Prevention and Treatment of High-altitude Illness in Travelers

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High-altitude illness is the collective term for acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE). These syndromes can affect unacclimatized travelers shortly after ascent to high altitude (especially higher than 2500 m). AMS is relatively common and usually is mild and self-limiting; HACE and HAPE are uncommon but life-threatening. Gradual ascent is the best strategy for preventing or minimizing high-altitude illness, although chemoprophylaxis may be useful in some situations. Acetazolamide remains the chemoprophylactic agent of choice, although other drugs, such as gingko biloba, are being investigated. Immediate descent remains the cornerstone of treatment for HACE and HAPE, although pharmacologic and hyperbaric therapies may facilitate this process.

Introduction

High-altitude illness is the collective term for the syndromes that are directly attributed to hypobaric hypoxia and can affect unacclimatized travelers shortly after ascent to high altitude. The term encompasses the predominantly cerebral syndromes of acute mountain sickness (AMS) and high-altitude cerebral edema (HACE), and the pulmonary syndrome high-altitude pulmonary edema (HAPE). AMS is a common, short-term affliction of high-altitude travelers. HACE and HAPE occur much less frequently than AMS but are potentially fatal.

In the medical literature, high altitude usually is defined as altitude higher than 2500 m because this is where objective physiologic changes become most evident. Given sufficient time, humans can successfully acclimatize to altitudes up to 5500 to 6000 m. Complete acclimatization does not occur above this height, and prolonged periods in this extreme altitude zone cause general deterioration with weight loss, worsening exercise tolerance, and general loss of condition. For this reason, members of expeditions to the world's highest mountains position base camps lower than 5500 m and try to avoid spending prolonged periods of time above this height. High-altitude acclimatization occurs at different rates in different people. Lack of acclimatization is indicated by poor exercise tolerance and, sometimes, by the development of high-altitude illness.

Epidemiology of High-altitude Illness

Humans travel to high altitudes for many reasons. An estimated 140 million people reside permanently at altitudes higher than 2500 m [1]. Large numbers of people travel to high altitudes for recreational pursuits such as mountaineering, trekking, and skiing, or as religious pilgrims. Miners, military personnel, porters, and other occupational groups are periodically deployed to work at high altitudes.

The most important risk factors for the development of high-altitude illness are rate of ascent, altitude reached (especially the sleeping altitude), and individual susceptibility. The incidence of AMS among conference delegates and skiers to moderate altitudes (1920–2957 m) in Colorado is 25% [2]. In the Mt. Everest region of Nepal, approximately 50% of trekkers who walk to altitudes higher than 4000 m over 5 or more days develop AMS [3••,4], whereas 84% of those who fly directly to 3860 m are affected [5]. The prevalence of AMS among climbers in the Swiss Alps ranged from 9% at 2850 m to 53% at 4559 m [6]. High-altitude illness is much more likely to occur at altitudes higher than 2500 m but is being increasingly recognized at altitudes between 1500 and 2500 m [7]. The incidence of HACE and HAPE is much lower than for AMS, with usual estimates less than 2%.

Exertion is a risk factor for AMS [8], but lack of physical fitness is not [9,10]. Children and adults appear to be equally affected [11•], although people aged older than 50 years may be less susceptible to AMS than younger people [2,12]. Although it is generally thought that there is no gender difference in susceptibility to AMS, some studies have indicated a higher incidence in women than in men [5,13,14]. Some people appear to be inherently more susceptible to AMS than others. Despite the efforts of many researchers, there is no satisfactory test to predict which individuals are more likely to develop high-altitude illness. Neck irradiation or surgery [15] and respiratory tract infection [16,17] also are potential risk factors for high-altitude illness.

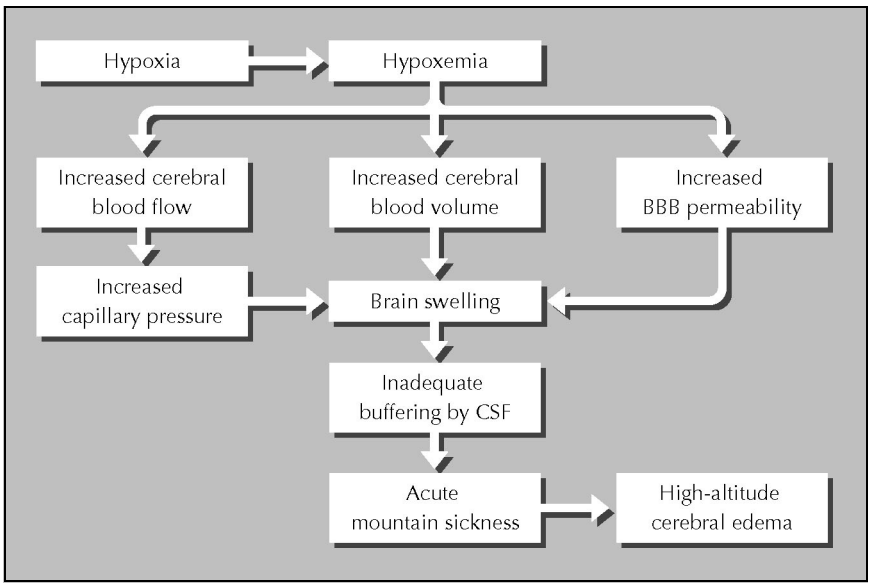

Figure 1. Proposed pathogenesis of acute mountain sickness and high-altitude cerebral edema [22••]. BBB—blood-brain barrier; CSF—cerebrospinal fluid. Reprinted with permission from Elsevier (*The Lancet*, 2003, 361, 1967–1974).

Clinical Presentation

Acute mountain sickness is characterized by relatively nonspecific symptoms and a paucity of physical findings. The principal symptoms are headache, anorexia, nausea, vomiting, fatigue, dizziness, and sleep disturbance, although all need not be present. Headache is regarded as the cardinal symptom, but the characteristics are not sufficiently distinctive to differentiate it from other causes of headache [18]. It often is throbbing in nature, aggravated by Valsalva's maneuver and stooping, and can be severe. Symptoms of AMS typically appear 6 to 12 hours after arrival at high altitude. Diagnostic signs are absent, and the presence of abnormal neurologic or respiratory signs may indicate progression to or development of HACE or HAPE. The lack of specific symptoms and signs of AMS can result in diagnostic confusion with other conditions such as exhaustion, dehydration, hypothermia, alcohol hangover, and migraine.

High-altitude cerebral edema is widely regarded as the end stage of AMS and usually is preceded by symptoms of AMS. HACE is characterized by ataxia and altered consciousness, which may progress to coma and death caused by brain herniation. Ataxia is an important early sign of HACE and can be readily tested in the field by heel-toe walking. Patients with concomitant HAPE may progress very rapidly from AMS to HACE. Clinical examination may reveal papilledema, ataxia, retinal hemorrhages, and occasionally, focal neurologic deficits.

High-altitude pulmonary edema typically occurs during the first 2 to 4 days after arrival at altitudes higher than 2500 m and is not necessarily preceded by AMS. Risk factors for HAPE are the same as for AMS and HACE. In addition, HAPE may be over-represented in males compared to females, and cold also is a risk factor. Patients with abnormalities of the cardiopulmonary circulation that are associated with increased pulmonary blood flow and/or pressure, such as unilateral absence of a pulmonary artery or primary pulmonary hypertension, are at increased risk for HAPE, even at moderate altitudes [19,20]. The first symptoms of HAPE usually are dyspnea on exertion and reduced exercise tolerance, more than expected for the altitude. Cough, initially dry and annoying, becomes productive later in the illness with blood-stained sputum. Physical findings initially may be subtle. Tachypnea and tachycardia are present at rest as the illness progresses, fever is common (rarely exceeding 38.3°C), and crackles are evident on chest auscultation. HAPE frequently is accompanied by signs of HACE. If a chest radiograph is able to be taken, it will show changes of pulmonary edema, although there is no radiographic feature specific to HAPE [21].

Pathophysiology

The exact mechanisms that cause AMS and HACE are unknown [22••]. Increasing evidence points to an underlying central nervous system process, and it is possible that mild cerebral edema is responsible for the symptoms of AMS, and that AMS and HACE represent different ends of the spectrum of a single disease process. Characteristics of established AMS include relative hypoventilation, impaired gas exchange, increased sympathetic activity, fluid retention and redistribution, and in moderate to severe AMS, raised intracranial pressure.

Hackett and Roach [23,24•] recently have proposed a model to explain the pathophysiology of AMS and HACE (Fig. 1). In this model, hypoxemia elicits various neurohumoral and hemodynamic responses that ultimately result in elevated cerebral blood flow, altered blood-brain barrier permeability, cerebral edema, and ultimately, brain swelling and raised intracranial pressure. According to the model, AMS occurs in people with inadequate cerebrospinal

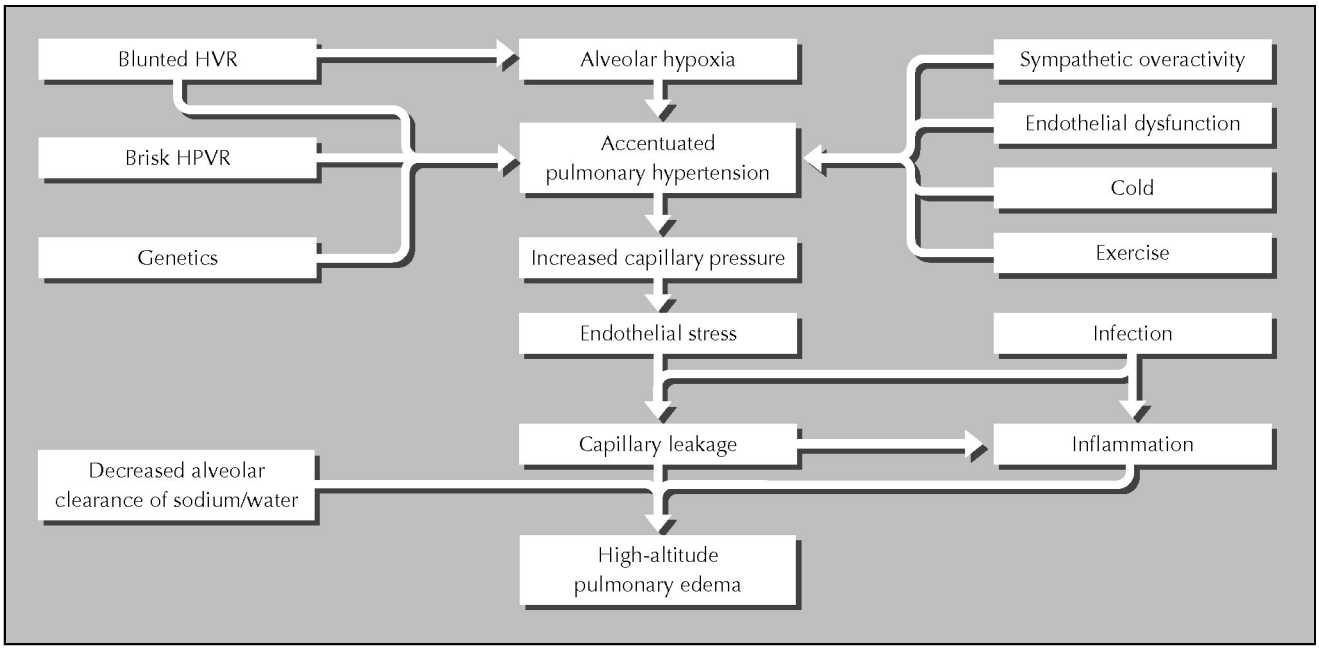

Figure 2. Proposed pathogenesis of high-altitude pulmonary edema [22••]. HVR—hypoxic ventilatory response; HPVR—hypoxic pulmonary vascular response. Reprinted with permission from Elsevier (*The Lancet*, 2003, 361, 1967–1974).

capacity to buffer the brain swelling; those with a greater ratio of cranial cerebrospinal fluid (CSF) to brain volume are better able to compensate for swelling through CSF displacement and are less likely to develop AMS. This hypothesis is attractive but very speculative.

High-altitude pulmonary edema is a noncardiogenic pulmonary edema characterized by exaggerated pulmonary hypertension resulting in vascular leakage through overperfusion and/or stress failure [22••]. The reason for the accentuated hypoxic pulmonary vasoconstriction is unclear, although it is likely because of several factors (Fig. 2). Recent evidence indicates that inflammation probably is not a primary event in the pathogenesis of HAPE, although it may occur as a secondary event in response to alveolar flooding [25]. Blunting of the clearance of alveolar fluid by the alveolar epithelium may predispose patients to pulmonary edema, and there is some indirect evidence to support this view [26].

Prevention of High-altitude Illness

Gradual ascent

Gradual ascent, which allows time for acclimatization to occur, is the best strategy for preventing high-altitude illness. However, determining an ideal ascent rate is difficult and varies with each person, depending on individual susceptibility to AMS. One historical rule of thumb is that above 3000 m, each night should average no more than 300 m above the last, with a rest day every 2 or 3 days (or every 1000 m) [27]. This recommendation was developed for trekkers in the Mt. Everest region of Nepal where the location of potential sleeping sites makes it well-suited. For other high-altitude regions, this ascent rate may appear painfully slow, and many people are able to tolerate a more rapid ascent schedule. As a consequence, more recent recommendations state that the height difference between consecutive sleeping sites should average no more than 600 m per day [28••]. Regardless of the specific recommendation, each formula emphasizes sleeping altitudes, which means that it is permissible to ascend more than the recommended daily rate, as long as descent occurs before sleeping (the "climb high, sleep low" adage). A night spent at an intermediate altitude (1500–2500 m) before ascent to high altitude also will aid acclimatization. For example, skiers who are resident at sea level will benefit from a night spent in Denver (1625 m) before a ski vacation in Aspen (base altitude 2400 m). Efforts are in progress to develop models of AMS that may be used to construct personalized ascent rates based on individual parameters [29], but this project is still in its infancy.

In addition to having a gradual ascent schedule, travelers also should be encouraged to have a flexible itinerary so that additional rest days can be incorporated if required. In Nepal, it was noted that trekkers who travel in organized groups arranged by commercial travel companies were more likely to die from high-altitude illness than were trekkers who travel independently. Part of the reason for this is likely because of the relatively fixed itinerary these groups follow, which makes it difficult for slow-acclimatizers to take additional rest days when needed. Travelers also should be familiar with the symptoms of high-altitude illness and be encouraged not to ascend further if they have these symptoms. Thus, if a traveler has symptoms of AMS after arriving at a new altitude and the

symptoms are still present the next morning, they should ascend no further until the symptoms have improved.

Realistically, the combination of a gradual ascent schedule and a flexible itinerary will be sufficient to provide adequate acclimatization for most travelers to high altitudes. A proportion of travelers who follow a sensible ascent schedule still will develop AMS, but few (if any) will progress to life-threatening HACE or HAPE. In this regard, it is beneficial to describe AMS as a useful warning sign that acclimatization is still occurring. I advise travelers that it is okay to get AMS, but it is not okay to ignore symptoms of AMS when they occur. By ignoring these symptoms and continuing to ascend, they run the risk for developing life-threatening HACE.

Chemoprophylaxis against acute mountain sickness

In some situations, pharmacologic prophylaxis against AMS may be warranted, although there is considerable debate as to exactly what these situations are. People ascending rapidly to altitudes higher than 3000 m (*eg,* flying from sea level to La Paz, Bolivia [3625 m]) and those with known increased susceptibility to AMS should certainly consider chemoprophylaxis. However, opinions vary considerably between experts about whether chemoprophylaxis should be recommended in other situations and, in practice, decisions usually are made on a case by case basis. Chemoprophylaxis can provide a false sense of security in some people and is never a substitute for a sensible graded ascent rate.

Acetazolamide

Acetazolamide is the preferred chemoprophylactic agent, and there is a considerable body of evidence supporting its use for preventing or minimizing the symptoms of AMS. Acetazolamide is a carbonic anhydrase inhibitor and probably exerts its prophylactic action at least partially by increasing renal bicarbonate excretion, thereby producing a metabolic acidosis and stimulating respiration. This drug also helps maintain oxygenation during sleep and prevents periods of extreme hypoxemia. The ideal prophylactic dosage of acetazolamide remains controversial. The standard recommendation is 250 mg twice daily, from 1 day before ascent above 2500 m. Although widely administered at 125 mg twice daily, only limited recent data support the efficacy of this dose regimen [30]. A recent systematic review suggested that acetazolamide is ineffective as a prophylactic at daily doses less than 750 mg [31]. This is contrary to clinical experience and probably reflects the strict criteria for inclusion of studies in this review and the fact that studies with different ascent rates were compared. Trials directly comparing different doses of acetazolamide in patients at similar rates of ascent are needed to clarify this issue. Until the results of such trials are available, the recommended prophylactic dosage of acetazolamide is 125 to 250 mg twice daily starting 1 day before ascent above 2500 m.

Acetazolamide is a sulfa drug and carries the usual precautions about hypersensitivity. Side effects of acetazolamide are common and usually mild in nature, although some patients have found them unacceptable. Most notable are mild diuresis and paresthesiae, both tending to diminish with continued use. Paresthesiae are most noticeable in the hands and feet, and especially on pressure points. Because of the effects of acetazolamide on carbonic anhydrase, carbonated drinks taste flat.

There is no evidence to suggest that the prophylactic use of acetazolamide masks symptoms of AMS, although some patients have reported the development of AMS after abrupt cessation of this drug.

Dexamethasone

Dexamethasone also is effective for AMS prophylaxis [32–34] and is the usual alternative if acetazolamide cannot be prescribed. Acetazolamide probably is slightly more effective than dexamethasone [35], and the combination of both drugs is more effective than either alone [36].

The mechanism of action of dexamethasone for preventing AMS is unknown, although it is generally thought that it does not actually aid acclimatization. Concerns about side effects have restricted the use of dexamethasone to the treatment of high-altitude illness and to situations in which prophylaxis is needed in patients who are allergic to acetazolamide. The usual prophylactic dosage of dexamethasone is 8 mg daily in divided doses, beginning at least 24 hours before ascent higher than 2500 m.

Gingko biloba

Recent studies provide preliminary evidence that gingko biloba has some prophylactic activity against AMS. During an ascent from 1800 to 5200 m over a 10-day period, no patients taking gingko extract (EGb 761) at a dosage of 80 mg twice daily experienced AMS, compared to 41% of patients taking placebo [37]. Gingko 120 mg twice daily taken for 5 days before exposure reduced the incidence and severity of AMS during ascent from 1400 to 4300 m over 2 hours [38]. In a third study, gingko 60 mg three times daily starting 1 day before rapid ascent from sea level to 4205 m reduced the severity (but not incidence) of AMS compared to placebo [39]. Gingko's effects may be because of its antioxidant activity. This concept is supported by data suggesting that ingestion of antioxidant vitamins may reduce the incidence and severity of AMS [40].

Other drugs

Several other drugs, including spironolactone and aspirin, have been investigated for their potential prophylactic properties against AMS, but none has become established.

Prevention of high-altitude cerebral edema and high-altitude pulmonary edema

As for AMS and HACE, the best way to prevent HAPE is to ascend gradually to allow sufficient time for acclimatization.

In patients with a past history of HAPE, nifedipine 20 mg slow release every 8 hours has been shown to prevent HAPE after rapid ascent to 4559 m [41]. There is recent evidence indicating that inhaled β-adrenergic agonists also may be useful in the prevention of HAPE [26].

Treatment of High-altitude Illness

Treatment of acute mountain sickness

The principles of treatment of AMS are to avoid further ascent until symptoms have resolved, to descend if there is no improvement or if symptoms worsen, and to descend immediately at the first signs of cerebral or pulmonary edema. Rest alone often is sufficient for mild AMS, and analgesics (such as aspirin and acetaminophen) and antiemetics may afford symptomatic relief. Descent and oxygen are the treatments of choice for moderate to severe AMS. Even a relatively small descent of 400 to 500 m may be sufficient to relieve symptoms. As a rule of thumb, descent to an altitude lower than where symptoms began usually will result in resolution of symptoms of AMS.

Additional pharmacotherapy may be used in conjunction with the therapies already mentioned for treating AMS, especially if descent is impossible and oxygen is unavailable. Acetazolamide (250 mg twice or three times daily) is helpful in established AMS, relieving symptoms and improving arterial oxygenation [42]. Dexamethasone (4 mg every 6 hours) relieves symptoms of AMS but does not improve objective physiologic abnormalities [32,43,44]. It may be a useful adjunct to descent and other therapy in severe AMS.

Treatment of high-altitude cerebral edema and high-altitude pulmonary edema

The treatment of HACE is immediate descent in conjunction with oxygen (if available) and dexamethasone, because this is a life-threatening condition. Early recognition is important, and most patients with HACE will have experienced preceding symptoms of AMS that worsened over time. As mentioned earlier, ataxia is an important early sign of HACE and can be readily tested by the heel-toe test; any deviation from a straight line should be taken seriously.

Early recognition also is the first key step in the treatment of HAPE. Death commonly results from an incorrect diagnosis and failure to descend. Descent is the treatment of choice for HAPE and should be initiated immediately when the condition is recognized. Exertion should be minimized, and the patient should be kept warm because exercise and cold can raise pulmonary artery pressure. Oxygen often produces immediate and dramatic improvement and can be life-saving. Continuous positive airways pressure (CPAP) also may be useful for the treatment of HAPE, and a portable CPAP device that can be used in the field recently has been developed [45]. Nifedipine (10 mg, followed by 20 to 30 mg slow release every 12 to 24 hours) may be useful as an adjunct to descent and oxygen [46].

Portable hyperbaric chambers

Portable hyperbaric chambers have become available since the late 1980s and have been used routinely to treat high-altitude illness in some locations. There are three commercially available portable hyperbaric chambers (the Gamow Bag [Hyperbaric Technologies, Ilion, NY], the CERTEC bag [CERTEC, Sourcieux Les Mines, France], and the Portable Altitude Chamber [CE Bartlett, Wendouree, Australia]), and all are constructed from lightweight fabric and inflated by foot- or hand-driven pumps that provide rapid pressurization of patients to above ambient pressure, thereby simulating descent. Continuous pumping of the chamber is required to maintain internal pressure and prevent the build-up of carbon dioxide.

Dramatic responses have been reported to hyperbaric treatment of AMS, HACE, and HAPE, although there have been few controlled trials. All of the trials have evaluated the efficacy of hyperbaric therapy for the treatment of AMS, and it is unlikely that there will be similar trials for the treatment of HACE and HAPE given the rarity of these conditions. It would take a considerable amount of time to recruit sufficient patients with HACE and HAPE for a controlled trial of adequate statistical power.

For the treatment of AMS, simulated descent in a portable hyperbaric chamber is effective at relieving symptoms [47–49] and may be particularly useful when descent is impossible. Unfortunately, the beneficial effects usually disappear within approximately 10 hours. Hyperbaric therapy may be life-saving for treatment of HACE and HAPE but always should be used to facilitate descent. For HAPE, the recumbent position necessary for operation may not be tolerated by the patient. There are no controlled data to support any particular treatment schedule, although pressurization for 1 to 2 hours is usually sufficient to relieve symptoms of AMS or to facilitate descent in patients with HACE or HAPE and can be repeated if necessary.

Conclusions

The key to preventing high-altitude illness, in particular HACE and HAPE, is education. Travelers to high altitudes should have a sensible gradual ascent schedule that incorporates enough flexibility to take additional rest days as needed. Travelers should be familiar with the symptoms of high-altitude illness and encouraged to stop ascending if symptoms of AMS develop. In some situations, chemoprophylaxis may be warranted, and acetazolamide 125 to 250 mg twice daily remains the drug of choice. However, newer chemoprophylactic agents are likely to appear in the near future. For the treatment of HACE and HAPE, the importance of immediate descent cannot be overstated, and other treatment modalities should be seen as facilitating this process. The next few years are likely to see several advances in the understanding of the causes and management of high-altitude illness.

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