Chapter 144

High-Altitude Medicine

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Epidemiology

High-altitude illness represents a spectrum of clinical entities that have hampered the activities of mountaineers, merchants, military forces, aviators, and explorers throughout time. This illness is seen clinically in one of several forms that overlap and share a common pathophysiologic mechanism. Acute mountain sickness (AMS) is the relatively benign and self-limited presentation, whereas high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) represent the potentially life-threatening manifestations of high-altitude illness.

Worldwide, it is estimated that approximately 40 million individuals live above 8000 feet, and 25 million live above 10,000 feet.1 Rather than these high-altitude residents, the groups at risk for acute altitude illnesses are those who ascend into mountainous regions. Mountain sports activities and tourism are attracting increasing numbers of participants each year. This, combined with the rapid ascent, made possible by air transportation results in more unacclimatized individuals at risk for high-altitude illness. More than 1 million visitors travel annually to the remote high mountain ranges of Asia, Africa, and South America.1 Approximately 35 million visitors travel annually to high-altitude recreation areas in the western United States.1

The incidence of high-altitude illness depends on many variables, including the rate of ascent, previous altitude exposure, and individual genetic susceptibility.2,3 Sleeping altitude, final altitude reached, and duration of stay at altitude are also risk factors for AMS development.4 AMS is common (67% incidence) among mountain climbers on Mt. Rainier who ascend quickly (1 or 2 days) to 14,410 feet.5 Trekkers who fly into the Khumbu region to explore the Mt. Everest area have a higher incidence of AMS (47%) compared with those who walk (23%).6 Skiers who visit resorts in the western United States from sea level generally fly or drive to the region but sleep at relatively lower altitudes than the other groups mentioned. Among this population, AMS occurs in approximately 25%.7 Given the large number of visitors (approximately 25 million) in Colorado each year, this is not a trivial matter. The incidence of HAPE varies from 0.01 to 2% in most studies but has reached 15.5% among soldiers flown directly to 14,500 feet without a chance to acclimatize at a lower altitude.8,9 The incidence of HACE is lower, and although it frequently occurs with HAPE, it can be seen as an isolated entity. Both HAPE and HACE are more common with a longer duration of visit and higher sleeping altitude.

Age may be a relative risk factor. Most studies of children suggest that they have the same incidence of AMS as adults do.9-12 One small study of tourists in Chile evaluated children 4 to 48 months old and found higher AMS scores and lower oxygen saturations compared with those of their parents.13 Younger individuals (<20 years old) are more likely to have HAPE, although HAPE is extremely rare in children younger than 2 years. Gender does not affect the incidence of AMS;1 however, women may have less risk for development of HAPE.6,7,14,15 No relationship appears to exist between AMS development and the menstrual cycle.16

The number of older travelers visiting mountain resorts is increasing. Many of these individuals have underlying health problems, including lung disease (10%), heart disease (25%), and hypertension (30%). Despite these conditions, the risk for AMS development in adults older than 50 years may be less than in younger age groups.2,17 One study found no difference in the incidence or severity of AMS in climbers older than 50 years compared with a matched cohort of younger climbers.18 Nevertheless, there are indications that elders may not react well to acute high-altitude exposure. Pulmonary vital capacity decreases almost one third in elders ascending from sea level to 14,000 feet for 1 week, producing a large decrease in both oxygen saturation and maximal oxygen uptake during exercise.

Definitions

Moderate altitude is between 8000 and 10,000 feet of elevation. Although most people do not experience significant arterial oxygen desaturation until they reach higher altitudes, high-altitude illness is common with rapid ascent above 8000 feet, and individuals with underlying medical problems may be predisposed to development of altitude illness at lower levels.

High altitude is between 10,000 and 18,000 feet. Most serious altitude illness occurs at these levels. The pathophysiologic effects of high altitude begin when the oxygen saturation of the arterial blood begins to fall below the 90% level. The sigmoidal shape of the oxyhemoglobin dissociation curve prevents a significant fall of arterial oxygen saturation (SaO₂) in most individuals until an altitude of approximately 12,000 feet. At this altitude, the steep portion of the curve is encountered, and marked oxygen desaturation may occur with relatively small increases in altitude (Fig. 144-1). Some predisposed individuals may desaturate to less than 90% at altitudes as low as 8000 feet.
Oxygen saturation (%)

**Box 144-1 Alveolar Gas Equation**

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\text{PAO}_2 = \text{P}_{102}(\text{PACO}_2/R)
\]

- **PAO**₂ Partial pressure of oxygen in alveolus
- **P**₁₀₂ Partial pressure of oxygen in inspired air
- **PACO**₂ Partial pressure of carbon dioxide in alveolus
- **R** Respiratory quotient

Acclimatization begins at the altitude that causes the oxygen saturation of arterial blood to fall below sea-level values. The altitude at which this occurs depends on the rate of ascent, the duration of exposure, and the individual’s physiology. People with preexisting conditions that reduce oxygen saturation or content may have a decreased altitude tolerance. Of particular importance are both acute and chronic cardiac and respiratory illnesses. Most healthy, unacclimatized visitors to high altitude will not desaturate significantly (to less than 90%) until they reach elevations higher than 8000 feet.

The risk of high-altitude illness also depends on an individual’s inherent ability to acclimatize. Some people acclimatize easily without having any clinical symptoms. Others may transiently have AMS during acclimatization, and a few have marked reactions to altitude exposure, developing severe altitude illness. This variability involves many genetic and epigenetic factors that moderate the process of acclimatization. Previous successful acclimatization may be predictive of future responses for adults in similar conditions, but this may not be the case for children.

One of the most important physiologic changes that occurs during acclimatization is an increase in minute ventilation, causing a decrease in the partial pressure of carbon dioxide (PACO₂). The alveolar gas equation states that as the PACO₂ decreases, a corresponding increase in PAO₂ occurs, thereby increasing arterial oxygenation (Box 144-1). Thus the level of ventilation determines alveolar oxygen for a given inspired oxygen tension.

When a person arrives at high altitude, the peripheral chemoreceptors in the carotid bodies respond to a decrease in PAO₂ and signal the respiratory control center in the medulla to increase ventilation. This increase in ventilation is known as the hypoxic ventilatory response (HVR), which may be inhibited or stimulated by numerous factors, including ethanol, sleep medications, caffeine, cocoa, prochlorperazine, and progesterone. The magnitude of the HVR varies among individuals and may be genetically predetermined.

As ventilation increases, a respiratory alkalosis occurs that acts as a negative feedback system on the central respiratory center, limiting any further increase in ventilation. Within 24 to 48 hours of ascent, the kidneys excrete bicarbonate in an effort to compensate for the alkalosis. As the pH normalizes, ventilation slows, reaching a maximum after 6 to 8 days. This process is enhanced by acetazolamide. The ability to achieve an adequate HVR varies and is related to the ability to acclimatize. A low HVR and relative hypoventilation are implicated in the pathogenesis of both AMS and HAPE. For the majority of people with intermediate HVRs, however, ventilatory drive probably has no predictive value for AMS development.

The release of catecholamines on ascent stimulates the circulatory system to increase cardiac output. This is manifested by an elevation in heart rate, blood pressure, cardiac output, and venous tone. Except at extreme altitudes, acclimatization results in the gradual return of the resting heart rate to near sea-level values. Resting relative tachycardia is evidence of poor acclimatization. As the altitude increases, a decrease in maximal heart rate capacity occurs, and at the limits of acclimatization, maximal and resting heart rates converge.

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**Figure 144-1.** Oxygen-hemoglobin dissociation curve. Approximate oxygen saturations are marked for several altitudes. P\text{O}_2, partial pressure of oxygen. (Data for 15,000-29,029 feet from Sutton JR, et al: Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. J Appl Physiol 64:1309, 1988.)

**Extreme altitude** is above 18,000 feet. At this height, complete acclimatization generally is not possible, and long visits above this level result in progressive deterioration.

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**ENVIRONMENTAL CONSIDERATIONS**

Barometric pressure decreases logarithmically as the altitude rises. The partial pressure of oxygen (P\text{O}_2) in the atmosphere also decreases as altitude rises, but it remains a constant 20.93% of the barometric pressure. The shape of the earth is slightly flat at the poles and bulging at the equator. The atmospheric envelope that surrounds the earth has a similar shape; therefore, the barometric pressure is lower at higher latitudes than it is at the equator. For example, it has been calculated that it would be impossible for a climber to reach the summit of Mt. Everest without supplemental oxygen if the mountain happened to be in a more northern latitude.

The atmospheric envelope also undergoes a seasonal tide that causes a variation in its local thickness. This results in barometric pressures that are lower and “relative altitudes” that are higher during the winter season. Local weather can also have a significant effect on barometric pressure from day to day. A low-pressure front can reduce the barometric pressure 12 to 40 mm Hg (500-2500 feet) and result in a significant temporary increase in relative altitude.

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**ACCLIMATIZATION**

The term *acclimatization* refers to the series of integrated adaptations that take place at high altitude, which tend to restore the oxygen pressures within the tissues toward normal sea-level values despite the lowered P\text{O}_2 of the atmosphere. These processes occur gradually and involve multiple systems from protein synthesis to respiratory, cardiovascular, and hematologic adjustments. Gradual ascents made by mountaineers during several weeks have allowed the successful summiting of many of the world’s highest peaks, including Mt. Everest (29,029 feet), without supplemental oxygen. Without this gradual approach to allow acclimatization, however, rapid exposure to extreme altitude results in loss of consciousness, and death may occur in a matter of minutes.
The hematopoietic response to high-altitude acclimatization consists of an increase in both hemoglobin and the number of red blood cells. An early increase of up to 15% occurs in mean corpuscular hemoglobin concentration after rapid ascent to high altitude. This is primarily a result of a fluid shift into the extravascular space. Long-term acclimatization leads to an increase in plasma volume and total blood volume. Erythropoietin is secreted in response to hypoxemia within hours of ascent, which in turn stimulates the production of red blood cells, leading to new circulatory red blood cells in 4 or 5 days. During the next 2 months, red blood cell mass increases in proportion to the degree of hypoxemia.

Hypoxemia also results in an increase in 2,3-diphosphoglycerate, causing a rightward shift of the oxyhemoglobin dissociation curve, which favors a release of oxygen from the blood to the tissues. This is counteracted by the leftward shift of the oxyhemoglobin dissociation curve caused by the respiratory alkalosis from hyperventilation. The result is a net null change in the oxyhemoglobin curve and an increase in oxygen-hemoglobin binding in the lung, which raises SaO₂. Some individuals with mutant hemoglobin and high oxygen-hemoglobin affinity are found to acclimatize more efficiently than their normal counterparts at moderate altitudes.

The symptoms of AMS develop several hours after arrival at high altitude, whereas the development of HAPE and HACE generally requires several days of altitude exposure. Because hypobaric hypoxemia occurs within minutes of arrival, it cannot be the direct cause of high-altitude illness. Instead, it appears to be the initiating factor for a complex pathologic process that leads to the development of the various clinical syndromes. The proposed mechanisms for the development of AMS, HAPE, and HACE are represented schematically in Figure 144-2.

A poor HVR resulting in relative hypoventilation may be due to either the individual's genetic predisposition or extrinsic factors, such as medications, that decrease the ventilatory drive. Whenever the HVR is decreased, the protective effects of hyperventilation are lost and the hypoxemia of high-altitude exposure is exacerbated.

The clinical syndromes of high-altitude illness are not discrete entities but represent a spectrum of intertwined pathophysiologic mechanisms. AMS and HACE appear to represent differing manifestations of altitude illness on the same continuum, whereas HAPE appears to have a somewhat independent pathophysiologic mechanism.

Figure 144-2. Proposed mechanisms for the development of acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). CNS, central nervous system; ICP, intracranial pressure.
The centrally mediated periodic breathing associated with high-altitude exposure may result in periods of apnea during sleep, causing severe arterial oxygen desaturation, which further exacerbates hypoxemia.\(^{31}\) Significant hypoxemia initiates multiple systemic responses that involve the circulatory, pulmonary, endocrine, and central nervous systems.

Hypoxemia alters fluid homeostasis, resulting in a generalized fluid retention followed by the shift of fluid into the intracellular spaces. This is manifested by peripheral edema, decreased urinary output, and increased body weight in patients with AMS. Several different mechanisms may account for these fluid shifts, including arginine vasopressin levels and sympathetic stimulation that may be centrally mediated.\(^{32,33}\) Arginine vasopressin levels are elevated in some cases of AMS and HAPE and decreased in others.\(^{34,35}\) Aldosterone, plasma renin, and atrial natriuretic levels are higher in people with AMS.\(^{35,37}\)

The hypoxemia that results from high-altitude exposure also causes an increase in pulmonary artery resistance, leading to pulmonary hypertension and elevated capillary pressures that play the cardinal role in the development of HAPE. Exercise and cold stress at altitude may increase hypoxemia and exacerbate pulmonary hypertension.\(^{36,59}\) Pulmonary blood volumes and pulmonary hypertension are increased by sympathetic nervous system stimulation and catecholamine release.\(^{40,41}\) In HAPE-susceptible individuals, pulmonary hypertension becomes severe, and an uneven distribution of pulmonary vasoconstriction results in overperfusion, increased capillary pressures, distention, and leakage in the remaining vessels.\(^{42-45}\) This explains the patchy nature of the infiltration seen on a chest radiograph with HAPE (Fig. 144-3). The mechanism for the uneven vasoconstriction in HAPE may be due to decreased nitric oxide bioavailability at the pulmonary tissue level, also leading to increased endothelial leakage and extracellular edema.\(^{46-48}\) Overperfusion of a restricted vascular bed as the pathogenesis of HAPE is supported by the observation that people born with congenital unilateral absence of a pulmonary artery are susceptible to HAPE.\(^{39}\) These individuals deliver their entire cardiac output to one lung, predisposing them to overperfusion injury.

The importance of the excessive rise in pulmonary artery pressure in HAPE is emphasized because lowering of the pressure during ascent prevents HAPE.\(^{50}\) This implicates increased vascular pressure rather than inflammation as the primary cause of the vascular leak. The resultant mechanical shear forces lead to endothelial damage and changes in membrane permeability.\(^{50}\) Inflammatory mediators appear to be a secondary response to the mechanical injury caused by overperfusion.\(^{44,51}\) Once the vascular leak occurs and alveolar fluid accumulates, a defect in transcapillary sodium transport impairs the clearance of alveolar fluid and contributes to HAPE development.\(^{52,54}\) Alveolar fluid clearance is upregulated by beta-adrenergic agonists, and inhaled beta-agonists may successfully prevent and treat HAPE.\(^{54,35}\)

Preexisting inflammation may also be a risk factor for HAPE. A preexisting respiratory infection during ascent to high altitude increases susceptibility to HAPE, particularly in children.\(^{34}\) Inflammation may “sensitize” the pulmonary endothelium to mechanical injury and increase susceptibility to alveolar fluid accumulation and HAPE during ascent.

The clinical manifestations of AMS and HACE are the result of central nervous system dysfunction. The mechanistic theories involve altered cerebral hemodynamics and inflammatory mediators.\(^{57,58}\) It is known that the vasodilatory response to hypoxia causes an increase of cerebral blood flow and volume.\(^{59,60}\) The resulting hypoxia leads to impaired vascular autoregulation, causing increased pressure transmission to the brain’s capillary beds.\(^{59,61,62}\) In addition, systemic hypertension from strenuous exercise at high altitude may overwhelm the brain vasculature, resulting in transcapillary leakage and vasogenic edema. In susceptible individuals, these hemodynamic changes are likely to contribute to clinical manifestations of AMS and HACE.\(^{63,64}\)

Additional circumstances, however, may be necessary for the development of vasogenic edema and clinical symptoms. Inflammatory mediators may contribute to edema formation. Vascular endothelial growth factor, the inducible form of nitric oxide synthase, reactive cytokines, and free radical formation may mediate brain endothelial permeability. The roles that these play in the pathophysiologic process of altitude illness remain unclear.\(^{57,66-69}\)

Whereas vasogenic edema has been implicated in the origin of AMS, magnetic resonance imaging (MRI) reveals signal changes present in subjects with and without clinical AMS. Thus the significance of vasogenic edema in AMS is questioned.\(^{70}\) In patients with HACE, MRI studies reveal white matter changes consistent with vasogenic edema that correlate with symptoms.\(^{71}\) Despite the unclear role of vasogenic edema, a breakdown of the blood–brain barrier remains the leading theory in AMS and HACE pathophysiology and is most likely due to a combination of mechanical factors and biochemical mediation of permeability.\(^{72,73}\)

MRI data do reveal that cytotoxic edema is also present in severe AMS.\(^{75,74}\) Cytotoxic edema results from hypoxic cell damage most often associated with ischemic hypoxic insults. Failure of the adenosine triphosphate–dependent sodium pump allows sodium to
accumulate within the cells, increasing intracellular water to maintain the osmotic equilibrium. Cytotoxic intracellular water accumulation may not be the primary mechanism for the development of HACE but rather the result of the increased cell ischemia initially caused by hemodynamic changes, vasogenic edema, biochemical mediators, and increased ratios of brain volume to intracranial space.71,75

Hypobaria also appears to play a role in the development of AMS. Sea-level experiments that expose subjects to hypoxia alone do not result in AMS; however, when hypoxia is combined with hypobaria, AMS does occur.76,77 Although microbubble formation and fluid retention may be a mechanism, the exact pathophysiologic role of hypobaria in altitude illness is unclear.75

These responses to hypoxia and altitude exposure occur in both susceptible individuals and those who remain free of AMS. Thus, there must be an overall factor in a subject at risk for AMS that fails to compensate for the changes associated with altitude exposure. The “tight fit” hypothesis is proposed to explain AMS development and its inherent individual susceptibility.59,78 This theory suggests that the development of AMS and HACE is due to a lack of intracranial space to accommodate increasing volume from brain swelling and edema that develop at altitude.8 The adequacy of the space to buffer changes in brain and cerebrospinal fluid (CSF) volume plays a key role in determining which individuals have symptoms of altitude illness. As brain volume increases from increased cerebral blood volume, the volume-buffering capacity of the central nervous system may prevent an immediate rise of intracranial pressure. As brain volume increases, the intracranial CSF is displaced through the foramen magnum into the space available in the spinal canal. Increased absorption of CSF by the arachnoid villi and decreased CSF production also occur. Individuals with less intracranial and intraspinal CSF buffering capacity have less compliance and become more symptomatic (i.e., develop AMS) from mild brain swelling. This tight fit hypothesis is supported by lumbar puncture, MRI, and computed tomography studies.59,78-80

ACUTE MOUNTAIN SICKNESS

Clinical Presentation

The symptoms of mild AMS are similar to those of a viral syndrome, an ethanol “hangover,” or simple physical exhaustion. The vague nature of this presentation results in many misdiagnoses. In the setting of recent high-altitude exposure, these symptoms warrant a presumptive diagnosis of AMS until it is proven otherwise.

For the diagnosis of AMS, a patient must be in the setting of a recent gain in altitude, be at the new altitude for at least several hours, and report a headache plus at least one of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), general weakness or fatigue, dizziness or lightheadedness, or difficulty in sleeping (Box 144-2).81 The headache may vary from mild to severe, is generally bitemporal and throbbing in nature, and is worse during the night and on waking or on suddenly becoming upright. Anorexia and nausea, with or without vomiting, are common, and the other symptoms described can range in severity from mild to incapacitating. The disturbance of sleep caused by periodic breathing is common in all visitors to high altitudes but is exacerbated in the setting of AMS. The symptoms of AMS develop within a few hours after arrival at high altitude and generally reach maximum severity between 24 and 48 hours, followed by a gradual resolution. Most individuals become symptom free by the third or fourth day. Those who do not resolve their symptoms should descend because they may develop more serious manifestations of altitude illness, especially if they continue to ascend.

Among infants and very young children, AMS is manifested by increased fussiness, decreased playfulness, decreased appetite, and sleep disturbance.10 In most cases of AMS in very young children, all of these symptoms are present. In children, many of the symptoms manifested by AMS can also result from the disruption of normal routine. A change in environment, sleeping accommodation, or eating habits can result in a fussy, unhappy child. In addition, the occurrence of an acute illness can also mimic AMS in young children. If occult bacteremia or another serious illness is suspected in a young child, descent to lower altitude is recommended to eliminate the confounding variable of altitude illness.

There are no diagnostic physical findings in cases of mild AMS. Although dyspnea on exertion is universal at high altitudes, dyspnea at rest is an early indication of HAPE, and a careful examination for pulmonary edema is indicated. Similarly, any evidence of cerebellar dysfunction, such as mild ataxia or alteration in mentation, mandates descent because of early evidence of HACE.

Ultrasoundography is emerging as an early, noninvasive diagnostic tool to assess intracranial pressure.82 Studies have demonstrated that elevated intracranial pressure is associated with AMS and HACE. Increasing intracranial pressure correlates directly with optic nerve sheath diameter.83 It is possible to demonstrate that subjects with symptoms and signs of AMS or HACE have enlarged optic nerve sheath diameters, which may be a useful adjunct in the diagnosis of AMS and HACE.84,85

Management

The management of AMS should include strict adherence to the principle that after the symptoms of altitude illness occur, further ascent to a higher sleeping altitude is contraindicated. Halting of ascent or activity to allow further acclimatization may reverse the symptoms; however, continuation of the ascent exacerbates the underlying pathologic processes and may lead to disastrous results. The presence of neurologic abnormalities (e.g., ataxia or altered mentation) or evidence of severe pulmonary edema mandates immediate descent because these signs indicate a progression of AMS to the more dangerous forms of altitude illness.

Most mild AMS is treated by stopping of further ascent and waiting for acclimatization. This may take 1 to 4 days. AMS that becomes worse or does not respond to maintenance of altitude, rest, and pharmacologic intervention necessitates descent. A descent of 1500 to 3000 feet effectively reverses high-altitude illness in most cases. Descent should be continued until improvement is seen, and efforts to minimize exertion should be instituted during the descent.

**Box 144-2 Acute Mountain Sickness**

**Incidence:** 12 to 67%, varies with rate of ascent and individual susceptibility; rare below 8000 feet, most common with rapid ascent to altitudes above 10,000 feet

**Symptoms and signs:** Headache, anorexia, nausea, fatigue, dizziness, difficulty sleeping

**Treatment:** Mild cases are usually self-limited and do not require treatment; discontinue ascent, rest; for moderate case, administer acetazolamide; ibuprofen, aspirin, or acetaminophen for headache; prochlorperazine for nausea; supplemental oxygen if available; descend if persistent or severe; add dexamethasone in severe cases

**Prevention:** Gradual ascent to allow acclimatization; high-carbohydrate diet, avoidance of ethanol or smoking; acetazolamide if ascent is rapid or known history of recurrent acute mountain sickness
Supplemental oxygen administration relieves AMS symptoms, including small amounts (1-2 L/min) during sleep. In the wilderness, oxygen tanks are heavy and are usually unavailable in adequate amounts; therefore, oxygen therapy is usually reserved for the more serious manifestations of high-altitude illness. In resort settings, oxygen may be readily available for use in the hotel or condominium. Hyperbaric therapy that simulates descent is also effective.

Treatment of headache, nausea, and insomnia can be beneficial during the course of mild AMS. Aspirin, ibuprofen, and acetaminophen are useful for the treatment of high-altitude headache. Narcotic analgesics should be avoided because of depression of the HVR and respiratory drive during sleep. For nausea and vomiting, prochlorperazine, unlike other antiemetics, stimulates the HVR. Periodic breathing causes insomnia, which is best treated with the respiratory stimulant acetazolamide. Doses of acetazolamide as low as 62.5 to 125 mg at bedtime may prevent periodic breathing and eradicate insomnia. Benzodiazepines and other sedative-hypnotics should be avoided because of their tendency to decrease ventilation during sleep. Some climbers experience unusual reactions to diazepam at high altitudes, including agitation, hallucinations, and disorientation. These reactions can occur in individuals who have previously used diazepam at lower altitudes without any difficulties. Some studies suggest that low doses of benzodiazepines alone or in combination with acetazolamide are safe at high altitude. Nonbenzodiazepine sleep agents (zolpidem and zaleplon) do not depress ventilation and may prove useful in AMS-related insomnia.

Acetazolamide accelerates acclimatization and, if it is given early in the development of AMS, rapidly resolves symptoms. A dose of 250 mg of acetazolamide at the onset of symptoms and repeated twice daily is effective therapy for AMS. The treatment of AMS in children is not formally studied, but anecdotal experience supports the use of acetazolamide in children. The dose for children is 2.5 mg/kg/dose given twice daily to a maximum of 250 mg.

Acetazolamide is a carbonic anhydrase inhibitor that induces a renal bicarbonate diuresis, causing a metabolic acidosis that increases ventilation and arterial oxygenation. This respiratory stimulation improves sleep when the hypoxemia caused by periodic breathing is eradicated by acetazolamide. The diuretic effects attenuate fluid retention common in patients with AMS. This agent also lowers CSF volume and pressure, which may play an additional role in its therapeutic and prophylactic use. Noncarbonic anhydrase inhibitory effects of acetazolamide include chemoreceptor effects on ventilatory drive, alterations of cerebral blood flow, relaxation of smooth muscles, and upregulation of fluid resorption in the lungs.

The most common adverse reactions to acetazolamide are paresthesias and polyuria. Less common reactions include nausea, drowsiness, tinnitus, and transient myopia. Carbonic anhydrase inhibition at the tongue causes dysgeusia, altering the flavor of carbonated beverages, including beer. Acetazolamide is a nonantibiotic sulfa compound that carries a low risk of cross-reactivity for individuals with an allergy to sulfa antibiotics. Those with known sulfonamide allergy may consider administration of a trial dose of acetazolamide in a controlled environment before ascent. A history of anaphylaxis or severe skin reactions to any sulfonamide-containing medication makes the use of acetazolamide contraindicated. Acetazolamide should be avoided in breast-feeding mothers and pregnant women.

Dexamethasone is an effective alternative treatment of AMS. An initial dose of 8 mg is followed by 4 mg every 6 hours. No significant adverse reactions are reported; however, symptoms can recur when the treatment is withdrawn. Although dexamethasone can resolve the symptoms of AMS, it does not play a role in acclimatization. Concurrent use with acetazolamide is advocated by some to promote acclimatization. It is known to have anti-inflammatory properties, possibly to reduce cerebral blood flow, and to block the action of vascular endothelial growth factor. Reduction of AMS symptoms with the use of dexamethasone may be the result of these or its euphoric effects. We believe that dexamethasone should generally be reserved for use in the setting of acetazolamide intolerance or in more advanced cases of AMS, especially to help facilitate descent. Individuals with AMS may resume their ascent after their symptoms resolve. Reascend with acetazolamide in these individuals is recommended. Caution in these susceptible individuals requires their understanding that should their symptoms recur, further ascent should be halted.

**Prevention**

Most of the symptoms of mild AMS are benign and well tolerated. These symptoms, however, can be unpleasant and debilitating to the point that travel, business, or vacation plans should be interrupted. Up to 50% of individuals with AMS report a decrease in activity.

Slow ascent, allowing adequate time for acclimatization, is the best method of prevention; however, the time constraints of many vacationers often make slow ascent unrealistic. The major concern lies in the sleeping altitude during any individual ascent. Ideally, the first night should not be spent at an altitude higher than 9200 feet, with a subsequent increase (to a new sleeping altitude) of not more than 1600 feet each night. One extra night of acclimatization (at the same sleeping altitude) should be added for every 3000 to 5000 feet of altitude gain above 10,000 feet. Excursions during the day to higher altitudes with a return to a lower sleeping altitude aid in acclimatization.

Altitude preexposure regimens in artificially hypoxic environments have been evaluated to facilitate acclimatization. It appears that little protection from subsequent altitude exposure occurs with preexposure regimens lasting less than 8 to 12 hours.

Mild to moderate exercise is thought to aid in acclimatization; however, overexertion can contribute to the development of AMS. Maintenance of adequate hydration is also recommended. Guidelines for adequate hydration should target relatively clear (unconcentrated) urine and normal volume of urine output. Recommendations for hyperhydration are frequently given in the lay literature, yet no evidence supports this advice. Drinking of excessive amounts of free water may lead to hyponatremia and possibly complicate altitude illness.

The rate of ascent and prior history of altitude illness should be considered in the assessment of the risk for development of altitude illness and the choice of prevention strategies. Individuals in low-risk situations should not need medications for prophylaxis, while those with a history of AMS and those who have previously used diazepam at lower altitudes without any difficulties are considered in the assessment of the risk for development of altitude illness. Ideally, the first night should not be spent at an altitude higher than 9200 feet, with a subsequent increase (to a new sleeping altitude) of not more than 1600 feet each night. One extra night of acclimatization (at the same sleeping altitude) should be added for every 3000 to 5000 feet of altitude gain above 10,000 feet. Excursions during the day to higher altitudes with a return to a lower sleeping altitude aid in acclimatization.

Prevention strategies should be individualized and based on the level of risk for altitude illness. The choice of prevention strategies should be based on the level of risk for altitude illness. The choice of prevention strategies should be based on the level of risk for altitude illness. The choice of prevention strategies should be based on the level of risk for altitude illness.
and this weight-based approach may reduce side effects in smaller adults. Ibuprofen compared with acetazolamide is equally efficacious in preventing headache.109 Dexamethasone also prevents AMS.103 The lowest effective dosage is 2 mg every 6 hours or 4 mg every 12 hours.43 Some patients experience the rapid onset of AMS after dexamethasone is discontinued. Dexamethasone does not facilitate acclimatization but rather reduces nausea and enhances mood. In most cases, dexamethasone use should be reserved for treatment of AMS rather than for prophylaxis. Military or rescue personnel rapidly ascending to high altitude and individuals with acetazolamide intolerance are candidates for prophylaxis with dexamethasone. The combination of acetazolamide and dexamethasone may be more effective than either drug alone.104

Because of its antioxidant properties, Ginkgo biloba was proposed for preventive therapy of AMS. The results of several studies are mixed, with some supporting the use of ginkgo and others showing no evidence to support a role in AMS management.111,112 These contradicting findings may be due to the variability of composition among commercially available ginkgo products, and thus determination of its clinical usefulness in the prevention or treatment of AMS is difficult.113 Acetazolamide remains the compound of choice for AMS prophylaxis.

Oxygen is an effective prophylactic modality for rescue personnel. Adequate supplies should be available to ensure the safety of all team members for the entire duration of the rescue. Air drops of oxygen can be lifesaving when weather or terrain prevents the immediate arrival of rescue personnel.

### High-Altitude Pulmonary Edema

HAPE is the most common fatal manifestation of severe high-altitude illness (Box 144-3). Although HAPE is uncommon below 10,000 feet, it can occur and even be fatal at altitudes as low as 8000 feet. Episodes occurring between 8000 and 10,000 feet are usually related to heavy exercise; but at higher altitudes, pulmonary edema can also occur at rest or with light activity.42

### Clinical Presentation

The initial symptoms of HAPE usually begin insidiously 2 to 4 days after arrival at high altitude. Most cases occur during the second night, but HAPE may develop rapidly, with early symptoms apparent after just a few hours at high altitude. Marked dyspnea on exertion, fatigue with minimal-to-moderate effort, tachycardia, and hemoptysis may be seen in severe cases. As the condition intensifies, cerebral edema or simply severe hypoxemia causes central nervous system dysfunction, such as ataxia and altered mentation. Coma may follow and precede death in a few hours if oxygen therapy or descent is not instituted.

The physical examination reveals a few rales in patients with mild HAPE, usually found in the region of the right middle lobe, progressing to unilateral or bilateral rales and then to diffuse bilateral rales and also rhonchi and gurgles audible without the stethoscope. Cyanosis of the nail beds alone may progress to severe central cyanosis. Tachypnea and tachycardia become more

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<tr>
<th>RISK CATEGORY</th>
<th>DESCRIPTION</th>
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<tr>
<td>Low</td>
<td>Individuals with no prior history of altitude illness and ascending to &lt;9200 ft</td>
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<tr>
<td></td>
<td>Individuals taking ≥2 days to arrive at 8200–9800 ft with subsequent increases in sleeping elevation &lt;1600 ft/day</td>
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<tr>
<td>Moderate</td>
<td>Individuals with prior history of AMS and ascending to 8200–9200 ft in 1 day</td>
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<td></td>
<td>No history of AMS and ascending to &gt;9200 ft in 1 day</td>
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<td></td>
<td>All individuals ascending &gt;1600 ft/day (increase in sleeping elevation) at altitudes above 9800 ft</td>
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<td>High</td>
<td>History of AMS and ascending to ≥9200 ft in 1 day</td>
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<td></td>
<td>All individuals with a prior history of HAPE or HACE</td>
</tr>
<tr>
<td></td>
<td>All individuals ascending &gt;11,500 ft in 1 day</td>
</tr>
<tr>
<td></td>
<td>All individuals ascending &gt;16000 ft/day (increase in sleeping elevation) above &gt;11,500 ft</td>
</tr>
<tr>
<td></td>
<td>Very rapid ascents (e.g., Mt. Kilimanjaro)</td>
</tr>
</tbody>
</table>


AMS, acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema.

Some individuals are susceptible and experience HAPE with each ascent to altitude. Rarely, the congenital absence of a pulmonary artery exaggerates the pulmonary vascular response to hypoxia, resulting in recurrent HAPE at elevations lower than expected.49 Many patients, however, have a single episode of HAPE and subsequently are able to return to high altitude without a recurrence. Conversely, those with previously uneventful high-altitude exposures may have HAPE develop in a future ascent.

Individuals who have been residents at high-altitude locations for extended periods may have HAPE develop on re ascent from a trip to low altitude. This phenomenon has been termed reentry HAPE. The incidence of reentry HAPE is not established; however, there seems to be an increased risk for children and young adults and possibly a greater incidence compared with HAPE experienced by low-altitude residents during their initial ascent.114,115 This apparent increased susceptibility among children for development of HAPE is probably the result of developmental changes in pulmonary vascular reactivity and tone.

### Incidence

Incidence: 0.01 to 15%, varies with rate of ascent; rare below 8000 feet and more common above 14,500 feet; usually occurs 2-4 days after arrival at high altitude. Some patients experience the rapid onset of AMS after dexamethasone is discontinued. Dexamethasone does not facilitate acclimatization but rather reduces nausea and enhances mood. In most cases, dexamethasone use should be reserved for treatment of AMS rather than for prophylaxis. Military or rescue personnel rapidly ascending to high altitude and individuals with acetazolamide intolerance are candidates for prophylaxis with dexamethasone. The combination of acetazolamide and dexamethasone may be more effective than either drug alone.104

Because of its antioxidant properties, Ginkgo biloba was proposed for preventive therapy of AMS. The results of several studies are mixed, with some supporting the use of ginkgo and others showing no evidence to support a role in AMS management.111,112 These contradicting findings may be due to the variability of composition among commercially available ginkgo products, and thus determination of its clinical usefulness in the prevention or treatment of AMS is difficult.113 Acetazolamide remains the compound of choice for AMS prophylaxis.

Oxygen is an effective prophylactic modality for rescue personnel. Adequate supplies should be available to ensure the safety of all team members for the entire duration of the rescue. Air drops of oxygen can be lifesaving when weather or terrain prevents the immediate arrival of rescue personnel.

###HIGH-ALTITUDE PULMONARY EDEMA

HAPE is the most common fatal manifestation of severe high-altitude illness (Box 144-3). Although HAPE is uncommon below 10,000 feet, it can occur and even be fatal at altitudes as low as 8000 feet. Episodes occurring between 8000 and 10,000 feet are usually related to heavy exercise; but at higher altitudes, pulmonary edema can also occur at rest or with light activity.42

### Clinical Presentation

The initial symptoms of HAPE usually begin insidiously 2 to 4 days after arrival at high altitude. Most cases occur during the second night, but HAPE may develop rapidly, with early symptoms apparent after just a few hours at high altitude. Marked dyspnea on exertion, fatigue with minimal-to-moderate effort, tachycardia, and hemoptysis may be seen in severe cases. As the condition intensifies, cerebral edema or simply severe hypoxemia causes central nervous system dysfunction, such as ataxia and altered mentation. Coma may follow and precede death in a few hours if oxygen therapy or descent is not instituted.

The physical examination reveals a few rales in patients with mild HAPE, usually found in the region of the right middle lobe, progressing to unilateral or bilateral rales and then to diffuse bilateral rales and also rhonchi and gurgles audible without the stethoscope. Cyanosis of the nail beds alone may progress to severe central cyanosis. Tachypnea and tachycardia become more
Pulmonary edema caused by elevation in hematocrit and dehydration. Venous thrombosis. The symptoms and signs of pulmonary embolism can mimic those of HAPE; however, embolic disease tends to have a more rapid onset, and pleuritic chest pain is a more prominent feature.

Differential Diagnosis

Pneumonia can be misdiagnosed in the setting of HAPE because the symptoms and signs of pneumonia are similar to those of HAPE. The incidence of pneumonia and the common organisms responsible for pneumonia at high altitude are unknown, but visitors to high altitudes may be predisposed to acquire bacterial infections because of impaired T-lymphocyte function. Patients who present with symptoms compatible with pneumonia at high altitude should be treated for HAPE. If any doubt exists about the diagnosis of HAPE versus pneumonia, empirical antibiotic therapy should be initiated. Because of the mild immunosuppression coincident with high-altitude exposure, the treatment of any serious pulmonary infection at high altitude requires oxygen, descent, and antibiotics.

High-altitude bronchitis and pharyngitis are common problems among climbers. They may result from the increased ventilation of cold, dry air across the upper airway mucosa, causing mucosal inflammation. Copious sputum production is sometimes seen, and antibiotic therapy usually is not helpful. Coughing spasms may be severe and require treatment with antitussives. Other therapeutic measures include hydration, lozenges, and steam inhalation.

Death from pulmonary embolism at high altitude is described. Hypercoagulability may result from altitude effects and hyperviscosity caused by elevation in hematocrit and dehydration. Venous stasis, caused by immobility when the individual is confined to a sleeping bag inside a tent, is also a predisposing factor for deep venous thrombosis. The symptoms and signs of pulmonary embolism can mimic those of HAPE; however, embolic disease is rare but may be present in severe cases. The extent of the edema on the chest radiograph roughly parallels the clinical severity. Of note, the radiographic findings of cardiomegaly, bat-wing distribution of infiltrates, and Kerley B lines, which are typical of cardiogenic pulmonary edema, are absent in cases of HAPE.

Radiographic evidence of HAPE clears rapidly after initiation of treatment; some mild cases may clear in 4 to 6 hours, and most clear by 24 hours. Radiographs of patients with severe HAPE may reveal infiltrates that persist for as long as 2 weeks, even though the clinical symptoms have resolved.

An electrocardiogram reveals tachycardia and evidence of right-sided heart strain, including right axis deviation, P wave abnormalities, tall R waves in the precordial leads, and S waves in the lateral leads. Hemodynamic studies reveal increased pulmonary vascular resistance, elevated pulmonary artery pressures, and normal pulmonary wedge pressures. Echocardiographic studies demonstrate high estimated pulmonary artery pressures, pulmonary vascular resistance, and normal left ventricular function.

Ultrasoundography to estimate pulmonary artery pressure is an emerging modality in the early detection and diagnosis of HAPE. Demonstration of high pulmonary artery pressures with normal left ventricular function is associated with HAPE and HAPE susceptibility.

Ultrasonography to estimate pulmonary artery pressure is an emerging modality in the early detection and diagnosis of HAPE. Demonstration of high pulmonary artery pressures with normal left ventricular function is associated with HAPE and HAPE susceptibility. Ultrasound lung comet tails, indicating extravascular water, may also be seen to support a HAPE diagnosis.

Management

In remote settings, where oxygen and medical expertise may be unavailable, immediate descent is a lifesaving measure after diagnosis of HAPE. Delay of descent while HAPE progresses or waiting for rescue personnel to initiate evacuation can prove fatal. Descents of 3000 feet are generally adequate for a rapid recovery; however, descent should continue until symptoms resolve.

Warmth and rest are also important in HAPE therapy for avoidance of cold- or exercise-induced pulmonary hypertension. Mild cases of HAPE can be treated without descent or oxygen with 1 or 2 days of bed rest. Oxygen administration increases the rate of improvement. Moderate cases can be treated without descent if bed rest and adequate supplies of supplemental oxygen are available. Any treatment plan that does not include descent necessitates serial examinations by clinicians with experience in management of high-altitude illness.

On difficult terrain or in weather conditions that hamper efforts to descend, oxygen administration (or hyperbaric therapy) can be a lifesaving measure. Rescue personnel should air drop oxygen supplies if immediate evacuation to lower altitudes will be delayed. High-flow rates of oxygen (6-8 L/min) by mask should be delivered initially to victims with severe HAPE until improvement is seen. Flow rates can then be lowered until recovery or descent is completed. Delivery of oxygen with a continuous positive airway pressure mask is more efficacious than normal oxygen delivery and may improve alveolar fluid clearance.

Hyperbaric therapy simulates descent without the administration of supplemental oxygen. Several portable, lightweight (approximately 15 pounds), fabric hyperbaric chambers are available and pressurized manually (Fig. 144-4). These chambers generate 103 mm Hg (2 psi) above the ambient pressure. This simulates a descent of 4000 to 5000 feet at moderate altitudes, and at the summit of Mt. Everest it would simulate a descent of approximately 9000 feet. These devices can be lifesaving in patients with HAPE and HACE. Some nonambulatory patients are able to descend under their own power after a few hours in hyperbaric chambers.

In treatment of HAPE, medications that lower pulmonary artery pressure, pulmonary blood volume, and pulmonary vascular resistance or enhance alveolar fluid clearance are useful but not as effective as oxygen and descent. Diuretic therapy is no longer recommended in the treatment of HAPE as it may result in a profound volume loss in patients who are already intravascularly

Figure 144-4. Gamow bag (left) and Certec bag (right): lightweight, portable hyperbaric chambers. Note the attached foot-operated pressure pump. (Courtesy Thomas Dietz, MD.)
The advent of pulmonary vasodilators has displaced the use of diuretics for HAPE. Nifedipine, a pulmonary vasodilator, is especially useful when oxygen is unavailable or descent is impossible. Nifedipine does not improve pulmonary hemodynamics as much as oxygen or descent does, and it does not have an additive effect when it is administered with oxygen. Treatment with 30 mg of a slow-release nifedipine preparation administered twice daily is effective. Patients should be monitored for the development of hypotension during nifedipine administration.

Phosphodiesterase type 5 inhibitors are less likely to produce hypotension. Although they are known to be useful for HAPE prevention, only anecdotal reports of treatment exist, and they remain unstudied for HAPE therapy. Alveolar fluid clearance is upregulated by beta-adrenergic agonists in animal models, and inhaled beta-agonists have been used anecdotally for therapy of HAPE (salmeterol 125 µg inhaled twice daily).

No evidence exists that the concurrent use of these medications with oxygen has any benefit beyond the use of oxygen alone. The mainstay of treatment remains immediate oxygen if it is available and descent. Should these treatments not be available, nifedipine should be initiated.

Disposition
Mild to moderate cases of HAPE can be treated with oxygen, rest, and careful monitoring. Resort physicians at moderate altitudes observe HAPE patients receiving oxygen therapy to ensure adequate oxygenation. These patients are then discharged to their hotel with supplemental oxygen and monitored for improvement or deterioration. In severe HAPE or milder cases that do not improve with therapy, descent is warranted. Rapid recovery is usually seen after descent to lower altitudes, and observation of the patient in the emergency department to ensure adequate room air oxygenation is generally adequate. On occasion, admission to the hospital is indicated to maintain the SaO2 greater than 90%. In the hospital, continuous positive airway pressure improves gas exchange in HAPE patients. Hypocapnia, alkalosis, and radiographic evidence of HAPE may persist for several days. After oxygen saturation remains greater than 90% on room air and clinical improvement is apparent, the patient can be discharged. If the patient requires air travel to return home (cabin pressures equal approximately 8000 feet), additional recovery time before travel or arrangement for supplemental oxygen administration is advised. Detection of a heart murmur in a patient with HAPE should lead to an evaluation searching for cardiac structural anomalies that may increase pulmonary vascular resistance. An evaluation for underlying congenital heart disease is warranted after an episode of HAPE in a young child.

The recovered victim may be able to reascend (generally in 2-3 days) when symptoms resolve and oxygen levels remain acceptable off supplemental oxygen at rest and with mild exercise. Reascend with pulmonary vasodilator medication should be considered.

Prevention
As with all forms of serious altitude illness, a gradual ascent that allows time to acclimatize and immediate cessation of further ascent at the onset of symptoms are the most effective means of prevention. Individuals with a prior history of HAPE should also avoid extreme exertion during the first 2 days at altitude. With a prior history of HAPE, prophylactic therapy should be considered. The preferred medication for HAPE prevention is the nonspecific pulmonary vasodilator nifedipine, 30 mg (controlled-release) two times daily before ascent and continued at altitude for 3 days. Less evidence exists to support the routine use of other pulmonary vasodilators for HAPE prevention.

Phosphodiesterase type 5 inhibitors are selective pulmonary vasodilators that increase cyclic guanosine monophosphate availability. Sildenafil (40 mg every 8 hours) and tadalafil (10 mg every 12 hours) are effective in preventing HAPE. The phosphodiesterase type 5 inhibitors have the added benefit that they are less likely than calcium channel blockers to induce systemic hypotension. A few additional medication options may be considered for prevention. Minimal data demonstrate that dexamethasone (8 mg every 12 hours) started 2 days before ascent also prevents HAPE. Unpublished data from animal models revealed that dexamethasone decreases pulmonary capillary leakage through down-regulation of the inflammatory cascade, decreasing alveolar fluid accumulation. To enhance alveolar clearance, salmeterol 125 µg inhaled twice daily may be used as an adjunct to nifedipine in patients with a clear history of HAPE recurrence, although side effects are common at this high inhaled dose. Finally, clinical experience suggests that acetazolamide aids in acclimatization and prevents HAPE, and it has utility in reduction of hypoxic pulmonary vasoconstriction.

HIGH-ALTITUDE CEREBRAL EDEMA
HACE is the least common but most severe form of high-altitude illness. Death from HACE at as low as 8200 feet is reported, although most cases occur above 12,000 feet. Mild AMS can progress to severe HACE with coma in as few as 12 hours. Although the usual time course is 1 to 3 days for the development of severe symptoms, it may occur in 5 to 9 days (Box 144-4).

Clinical Presentation
HACE is characterized by evidence of global cerebral dysfunction. The symptoms of severe AMS (headache, fatigue, and vomiting) as well as those of HAPE (cough and dyspnea) are often present. HACE-specific signs include ataxia, generalized seizures, slurred speech, rarely focal neurologic deficits, and altered mentation, which can range from mild emotional lability or confusion to hallucinations and decreased levels of consciousness that may proceed to coma and death. MRI of patients with HACE reveals white matter changes consistent with vasogenic edema (Fig. 144-5).

Altered consciousness and cerebellar ataxia are the most sensitive signs for early recognition of HACE. The early appearance of ataxia reflects the particular sensitivity of the cerebellum to hypoxia. Ataxia alone is an indication for immediate descent. Retinal hemorrhages are common but often occur as an isolated finding. Papilledema and occasionally cranial nerve palsy also occur in the setting of increased intracranial pressure. Differentiation between HACE and stroke may be difficult. Although it is rare, the occurrence of cerebral thrombosis and transient ischemic attacks, in the absence of high-altitude illness, is documented at

**Box 144-4** High-Altitude Cerebral Edema

**Incidence:** Lower than 1 or 2%, uncommon as a pure entity; usually associated with the presence of severe AMS and HAPE

**Symptoms and signs:** Ataxia, severe headache, nausea and vomiting, altered mentation, seizures, coma

**Treatment:** Immediate evacuation to a lower altitude; oxygen, bed rest, dexamethasone, and hyperbaric therapy while awaiting descent

AMS, acute mountain sickness; HAPE, high-altitude pulmonary edema.
The absence of any other evidence for high-altitude illness or the persistence of signs despite adequate treatment of high-altitude illness suggests the presence of a vascular lesion.

**Management**

Early recognition and initiation of descent are the keys to successful therapy for HACE. High-flow oxygen should be administered if it is available because oxygen alone reduces intracranial blood flow at high altitude. Steroid therapy is recommended and may result in recovery from HACE without neurologic deficits. The initial dose of dexamethasone is 8 mg parenterally or orally in mild cases, followed by 4 mg every 6 hours.

Patients with severely altered levels of consciousness require tracheal intubation. Hyperventilation, diuretics (e.g., furosemide), and hypertonic solutions (e.g., mannitol) may be used to manage severely elevated intracranial pressure. Caution is warranted because many patients with HACE are already volume depleted from poor fluid intake; diuretic use could compromise adequate intravascular volume and reduce cerebral perfusion pressure.

Hyperbaric treatment of HACE is also effective and may result in temporary improvement and allow self-rescue. Conversely, coma may persist for several days after descent to lower altitudes, so placement of HACE patients in a hyperbaric device may only delay the more comprehensive care available in the hospital setting.

Long-term neurologic deficits, such as ataxia and cognitive impairment, are reported after recovery from acute episodes of HACE. Both transient and long-lasting neurobehavioral impairments can occur in mountaineers after climbing to extreme altitude without experiencing clinical HACE. Some of these sequelae can persist for 1 year. Because of the potential for long-lasting neurologic injury, the clinician who treats high-altitude illness should be extremely sensitive to the early manifestations of HACE. Early treatment of HACE generally results in good outcomes, but after coma is present, the mortality rate exceeds 60%.

**HIGH-ALTITUDE RETINAL HEMORRHAGE**

High-altitude retinal hemorrhage (HARH) is the most common type of retinopathy in visitors to high altitude. These hemorrhages are common at altitudes above 17,500 feet, although they can occur at lower levels.

The exact incidence of HARH is unknown because most patients are asymptomatic, with HARH noted only on retinoscopy. HARH is not generally related to the presence of mild AMS but does seem to be related to strenuous exercise at high altitude. At any altitude, in the setting of severe HAPE or HACE, retinal hemorrhages are commonly noted, but the mechanism remains unclear.

Hemorrhages usually spare the macula (Fig. 144-6). Retinal hemorrhages usually resolve without treatment in 2 or 3 weeks. With macular involvement, central scotomas may be noticed for several years, gradually resolving. In some cases, however, these visual defects are permanent. HARH is more likely to occur among individuals with a previous history of these hemorrhages, but the underlying risk remains unclear. This usually does not pose a contraindication to return to high altitude unless the macular region is involved.
Carbon monoxide (CO) poisoning can occur at altitude from the use of fires and combustion stoves to keep warm and to prepare food in the high-altitude environment. If CO poisoning occurs at altitude, it can be more devastating because of the lower oxygen pressures and the body’s baseline hypoxic state. CO binds to hemoglobin and prevents oxygen release to the body’s tissues that are already, relative to sea level, hypoxic. It is easy to confuse the symptoms and signs of CO poisoning and AMS as both include headache, nausea, dizziness, dyspnea, and lassitude.\textsuperscript{145,146} If there is doubt, a person should leave the enclosed space and descend or use supplemental oxygen if it is available.\textsuperscript{147,149}

ALTITUDE AND UNDERLYING MEDICAL CONDITIONS

Individuals with diseases such as moderate to severe chronic obstructive pulmonary disease (COPD) and coronary artery disease may have a more difficult time acclimatizing because these disease states are often aggravated by the hypoxic atmosphere at higher elevations. They may predispose these individuals to the development of high-altitude illness. Table 144-2 describes the risk associated with travel to altitude in individuals with a variety of underlying comorbidities.

### Table 144-2

<table>
<thead>
<tr>
<th>Risk Associated with Travel to Altitude in Individuals with a Variety of Underlying Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advisability of Exposure to High Altitude for Common Conditions (Without Supplemental Oxygen)</strong></td>
</tr>
<tr>
<td><strong>Probably No Extra Risk</strong></td>
</tr>
<tr>
<td>Young and old</td>
</tr>
<tr>
<td>Fit and unfit</td>
</tr>
<tr>
<td>Mild obesity</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Previous coronary artery bypass grafting (without angina)</td>
</tr>
<tr>
<td>Mild chronic obstructive pulmonary disease (COPD)</td>
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<tr>
<td>Asthma</td>
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<tr>
<td>Low-risk pregnancy</td>
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<tr>
<td>Controlled hypertension</td>
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<tr>
<td>Controlled seizure disorder</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>Neoplastic diseases</td>
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<tr>
<td>Inflammatory conditions</td>
</tr>
<tr>
<td><strong>Caution</strong></td>
</tr>
<tr>
<td>Moderate COPD</td>
</tr>
<tr>
<td>Asymptomatic pulmonary hypertension</td>
</tr>
<tr>
<td>Compensated congestive heart failure</td>
</tr>
<tr>
<td>Morbid obesity</td>
</tr>
<tr>
<td>Sleep apnea syndromes</td>
</tr>
<tr>
<td>Troublesome arrhythmias</td>
</tr>
<tr>
<td>Stable angina or coronary artery disease</td>
</tr>
<tr>
<td>High-risk pregnancy</td>
</tr>
<tr>
<td>Sickle cell trait</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
</tr>
<tr>
<td>Any cause of restricted pulmonary circulation</td>
</tr>
<tr>
<td>Seizure disorder (not taking medication)</td>
</tr>
<tr>
<td>Radial keratotomy</td>
</tr>
<tr>
<td><strong>Contraindicated</strong></td>
</tr>
<tr>
<td>Sickle cell anemia (with history of crises)</td>
</tr>
<tr>
<td>Severe COPD</td>
</tr>
<tr>
<td>Symptomatic pulmonary hypertension</td>
</tr>
<tr>
<td>Uncompensated congestive heart failure</td>
</tr>
</tbody>
</table>


Respiratory Illnesses

Travelers with COPD to moderate altitudes have underlying anatomic and physiologic changes that predispose them to development of hypoxemia, sleep apnea, pulmonary hypertension, and ventilation disorders. COPD is a risk factor for the development of AMS.\textsuperscript{7} Although oxygen saturation remains more than 90% in a healthy, awake individual until an altitude of 8000 feet, patients with COPD may desaturate below 90% at lower altitudes. Travel to 5000 feet did not result in significant desaturation below 90% in one group of COPD patients and did not produce significant adverse effects on the systemic circulation in another group at 8000 feet.\textsuperscript{150} High altitude increases hypoxic pulmonary vasconstriction and may potentiate the development of cor pulmonale, which is known to adversely affect survival at sea level.\textsuperscript{151} Colorado, for example, has a relatively low incidence of COPD but a higher mortality rate than expected from emphysema.\textsuperscript{152} Individuals with chronic COPD should be advised of the potential need for oxygen supplementation when traveling to moderate altitude, especially if they are already using oxygen at sea level or if dyspnea or fatigue becomes worse. Use of a pulse oximeter can guide the need for increased oxygen supplementation.

Patients with asthma, on the other hand, may have fewer problems at altitude because of decreased allergens and pollutants and decreased airflow turbulence. There are no descriptions of asthma exacerbations due to altitude, although oxygen saturations might be lower at elevation. Even those with exercise-induced bronchospasm do not have worsening symptoms while exercising at 5000 feet.\textsuperscript{153} In addition, AMS incidence is not increased in asthmatics.\textsuperscript{153} People with asthma traveling to higher elevations should continue their usual medications and carry a rescue supply of bronchodilators and steroids.

Patients who ascend to high altitude with preexisting primary or secondary pulmonary hypertension should be considered HAPE susceptible, and those with primary pulmonary hypertension should be advised of increased risk for HAPE.\textsuperscript{154} Patients with known primary pulmonary hypertension should be advised against travel to higher elevations. If travel cannot be avoided, supplemental oxygen should be used. Prophylactic nifedipine SR, 30 mg twice daily for the duration of the stay at altitude, can prevent HAPE.\textsuperscript{126} Phosphodiesterase type 5 inhibitors and steroids may also be used.\textsuperscript{30}

Cardiovascular

Individuals with a history of congestive heart failure, coronary artery disease, dysrhythmias, or coronary bypass surgery are rarely studied in the high-altitude setting. In theory, people with diseased myocardium should be advised to avoid high altitude because of decreased environmental oxygen availability. No studies report increased mortality in visitors to these locations. To the contrary, long-term residents at high altitude may be protected from coronary artery disease by increased collateral vessel formation or a decrease in the development of atherosclerosis.\textsuperscript{155-157}

Many elderly people with known or suspected coronary artery disease have been safely exposed to acute hypoxia at altitude while breathing low oxygen mixtures or when being placed in a hypobaric chamber.\textsuperscript{158} In contrast, another investigation of elderly people with known coronary disease does demonstrate some risk.\textsuperscript{139}

Patients with heart disease have increased sympathetic activity during the first 3 days at altitude, as do all travelers. The resultant increase in heart rate and blood pressure increases cardiac work and myocardial oxygen consumption, and this could increase dysrhythmias. Although both cardiac rhythm abnormalities and ST segment and T wave electrocardiographic changes are reported, none of these changes are associated with any clinical evidence of
myocardial ischemia. Limited data suggest no increased risk for sudden cardiac death or myocardial infarction at altitudes up to 8000 feet.

The small increase in heart rate and blood pressure that occurs on first visiting altitude might exacerbate angina in patients with known disease. Even when individuals with stable angina are exercised, there is conflicting evidence for the probability of inducing malignant arrhythmias. In a study of 22 patients with recent percutaneous coronary intervention or coronary artery bypass graft with a submaximal exercise routine at 11,400 feet, there is no evidence of myocardial ischemia or significant arrhythmias despite an elevated oxygen demand, heart rate, and lactate level. Travelers with heart disease who ascend to moderate altitudes do not appear to have an increased incidence of AMI. Travelers with mild stable coronary artery disease should be advised to ascend gradually, to limit activity especially in the first few days at elevation, and to continue antianginal and antihypertensive medications. Individuals who have more severe, symptomatic coronary disease or those in a high-risk group (low ejection fraction, abnormal stress test results, and high-grade ventricular ectopy) should avoid travel to high altitudes. Ascent to moderate elevations can be suggested on an individual basis with the previously mentioned precautions. Individuals with heart failure who travel to altitude may require increased use of diuretics to promote diuresis and acclimatization. Acetazolamide prophylaxis may be useful to speed acclimatization and to prevent AMS and its accompanying fluid retention. If the anticipated workload at altitude is greater than the individual is accustomed to at sea level, exercise stress testing at this increased workload before ascent should be considered.

Hypertension

High-altitude travel produces a mild increase in blood pressure and heart rate in healthy individuals because of increased catecholamine activity and resultant sympathetic tone. This increase begins in the first few days after ascent, is maximal at 2 or 3 weeks, and returns to baseline values over time because of a downregulation of adrenergic receptors if one stays at high altitude or on descent to sea level. No studies demonstrate an increased predisposition for altitude illness in patients with underlying hypertension.

The incidence of hypertension in sea-level dwellers traveling to high altitude is 10 to 25%. Although there is no difference in blood pressure readings in either normotensive or hypertensive individuals when blood pressure is measured at low altitudes (3000 feet), significant increases occur in both blood pressure and heart rate at altitudes above 9800 feet. This suggests that people with severe hypertension should travel only to moderate altitudes. For individuals who have mild hypertension while traveling at altitude, treatment is not routinely necessary because the hypertension will rarely become dangerously high and will improve on descent. Although individual variability exists, patients with hypertension should be monitored frequently in the first few days at altitude and antihypertensive medications continued. For hypertensive patients with a rapid rise in blood pressure and who will be staying for several weeks, an alpha-blocker, nifedipine, or angiotensin-converting enzyme inhibitor should be considered.

Seizures

Travel to altitude is implicated as a precipitant for seizure activity. There are numerous reports of altitude-provoked seizures, but epidemiologic data are lacking. Seizures attributable to high altitude are typically generalized tonic-clonic in nature. A focal seizure at altitude should prompt a thorough workup for a space-occupying lesion. Several pathophysiologic mechanisms are implicated. These include sleep deprivation from periodic breathing, hyperventilation, and the direct effect of hypobaric hypoxia. These mechanisms are postulated to induce a metabolic state that lowers the seizure threshold. Seizures not responding to supportive care can be treated with benzodiazepines. Should an epileptic who is already taking seizure medicine experience a breakthrough seizure at altitude, standard seizure evaluation is warranted, and acetazolamide at 250 mg twice daily may be added. Acetazolamide itself has antiepileptic properties and may ameliorate the altitude-related metabolic derangements.

Sickle Cell Disease

Patients with sickle cell disease are affected by the hypoxemia occurring at low to moderate altitudes (5000-6500 feet). Up to 20% of patients with hemoglobin sickle cell and sickle cell–thalassemia disease may experience a vaso-occlusive crisis, even under pressurized aircraft conditions. Oxygen is therefore advised for air travelers who have sickle cell disease. Although most people with sickle cell trait remain asymptomatic, this subgroup can experience the development of left upper quadrant pain as a result of splenic ischemia or infarction. Non-blacks, usually of Mediterranean origin, who have sickle cell trait may be more prone to the development of splenic infarctions than are blacks.

Pregnancy

Studies of permanent high-altitude residents in Colorado and Peru show an increased incidence of complications in maternal, fetal, and neonatal life. Infants born at high altitude have a lower birth weight compared with infants born at sea level because of a combination of factors, including altitude-related effects on fetal growth, changes in uterine blood flow, and increased premature births.

Pregnancy-induced hypertension, proteinuria, and peripheral edema (manifestations of toxemia and preeclampsia) are more common at high altitudes and may also be related to maternal and uterine hypoxemia. Although hypertension in pregnancy is more common at high altitudes, no evidence exists for an increase in spontaneous abortions, abruptio placenta, or placenta previa.

Travel by pregnant women to moderate altitudes appears to be safe, but caution is advised for lowland women with normal pregnancies who wish to travel above 13,000 feet, for pregnant women who wish to remain at high altitude for a prolonged period, and for women with complicated pregnancies.

Radial Keratotomy

Although it is currently less popular, radial keratotomy may cause individuals to experience hyperopic (farsighted) visual changes with ascent above 9000 feet. This results from corneal swelling from ambient hypoxia because the cornea is markedly sensitive to both systemic and ambient oxygen tension. In normal corneas, this swelling is uniform. After radial keratotomy, the swelling is exacerbated and inconsistent secondary to the pattern of the incisions. Photorefractive keratotomy and LASIK, which use laser techniques that do not produce incisions but instead shave the cornea and corneal stroma, respectively, do not result in similar problems.

ACKNOWLEDGMENT

The authors would like to acknowledge Dr. Benjamin Honigman for his contributions to previous editions of this chapter.
The symptoms of AMS can resemble a viral syndrome and include headache, nausea, anorexia, fatigue, and insomnia.

The management of altitude illness must include adherence to the principle that after the symptoms occur and until symptoms resolve, further ascent is contraindicated.

Dyspnea at rest is an early symptom of HAPE. As the HAPE patient’s condition deteriorates, the dyspnea intensifies with effort and is unrelieved by rest.

Altered consciousness and cerebellar ataxia must be recognized as early signs of HACE, and descent is mandatory.

Effective prophylaxis options for altitude illness include acetazolamide for AMS and nifedipine for HAPE. Phosphodiesterase type 5 inhibitors are selective pulmonary vasodilators that increase cyclic guanosine monophosphate availability. Sildenafil (40 mg every 8 hours) and tadalafil (10 mg every 12 hours) are effective in preventing HAPE.

Narcotic analgesics should be avoided because of depression of the HVR and respiratory drive during sleep. For nausea and vomiting, prochlorperazine, unlike other antiemetics, stimulates the HVR.


