INCREASING NUMBERS OF PEOPLE are traveling to high altitude for work or pleasure. The rewards of such travel can be high but do come at the risk of developing one of several forms of acute altitude illnesses and/or worsening of underlying medical problems. In response to these risks, many individuals planning high-altitude travel present to their primary care providers or travel medicine clinic seeking advice about how to ensure a successful sojourn. The purpose of this Physiology in Medicine article is to provide information that providers can use when counseling patients who present to primary care or travel medicine clinics seeking advice about how to prevent these problems. After discussing the primary physiologic responses to acute hypoxia from the organ to the molecular level in normal individuals, the review describes the main forms of acute altitude illness—acute mountain sickness, high-altitude cerebral edema, and high-altitude pulmonary edema—and the basic approaches to their prevention and treatment of these problems, with an emphasis throughout on the physiologic basis for the development of these illnesses and their management.

The review begins by describing the physiologic responses to acute hypoxia from the organ to the molecular level and then uses this information to describe the main forms of acute altitude illness, acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE), with a particular emphasis on how alterations in the normal physiologic responses to hypoxia contribute to their development. The review then examines the main pharmacologic and nonpharmacologic approaches to prevention and treatment of acute altitude illness, again emphasizing the physiologic basis for these approaches. General approaches to altitude illness prevention and treatment are described along with a brief discussion of how the standard approaches for prevention no longer apply at the extremes of high altitude. The focus throughout the review will be on healthy individuals traveling to high altitude rather than individuals with underlying cardiopulmonary diseases. For further information on such patients, the reader is referred to an earlier Physiology in Medicine article on that topic (57).

PHYSIOLOGIC RESPONSES TO ACUTE HYPOXIA

With ascent to high altitude, there is a nonlinear decrease in barometric pressure, which leads to a decrease in the ambient partial pressure of oxygen (Po2) and, subsequently, a decrease in the Po2 at every point along the oxygen transport cascade from inspired air to the alveolar space, arterial blood, the tissues, and venous blood. The higher the elevation attained, the greater the drop in Po2 at each of these points.

These declines in oxygen tensions trigger a variety of physiologic responses in multiple organ systems (Fig. 1) over a period of minutes to weeks after the initial exposure (Fig. 2) that are designed to help the individual adapt to or compensate for the hypoxic conditions. Several important responses are described below.

GAS EXCHANGE

Because of the decrease in barometric pressure and thus alveolar Po2, the partial pressure difference for oxygen between the alveolus and pulmonary capillary is decreased, thereby slowing the rate of diffusion of oxygen across the alveolar-capillary membrane. The time necessary to reach equilibration between the alveolar and capillary Po2 is further increased, because hypoxia results in gas exchange taking place on the steep part of the hemoglobin-oxygen dissociation curve. As a result, more oxygen must be loaded onto hemo-
globin before the Po$_2$ rises, delaying equilibration. At rest, however, red blood cell capillary transit time in hypoxia is still sufficient for full equilibration of oxygen between the alveolar gas and end-capillary blood, and the alveolar-arterial oxygen difference ([A – a]O$_2$) remains normal. However, during exercise, with reduced red cell transit time, arterial Po$_2$ drops substantially as pulmonary oxygen exchange now becomes diffusion limited—even in normal individuals.

VENTILATORY RESPONSES

Arterial hypoxemia triggers an increase in minute ventilation known as the ventilatory response to hypoxia. Mediated by the carotid bodies and determined by the Po$_2$ rather than the content (CaO$_2$) of arterial blood, the magnitude of ventilatory response to hypoxia varies between individuals and over time because the initial ventilatory responses is blunted by the concurrent respiratory alkalosis before subsequent large increases in ventilation occur due to further changes in acid-base status (described below) and increased sensitivity of the peripheral chemoreceptors (16, 53).

ACID-BASE PHYSIOLOGY

With the onset of the ventilatory response to hypoxia, individuals develop an uncompensated respiratory alkalosis. This blunts the initial ventilatory responses, because the increase in arterial pH decreases peripheral chemoreceptor output, whereas a decrease in diffusion of carbon dioxide across the blood-brain barrier causes a fall in cerebrospinal fluid hydrogen ion concentration that decreases central chemoreceptor responses. Over a period of several days, renal excretion of bicarbonate leads to a compensatory metabolic acidosis and subsequent decrease in the pH toward normal, which contributes to later increases in ventilation.

CARDIOVASCULAR RESPONSES

Cardiac output increases in acute hypoxia to maintain tissue oxygen delivery in the face of the lower Pa$_2$. This increase is due largely to increases in heart rate (from sympathetic activation) rather than stroke volume, because the latter actually declines after exposure to high altitude because of a decrease in plasma volume.
Myocardial contractility is preserved in hypoxia (45), whereas systemic blood pressure is increased to a variable extent in many individuals (34). The change in blood pressure is also a result of augmented sympathetic nervous system activity (71), which increases continuously over several weeks above 4,000 m.

**PULMONARY VASCULAR RESPONSES**

Exposure to environmental hypoxia also triggers hypoxic pulmonary vasoconstriction, which, in conjunction with increased cardiac output, leads to a rise in pulmonary artery (PA) pressure. Hypoxic pulmonary vasoconstriction occurs within minutes of exposure to hypoxia (63) and is determined primarily by the alveolar rather than the arterial PO2, although the bronchial artery PO2 (40) and increased sympathetic activity (15) may also play a role. As with the other responses described in this article, there is considerable interindividual variability in the magnitude of hypoxic pulmonary vasoconstriction (11, 20) that plays a key role in the development of one form of acute altitude illness (HAPE, described below).

**FLUID HOMEOSTASIS**

With acute hypoxia, individuals experience diuresis and natriuresis. This response, which also shows significant interindividual variability, is mediated by the peripheral chemoreceptors and does not appear to be related to changes in renin, angiotensin, aldosterone, or atrial natriuretic peptide levels (60). Together with the decrease in humidity at high altitude and increased fluid losses via the respiratory tract due to hyperventilation, the decrease in plasma volume increases the risk of dehydration in those with inadequate fluid intake.

**HEMATOLOGIC RESPONSES**

Hemoglobin concentrations increase within 24–48 h of ascent and continue to rise in the weeks that follow. The initial changes are due to the reduction in plasma volume, whereas later changes are related to increases in red cell mass resulting from early rises in serum erythropoietin (EPO) concentrations (42). These responses are important for maintaining tissue oxygen delivery in the setting arterial hypoxemia (69). The position of the hemoglobin oxygen dissociation curve at high altitude is affected by the respiratory alkalosis and changes in 2,3-diphosphoglycerate concentrations with the ultimate position likely a function of the altitude attained and the duration of stay. Studies have documented, for example, a rightward shift in the curve at 2,500–3,000 m (38), no change in overall position at 4,500 m (39), and a leftward shift at extremely high elevations (>8,000 m) in acclimatized individuals, likely due to the marked respiratory alkalosis (70).

**CELLULAR LEVEL RESPONSES**

Many of the physiologic responses to hypoxia occur at the cellular, molecular, and genetic level, with the major driver of these responses being hypoxia inducible factor (HIF) 1-α (58). Whereas this transcription factor is degraded in normoxia by prolyl hydroxylases, it avoids degradation in hypoxia and enters the nucleus where it binds to HIF 1-β and coactivator proteins (Fig. 3). These complexes then combine with hypoxia response elements to activate transcription of genes related to mitochondrial function, glycolytic pathways, angiogenesis (especially via vascular endothelial growth factor), endothelial function via inducible nitric oxide synthetase, erythropoiesis via EPO, and tyrosine hydroxylases with subsequent downstream effects on a variety of processes including energy utilization, angiogenesis, erythropoiesis, nitric oxide metabolism, and chemoreceptor function.

**SLEEP**

Sleep disturbances are common at high altitude with an increased incidence of poor sleep quality, increased arousals, and changes in sleep architecture (66). The most noteworthy feature, however, is the increased incidence of central sleep apnea, similar to that seen in heart failure patients at sea level, that develops as a result of an interaction between the ventilatory response to hypoxia and the feedback-control system that governs breathing during sleep when cortical influences on breathing are absent. Periodic breathing may be more common in individuals with stronger ventilatory responses to hypoxia (41) and can persist or worsen during long stays at high altitude as ventilatory responses continue to increase (5).

**EXERCISE**

For any given submaximal work rate, heart rate, cardiac output, and minute ventilation are higher at high altitude than at sea level. For most normal individuals, and in contrast to sea level exercise, PaO2 and oxygen saturation (SaO2) decline with progressive exercise (68), because the rise in cardiac output shortens red blood cell transit time in the pulmonary capillaries, thereby preventing full equilibration of oxygen between the alveolar and capillary spaces. Maximum exercise capacity is decreased and does not return to sea level values even with prolonged stays at high altitude (68) despite [Hb] being increased to mitigate reduced SaO2. Multiple factors such as redistribution of blood flow to nonexercising muscles (6), increases in right ventricular afterload, and impaired right ventricular function (19) and others have been implicated in this phenomenon, but the precise mechanism remains unclear.

**HOW TRAVELERS TO ALTITUDE EXPERIENCE THE PHYSIOLOGIC RESPONSES**

As a result of these and other physiologic responses, travelers often feel different at high altitude than they do at sea level. It is useful to review these differences (Table 1) as part of pretravel counseling, because it will prevent travelers from misinterpreting normal responses as signs of illness and allow them to better recognize when they or fellow travelers manifest abnormal responses.

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**Key Points**

- Ascent to high altitude leads to a decrease in the PO2 at all points along the oxygen transport cascade.
- Decreased alveolar and arterial oxygen tensions trigger physiologic responses across multiple organ systems over varying time frames.
- The magnitude of the physiologic responses varies significantly between individuals.
- Because of the physiologic responses, individuals feel different at high altitude than at sea level and should be counseled about what to expect in this regard.
ACUTE ALTITUDE ILLNESS: CLINICAL FEATURES AND PATHOPHYSIOLOGY

The majority of individuals ascending to high altitude manifest the physiologic responses noted above and complete their sojourn without significant health problems. In other cases, maladaptive responses occur and individuals develop one of three forms of acute altitude illness, AMS, HACE, or HAPE. The clinical features of these illnesses are described in Table 2 and have been reviewed extensively elsewhere (4, 22). Of these entities, AMS is by far the most common, with reported incidence rates varying between 25 and 78% depending on the study population, location, altitude reached, and rate of ascent. HACE and HAPE are far less common but are potentially fatal if not recognized and addressed promptly, thereby making it important to counsel all high-altitude travelers about how to recognize these entities at an early stage of illness. A variety of other problems have been described in travelers at high altitude such as transient cortical blindness and other visual defects, global amnesia, and cranial nerve palsies, but there is insufficient evidence to suggest these are distinct altitude-related illnesses like AMS, HACE, or HAPE.

GENERAL PATHOPHYSIOLOGY PRINCIPLES

In general, the main reason individuals become ill is they ascend too high too fast. For example, an individual who ascends over only 3 days to 5,000 m and remains at this altitude is far more likely to develop acute altitude illness than an individual who ascends to the same elevation over a period of 7 days. Overly rapid ascent essentially prevents adequate acclimatization, the series of organ and cellular level responses mentioned above that, in broad terms, serve to limit the fall in Po2 at every step along the oxygen cascade and, as a result, decrease the risk of acute altitude illness.

In considering this issue, it is important to note, that there is significant interindividual variability in the pace of acclimatization, such that some individuals acclimatize quickly and tolerate fast ascent rates, whereas others have difficulty even with slower ascent profiles. This is likely a multigenetic trait and many polymorphisms contribute to this phenotype, but the full array of polymorphisms have yet to be identified. There is also an important interaction between altitude reached and the time spent at that altitude that affects risk, whereby individuals...
Table 2. Summary of clinical features and management of acute high altitude illnesses in the general population

<table>
<thead>
<tr>
<th>Acute Altitude Illness</th>
<th>Epidemiology</th>
<th>Clinical Features</th>
<th>Prevention</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Acute Mountain Sickness (AMS)</td>
<td>Affects 22–77% of travelers to 1850 to 5895 m Increased incidence at higher elevations and with faster ascent Onset of symptoms within 6–10 h of ascent</td>
<td>Headache plus one or more of the following: nausea, vomiting, lethargy, sustained light-headedness Normal neurologic exam and normal mental status</td>
<td>Slow ascent (above 3000 m, limit increases in sleeping elevation to 500 m/day Avoid overexertion Acetazolamide or dexamethasone with moderate-high risk ascent profiles</td>
<td>Stop ascending Acetaminophen or NSAIDs for headache; Antiemetics; Mild to moderate illness: Acetazolamide Severe cases: dexamethasone Descend if symptoms do not improve in 1–2 days or worsen on appropriate treatment Further ascent possible if symptoms resolve</td>
</tr>
<tr>
<td>High Altitude Cerebral Edema (HACE)</td>
<td>Affects &lt;1% of travelers to elevations above 3000 m Many affected individuals have preceding AMS symptoms Preexisting AMS or HAPE symptoms (not universally present) Ataxia, altered mental status Severe lassitude, somnolence, coma Focal neurologic deficits uncommon and should prompt consideration of other diagnoses Potentially fatal if not recognized and treated promptly</td>
<td>Slow ascent Avoid overexertion Acetazolamide or dexamethasone with moderate-high risk ascent profiles</td>
<td></td>
<td>Descend until symptoms resolve If descent not possible, supplemental oxygen or a portable hyperbaric chamber Dexamethasone No further ascent until individual is asymptomatic while off treatment medications</td>
</tr>
<tr>
<td>High Altitude Pulmonary Edema (HAPE)</td>
<td>Affects 0.2 to 8% of travelers between 2500 and 5500 m with greater incidence at higher elevations and with faster ascent Onset within 2–5 days of ascent Can occur without preceding AMS symptoms Mild disease: dyspnea and arterial O₂ desaturation out of proportion to that expected among normals with similar ascent rates at a given elevation; decreased exercise performance, dry cough Severe disease: dyspnea with mild exertion or at rest; cough with pink, frothy sputum; cyanosis May see concurrent signs or symptoms of AMS or HACE Potentially fatal if not recognized promptly</td>
<td>Slow ascent Avoid overexertion Nifedipine for individuals with prior history of HAPE (alternative: phosphodiesterase inhibitors)</td>
<td></td>
<td>Descend until symptoms resolve; avoid over-exertion on descent If descent not possible, supplemental oxygen or a portable hyperbaric chamber Nifedipine or phosphodiesterase inhibitor (may not be necessary if supplemental oxygen available). Avoid concurrent use of nifedipine and phosphodiesterase inhibitor No further ascent until individual is asymptomatic while off treatment medications</td>
</tr>
</tbody>
</table>

who quickly ascend to very high elevations but descend soon thereafter may avoid altitude illness, whereas individuals who remain longer at the peak elevation after a similar ascent profile often become ill.

**DISEASE-SPECIFIC PATHOPHYSIOLOGY**

Beyond the general issues noted above, more specific pathophysiologic issues warrant consideration for each form of altitude illness.

AMS and HACE. Despite considerable research in this area, there is still no unified explanation for why individuals develop these entities and whether they represent different manifestations and severity of the same underlying process or result from distinct pathophysiologic mechanisms. Some studies suggest that individuals with a lower SaO₂ after arrival at high altitude are at greater risk for developing AMS later in their sojourn (48, 64), whereas others have noted a correlation between SaO₂ and simultaneously measured AMS scores (29, 44). Because the SaO₂ can be related to the PaO₂ through the hemoglobin-oxygen dissociation curve, assuming equal hemoglobin-oxygen affinity between healthy and sick individuals, this would imply that individuals who become sick either have lower ventilation and, therefore, lower alveolar and arterial P O₂ than healthy individuals or have abnormal ventilation-perfusion matching leading to a lower PaCO₂.

Blunted ventilatory responses might play a role in the development of AMS, because the lower PaO₂ and higher PaCO₂ may cause higher cerebral blood flow with subsequent increases in intracranial volume and, potentially, intracranial pressure. According to the tight-fit hypothesis, which posits that individuals with a greater ratio of cerebrospinal fluid to blood and brain tissue volume have increased ability to compensate for cerebral swelling or increasing intracranial blood volume, these effects might be magnified in individuals with less intracranial volume, further increasing the risk of altitude illness (28, 50). The fact that decreased ventilation during hypoxia at rest or with exercise is associated
with a greater risk of AMS (7, 43, 47), and the fact that medications that increase ventilation such as acetazolamide (discussed further below) and theophylline also decrease the incidence of the disorder would provide support for this argument. However, because the ventilatory response to hypoxia is highly variable between individuals and is just one of several factors contributing to the development of AMS, measurement of this response has limited utility for assessing risk in a particular individual. It should also be noted that although the tight-fit hypothesis is appealing from a theoretical standpoint, supportive data are lacking. Studies using brain MRI, for example, have not shown a relationship between changes in brain volume in acute hypoxia and subsequent development of AMS (14, 51).

Ventilation-perfusion mismatch could possibly arise from subclinical pulmonary edema, but although a study of changes in closing volume in climbers ascending to 4,559 m suggested there was a high incidence of subclinical edema (9), other studies examining changes in diffusion capacity for carbon monoxide, a marker of the surface area for gas exchange, and the development of AMS after ascent have yielded conflicting evidence regarding this phenomenon (12, 18, 59).

Alterations in fluid balance have also been invoked as a potential mediator of AMS. Clinical observations and controlled studies suggest, for example, that individuals who develop AMS develop expanded plasma and extracellular volume in contrast to the mild diuresis that occurs in individuals who remain healthy (21, 31). Studies have examined the role of antidiuretic hormone, the renin-angiotensin system, and atrial natriuretic peptide levels in this phenomenon, but the precise mechanism remains unclear.

Beyond these derangements in organ-level physiologic responses noted earlier, other molecular-level mechanisms promoting inflammation, reactive oxygen species generation, vascular endothelial growth factor upregulation have been examined for a role in AMS and/or HACE pathophysiology, but this work has not sufficiently clarified the pathophysiology of these disorders to translate into clinical management.

HAPE. In contrast to AMS and HACE, the pathophysiology of HAPE is well understood. Multiple studies have established that compared with healthy controls HAPE-susceptible individuals have abnormal pulmonary vascular responses to hypoxia as well as exercise in both normoxia and hypoxia (11, 20, 37). At high altitude, exaggerated hypoxic pulmonary vasoconstriction leads to elevated pulmonary artery pressure and subsequent edema formation. High pulmonary artery pressure alone is not sufficient to cause HAPE, however. Instead, the key feature of this process is the fact that hypoxic pulmonary vasoconstriction occurs unevenly throughout the lung. As a result of this heterogeneity, regions of the pulmonary vasculature where vasoconstriction does not occur experience both increased pressure and increased blood flow, leading to capillary stress failure and subsequent leakage of fluid and protein from the vascular space to the interstitial and alveolar spaces (3, 25). This concept, which is supported by the patchy radiographic opacities in many HAPE patients and MRI studies demonstrating that HAPE-susceptible individuals develop increased heterogeneity of pulmonary blood flow during hypoxic breathing (13, 24) helps account for the observation that edema is seen with very high PA pressure at altitude but is not a feature of other forms of pulmonary arterial hypertension, where pathophysiologic changes are more even throughout the lung, even in patients with severe forms of the disease. Heavy exercise contributes further to the risk of edema formation at altitude by increasing pulmonary blood flow and worsening overperfusion in the unprotected regions.

At the molecular level, exaggerated hypoxic pulmonary vasoconstriction appears to be the result of impaired endothelial function and decreased bioavailability of nitric oxide, but additional factors, including increased sympathetic activity and altered levels of other vasoactive mediators such as endothelin and angiotensin II may also play a role (3).

Beyond these hemodynamic factors, alterations in alveolar fluid clearance also contribute to edema formation. By decreasing the activity and expression of apical and basolateral membrane sodium channels and sodium-potassium (Na⁺-K⁺) ATPases, hypoxia decreases sodium transport across the alveolar wall and reduces reabsorption of fluid that accumulates in the alveolar space (52, 65). Although earlier studies suggested inflammatory responses might affect edema formation (55), more recent studies using bronchoalveolar lavage in the early stages of HAPE demonstrated that edema formation is driven by imbalances in hydrostatic forces rather than inflammation (61).

Key Points

- There is significant interindividual variability in susceptibility to acute altitude illness.
- Overly rapid ascent is the main reason that individuals develop acute altitude illness.
- The pathophysiology of acute mountain sickness and high-altitude cerebral edema is not well understood but may be related to alterations in ventilation, gas exchange, cerebral blood flow, fluid homeostasis, and a variety of molecular-level processes.
- High-altitude pulmonary edema occurs as a result of excessive hypoxic pulmonary vasoconstriction that occurs unevenly throughout the lung and leads to leakage of fluid from the vascular into the alveolar and interstitial spaces of the lung.

A PHYSIOLOGIC PERSPECTIVE ON PREVENTING ACUTE ALTITUDE ILLNESS

A variety of nonpharmacologic and pharmacologic measures are available for preventing acute altitude illness after ascent. The basis for many of these interventions can be understood in light of the physiologic and pathophysiologic responses described above.

NONPHARMACOLOGIC MEASURES FOR ALTITUDE ILLNESS PREVENTION

Because overly rapid ascent is a critical risk factor for acute altitude illness, the best preventive measure is to undertake a slow ascent to the target altitude, where the term “slow” refers to the rate at which one increases her sleeping elevation rather than the walking or climbing pace at any given time (35). Although the molecular level details of what happens with slow, compared with fast, ascent remain unclear, slow ascent essentially provides more time for protective physiologic responses while blunting pathophysiologic responses that contribute to illness, a concept is demonstrated nicely by data showing that PA pressure at 4,300 m is lower when ascent is
interrupted by a 7-day stay at an intermediate altitude compared with immediate exposure to this altitude in a hypobaric chamber (1).

Avoiding overexertion at altitude is another common recommendation for preventing altitude illness, although the evidence supporting this is mixed (49, 56). The mechanism by which overexertion affects risk is not clear but may relate to decreases in $\text{PaO}_2$ that occur with progressive exercise at altitude and subsequent downstream consequences of increased hypoxemia or to increases in cerebral and pulmonary blood flow, with the latter being an important contributor to the development of HAPE. Overexertion also increases the risk of dehydration, whose symptoms mimic those of AMS. Forced dehydration is often recommended in lay publications as a means to decrease the risk of altitude illness, but the available evidence does not support a relationship between hydration status and AMS (8) and forced hydration might actually increase the risk of problems such as hyponatremia or, when combined with heavy sodium intake, pulmonary edema (32).

PHARMACOLOGIC MEASURES FOR ALTITUDE ILLNESS PREVENTION

Several medications have an established benefit in prevention of AMS, HACE, and HAPE. The appropriate doses are listed in Table 3 and their physiologic rationale is described below.

**Acetazolamide.** The mainstay of pharmacologic prophylaxis, acetazolamide decreases the risk of AMS by initiating a renal bicarbonate loss and causing a metabolic acidosis. This counteracts the dampening effect of hypocapnia on the full ventilatory response upon initial exposure to hypoxia. With the decrease in pH, peripheral chemoreceptor output increases, leading to a rise in minute ventilation. Renal bicarbonate losses also lead to increased efflux of bicarbonate from the CSF, leading to a decrease in CSF pH and further stimulation to ventilation via the central chemoreceptors. Beyond these primary effects, acetazolamide may also play a role through direct effects on the cerebrovascular endothelium, peripheral chemoreceptors and central chemoreceptors with subsequent downstream effects on minute ventilation (62). Animal (23) and human studies (64a) have demonstrated that acetazolamide can blunt hypoxic pulmonary vasoconstriction and suggest the medication may have a role in HAPE prophylaxis. Prevention studies have yet to confirm a benefit in this regard, however, and the medication is not currently used specifically for HAPE prophylaxis.

**Dexamethasone.** Although its role in AMS prevention has been established in research studies (26) and clinical experience, the mechanism by which it plays this role remains unexplained. In a study of HAPE-susceptible individuals ascending to 4,559 m, dexamethasone was also shown to decrease PA pressure and prevent HAPE (36). The mechanism underlying this surprising finding is unclear but may relate to effects on endothelial nitric oxide synthetase activity and nitric oxide availability as well as effects on sympathetic activity, pulmonary capillary permeability, and epithelial sodium transport (3).

**Nifedipine.** Based on a single, small, randomized study (2), nifedipine has been the primary option for preventing HAPE in known susceptible individuals. By inhibiting calcium channels on the surface of vascular smooth muscle cells, the medication limits the rise in intracellular calcium concentrations necessary for smooth muscle contraction, thereby interfering with hypoxic pulmonary vasoconstriction and decreasing PA pressure, the key issues driving edema formation in HAPE. Nifedipine has no known role in AMS prevention.

**Phosphodiesterase-5 inhibitors.** Sildenafil and tadalafil can be used as alternatives to nifedipine for HAPE prevention (36). These agents enhance the role of nitric oxide by blocking the degradation of cyclic GMP in vascular smooth muscle. Higher cGMP concentrations, in turn, decrease inflx and increase efflux of calcium from smooth muscle cells, promoting vasodilatation and decreasing PA pressure. These medications may also improve gas exchange at altitude and partially mitigate the altitude-induced decrease in maximum exercise capacity (19, 46). The mechanism for the former effect is unclear, whereas the latter is the result of diminished pulmonary artery pressure responses to hypoxia and improvements in right ventricular function.

**Salmeterol.** This long-acting β-agonist increases sodium and fluid transport out of the alveolar space by stimulating amiloride-sensitive sodium channels on the apical membrane and possibly increasing Na$^+$/K$^+$/ATPase activity on the basolateral membrane. Although it has been shown in a randomized, controlled trial to reduce the incidence of HAPE in susceptible individuals (52), nifedipine or the phosphodiesterase-5 (PDE-5) inhibitors remain the preferred first-line agents for HAPE prevention (35), because lowering pulmonary artery pressure appears to be a more effective prophylaxis strategy.

**Ibuprofen.** Recent data suggest ibuprofen may also be effective in the prevention of AMS (30). However, a clear mechanism of action has not been elucidated and the agent has not yet supplanted acetazolamide or dexamethasone in prevention guidelines.

### Table 3. Medications used for prevention and treatment of acute altitude illness

<table>
<thead>
<tr>
<th>Medication</th>
<th>Primary Mechanism</th>
<th>Use</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>Increase in ventilation by generation of a metabolic acidosis</td>
<td>AMS Prevention</td>
<td>125 or 250 mg every 12 h</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Unclear mechanism of action</td>
<td>AMS Treatment*</td>
<td>250 mg every 12 h</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Pulmonary vasodilation</td>
<td>AMS Prevention</td>
<td>2 mg every 6 h or 4 mg every 12 h</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Alterations in alveolar epithelial sodium and water transport</td>
<td>AMS Treatment</td>
<td>4 mg every 6 h</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Pulmonary vasodilation</td>
<td>HACE Treatment</td>
<td>8 mg once then 4 mg every 6 h (22)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Pulmonary vasodilation</td>
<td>HAPE Prevention and Treatment</td>
<td>30 mg sustained release version every 12 h</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Pulmonary vasodilation</td>
<td>HAPE Prevention and Treatment†</td>
<td>125 μg every 12 h</td>
</tr>
</tbody>
</table>

*Role of acetazolamide in AMS treatment is not well-documented compared to its role in prevention. †Clinical studies have not documented a benefit for prevention or treatment of HAPE. ‡Clinical studies have only shown benefit in prevention of HAPE.
GENERAL APPROACH TO ALTITUDE ILLNESS PREVENTION

All individuals ascending to high altitude should adhere to the nonpharmacologic measures mentioned above. To limit the rate of ascent, once above 3,000 m individuals should not increase their sleeping elevation by more than 300–500 m per night and should include a rest day every 3–4 days or before or after any very large gains in elevation mandated by local terrain factors. Pharmacologic prophylaxis is not warranted in all high-altitude travelers and, instead, should be used based on the individual’s prior history of performance at altitude, if known, and the planned ascent profile as specified in published guidelines on this topic (35). Those individuals with a prior history of altitude illness, very high sleeping elevations on the first night of the trip, or planned fast ascent rate above 3,000 m should strongly consider pharmacologic prophylaxis for AMS, with acetazolamide being the first-line agent for this purpose. Because it is an uncommon entity, pharmacologic prophylaxis for HAPE is reserved for those with a prior history of the disorder. Because of genetic differences in susceptibility, individuals making repeated ascents to high altitude over time can adapt these recommendations as they learn more about their personal tolerance of hypoxia.

Key Points
- Undertaking a gradual ascent is the primary nonpharmacologic means of preventing acute altitude illness.
- The decision to initiate pharmacologic prophylaxis should be based on the individual’s planned ascent profile and prior history of illness at high altitude.
- Acetazolamide is the standard medication for preventing acute mountain sickness and works primarily by increasing ventilation through effects on acid-base balance.
- By blunting hypoxic pulmonary vasoconstriction, pulmonary vasodilators such as nifedipine can be used to prevent HAPE in known susceptible individuals.

EXTREME ALTITUDE: WHERE THE STANDARD APPROACH NO LONGER APPLIES

The majority of individuals who travel to altitude for work or pleasure do not ascend higher than 5,500–6,000 m, an altitude range that encompasses the highest altitude of permanent human habitation and common trekking destinations such as Mt. Kilimanjaro (5,895 m) and Everest Base Camp (5,350 m). Most of the discussion of physiologic responses and prevention of acute altitude illness described above largely applies to travel up to such elevations. Select individuals, most commonly as part of climbing expeditions, however, do travel above these elevations and enter an environment of profound hypoxia where many of the physiologic responses are pushed to the extremes (67).

Importantly, individuals cannot tolerate acute exposure to these marked degrees of hypoxemia and can only do so if they take the appropriate amount of time to acclimatize and allow for adaptive responses at the organ and molecular levels. The bulk of the acclimatization work must take place at more modest elevations and through short-duration trips to higher elevations, however, because above ~7,000 m (~23,000 ft), acclimatization does not occur and stays of more than just a few days in succession are associated with physical deterioration and impaired physical performance. It is for this reason that with climbing at the extremes of high altitude, the commonly held notion of ensuring a slow ascent to decrease the risk of altitude illness ceases to apply. Climbers must do the bulk of their acclimatizing at more moderate elevations and minimize the time spent in the “death zone” above ~7,000 m by making a fast move to and from the summit when conditions permit. Medications used for prophylaxis against the acute altitude illnesses have also never been studied at these extreme elevations and it remains unclear if they provide a benefit in this environment, although anecdotal reports suggest some climbers use them for this purpose (10).

Key Points
- Individuals do not tolerate acute exposure to the extremes of high altitude (>7,000 m) and can only do so if they take the appropriate time to acclimatize at more moderate elevations.
- Above about 7000 m, acclimatization is no longer feasible and prolonged stays are associated with physical deterioration.
- The usual rules of ensuring slow ascent and pharmacologic prophylaxis no longer apply at elevations above 7,000 m.

A PHYSIOLOGIC PERSPECTIVE ON TREATING ACUTE ALTITUDE ILLNESS

As with altitude illness prevention, treatment involves a combination of both nonpharmacologic and pharmacologic measures.

NONPHARMACOLOGIC MEASURES FOR TREATMENT OF ALTITUDE ILLNESS

Descent. With descent, barometric pressure increases, leading to an increase in the Po2 at every step along the oxygen transport cascade that effectively “shuts off” the pathophysiologic processes contributing to acute altitude illness. Although beneficial responses to hypoxia, such as hyperventilation, are eliminated over time after descent, these effects are far outweighed by the increase in the ambient Po2. How far an individual must descend is unclear and varies between individuals and with the severity of illness. Although it is the definitive form of treatment, it is not necessary in mild AMS and is reserved for HACE, HAPE, or those with AMS who are not responding to appropriate treatment.

Portable hyperbaric chambers. When descent is not feasible because of weather or other logistical factors, patients with severe illness can be treated in a tight-sealing fabric pressure bag, often called a Gamow bag in reference to its inventor. With inflation by manual air pump, the barometric pressure inside the bag rises and effectively brings the ill individual to a lower elevation, with the magnitude of simulated descent a function of the inflation pressure and altitude at which it is used. After initial inflation, the bag must be pumped on a continual basis to maintain pressure and ensure adequate ventilation and removal of exhaled CO2. When patients are removed from the bag, they are, of course, immediately back at the original altitude but symptoms do not return immediately, providing time for the patient to descend under their own power or by other means.

Supplemental oxygen. When available, administration of supplemental oxygen can facilitate resolution of altitude illness.
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Most of the medications used for prevention of altitude illness can also be used for treatment of active disease (Table 3). The physiologic rationale underlying their use is the same as described above, although the evidence base supporting their use for this purpose is not as extensive as the evidence for use in prevention. Because dexamethasone has not been studied in HAPE treatment, it cannot be recommended for this purpose. Case series describe the use of β-agonists in treatment of HAPE (17, 27), but they have not been studied for this purpose and are not part of standard treatment protocols.

GENERAL APPROACH TO ALTITUDE ILLNESS TREATMENT

Descent is the definitive treatment for all altitude illness but is not required in all situations. In fact, the majority of patients with AMS, the most common form of acute altitude illness, can be treated with rest, symptomatic relief (e.g., acetaminophen or nonsteroidal anti-inflammatory medications for headache), and possibly acetazolamide or dexamethasone while remaining at the same elevation. Failure to improve or worsening symptoms with this conservative approach are indications for descent.

Descent should be initiated up front, however, in patients with incapacitating symptoms of AMS or symptoms and signs of HACE or HAPE. If descent is not feasible, patients should be treated with either supplemental oxygen or a portable hyperbaric chamber when available. Dexamethasone should be started for patients with HACE, whereas nifedipine or a phosphodiesterase inhibitor should be initiated in patients with HAPE. Dual pulmonary vasodilatory therapy should be avoided, however, because of a risk of hypotension. Patients with HAPE who access a health care facility may not require descent or pulmonary vasodilator therapy and, in many cases, can be treated with supplemental oxygen, bed rest, and close observation alone (33).

Key Points
- Descent is the best treatment for acute altitude illness.
- When descent is not feasible, supplemental oxygen and portable hyperbaric chambers can be used for management of HACE, HAPE and very severe AMS.
- With limited exceptions, the same medications used for altitude illness prevention can be used in altitude illness treatment.

SUMMARY

Upon ascent to high altitude, individuals are exposed to acute hypoxia and experience a decrease in oxygen tensions at all points along the oxygen transport cascade. This triggers a series of physiologic responses that help the body adapt to the lower oxygen tensions and lead individuals to feel different than they would at sea level. Although most high-altitude travelers tolerate the hypoxic conditions without difficulty, some individuals manifest maladaptive responses that can lead to one of several forms of acute altitude illness, including AMS, HACE, and HAPE. Drawing on an understanding of the major physiologic responses to acute hypoxia, providers can counsel patients about changes to expect after ascent, the reasons individuals develop acute altitude illness, and the appropriate pharmacologic and nonpharmacologic measures for preventing and treating these disorders should they develop.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: A.M.L. prepared figures; A.M.L. drafted manuscript; A.M.L. approved final version of manuscript.

REFERENCES

8. Castellani JW, Muza SR, Cheuvront SN, Sills IV, Fulco CS, Kenefick RW, Beidleman BA, Sawka MN. Effect of hyohydration and altitude


