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Strengthening Public and Political Support Implementing Policies for Mitigation (Primary Prevention) Improving the Public’s Understanding of Climate Change Policymaking Process Energy Policy Building Movements for Addressing Climate Change Transportation Policy Agriculture Policy Promoting Climate Justice Increased Greenhouse Gas Levels Fossil Fuel Combustion Carbon Dioxide Other Greenhouse Gas Sources Methane Loss of Carbon Sinks Nitrous oxide Other GHGs FIGURE 474-11 Conceptual framework of climate change and its health impacts. (Reproduced with permission from JA Patz, BS Levy.) PART 15 Disorders Associated with Environmental Exposures ■ ■FURTHER READING Caminade C et al: Global risk model for vector-borne transmission of Zika virus reveals the role of El Niño 2015. Proc Natl Acad Sci USA 114:119, 2017. Colón-González FJ et al: The effects of weather and climate change on dengue. PLoS Negl Trop Dis 7:e2503, 2013. Glass GE et al: Satellite imagery characteristics local animal reservoir populations of Sin Nombre virus in the southwestern United States. Proc Natl Acad Sci USA 99:16817, 2002. Goren A et al: The emergence and shift in seasonality of Lyme bor reliosis in Northern Europe. Proc Biol Sci 290:20222420, 2023. Levy BS, Patz JA (eds): Climate Change and Public Health, 2nd ed. Oxford University Press, 2024. Mora C et al: Over half of known human pathogenic diseases can be aggravated by climate change. Nat Climate Change 12:869, 2022. Ogden NH: Risk maps for range expansion of the Lyme disease vec tor, Ixodes scapularis, in Canada now and with climate change. Int J Health Geogr 7:1, 2008. Paaijmans KP et al: Temperature-dependent pre-bloodmeal period and temperature-driven asynchrony between parasite development and mosquito biting rate reduce malaria transmission intensity. PLoS One 8:e55777, 2013. Patz JA et al: Impact of regional climate change on human health. Nature 438:310, 2005. Patz JA et al: Climate change and waterborne disease risk in the Great Lakes region of the U.S. Am J Prev Med 35:451, 2008. Ryan SJ et al: Warming temperatures could expose more than 1.3 billion new people to Zika virus risk by 2050. Glob Change Biol 27:84, 2021. Trtanj J et al: Climate impacts on water-related illness, in The Impacts of Climate Change on Human Health in the United States: A Scientific Assessment. U.S. Global Change Research Program, Washington, DC, 2016, pp 157–188.

Implementing Actions for Adaptation (Secondary Prevention) Implementing Health Adaptation *Also supports GHG mitigation Planning Healthy and Sustainable Built Environments* Promoting Nature-Based Climate Solutions* Health Impacts Climate Change Heat-related Disorders Temperature Rise Respiratory Disorders Sea-level Rise Vectorborne Diseases Hydrologic Extremes: Waterborne Diseases • Droughts Food Insecurity & Malnutrition • Floods Mental Health Impacts • Wildfires Violence Buddha Basnyat, Geoffrey Tabin, Steven Roy

Altitude Illness ■ ■EPIDEMIOLOGY Mountains cover one-fifth of the earth’s surface; 140 million people live permanently at altitudes ≥2500 m, and 100 million people travel to high-altitude locations each year. Skiers in the Alps or Aspen; tourists to La Paz, Ladakh, or Lahsa; religious pilgrims to Kailash-Manasarovar or Gosainkunda; trekkers and climbers to Kilimanjaro, Aconcagua, or Everest; miners working in high-altitude sites in South America; and military personnel deployed to high-altitude locations are all at risk of developing acute mountain sickness (AMS), high-altitude cerebral edema (HACE), high-altitude pulmonary edema (HAPE), and other altitude-related problems. AMS is the benign form of altitude illness, whereas HACE and HAPE are life-threatening. Altitude illness is likely to occur above 2500 m but has been documented even at 1500–2500 m. In the Mount Everest region of Nepal, ~50% of trekkers who walk to altitudes >4000 m over ≥5 days develop AMS, as do 84% of people who fly directly to 3860 m. The incidences of HACE and HAPE are much lower than that of AMS, with estimates in the range of 0.1–4%. Finally, reentry HAPE, which in the past was generally limited to highlanders (long-term residents of altitudes >2500 m) in the Americas, is now being seen in Himalayan and Tibetan highlanders—and often mis diagnosed as a viral illness—as a result of recent rapid air, train, and motorable-road access to high-altitude settlements. ■ ■PHYSIOLOGY Ascent to a high altitude subjects the body to a decrease in barometric pressure that results in a decreased partial pressure of oxygen in the inspired gas in the lungs. This change leads in turn to less pressure, driving oxygen diffusion from the alveoli and throughout the oxygen cascade. A normal initial “struggle response” to such an ascent includes increased ventilation—the cornerstone of acclimatization—mediated

by the carotid bodies. Hyperventilation may cause respiratory alkalosis and dehydration. Respiratory alkalosis may be extreme, with an arterial blood pH of >7.7 (e.g., at the summit of Everest). Alkalosis may depress the ventilatory drive during sleep, with consequent periodic breathing and hypoxemia. During early acclimatization, renal suppression of car bonic anhydrase and excretion of dilute alkaline urine combat alkalosis and tend to bring the pH of the blood to normal. Other physiologic changes during normal acclimatization include increased sympathetic tone; increased erythropoietin levels, leading to increased hemoglobin levels and red blood cell mass; increased tissue capillary density and mitochondrial numbers; and higher levels of 2,3-bisphosphoglycerate, enhancing oxygen utilization. Even with normal acclimatization, how ever, ascent to a high altitude decreases maximal exercise capacity (by ~1% for every 100 m gained above 1500 m) and increases susceptibility to cold injury due to peripheral vasoconstriction. If the ascent is made faster than the body can adapt to the stress of hypobaric hypoxemia, altitude-related disease states can result. ■ ■GENETICS Hypoxia-inducible factor, which acts as a master switch in highaltitude adaptation, controls transcriptional responses to hypoxia throughout the body and is involved in the release of vascular endothelial growth factor (VEGF) in the brain, erythropoiesis, and other pulmonary and cardiac functions at high altitudes. In particular, the gene EPAS1, which codes for transcriptional regulator hypoxiainducible factor 2α, appears to play an important role in the adaptation of Tibetans living at high altitude, resulting in lower hemoglobin con centrations than are found in Han Chinese or South American high landers. Other genes implicated include EGLN1 and PPARA, which are also associated with hemoglobin concentration. Some evidence indi cates that these genetic changes occurred within the past 3000 years, which is very fast in evolutionary terms. An intriguing question is whether the Sherpas’ well-known mountain-climbing ability is par tially attributable to their Tibetan ancestry, with overrepresentation of variants of EPAS. A striking recent finding is that some of these genetic characteristics may stem from those of Denisovan hominids who were contemporaries of the

Neanderthals. For acute altitude illness, a single gene variant is unlikely to be found, but differences in the susceptibility of individuals and popula tions, familial clustering of cases, and a positive association of some genetic variants all clearly support a role for genetics. ■ ■ACUTE MOUNTAIN SICKNESS AND HIGHALTITUDE CEREBRAL EDEMA AMS is a neurologic syndrome characterized by nonspecific symptoms (headache, nausea, fatigue, and dizziness), with a paucity of physical findings, developing 6–12 h after ascent to a high altitude. AMS is a clinical diagnosis. For uniformity in research studies, the Lake Louise Scoring System, created at the 1991 International Hypoxia Symposium, is generally used without the sleep disturbance score. AMS must be distinguished from exhaustion, dehydration, hypothermia, alcoholic hangover, and hyponatremia. AMS and HACE are thought to represent opposite ends of a continuum of altitude-related neurologic disorders. HACE (but not AMS) is an encephalopathy whose hallmarks are ataxia and altered consciousness with diffuse cerebral involvement but generally without focal neurologic deficits. Progression to these signal manifestations can be rapid. Papilledema and, more commonly, retinal hemorrhages may develop. In fact, retinal hemorrhages occur frequently at ≥5000 m, even in individuals without clinical symptoms of AMS or HACE. Risk Factors The most important risk factors for the development of altitude illness are the rate of ascent and a prior history of highaltitude illness. Exertion is a risk factor, but lack of physical fitness is not. An attractive but still speculative hypothesis proposes that AMS develops in people who have inadequate cerebrospinal capacity to buffer the brain swelling that occurs at high altitude. Children and adults seem to be equally affected, but people >50 years of age may be less likely to develop AMS than younger people. In general, there is no gender difference in AMS incidence. Sleep desaturation—a common

phenomenon at high altitude—is associated with AMS. Debilitating fatigue consistent with severe AMS on descent from a summit is an important risk factor for death in mountaineers. A prospective study involving trekkers and climbers who ascended to altitudes between 4000 and 8848 m showed that high oxygen desaturation and low venti latory response to hypoxia during exercise are independent predictors of severe altitude illness. However, because there may be a large overlap between groups of susceptible and nonsusceptible individuals, accu rate cutoff values are hard to define. Prediction is made more difficult because the pretest probabilities of HAPE and HACE are low. Neck irradiation or surgery damaging the carotid bodies, respiratory tract infections, and dehydration appear to be other potential risk factors for altitude illness. Unless guided by clinical signs and symptoms, pulse oximeter readings alone on a trek should not be used to predict AMS.

Pathophysiology Hypobaric hypoxia is the main trigger for alti tude illness. In established AMS, raised intracranial pressure, increased sympathetic activity, relative hypoventilation, fluid retention and redistribution, and impaired gas exchange have all been well noted; these factors may play an important role in the pathophysiology of AMS. Severe hypoxemia can lead to a greater than normal increase in cerebral blood flow. However, the exact mechanisms underlying AMS and HACE are unknown. Evidence points to a central nervous system process. Magnetic resonance imaging (MRI) studies have sug gested that vasogenic (interstitial) cerebral edema is a component of the pathophysiology of HACE. In the setting of high-altitude illness, the MRI findings shown in Fig. 475-1 are confirmatory of HACE, with increased signal in the white matter and particularly in the sple nium of the corpus callosum. In addition, hemosiderin deposits in the corpus callosum have been characterized as long-lasting footprints of HACE. Quantitative analysis in an MRI study revealed that hypoxia is associated with mild vasogenic cerebral edema irrespective of AMS. This finding is in keeping with case reports of suddenly symptomatic brain tumors and of cranial nerve palsies

without AMS at high alti tudes. Vasogenic edema may become cytotoxic (intracellular) in severe HACE. CHAPTER 475 Altitude Illness Impaired cerebral autoregulation in the presence of hypoxic cerebral vasodilation and altered permeability of the blood-brain barrier due to hypoxia-induced chemical mediators like histamine, arachidonic acid, and VEGF may all contribute to brain edema. In 1995, VEGF was first proposed as a potent promoter of capillary leakage in the brain at FIGURE 475-1 T2 magnetic resonance image of the brain of a patient with highaltitude 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. (From B Basnyat et al: Clinical images. A mystery. Wilderness Environ Med 15: 53, 2004. Reused with permission from the Wilderness Medical Society. ©2004 Wilderness Medical Society.)

high altitude, and studies in mice have borne out this role. Although studies of VEGF in climbers have yielded inconsistent results regard ing 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 calciummediated nitric oxide and neuronally mediated adenosine, which may promote cerebral vasodilation. Venous outflow obstruction resulting in increased brain capillary pressure is also thought to play an impor tant role in the development of HACE. Lesions in the globus pallidum (which is sensitive to hypoxia) leading to Parkinson’s disease have been reported to be complications of HACE.

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. Prevention and Treatment (Table 475-1) Gradual ascent, with adequate time for acclimatization, is the best method for the preven tion of altitude illness. Even though there may be individual variation in the rate of acclimatization, a conservative approach would be a graded ascent of ≤300 m from the previous day’s sleeping altitude above 3000 m, and taking every third day of gain in sleeping altitude as an extra day for acclimatization is helpful. Spending one night at an inter mediate altitude before proceeding to a higher altitude may enhance acclimatization and attenuate the risk of AMS. Another protective fac tor in AMS is recent high-altitude exposure; for example, the incidence PART 15 Disorders Associated with Environmental Exposures TABLE 475-1 Management of Altitude Illness CONDITION MANAGEMENT Acute mountain sickness (AMS), milda Discontinuation of ascent Treatment with acetazolamide (250 mg q12h) Descentb AMS, moderatea 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 therapyd 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 O2 saturation to >90% Adjunctive therapy with nifedipinee (30 mg, extended-release, q12h) Hyperbaric therapy if descent is not possible aCategorization 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). bNo fixed altitude is specified; the patient should descend to a point below that at which symptoms developed. cAcetazolamide treats and dexamethasone masks symptoms. For prevention (as opposed to treatment) of AMS, 125 mg of acetazolamide q12h or (when acetazolamide is contraindicated— e.g., in people with a history of sulfa anaphylaxis) 4 mg of dexamethasone q12h may be used. dIn hyperbaric therapy (Fig. 475-2), the patient is placed in a portable altitude chamber or bag to simulate descent. eNifedipine at this dose is also effective for the prevention of HAPE, as are tadalafil (10 mg twice daily), sildenafil (50 mg three times per day), and dexamethasone (8 mg twice daily). Preventative therapy should be continued for about 3 days after arriving at the target altitude. If prompt descent follows arrival at target altitude, continuation of preventative therapy is unnecessary.

and severity of AMS at 4300 m are reduced by 50% with an ascent after 1 week at an altitude ≥2000 m rather than with an ascent from sea level. However, regarding the benefits of acclimatization, clear-cut randomized studies are lacking. Repeated exposure at low altitudes to hypobaric or normobaric hypoxia is termed preacclimatization. Preac climatization is gaining popularity with commercially available normo baric hypoxia “tents” used for weeks to months in preparation for the climb. However, current evidence has not shown significant effects of such technology. 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. Proper hydration (but not overhydration) in high-altitude trekking and climbing, aimed at countering fluid loss due to hyperventilation and sweating, may 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 acclimatization are not possible—e.g., when rapid ascent is neces sary 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 prompt bicarbonate diuresis that leads to metabolic acidosis and hyperventilation. Acetazolamide (125 mg twice daily), administered for 1 day before ascent and con tinued for about 3 days at the same altitude, is effective. Treatment can be restarted if symptoms return after discontinuation of the drug. 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 reduc tion of ~48% from values obtained with placebo. Paresthesia and a tingling sensation are common side effects of acetazolamide. Some other uncommon side effects are myopia and drowsiness. 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, placebo-controlled trial in partially acclimatized trekkers clearly showed that Ginkgo biloba is ineffective in the prevention of AMS. In randomized studies, ibuprofen (600 mg three times daily) has been shown to be beneficial in the prevention of AMS. Recently, acet aminophen (1 g three times daily) was as effective as ibuprofen at the above dosage in a randomized, double-blind study, which did not have a placebo arm. However, more definitive studies are needed to clarify whether these medications mask the symptoms of altitude illness or whether they prevent the pathophysiology of AMS and assess the risk profile of side effects before these drugs can be routinely recommended for AMS prevention. Many drugs, including spironolactone, medroxy progesterone, magnesium, calcium channel blockers, and antacids, confer no benefit in the

prevention of AMS. Starkly conflicting results from a number of trials of inhaled budesonide for the prevention of AMS have recently been published, but, in all likelihood, the drug is ineffective. Similarly, no efficacy studies are available for coca leaves (a weak form of cocaine), which are offered to high-altitude travelers in the Andes, or for soroche pills, which contain aspirin, caffeine, and acetaminophen and are sold over the counter in Bolivia and Peru. Finally, a word of caution applies in the pharmacologic prevention of altitude illness. A fast-growing population of climbers in pursuit of a summit are injudiciously using prophylactic drugs such as gluco corticoids in an attempt to improve their performance; the outcome can be tragic because of potentially severe side effects of these drugs, especially if taken for a long duration. For the treatment of mild AMS, rest alone with analgesic use may be adequate. Descent and the use of acetazolamide and (if available) oxy gen are sufficient to treat most cases of moderate AMS. Even a minor descent (400–500 m) may be adequate for symptom relief. For moder ate AMS or early HACE, dexamethasone (4 mg orally or parenterally) is highly effective. For HACE, immediate descent is mandatory. When descent is not possible because of poor weather conditions or darkness, a simulation of descent in a portable hyperbaric chamber (Fig. 475-2) can be very effective. Pressurization in the bag for 1–2 h often leads

FIGURE 475-2 A hyperbaric bag. The cylindrical, portable (<7 kg) nylon bag has a one-way valve to prevent carbon dioxide buildup. A patient with severe acute mountain sickness (AMS), high-altitude cerebral edema (HACE), or high-altitude pulmonary edema (HAPE) is zipped inside the bag, which is continuously inflated with a foot pedal. The increased barometric pressure (2 psi) inside the bag simulates descent; for example, at 4250 m, the equivalent “elevation” inside the bag is ~2100 m. No supplemental oxygen is required. to spectacular improvement and, like dexamethasone administration, “buys time.” Thus, in certain high-altitude locations (e.g., remote pil grimage sites), the decision to bring along the lightweight hyperbaric chamber may prove lifesaving. Like nifedipine, phosphodiesterase-5 inhibitors have no role in the treatment of AMS or HACE. Finally, short-term oxygen inhalation using small cannisters of oxygen or by visiting oxygen bars is unhelpful in the prevention of AMS. ■ ■HIGH-ALTITUDE PULMONARY EDEMA Risk Factors and Manifestations Unlike HACE (a neurologic disorder), HAPE is primarily a pulmonary problem and therefore is not necessarily preceded by AMS. HAPE develops within 2–4 days after arrival at high altitude; it rarely occurs after >4 or 5 days at the same altitude, probably because of remodeling and adaptation that render the pulmonary vasculature less susceptible to the effects of hypoxia. A rapid rate of ascent, a history of HAPE, respiratory tract infections, and cold environmental temperatures are risk factors. Men are more susceptible than women. People with abnormalities of the cardiopul monary circulation leading to pulmonary hypertension—e.g., mitral stenosis, primary pulmonary hypertension, and unilateral absence of the pulmonary artery—may be at increased risk of HAPE, even at moderate altitudes. Although patent foramen ovale, a common condi tion, is four times more common among HAPE-susceptible individu als than in the general population, there is no compelling evidence to suggest causal effect. Echocardiography is recommended when HAPE develops at relatively low altitudes (<3000 m) and whenever cardio pulmonary abnormalities predisposing to HAPE are suspected. The differential diagnosis of HAPE includes anxiety attack, pneumonia, pneumothorax, and pulmonary embolism. The initial manifestation of HAPE may be a reduction in exercise tolerance greater than that expected at the given altitude. Although a dry, persistent cough may presage HAPE and may be followed by the production of blood-tinged sputum, cough in the mountains is almost universal and the mechanism is poorly understood. Tachypnea and tachycardia, even at rest, are important markers as illness progresses. Crackles

may be heard on auscultation but are not diagnostic. HAPE may be accompanied by signs of HACE. Patchy or localized opaci ties (Fig. 475-3) or streaky interstitial edema may be noted on chest radiography. In the past, HAPE was mistaken for pneumonia due to the cold or for heart failure due to hypoxia and exertion. Kerley B lines or a bat-wing appearance are not seen on radiography. Electro cardiography may reveal right ventricular strain or even hypertro phy. Hypoxemia and respiratory alkalosis are consistently present in patients with HAPE. Alkalemia is often present, unless the patient is

FIGURE 475-3 Chest radiograph of a patient with high-altitude pulmonary edema shows opacity in the right middle and lower zones simulating pneumonic consolidation. The opacity cleared almost completely in 2 days with descent and supplemental oxygen. taking acetazolamide, in which case metabolic acidosis may super vene. Assessment of arterial blood gases is not necessary in the evalu ation of HAPE; an oxygen saturation reading with a pulse oximeter is generally adequate. The existence of a subclinical form of HAPE has been suggested by an increased alveolar-arterial oxygen gradient in Everest climbers near the summit, but hard evidence correlating this abnormality with the development of clinically relevant HAPE is lack ing. Comet-tail scoring—an ultrasound technique initially validated in cardiogenic pulmonary edema—has been used for evaluation of extravascular lung water at high altitude. However, B-lines are not just seen in patients with HAPE and are frequently detected in individuals who never go on to develop clinical HAPE. For this reason, comet-tail scoring is sensitive but not specific for HAPE, and clinical correlation is important. CHAPTER 475 Altitude Illness Pathophysiology HAPE is a noncardiogenic pulmonary edema with normal pulmonary artery wedge pressure. It is characterized by patchy pulmonary hypoxic vasoconstriction that leads to overperfu sion in some areas. This abnormality leads in turn to increased pul monary capillary pressure (>18 mmHg) and capillary “stress” failure. The exact mechanism for this hypoxic vasoconstriction is unknown. Endothelial dysfunction due to hypoxia may play a role by impairing the release of nitric oxide, an endothelium-derived vasodilator. At high altitude, HAPE-prone persons have reduced levels of exhaled nitric oxide. The effectiveness of phosphodiesterase-5 inhibitors in allevi ating altitude-induced pulmonary hypertension, decreased exercise tolerance, and hypoxemia supports the role of nitric oxide in the patho genesis of HAPE. One study demonstrated that prophylactic use of tadalafil, a phosphodiesterase-5 inhibitor, decreases the risk of HAPE by 65%. In contrast, the endothelium also synthesizes endothelin-1, a potent vasoconstrictor whose concentrations are higher than average in HAPE-prone mountaineers. Exercise and cold lead to increased pulmonary intravascular pres sure and may predispose to HAPE. In addition, hypoxia-triggered increases in sympathetic drive may lead to pulmonary venoconstric tion and extravasation into the alveoli from the pulmonary capillaries. Consistent with this concept, phentolamine, which elicits α-adrenergic blockade, improves hemodynamics and oxygenation in HAPE more than do other vasodilators. The study of tadalafil cited above also inves tigated dexamethasone in the prevention of HAPE. Surprisingly, dexa methasone reduced the incidence of HAPE by 78%—a greater decrease than with tadalafil. Besides possibly increasing the availability of endo thelial nitric oxide, dexamethasone may have altered the excessive sym pathetic activity associated with HAPE: the heart rate of participants in the dexamethasone arm of the study was significantly lowered. Finally, people susceptible to HAPE also display enhanced sympathetic activity during short-term hypoxic breathing at low altitudes. Because many patients with HAPE have fever, peripheral leukocy tosis, and an increased erythrocyte sedimentation rate, inflammation

has been considered an etiologic factor in HAPE. However, strong evidence suggests that inflammation in HAPE is an epiphenomenon rather than the primary cause. Nevertheless, inflammatory processes (e.g., those elicited by viral respiratory tract infections) do predispose persons to HAPE—even those who are constitutionally resistant to its development.

Another proposed mechanism for HAPE is impaired transepithelial clearance of sodium and water from the alveoli. β-Adrenergic agonists upregulate the clearance of alveolar fluid in animal models. In a single double-blind, randomized, placebo-controlled study of HAPE-suscep tible mountaineers, prophylactic inhalation of the β-adrenergic agonist salmeterol reduced the incidence of HAPE by 50%. However, the dos age of salmeterol (125 μg twice daily) used was very high, which could result in excessive tachycardia and tremors. Other effects of β agonists may also contribute to the prevention of HAPE, and these findings are in keeping with the concept that alveolar fluid clearance may play a pathogenic role in this illness. Prevention and Treatment (Table 475-1) Allowing sufficient time for acclimatization by ascending gradually (as discussed above for AMS and HACE) is the best way to prevent HAPE. Sustained-release nifedipine (30 mg), given twice daily, prevents HAPE in people who must ascend rapidly or who have a history of HAPE. Other drugs for the prevention of HAPE are listed in Table 475-1 (footnote e). Although dexamethasone is listed for prevention, its adverse effect profile requires close monitoring. Acetazolamide has been shown to blunt hypoxic pulmonary vasoconstriction in animal models, and this observation warrants further study in HAPE prevention. However, one large study failed to show a decrease in pulmonary vasoconstric tion in partially acclimatized individuals given acetazolamide. Inhaled salmeterol is not recommended as clinical experience with this drug is limited at high altitude. Finally, potent diuretics like furosemide should be avoided in the treatment of HAPE. Early recognition is para mount in the treatment of HAPE, especially when it is not preceded by the AMS symptoms of headache and nausea. Fatigue and dyspnea at rest may be the only initial manifestations. Descent and the use of supplementary oxygen (aimed at bringing oxygen saturation to >90%) are the most effective therapeutic interventions. Exertion should be kept to a minimum, and the patient should be kept warm. Hyperbaric therapy (Fig. 475-2) in a portable altitude chamber may be lifesav ing, especially if descent is not possible and oxygen is not available. Oral sustained-release nifedipine (30 mg twice daily) can be used as adjunctive therapy. No studies have investigated phosphodiesterase-5 inhibitors in the treatment of HAPE, but reports have described their use in clinical practice. The mainstays of treatment remain descent and (if available) oxygen. PART 15 Disorders Associated with Environmental Exposures In AMS, if symptoms abate (with or without acetazolamide), the patient may reascend gradually to a higher altitude. Unlike that in acute respiratory distress syndrome (another noncardiogenic pulmonary edema), the architecture of the lung in HAPE is usually well preserved, with rapid reversibility of abnormalities (Fig. 475-3). This fact has allowed some people with HAPE to reascend slowly after a few days of descent and rest. In HACE, reascent after a few days may not be advis able during the same trip. ■ ■OTHER HIGH-ALTITUDE PROBLEMS Sleep Impairment The mechanisms underlying sleep problems, which are among the most common adverse reactions to high altitude, include increased periodic breathing; changes in sleep architecture, with increased time in lighter sleep stages; and changes in rapid eye movement sleep. Sojourners should be reassured that sleep qual ity improves with acclimatization. In cases where drugs do need to be used, acetazolamide (125 mg before bedtime) is especially use ful because this agent decreases hypoxemic episodes and alleviates sleeping disruptions caused by excessive periodic breathing. Whether combining acetazolamide with temazepam or zolpidem is more effec tive than administering acetazolamide alone is unknown. In com binations,

the doses of temazepam and zolpidem should not be increased by >10 mg at high altitudes. Limited evidence suggests that

diazepam causes hypoventilation at high altitudes and therefore is con traindicated. For trekkers with obstructive sleep apnea who are using a continuous positive airway pressure (CPAP) machine, the addition of acetazolamide, which will decrease centrally mediated sleep apnea, may be helpful. There is evidence to show that obstructive sleep apnea at high altitude may decrease and “convert” to central sleep apnea. Gastrointestinal Issues High-altitude exposure may be associ ated with increased gastric and duodenal bleeding, but further studies are required to determine whether there is a causal effect. Because of decreased atmospheric pressure and consequent intestinal gas expan sion at high altitudes, many sojourners experience abdominal bloating and distension as well as excessive flatus expulsion. In the absence of diarrhea, these phenomena are normal, if sometimes uncomfortable. Accompanying diarrhea, however, may indicate the involvement of bacteria or Giardia parasites, which are common at many high-altitude locations in the developing world. Prompt treatment with fluids and empirical antibiotics may be required to combat dehydration in the mountains. Hemorrhoids are common on high-altitude treks; treat ment includes hot soaks, application of hydrocortisone ointment, and measures to avoid constipation. High-Altitude Cough High-altitude cough can be debilitating and is sometimes severe enough to cause rib fracture, especially at

> 5000 m. The etiology of this common problem is probably multifac torial. Although high-altitude cough has been attributed to inspiration of cold dry air, this explanation appears not to be sufficient by itself; in long-duration studies in hypobaric chambers, cough has occurred despite controlled temperature and humidity. The implication is that hypoxia also plays a role. Exercise can precipitate cough at high alti tudes, possibly because of water loss from the respiratory tract. In gen eral, infection does not seem to be a common etiology. Many trekkers find it useful to wear a balaclava to trap some moisture and heat. In most situations, cough resolves upon descent. High-Altitude Neurologic Events Unrelated to “Altitude Illness” Transient ischemic attacks (TIAs) and strokes have been well described in high-altitude sojourners outside the setting of altitude sickness. However, these descriptions are not based on cause (hypoxia) and effect. In general, symptoms of AMS present gradually, whereas many of these neurologic events happen suddenly. The population that suffers strokes and TIAs at sea level is generally an older age group with other risk factors, whereas those so afflicted at high altitudes are gener ally younger and probably have fewer risk factors for atherosclerotic vascular disease. Other mechanisms (e.g., migraine, vasospasm, focal edema, hypocapneic vasoconstriction, hypoxia in the watershed zones of minimal cerebral blood flow, or cardiac right-to-left shunt) may be operative in TIAs and strokes at high altitude. Subarachnoid hemorrhage, transient global amnesia, delirium, and cranial nerve palsies (e.g., lateral rectus palsy) occurring at high altitudes but outside the setting of altitude sickness have been well described. Syncope is common at moderately high altitudes, gener ally occurs shortly after ascent,

> usually resolves without descent, and appears to be a vasovagal event related to hypoxemia. Seizures occur rarely with HACE, but hypoxemia and hypocapnia, which are prevalent at high altitudes, are well-known triggers that may contribute to new or breakthrough seizures in predisposed individuals. Nevertheless, the consensus among experts is that sojourners with well-controlled seizure disorders can ascend to high altitudes. Finally, persons with hypercoagulable conditions (e.g., antiphos pholipid syndrome, protein C deficiency) who are asymptomatic at sea level may experience cerebral venous thrombosis (possibly due to enhanced blood viscosity triggered by polycythemia and dehydration) at high altitudes. Proper history taking, examination, and prompt investigations where possible will help define these conditions as enti ties separate from altitude sickness. Administration of oxygen (where available) and prompt descent are the cornerstones of treatment of most of these neurologic conditions. Ocular Problems Ocular issues are common in sojourners to high altitudes. Hypoxemia induced by altitude leads to increased retinal

blood flow, which can be visible as engorged retinal veins on ophthal moscopic examination. Both high flow and hypoxemic vascular dam age causing permeability have been implicated in a breakdown of the blood-retina barrier and the formation of retinal hemorrhages. Blot, dot, flame, and white-centered hemorrhages can be observed. These hemorrhages usually resolve spontaneously with descent, with only mild symptoms and no lasting visual damage in most healthy eyes. The exception is hemorrhage in the macular area. Macular hemor rhages can cause devastating initial visual loss, particularly if bilateral, and have been reported to cause permanently decreased vision in a few cases. Stroke syndromes such as retinal vein occlusion, retinal artery occlusion, ischemic optic neuropathy, and cortical visual loss have all been reported. With unilateral vision loss, it is always important to check for a relative afferent pupillary defect. Increased hematocrit combined with dehydration may contribute to these maladies. Glauco matous optic nerve damage may progress with hypoxemia of altitude. Acetazolamide is helpful both in combating the respiratory alkalosis that comes with increased ventilation at high altitude and in lower ing the interocular pressure; its use should be considered in patients with stable controlled glaucoma. Macular degeneration and diabetic eye disease are not directly exacerbated by ascent to high altitude. Dry eye and solar damage to the cornea, known as “snow blindness,” are common. Wearing of high-quality UV-blocking sunglasses, even on cloudy days, and attention to protecting and supplementing the tear film with artificial tear drops can greatly improve comfort and vision. Although modern refractive surgeries, such as photorefractive keratec tomy (PRK) and laser in situ keratomileusis (LASIK), are stable at high altitude, patients who have undergone radial keratotomy should be cautioned that hypoxemia to the cornea can lead to swelling that shifts the refraction during ascent. Psychological/Psychiatric Problems Delirium characterized by a sudden change in mental status, a short attention span, disorga nized thinking, and an agitated state during the period of confusion has been well described in mountain climbers and trekkers without a prior history. In addition, anxiety attacks, often triggered at night by excessive periodic breathing, are well documented. The contribution of hypoxia to these conditions is unknown. Expedition medical kits need to include antipsychotic injectable drugs to control psychosis in patients in remote high-altitude locations. ■ ■PREEXISTING MEDICAL ISSUES Because travel to high altitudes

is increasingly popular, common con ditions such as hypertension, coronary artery disease, and diabetes are more frequently encountered among high-altitude sojourners. This situation is of particular concern for the millions of elderly pilgrims with medical problems who visit high-altitude sacred areas (e.g., in the Himalayas) each year. In recent years, high-altitude travel has attracted intrepid trekkers who are taking immunosuppressive medications (e.g., kidney transplant recipients or patients undergoing chemotherapy). Recommended vaccinations and other precautions (e.g., hand wash ing) may be especially important for this group. Although most of these medical conditions do not appear to influence susceptibility to altitude illness, they may be exacerbated by ascent to altitude, exertion in cold conditions, and hypoxemia. Advice regarding the advisability of high-altitude travel and the impact of high-altitude hypoxia on these preexisting conditions is becoming increasingly relevant, but there are no evidence-based guidelines. In addition, recommendations made for relatively low altitudes (~3000 m) may not hold true for higher altitudes (>4000 m), where hypoxic stress is greater. Personal risks and benefits must be clearly thought through before ascent. Hypertension At high altitudes, enhanced sympathetic activity may lead to a transient rise in blood pressure. Occasionally, nonhyper tensive, healthy, asymptomatic trekkers have pathologically high blood pressure at high altitude that rapidly normalizes without medicines on descent. Sojourners should continue to take their antihypertensive medications at high altitudes. Importantly, hypertensive patients are not more likely than others to develop altitude illness. Because the

probable mechanism of high-altitude hypertension is α-adrenergic activity, anti-α-adrenergic drugs such as prazosin have been suggested for symptomatic patients and those with labile hypertension. It is best to start taking the drug several weeks before the trip and to carry a sphygmomanometer if a trekker has labile hypertension. Sustainedrelease nifedipine may also be useful. A recent observational cohort study of 672 hypertensive and nonhypertensive trekkers in the Hima layas showed that most travelers, including those with well-controlled hypertension, can be reassured that their blood pressure will remain relatively stable at high altitude. Although blood pressure may be extremely elevated at high altitude in normotensive and hypertensive people, it is unlikely to cause symptoms.

Coronary Artery Disease Myocardial oxygen demand and maxi mal heart rate are reduced at high altitudes because the VO2 max (maximal oxygen consumption) decreases with increasing altitude. This effect may explain why signs of cardiac ischemia or dysfunction usually are not seen in healthy persons at high altitudes. Asymptom atic, fit individuals with no risk factors need not undergo any tests for coronary artery disease before ascent. For persons with ischemic heart disease, previous myocardial infarction, angioplasty, and/or bypass surgery, an exercise treadmill test is indicated. A strongly positive treadmill test is a contraindication for high-altitude trips. Patients with poorly controlled arrhythmias should avoid high-altitude travel, but patients with arrhythmias that are well controlled with antiarrhyth mic medications do not seem to be at increased risk. Sudden cardiac deaths are not noted with a greater frequency in the Alps than at lower altitudes; although sudden cardiac deaths are encountered every trek king season in the higher Himalayan range, accurate documentation is lacking. CHAPTER 475 Cerebrovascular Disease Patients with TIAs should avoid travel to high altitude for at least 3 months. Patients with known cerebral aneurysm should also avoid high-altitude travel because of possible rupture of the aneurysm due to increased cerebral blood flow at high altitude. Altitude Illness Migraine Trekkers with a history of migraine may have an increased likelihood of suffering from AMS and may also be predisposed to headaches including altered character of their migraine presenting with focal

neurologic deficits. Oxygen inhalation may reduce AMStriggered headache, whereas a migraine headache usually persists even after 10–15 min of oxygen inhalation. Asthma Although cold air and exercise may provoke acute bron choconstriction, asthmatic patients usually have fewer problems at high than at low altitudes, possibly because of decreased allergen levels and increased circulating catecholamine levels. Nevertheless, asthmatic individuals should carry all their medications, including oral gluco corticoids, with proper instructions for use in case of an exacerbation. Severely asthmatic persons should be cautioned against ascending to high altitudes. Pregnancy In general, low-risk pregnant women ascending to 3000 m are not at special risk except for the relative unavailability of medical care in many high-altitude locations, especially in developing coun tries. Despite the lack of firm data on this point, venturing higher than 3000 m to altitudes at which oxygen saturation drops steeply seems unadvisable for pregnant women. Obesity Although living at a high altitude has been suggested as a means of controlling obesity, obesity has also been reported to be a risk factor for AMS, probably because nocturnal hypoxemia is more pro nounced in obese individuals. Hypoxemia may also lead to greater pul monary hypertension, thus possibly predisposing the trekker to HAPE. Sickle Cell Disease High altitude is one of the rare environmental exposures that occasionally provokes a crisis in persons with sickle cell anemia. Even when traversing mountain passes as low as 2500 m, peo ple with sickle cell anemia have been known to have a vaso-occlusive crisis. Patients with known sickle cell anemia who need to travel to high altitudes should use supplemental oxygen and travel with caution. Thalassemia has not been known to cause problems at high altitude.

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