abnormal for days to weeks.

HACE: high altitude cerebral edema; MRI: magnetic resonance imaging.

Graphic 53871 Version 4.0

Pharmacologic treatment and prevention of high altitude illness (HAI)

Condition		Preferred agent	Alternatives
AMS/HACE	Prevention*	**Acetazolamide:** 125 mg orally every 12 hours Children: 2.5 mg/kg (maximum single dose: 125 mg) orally every 12 hours[¥] Duration: Start day before ascent and continue 2 to 3 days at maximum altitude; may use once at night thereafter to improve sleep	**Dexamethasone:** 2 mg orally every 6 hours or 4 mg orally every 12 hours Children: Acetazolamide preferred; do not use for prophylaxis Duration: Start day of ascent and continue 2 to 3 days at maximum altitude but for no more than 7 days total
	Treatment of mild AMS[¶]	**Acetazolamide:** 125 to 250 mg orally every 12 hours Children: 2.5 mg/kg (maximum single dose: 250 mg) orally every 12 hours[¥] Duration: Continue for 24 hours after symptoms resolve or descent completed	**Dexamethasone:** 2 to 4 mg orally every 6 hours Children: 0.15 mg/kg (maximum single dose: 4 mg) orally every 6 hours Duration: Continue until 24 hours after symptoms resolve or descent completed but for no more than 7 days total
	Treatment of moderate to severe AMS	**Dexamethasone:**[Δ] 4 mg orally every 6 hours Children: 0.15 mg/kg (maximum single dose: 4 mg) orally every 6 hours Duration: Continue for 24 hours after symptoms resolve or descent completed but for no more than 7 days total	**Acetazolamide:** 125 to 250 mg orally every 12 hours Children: 2.5 mg/kg (maximum single dose: 250 mg) orally every 12 hours[¥] Duration: Continue for 24 hours after symptoms resolve or descent completed

	Treatment of HACE	**Dexamethasone:**[Δ] 8 to 10 mg orally /IM/IV once, then 4 mg orally/IM/IV every 6 hours Children: 0.15 mg/kg (maximum single dose: 4 mg) every 6 hours Duration: Continue until 24 hours after symptoms resolve or descent completed but for no more than 7 days total	**Acetazolamide:** 250 mg orally every 12 hours; may use as adjunct with dexamethasone; **not** for monotherapy Children: 2.5 mg/kg (maximum single dose: 250 mg) orally every 12 hours[¥] Duration: Continue until 24 hours after symptoms resolve or descent completed
HAPE	Prevention*	**Nifedipine:** 60 mg extended-release orally divided daily (30 mg orally every 12 hrs; or 20 mg orally every 8 hours)[◇] Children: 0.5 mg/kg (maximum single dose: 20 mg) extended-release orally every 8 hours[◇] Duration: Start day before ascent and continue for 5 days at maximum altitude	Further research is needed before the medications listed below can be recommended for routine use in HAPE prevention: **Tadalafil:** 10 mg orally every 12 hours; start day of ascent and continue 3 to 5 days at maximum altitude **Sildenafil:** 50 mg orally every 8 hours; start day of ascent and continue 3 to 5 days at maximum altitude **Dexamethasone:** 8 mg orally every 12 hours; start day of ascent and continue 48 to 72 hours at maximum altitude **Acetazolamide:** 125 to 250 mg orally every 12 hours; start day before ascent and continue 48 to 72 hours at maximum altitude
	Treatment[§]	**Nifedipine:** 60 mg extended-release orally divided daily (30 mg orally every 12 hours or 20 mg orally every 8 hours)[◇] Children: 0.5 mg/kg (maximum single dose: 20 mg) extended-release orally every 8 hours[◇] Duration: Continue until descent completed, symptoms resolved, and SpO_2 normal for altitude	Further research is needed before the medications listed below can be recommended for routine use in HAPE treatment: **Tadalafil:** 10 mg orally every 12 hours **Sildenafil:** 50 mg orally every 8 hours Duration: Continue until descent completed, symptoms resolved,

			and SpO_2 normal for altitude

AMS: acute mountain sickness; HACE: high altitude cerebral edema; HAPE: high altitude pulmonary edema; IM: intramuscular; NSAID: nonsteroidal antiinflammatory drug; HAI: high-altitude illness; SpO_2: oxygen saturation.

* Gradual ascent is the best strategy for prevention of HAI. Early recognition of symptoms and prompt treatment are critical to reduce risk of progression to serious HAI (such as HAPE and HACE). Reserve pharmacologic prophylaxis for patients who have a history of HAPE or recurrent AMS and patients at high risk (as well as selected patients at moderate risk) of developing AMS/HACE according to criteria listed in the separate UpToDate content. Provision of these medications for "rescue" treatment is also reasonable.

¶ May not require pharmacologic treatment. Rest, halt ascent, and symptomatic treatment (eg, acetaminophen or NSAID for headache and ondansetron for nausea/vomiting) may be sufficient. Refer to accompanying UpToDate text.

Δ Treatment with dexamethasone alleviates symptoms of AMS/HACE but does not improve acclimatization. Dexamethasone is not a substitute for immediate descent in HACE.

◇ In United States the lowest strength extended-release nifedipine oral preparation available is 30 mg. In some other countries, 10 and 20 mg extended-release preparations are available.

§ May not require any pharmacologic intervention. In proper setting, rest and supplemental oxygen may be sufficient. Refer to accompanying UpToDate text.

¥ For immediate administration in children, a liquid acetazolamide solution can be made by crushing a 125 mg or 250 mg tablet and suspending it in cherry, chocolate, or other flavored syrup to hide the bitter taste. A flavored oral suspension useful in patients who cannot swallow pills or for measurement of doses used in smaller children (eg <125 mg) can also be compounded by a pharmacy. Detail is available in the acetazolamide pediatric drug monograph.

Courtesy of Scott Gallagher, MD and Peter Hackett, MD, with additional data from:

1. *Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society Consensus Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med 2019; 30:S3.*
2. *Pollard A, Niermeyer S, Barry P, et al. Children at high altitude: an international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, March 12, 2001. High Alt Med Biol 2001; 2:389.*

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