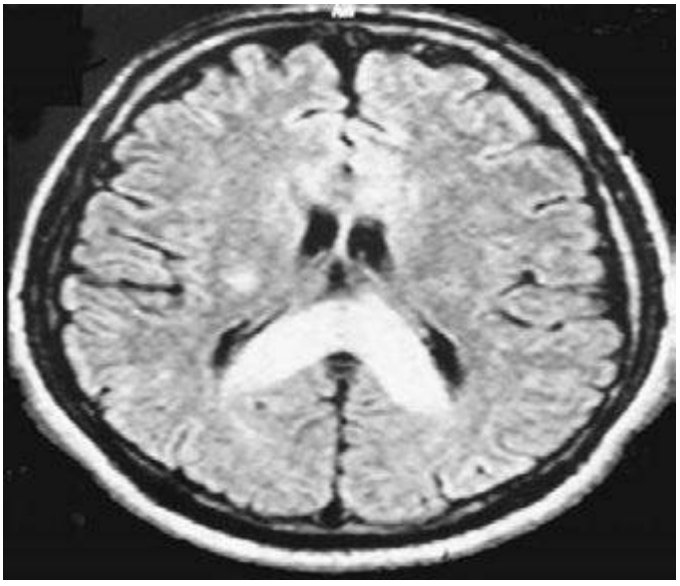

FIGURE 476e-1 T2 magnetic resonance image of the brain of a patient with high-altitude cerebral edema (HACE) shows marked swelling and a hyperintense posterior body and splenium of the corpus callosum (area with dense opacity). The patient, a climber, went on to climb Mount Everest about 9 months after this episode of HACE. *(With permission from Wilderness Environ Med 15:53–55, 2004.)*

TABLE 476e-1 MANAGEMENT OF ALTITUDE ILLNESS

Condition	Management
Acute mountain sickness (AMS), mild[a]	Discontinuation of ascent
	Treatment with acetazolamide (250 mg q12h)
	Descent[b]
AMS, moderate[a]	Immediate descent for worsening symptoms
	Use of low-flow oxygen if available
	Treatment with acetazolamide (250 mg q12h) and/or dexamethasone (4 mg q6h)[c]
	Hyperbaric therapy[d]
High-altitude cerebral edema (HACE)	Immediate descent or evacuation
	Administration of oxygen (2–4 L/min)
	Treatment with dexamethasone (8 mg PO/IM/IV; then 4 mg q6h)
	Hyperbaric therapy if descent is not possible
High-altitude pulmonary edema (HAPE)	Immediate descent or evacuation
	Minimization of exertion while patient is kept warm
	Administration of oxygen (4–6 L/min) to bring O_2 saturation to >90%
	Adjunctive therapy with nifedipine[e] (30 mg, extended-release, q12h)
	Hyperbaric therapy if descent is not possible

[a]Categorization of cases as mild or moderate is a subjective judgment based on the severity of headache and the presence and severity of other manifestations (nausea, fatigue, dizziness, insomnia). [b]No fixed altitude is specified; the patient should descend to a point below that at which symptoms developed. [c]Acetazolamide treats and dexamethasone masks symptoms. For prevention (as opposed to treatment), 125–250 mg of acetazolamide q12h or (when acetazolamide is contraindicated—e.g., in people with sulfa allergy) 4 mg of dexamethasone q12h may be used. [d]In hyperbaric therapy, the patient is placed in a portable altitude chamber or bag to simulate descent. [e]Nifedipine at this dose is also effective for the prevention of HAPE, as is salmeterol (125 mg inhaled twice daily), tadalafil (10 mg twice daily), or dexamethasone (8 mg twice daily).

in the brain at high altitude, and studies in mice have borne out this role. Although preliminary studies of VEGF in climbers have yielded inconsistent results regarding its association with altitude illness, indirect evidence of a role for this growth factor in AMS and HACE comes from the observation that dexamethasone, when used in the prevention and treatment of these conditions, blocks hypoxic upregulation of VEGF. Other factors in the development of cerebral edema may be the release of calcium-mediated nitric oxide and neuronally mediated adenosine, which may promote cerebral vasodilation.

Increased sympathetic activity triggered by hypoxia may also contribute to blood-brain barrier leakage. Enhanced optic-nerve sheath diameter with increasing severity of AMS has been noted and suggests an important role for increased intracranial pressures in the pathophysiology of AMS. Microhemorrhage formation caused by cytokines or damage through increased hydrostatic pressure is an important feature of HACE. Lesions in the globus pallidum (which is sensitive to hypoxia) leading to Parkinson's disease have also been reported to be complications of HACE. Finally, the effect of hypoxia on reactive oxygen species and the role of these species in clinical AMS are unclear.

The pathophysiology of the most common and prominent symptom of AMS—headache—remains unclear because the brain itself is an insensate organ; only the meninges contain trigeminal sensory nerve fibers. The cause of high-altitude headache is multifactorial. Various chemicals and mechanical factors activate a final common pathway, the trigeminovascular system. In the genesis of high-altitude headache, the response to nonsteroidal anti-inflammatory drugs and glucocorticoids provides indirect evidence for involvement of the arachidonic acid pathway and inflammation. Although the International Headache Society acknowledges that high altitude may be a trigger for migraine, it is unclear whether high-altitude headache and migraine share the same pathophysiology.

Prevention and Treatment (Table 476e-1) Gradual ascent, with adequate time for acclimation, is the best method for the prevention of altitude illness. Even though there may be individual variation in the rate of acclimation, a graded ascent of ≤400 m from the previous day's sleeping altitude is recommended above 3000 m, and taking every third day of gain in sleeping altitude as an extra day for acclimation is helpful. Spending one night at an intermediate altitude before proceeding to a higher altitude may enhance acclimation and attenuate the risk of AMS. Another protective factor in AMS is high-altitude exposure during the preceding 2 months; for example, the incidence and severity of AMS at 4300 m are reduced by 50% with an ascent after 1 week at an altitude of ≥2000 m rather than with an ascent from sea level. Studies have examined whether exposure to a normobaric hypoxic environment (in a room or a tent) before an ascent can provide protection against AMS. In double-blind placebo-controlled trials, repeated intermittent exposure (60–90 min) to normobaric hypoxia (up to 4500 m) or continuous exposure to 3000 m during 8 h of sleep for 7 consecutive days failed to reduce the incidence of AMS at altitudes of 4300–4559 m.

Clearly, a flexible itinerary that permits additional rest days will be helpful. Sojourners to high-altitude locations must be aware of the symptoms of altitude illness and should be encouraged not to ascend further if these symptoms develop. Any hint of HAPE (see below) or HACE mandates descent. Finally, proper hydration (but not overhydration) in high-altitude trekking and climbing, aimed at countering fluid loss due to hyperventilation and sweating, may also play a role in avoiding AMS. Pharmacologic prophylaxis at the time of travel to high altitudes is warranted for people with a history of AMS or when a graded ascent and acclimation are not possible—e.g., when rapid ascent is necessary for rescue purposes or when flight to a high-altitude location is required. Acetazolamide is the drug of choice for AMS prevention. It inhibits renal carbonic anhydrase, causing a prompt bicarbonate diuresis that leads to metabolic acidosis and hyperventilation. Acetazolamide (125–250 mg twice a day), administered for 1 day before ascent and continued for 2 or 3 days, is effective. Higher doses are not required. A meta-analysis limited to randomized controlled trials revealed that 125 mg of acetazolamide twice daily was effective in the prevention of AMS, with a relative-risk reduction of ~48% from values obtained with placebo. Paresthesia and a tingling sensation are common side effects of acetazolamide. This drug is a nonantibiotic sulfonamide that has low-level cross-reactivity with sulfa antibiotics; as a result, severe reactions are rare. Dexamethasone (8 mg/d in divided doses) is also effective. A large-scale, randomized, double-blind,