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# High-altitude illness: Physiology, risk factors, and general prevention

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## INTRODUCTION

The beauty and recreational opportunities of the mountains attract millions of visitors to high-altitude destinations worldwide. Resort towns in the Western United States alone attract over 30 million visitors annually, generally to sleeping elevations in the 2000 to 3000 m (6500 to 9800 feet) range. Many millions more visit destinations at these elevations, including several large cities in South America and Asia situated above 3000 m [1]. Most of these destinations can be reached within a day.

In addition, tens of thousands of climbers, trekkers, and skiers worldwide ascend to elevations in the 3000 to 5500 m (9800 to 18,000 feet) range, often at an ascent rate that exceeds an individual's ability to acclimatize. A growing number of mountaineers seek the summits of peaks over 5500 m. Military, rescue, and other professional personnel may also be called upon to ascend to high altitudes with little or no time for acclimatization. Such rapid ascents place the unacclimatized traveler at risk for developing high-altitude illness (HAI).

Clinicians working in or near mountainous areas should familiarize themselves with the presentation and management of HAI, while all health care workers who advise travelers should understand the best prevention strategies and treatment options. High altitude physiology, the different types of HAI and associated risk factors, and general methods for

prevention will be reviewed here. The pathophysiology, diagnosis, treatment, and prevention of specific types of HAI are discussed separately.

- (See "Acute mountain sickness and high-altitude cerebral edema".)
- (See "High-altitude pulmonary edema".)
- (See "High altitude, air travel, and heart disease".)

## HIGH ALTITUDE PHYSIOLOGY

**Hypobaric hypoxia** — The partial pressure of oxygen ($PO_2$) is the driving force for the diffusion of oxygen down the oxygen cascade. Oxygen moves from inspired air to the alveolar space via the airways and then diffuses across the alveoli into the blood (figure 1 and figure 2), where it is carried mainly bound to hemoglobin but also in dissolved form. At the level of the capillaries, oxygen diffuses across vessel walls, through the tissues and into cells, and ultimately into the mitochondria. (See "Oxygen delivery and consumption" and "Measures of oxygenation and mechanisms of hypoxemia".)

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Barometric pressure and oxygenation diminish in a curvilinear fashion with increasing altitude (table 1 and table 2 and table 3). Barometric pressure also decreases with lower temperature, higher latitude, inclement weather, and during winter. Although the effect of these variables upon barometric pressure is not nearly as significant as altitude, it becomes physiologically significant at elevations over approximately 2800 m (9200 feet) [1].

At sea level there is a large pressure gradient for oxygen between inspired air and tissue. However, as barometric pressure falls so does the available oxygen. At high altitudes, especially when tissue oxygen demands are high during athletic or work activities, the marked reduction in the pressure gradient and available oxygen can lead to tissue hypoxia. This form of hypoxia is termed hypobaric hypoxia, and it represents the initial cause of HAI.

### Acclimatization

**Overview** — As $PIO_2$ decreases with ascent, the driving pressure of $PO_2$ down the oxygen cascade diminishes, resulting in progressive hypoxemia and tissue hypoxia (figure 3) [1-3]. The normal compensatory responses to acute hypobaric hypoxia are termed "acclimatization," an incompletely understood, complex series of physiologic changes involving multiple organ systems that occurs over varying periods (from minutes to weeks).

Acclimatization improves tissue oxygenation by increasing alveolar $PO_2$ and the efficiency with which oxygen moves down the oxygen cascade and by optimizing the utilization of oxygen at the cellular level.

Acclimatization differs from "adaptation," which refers to physiologic changes that take place in response to chronic exposure to hypobaric hypoxia over generations and are observed in some populations permanently situated at high altitude. It should be stressed that the capacity to acclimatize varies greatly among individuals and is dependent upon many factors, including the degree of hypoxic stress (rate of ascent, altitude attained), the intrinsic capacity of the individual to compensate for diminished $PaO_2$ (genetic and anatomic variation, medical conditions), and extrinsic factors, which may enhance or interfere with compensatory mechanisms (eg, alcohol, medications, temperature) [4].

The process of acclimatization begins within minutes of ascent but requires several weeks to complete. Hypoxia-inducible factors (HIFs) are transcription factors that respond to decreases in available cellular oxygen. HIF-1-alpha regulates more than 3000 genes in response to hypoxia and plays a major role in activating the cellular mechanisms responsible for acclimatization. Other factors and genes are likely be involved as well [5].

Although the complex compensatory changes that occur cannot fully restore tissue $PO_2$ to sea-level values, acclimatization can substantially improve oxygen delivery and utilization. In fact, acclimatization enables some climbers to function with only minor difficulty on the peak of Mount Everest (8848 m or 29,029 feet) without supplemental oxygen [2].

At 8848 m, $PIO_2$ is 43.1 mmHg, equivalent to breathing 6 percent oxygen at sea level. Sudden exposure to such high altitude (eg, pilot's cockpit suddenly decompresses) results in loss of consciousness and death [1]. A detailed discussion of acclimatization is beyond the scope of this review, but can be found in several excellent sources [1,6]. A brief review of the beneficial changes that occur during acclimatization is provided below. Other aspects of respiratory physiology are discussed separately. (See "Control of ventilation" and "Physiology of dyspnea".)

**Ventilation, arterial blood gases, and renal compensation** — The first and most important step in improving oxygen delivery is an increase in ventilation. Without increased ventilation, humans could not tolerate altitudes higher than 5000 m (16,400 feet) [1-3].

Hypoxic stimulation of the peripheral chemoreceptors (in the carotid and aortic bodies) results in increased minute ventilation and is termed the hypoxic ventilatory response (HVR). HVR increases in sensitivity over several days spent at altitude (figure 4). Overall, minute

ventilation increases in a nearly linear fashion with diminishing $SaO_2$. The increase in ventilation raises alveolar $PO_2$ and lowers alveolar $CO_2$, resulting in a respiratory alkalosis. Ventilation reaches a maximum only after four to seven days at the same altitude, as renal compensation for the respiratory alkalosis takes place. (See "Control of ventilation", section on 'Peripheral chemoreceptors'.)

HVR is genetically determined and quite variable among individuals. HVR is not influenced by athletic training but is affected by extrinsic factors, such as respiratory depressants (eg, alcohol and sedative/hypnotics) and fragmented sleep. Conversely, respiratory stimulants (eg, progesterone) and sympathomimetics (eg, coca, caffeine) increase HVR.

While one might assume that a brisk HVR would reduce the degree of hypoxemia and protect against acute mountain sickness (AMS), studies have failed to demonstrate this finding consistently. Some elite climbers, endurance athletes, and high-altitude residents (Sherpas and Andean peoples) have low HVR and perform well at altitude. However, a low HVR is associated with an increased risk of HAPE, perhaps because it augments hypoxia-induced pulmonary vasoconstriction, leading to an exaggerated increase in pulmonary artery (PA) pressure [1,6].

As ventilation rises in response to hypoxia, $PaCO_2$ falls and pH rises. The central chemoreceptors in the medulla of the brain respond to alkalosis in the cerebral spinal fluid (CSF) by inhibiting ventilation, such that the full hypoxic ventilatory response is attenuated. While peripheral chemoreceptors are sensitive to changes in pH, central chemoreceptors play the major role in this response. (See "Control of ventilation", section on 'Central chemoreceptors'.)

Partial renal compensation for respiratory alkalosis occurs within 24 to 48 hours of ascent as the kidneys excrete bicarbonate, decreasing the pH toward normal, and allowing ventilation to again increase as the alkalosis is reduced. Plasma bicarbonate concentration continues to drop and ventilation to rise with further increases in altitude. Acetazolamide rapidly facilitates this process. (See "Simple and mixed acid-base disorders", section on 'Compensatory respiratory and renal responses'.)

**Circulatory changes** — Circulatory changes following ascent involve the systemic, cerebral, and pulmonary vasculatures. Following a rapid and sustained increase in altitude, increased sympathetic activity transiently increases cardiac output, blood pressure, heart rate, and venous tone. Heart rate remains elevated while stroke volume is diminished due to decreased plasma volume, which can drop as much as 12 percent over the first 24 hours

from bicarbonate diuresis, fluid shift from the intravascular space, and suppression of aldosterone [1]. The reduction in plasma volume cannot be offset by increased fluid intake. The effects of altitude upon cardiac function are discussed in detail separately. (See "High altitude, air travel, and heart disease".)

The cerebral vasculature is highly autoregulated in response to changes in both oxygen and $CO_2$. In the brain, oxygen delivery is dependent upon cerebral blood flow (CBF), which in turn depends upon a balance of vasodilation (in response to hypoxia), vasoconstriction (in response to hypocapnia), and changes in autoregulation. While there is considerable variation of cerebral autoregulation and cerebral blood flow among hypoxic individuals, oxygen delivery is generally maintained down to $SpO_2$ levels of 70 to 80 percent despite marked hypocapnia. Although hypocapnia attenuates hypoxic vasodilation, the net change in response to hypoxia is an increase in CBF. Individual variation in cerebral blood flow is linked to differences in ventilatory responses to hypoxia and hypocapnia. Despite mild regional brain tissue hypoxia revealed by near infrared spectroscopy, overall global cerebral metabolism is well-maintained during moderate hypoxia [7].

The pulmonary vasculature constricts in response to hypoxia (Hypoxic Pulmonary Vasoconstriction (HPV)), resulting in prompt increases in pulmonary vascular resistance and pulmonary artery (PA) pressure. Increased flow to usually under-perfused areas may augment gas exchange by improving ventilation/perfusion matching. There is marked individual variation of HPV. An exaggerated increase in PA pressure and pulmonary vascular resistance (PVR) is associated with susceptibility to HAPE, as is markedly inconsistent vasoconstriction of pulmonary arterioles. (See "High-altitude pulmonary edema", section on 'Pathophysiology'.)

At altitude, mild pulmonary hypertension at rest can be markedly increased by vigorous exercise, with pulmonary pressure reaching near-systemic levels, especially in people with a history of HAPE. Cold ambient temperatures at high altitude also increase pulmonary artery pressure. To what extent increased pulmonary vascular resistance limits exercise at altitude is debated [8,9]. The effect of PDE-5 inhibitors to increase exercise capacity in some persons suggests that those with exaggerated hypoxic pulmonary vasoconstriction may have exercise limitations [10].

**Hematologic changes** — Increased hemoglobin concentration ([Hb]) is a well-known component of high altitude acclimatization. A modest increase in [Hb] is beneficial by increasing the oxygen-carrying capacity of blood.

In the first few days at altitude, [Hb] is increased due to plasma volume contraction. Within a few hours, hypoxemia stimulates increased production of erythropoietin from specialized renal cells, which increases the production of red blood cells (RBCs), resulting in an increased [Hb] within two to four weeks. Up to altitudes of approximately 4000 m, this increase is sufficient to balance the reduction in oxygen saturation and restore the oxygen content of arterial blood to sea level values (though now at a lower $PO_2$).

The oxyhemoglobin dissociation curve (ODC) plays a crucial role in oxygen transport and delivery. Because of the sigmoid shape of the curve, arterial oxygen saturation ($SpO_2$) is well-maintained up to 3000 m, despite a significant decrease in arterial $PO_2$ ($PaO_2$). This correlates with an oxygen saturation of about 88 to 89 percent. Above that altitude, small changes in $PaO_2$ result in large changes in $SpO_2$. (See "Structure and function of normal hemoglobins".)

While $SpO_2$ is the major determinant of blood oxygen content, $PaO_2$ determines diffusion of oxygen from the capillary to the cell. Intraerythrocytic alkalosis causes a leftward shift of the ODC, but alkalosis is a major stimulus for the production of 2,3 DPG, which shifts the ODC rightward, back toward its normal position. This balance between alkalosis (left shift) and increased 2,3 DPG (right shift) is maintained until sojourners reach very high altitudes. There, the effect of the alkalosis far outstrips the capacity of the RBC to produce more 2,3 DPG, leading to a leftward shift of the ODC.

As an example, in climbers at the summit of Mount Everest the $PaCO_2$ is 8 to 10 mmHg and the pH rises above 7.6. The resulting shift of the ODC to the left facilitates oxygen-hemoglobin binding in the lung, which results in an advantageous rise in $SpO_2$. Also, animals adapted to high altitude (eg, yaks, llamas, bar-headed geese) have left-shifted ODCs compared with their low-altitude counterparts [11].

**Oxygen delivery and utilization** — Diffusion of oxygen from the capillaries to the mitochondria and its subsequent use by these organelles constitutes the final step of the oxygen cascade. Diffusion distance from capillary wall to mitochondria is decreased at high altitude, mainly because of reduction in the diameter of muscle fibers, which atrophy during high altitude expeditions. This atrophy occurs due to a net energy deficit and deconditioning effect [12].

At the tissue level, HIF-1-a stimulates vascular endothelial growth factor (VEGF), which stimulates angiogenesis and nitric oxide synthesis. This results in greater blood flow and oxygen delivery to tissues. Improvements in oxidative metabolism and tissue gas exchange also occur [13].

## DEFINITIONS

**High-altitude illness** — HAI is the collective term for the unique cerebral and pulmonary syndromes that can occur following an initial ascent to high altitude (generally above 2000 to 2500 m, 6500 to 8200 feet) or following a further ascent while already at high altitude. HAI includes acute mountain sickness (AMS) and high altitude cerebral edema (HACE), which afflict the brain, and high altitude pulmonary edema (HAPE), which afflicts the lungs. They are induced by the hypoxic stress of high altitude and are characterized by extravascular fluid accumulation in the brain (AMS/HACE) and lungs (HAPE). All respond to descent, oxygen therapy, or both. Patients with possible AMS, HAPE, or HACE require careful evaluation to exclude other potential diagnoses, such as severe dehydration, hyponatremia, pneumonia, carbon monoxide poisoning, and hypoglycemia.

**Acute mountain sickness and high altitude cerebral edema** — Most experts consider acute mountain sickness (AMS) and high altitude cerebral edema (HACE) to represent different points of severity along the same pathophysiologic process in the brain. This process may collectively be referred to as AMS/HACE.

AMS is the most common form of HAI and may occur following rapid ascent [1,4,6,14]. It is characterized by headache in combination with other nonspecific symptoms, such as malaise and anorexia.

HACE is the least common form of HAI but is rapidly fatal without prompt recognition and treatment. AMS/HACE are discussed in detail separately. (See "Acute mountain sickness and high-altitude cerebral edema".)

**High altitude pulmonary edema** — High altitude pulmonary edema (HAPE) is an uncommon, life-threatening noncardiogenic pulmonary edema that develops two to four days following rapid ascent above 2500 m (8000 feet) [15]. HAPE, which may accompany AMS/HACE, is the most common cause of death among the HAIs. Individuals who have had HAPE are at high risk for recurrence if they ascend to the same altitude, particularly if they do so at the same rate of ascent. HAPE is discussed in detail separately. (See "High-altitude pulmonary edema".)

**Other altitude-related illnesses** — Altered breathing during non-REM sleep, a phenomenon known as periodic breathing of altitude, is encountered at altitudes over 2500 m and becomes very common at higher altitudes [16-18]. It is a form of Cheyne-Stokes respiration and reflects changes in neural signaling due to hypoxia (respiratory stimulant) and alkalosis

(respiratory depressant) during sleep. Periodic breathing of altitude may occur at altitudes as low as 1400 m but generally does not disrupt sleep until visitors or climbers reach altitudes above 2750 m. (See "Disorders of ventilatory control".)

High altitude retinal hemorrhage occurs when there is rupture of retinal arterioles leading to extravasation of blood into the retina [19-21]. The retinal circulation develops many of the same changes seen in the cerebral circulation at altitude. It is most common at elevations above 5000 m (16,400 feet), particularly among those engaged in strenuous activity. Symptoms rarely develop unless hemorrhage extends to the macula.

Numerous medical illnesses other than AMS/HACE and HAPE may be caused or exacerbated by high altitude (table 4). Examples include: problems resulting from chronic altitude exposure, such as chronic mountain sickness and high altitude pulmonary hypertension; preexisting medical conditions exacerbated by hypoxia, such as ischemic heart disease; and conditions arising at altitude unrelated to hypoxia, such as frostbite and photokeratitis. Many of these conditions are discussed separately. (See "High altitude, air travel, and heart disease" and "Photokeratitis" and "Frostbite: Emergency care and prevention" and "Accidental hypothermia in adults".)

## RISK FACTORS

**Individual** — Individual susceptibility to HAI varies widely for reasons that remain largely unexplained. Given adequate time, some individuals can acclimatize sufficiently to tolerate severe hypoxia, such as that found at the summit of Mount Everest (8848 m or 29,029 feet; approximate $PaO_2$ 20 to 30 mmHg). Others consistently develop debilitating AMS or HAPE during rapid ascent to elevations as low at 2500 m (approximate $PaO_2$ 60 to 70 mmHg).

No reliable and easily available genetic or physiologic markers are able to predict an individual's susceptibility to HAI. Despite extensive research, susceptibility to AMS cannot be predicted accurately prior to ascent. Some researchers have reported an association between AMS and a variety of physiologic markers (eg, resting and post-exercise SaO at altitude, hypoxic ventilatory response [HVR], hypercapnic ventilatory response [HCVR], hyperventilation capacity, heart rate variability, and apneic diving response), but others have failed to confirm these findings [22-29].

Individual factors associated with an increased risk of developing HAI include (table 5) [1,30,31]:

- Past history of HAI (strongly predictive if conditions are similar)
- Rate of ascent
- Vigorous exertion at altitude before adequate acclimatization
- Lack of acclimatization (see 'Acclimatization' above)
- Substances (eg, alcohol) or conditions that interfere with acclimatization
- Comorbidities that interfere with respiration (eg, neuromuscular disease) or circulation (eg, pulmonary hypertension)

HAI can be induced in any subject if the altitude is sufficiently high or the rate of ascent is sufficiently rapid, regardless of the person's capacity to acclimatize. Thus, the most important variables determining whether HAI develops are an individual's genetic susceptibility and the degree of hypoxic stress. The elevation attained (particularly the sleeping elevation) and the rate of ascent is of greatest importance when considering hypoxic stress. Conditions that further contribute to hypoxic stress, such as vigorous exertion prior to acclimatization, also increase the risk of HAI.

Other factors that alter ventilation and the ventilatory response may impair acclimatization. Examples include sedative-hypnotic medications, alcohol, and sleep apnea. Comorbid conditions that impair ventilation, respiration, or oxygen-carrying capacity increase the risk for HAI. Examples include neuromuscular disease, chronic obstructive pulmonary disease (COPD), restrictive lung disease, cystic fibrosis, pneumonia, pulmonary hypertension, carotid artery surgery or neck radiation that ablates the carotid bodies, and congenital cardiac anomalies involving right-to-left shunts [32-42]. Of note, neither anemia nor asthma is associated with an increased risk for HAI (in fact, asthma generally improves at high altitude). Sickle cell disease is exacerbated by hypoxic environments. Sickle cell disease and its complications are discussed separately. (See "Overview of the clinical manifestations of sickle cell disease".)

HAI afflicts all ages and both sexes, regardless of physical fitness. In fact, younger athletes, particularly males, may be at greater risk of HAI for behavioral reasons. They are likely to engage in strenuous exertion prior to acclimatization or to pursue continued ascent, despite the presence of symptoms suggestive of HAI. Such behaviors feature prominently in severe and fatal cases of HAI.

**Pediatric** — The risk factors for HAI are the same in healthy children as in adults. Expert opinion is that lowland infants less than six weeks of age should avoid overnight exposure to more than 2500 m [43]. Shared risk factors among children and adults include the rate of ascent, absolute altitude achieved, degree of physical exertion, and colder ambient

temperatures. Risk factors of greater importance for the pediatric population relate to the unique physiology of hypoxia in infants and young children, as well as the effects of concurrent acquired or congenital conditions that are more prevalent in this age group (eg, upper respiratory infection, congenital cardiopulmonary disease, cystic fibrosis, Down syndrome). These issues are discussed in greater detail separately. (See "High-altitude disease: Unique pediatric considerations", section on 'High-altitude physiology'.)

**Environmental** — High altitude is commonly categorized according to the physiologic stress it produces (table 2 and table 3). Although there is no consensus about such classification, the main concept is that progressive ascent results in increased hypoxic stress, requiring greater degrees of physiologic and behavioral adjustments in order to preserve function.

In terms of HAI, symptoms generally do not manifest below 1500 m (5000 feet). From about 1500 to 2500 m (5000 to 8200 feet), symptoms are generally mild, if experienced at all. At 2500 m, symptoms of mild to moderate AMS become quite common among unacclimatized visitors after rapid ascent. At this altitude HAPE may also occur, but it is more common above 3000 m (9800 feet). Above 3000 to 4000 m (9800 to 13,100 feet), AMS is common among people who have not properly acclimatized, and the risk of severe HAI, including life-threatening HAPE and HACE, is substantial.

**Pregnancy is not a risk factor** — There is no evidence of a relationship between pregnancy and HAI. In fact, high progesterone, a potent respiratory stimulant, results in higher $SpO_2$ in pregnant persons at altitude. Travel to moderate altitudes (up to 2500 m) during normal pregnancies appears safe. This issue is discussed in greater detail separately. (See "Prenatal care: Patient education, health promotion, and safety of commonly used drugs", section on 'Travel to moderate and high altitudes'.)

Women residing at high altitudes have a greater risk of pregnancy-induced hypertension, proteinuria, and preeclampsia, and their newborns have lower birth weights [1]. (See "Fetal growth restriction: Evaluation".)

## RISK STRATIFICATION OF THE TRAVELER TO HIGH ALTITUDE

**Determining overall risk** — Determining the risk of an individual traveler for developing HAI is difficult, but depends primarily upon the ascent profile (ie, how high and how fast), whether there is a history of HAI during previous trips to altitude, and whether the patient has comorbidities that predispose to HAI [44]. Of note, clinicians assessing patient risk must

distinguish between the risk for developing HAI (most notably high altitude cerebral edema [HACE] and high altitude pulmonary edema [HAPE]) and the risk that the conditions of high altitude (eg, relative hypoxia) will exacerbate a specific comorbidity (eg, coronary heart disease, sickle cell anemia). This discussion will address only the former; risks associated with the exacerbation of comorbidities are reviewed separately. (See "High altitude, air travel, and heart disease" and "Evaluation of patients for supplemental oxygen during air travel".)

Developing HAI during a previous trip to altitude places a patient at high risk for recurrence during subsequent trips. However, risks are distinct: the patient with a history of HAPE is at risk for a recurrence of HAPE, but may not be at increased risk for AMS/HACE. When inquiring about a patient's history, clinicians must be careful to clarify what the patient means by altitude-related illness. As an example, some patients may confuse a case of infectious diarrhea contracted at high altitude with HAI.

**Assessing the proposed trip** — The itinerary of a trip must be considered when determining the risk for developing HAI. Rapid ascents without adequate time provided for acclimatization and ascents to extremely high altitudes increase the risk for HAI in all travelers.

A useful exercise for determining the risk of HAI is to make a graph, with the patient, of the proposed ascent profile for the trip. A graphic representation showing the daily gain in sleeping elevation makes clear to everyone when the rate of ascent is too fast, and the corresponding risk of developing HAI too great. The risks of developing HAI associated with different rates of ascent are described in the following table (table 5).

Other important factors to consider when planning a trip include the ease with which the traveler can descend to lower altitude and the availability of oxygen or medical care. For travelers at significantly increased risk for HAI, descent from a resort hotel may be reasonable whereas descent from a remote mountainside by yak is probably not. Considerations about the availability of oxygen and medical resources should include not only nearby clinics but also whether the travel group will include someone experienced in the recognition and acute management of HAI.

**Diseases and medical conditions that increase risk** — There are relatively few diseases that predispose the traveler to developing HAI. Such conditions include those that impair the body's ability to increase ventilation and acclimatize to high altitude, such as the absence of carotid bodies due to surgical resection or the effects of radiation, neuromuscular disease affecting the thorax and diaphragm, and moderate to severe chronic obstructive pulmonary

disease (COPD) [32-42,44]. Although the evidence is less clear, conditions that exaggerate the effects of hypoxemia are likely to increase the risk for HAI. Such diseases include obstructive sleep apnea, interstitial lung disease, cystic fibrosis, pneumonia, and congenital cardiac anomalies involving right-to-left shunts (whether patent foramen ovale increases risk is arguable). Pulmonary hypertension clearly predisposes patients to HAPE but not to AMS/HACE. Down's syndrome is a distinct risk factor for HAPE [45-47]. In small observational studies, obesity is associated with an increased risk of AMS [48,49]. Patients with various respiratory conditions may benefit from oxygen or acetazolamide when going to high latitude, such as those with OSA [50]. (See "Acute mountain sickness and high-altitude cerebral edema" and "High-altitude pulmonary edema".)

Diseases of the central nervous system that increase the risk of developing HAI include idiopathic intracranial hypertension (ie, pseudotumor cerebri) and virtually any space-occupying lesion. In addition, patients with chronic headaches are more likely to develop headaches and AMS at altitude.

There are several common diseases and conditions that some clinicians might intuitively expect to increase the risk for HAI but in fact do not. As examples, asthma often improves at altitude, while anemia is not associated with increased risk. Pregnant patients are less likely to develop HAI. In addition, patients over the age of 50 years, assuming they do not have any of the conditions described immediately above, are at lower risk of developing HAI. Most other common chronic diseases, such as hypertension or diabetes, do not appear to be associated with increased risk.

**Assessing the patient** — Patient assessment begins with a careful history, including questions about any problems that developed during previous trips to altitude and whether the patient has any medical conditions that predispose to HAI. (See 'Diseases and medical conditions that increase risk' above.)

As part of the history, it is important to ask about exercise. A patient who exercises regularly, particularly at high intensity, is more than likely to have the physical capacity necessary to travel, climb, or ski at altitude, and is unlikely to have a significant underlying medical condition that might be aggravated by altitude. It is worth inquiring about medical conditions that can be exacerbated by conditions at altitude, such as ischemic heart disease, sleep apnea, and chronic lung disease, and symptoms commonly associated with such ailments, such as chest discomfort or dyspnea with mild exertion, wheezing, or any other breathing difficulty. The risks associated with the exacerbation of comorbidities at altitude are reviewed in greater detail separately. (See "High altitude, air travel, and heart disease"

and "Evaluation of patients for supplemental oxygen during air travel".)

We ask whether there is a family history of migraine, as altitude may precipitate a first migraine headache. Patients with systemic scleroderma, rheumatoid arthritis, or other connective tissue diseases associated with pulmonary manifestations warrant careful screening for pulmonary complications before traveling to altitude. (See "Clinical manifestations, evaluation, and diagnosis of interstitial lung disease in systemic sclerosis (scleroderma)" and "Interstitial lung disease in rheumatoid arthritis".)

During the physical examination, special attention should be paid to detecting jugular venous distention, heart murmurs, and abnormal pulmonary findings. Such findings may reflect the presence of underlying cardiac or pulmonary disease that increases the risk associated with travel to altitude and thus warrant further evaluation. The presence of thoracic irregularities, such as kyphoscoliosis, which may affect pulmonary function, and obesity should be noted.

Some patients who travel on commercial airlines require supplemental oxygen. It is generally safe to assume that patients who require supplemental oxygen for air travel are at increased risk for developing problems at altitude. Although in some cases potential problems may be avoided if the patient is not traveling to extreme altitudes and has sufficient time to acclimatize, commercial airline travelers who require supplemental oxygen and live at or near sea level may be at risk for significant hypoxemia at high altitude. Cabin pressures are typically the equivalent of 1400 to 2500 m, or 4000 to 8000 feet. As an example, a chronic obstructive pulmonary disease (COPD) patient who requires supplemental oxygen for air travel will certainly require it if he or she ascends to a comparable altitude. Screening for these patients begins with pulse oximetry and is discussed in detail separately. (See "Evaluation of patients for supplemental oxygen during air travel".)

**Prophylactic medication: Who needs it and what to give** — Gradual ascent remains the primary method for preventing all forms of HAI. However, in some cases prophylactic medication may be warranted. We recommend prophylactic treatment for all patients at high risk of developing HAI according to the criteria listed in the attached table (table 5). For healthy patients with no history of medical problems at high altitude, the risk of HAI is low with gradual ascent and routine prophylaxis with medication is not warranted. However, gradual ascent is not always possible and sometimes patients at increased risk wish to travel to altitude. In such cases and for others deemed to be at moderate risk for developing HAI, prophylactic medication may be helpful. However, no medication is completely without risk and we prefer to discuss the use of prophylactic medication with patients at moderate risk

and reach a decision with their input. In all cases, rescue medication (given when symptoms begin but not before) is a reasonable alternative to prophylactic medication.

The medication given for prophylaxis depends upon the individual risk of the patient. The risk for HAPE is typically low, unless the patient has a history of HAPE or is susceptible due to specific underlying pulmonary disease (eg, pulmonary hypertension). Therefore, outside such circumstances, we do not routinely recommend medication prophylaxis for HAPE. If such risk factors are present and prophylaxis is indicated, the preferred prophylactic medication is nifedipine. Dosing for the medications used for prophylaxis and treatment of HAI are described in the following table (table 6). Prevention of HAPE, including the medications used for prophylaxis, is discussed in greater detail separately. (See "High-altitude pulmonary edema", section on 'Prevention'.)

For patients at moderate risk of developing AMS/HACE based on the criteria listed in the attached table (table 5) who decide after appropriate discussion that they wish to use prophylactic medication, acetazolamide is the preferred drug, but dexamethasone is also a reasonable option (table 6). Prevention of AMS/HACE, including the medications used for prophylaxis, is discussed in greater detail separately. (See "Acute mountain sickness and high-altitude cerebral edema", section on 'Pharmacologic prevention of AMS/HACE'.)

In the rare instance when medication prophylaxis against both AMS/HACE and HAPE is needed, it is best to seek input from a physician with experience managing HAI.

## PREVENTION OF HIGH-ALTITUDE ILLNESS

**General approach** — Most individuals ascend to high altitude with minimal or no symptoms by allowing sufficient time to acclimatize [44,51]. A subset of patients benefits from pharmacologic prophylaxis. This includes those with a known predilection for HAI despite gradual ascent, and those who must ascend rapidly for convenience (eg, tourists traveling to mountain resort) or work (eg, rescue and military personnel). Pharmacologic prophylaxis is discussed separately. (See "Acute mountain sickness and high-altitude cerebral edema", section on 'Pharmacologic prevention of AMS/HACE'.)

When determining the optimal preventive strategy, factors to consider include the following [52]:

- Patient susceptibility (history of previous HAI)
- Elevation of the person's usual residence

- Recent exposure to altitude
- Intended ascent profile (ie, rapid or gradual ascent)
- Medical history
- Medications and allergies
- Purpose of ascent

**Behavioral methods**

**Gradual or staged ascent** — Gradual or staged ascents are the surest and safest methods of preventing or ameliorating HAI [31,51,53,54]. As a general guideline, individuals who normally reside below 1500 m (5000 feet) elevation should avoid an abrupt ascent to sleeping altitudes above 2800 m (9200 feet). This is best accomplished by spending one night at an intermediate altitude (particularly when traveling to an elevation that caused symptoms previously).

If further ascent above 3000 m (9800 feet) is planned, we suggest not spending subsequent nights at elevations over 500 m higher than the previous night, and including a rest day (no ascent and no vigorous activity) for every 1000 m (3280 feet) climbed (figure 5). Even this conservative approach may prove too aggressive for individuals particularly susceptible to HAI [55]. For others, it may be agonizingly slow.

A common adage among mountaineers is "climb high, sleep low." Day trips to higher elevation with a return to a lower altitude for sleep may accelerate acclimatization and help to prevent HAI.

If time is available, staged ascent is another approach to acclimatization that reduces the risk of developing HAI [56]. Staged ascent involves ascending to altitude in stages. Five to seven days is spent at an intermediate altitude (typically 3000 to 4000 m, 9800 to 13,000 feet) before proceeding to higher elevations. Individuals who reside at low elevation and are traveling to moderate altitudes may stop at an intermediate elevation (approximately 1500 m) to reduce the risk of AMS [57].

**Preacclimatization** — Preacclimatization involving preexposure to higher altitudes (hypobaric hypoxia) or environments that simulate high altitude (normobaric hypoxia) is an effective strategy for preventing HAI. Residing at a site above 2500 m (8200 feet) or participating in brief climbs to actual elevations over 2500 to 3000 m (8200 to 9840 feet) in the weeks leading up to a trip to higher elevations (approximately 4500 m [14,800 feet], or higher) provides a degree of preacclimatization, and may allow for a faster rate of ascent without AMS [1,56-58]. However, evidence is limited about whether brief exposures to high

altitude are effective and the optimal strategy for preacclimatization remains unproven. As a general rule of thumb, the altitude of preexposure climbs, real or simulated, should reach within approximately 2000 m or closer of the ultimate altitude and involve longer exposure (eg, >8 hours daily for over 7 days) to yield benefit [59]. If extended preexposure is not feasible, a reasonable alternative would be to travel to such altitudes for two or three weekends during the two months prior to the trip.

While hypobaric hypoxia is more effective, an alternative approach to preacclimatization involves using normobaric hypoxia to simulate the relative hypoxia of high altitudes [54,59-61]. Such programs are sometimes called intermittent normobaric hypoxic exposure (INHE). INHE programs use commercially-available devices involving face masks or sealed tents or chambers that allow users to decrease the percentage of inhaled oxygen from 21 percent (sea level) to below 16 percent during sleep or while exercising for variable intervals of time and duration. While INHE is more convenient than traveling to altitude and the physiologic basis appears sound, there is less evidence that this approach is effective at reducing the risk for HAI, unless exposure is for more than seven to eight hours per day for at least a week. A small randomized, placebo-controlled trial showed that two weeks of sleeping at a **simulated** altitude of 2200 to 2600 m was required to prevent AMS at 4600 m [58]. Brief exposures of minutes or hours per day, at rest or during exercise, have not been effective in preventing HAI in the few studies to date. Studies assessing a range of preacclimatization strategies have reported mixed results, and further research is needed to determine the optimal protocols for both preacclimatization and staged ascent [60-66].

**Education** — Individuals with a history of HAI or significant cardiopulmonary disease should be counseled regarding their increased risk and be provided with a conservative ascent plan (or profile). The clinician and patient should review this profile and discuss the relative risks associated with each elevation, as well as the risks of limited accessibility to medical care and evacuation.

Educating patients about the early symptoms and signs of HAI and the need for prompt intervention, particularly with regard to HAPE and HACE, can be life-saving [4,6,51,67]. Patients should commit to memory the mantra that no one with symptoms of HAI should continue to ascend, and that descent is mandatory if symptoms do not improve. A plan of action in the event that immediate descent is not possible should be discussed. Trekkers going to remote areas should be encouraged to descend while still able to do so under their own power if they are not acclimatizing well or are deteriorating. Evacuations are especially difficult in remote areas.

Health care workers who advise travelers need to understand the best prevention strategies and treatment options based upon variables, such as ascent profile (rate of ascent, ultimate elevation attained, time spent at various elevations), previous history of HAI, comorbidities, medication allergies, severity of illness HAPE or AMS/HACE, treatment setting (eg, terrain, weather, remoteness), and available treatment options (eg, field, clinic, hospital) (table 3). Individuals should be informed that the process of acclimatization is hindered by the use of respiratory depressants (eg, sedatives) or alcohol and by overexertion during the first few days at high altitude.

**Alcohol and drug use** — Sedative-hypnotics and moderate to heavy alcohol intake should be avoided during the acclimatization process, particularly during the first two nights at a new elevation. Both types of agents depress respiratory function and interfere with normal sleep patterns and physiologic responses to altitude, which are necessary for acclimatization.

Studies of alcohol's effect on acclimatization and HAI risk are methodologically limited and show mixed results [56,57,68]. While abstinence from alcohol early during acclimatization is the safest course, traditional proscriptions may be overstated and a single drink is unlikely to cause significant problems.

Mild sleeping aids such as zolpidem (Ambien), taken in appropriate doses, do not depress ventilation or affect acclimatization to high altitude and are safe. High-altitude travelers who have slept poorly due to altitude-related periodic breathing may benefit from acetazolamide.

**Diet and hydration** — Various diets, including high carbohydrate, have been touted to reduce the incidence of HAI, but data are inconclusive [1]. Similarly, vigorous hydration, beyond the amount required to maintain adequate hydration, has not been shown to reduce the incidence of HAI [6,69,70]. Climbers or visitors to high altitude sites should be aware of the risk of hyponatremia when following "conventional wisdom" about vigorous hydration. (See "Causes of hypotonic hyponatremia in adults".)

**Exertion** — Vigorous exertion at altitude contributes to the development of AMS as well as HAPE, although sedentary persons also develop these illnesses [71]. Modest exercise may aid acclimatization [1,6,71,72]. Patients with a previous history of HAI should be particularly wary of vigorous exertion during the first few days at high altitude.

**Pharmacologic prophylaxis** — Clinicians should reserve prophylactic medications for individuals with a history of altitude intolerance and those who must make a planned rapid ascent to high altitude [51]. Even in individuals with a previous history of HAI, gradual ascent should be emphasized over pharmacologic prophylaxis. Often, ascending at a slower rate

than the previous offending ascent allows individuals to avoid illness.

Patients with comorbid conditions that are exacerbated by hypoxic environments (eg, ischemic heart disease, COPD, sleep apnea, sickle cell disease, cystic fibrosis) who wish to travel to moderate altitudes may warrant prophylactic oxygen therapy. (See "High altitude, air travel, and heart disease" and "Evaluation of patients for supplemental oxygen during air travel" and "Stable COPD: Initial pharmacologic management" and "Overview of the clinical manifestations of sickle cell disease".)

Pharmacologic prophylaxis against HAI is discussed separately. (See "Acute mountain sickness and high-altitude cerebral edema", section on 'Pharmacologic prevention of AMS/HACE'.)

**Other prevention methods including medications, supplements, and plants** — Numerous other agents and methods are purported to help prevent HAI, including antioxidants, iron, dietary nitrates, leukotriene receptor blockers, phosphodiesterase inhibitors, salicylic acid, spironolactone, sumatriptan, forced overhydration, nocturnal expiratory positive airway pressure (EPAP), short-term oxygen use in the form of oxygen bars, and over-the-counter oxygen canisters. While preliminary study of some interventions has been performed, there is no high-quality evidence to support any of these interventions [73-82].

Among some local Andean populations, coca is felt to enhance physical performance at altitude, but formal studies of this claim are limited [83,84]. When assessing the effects of coca, it is important to distinguish between coca tea (mate de coca) and coca leaves. Coca tea typically contains only a tiny amount of cocaine alkaloid and is unlikely to have any impact on preventing HAI, although it may slightly enhance exercise tolerance and provide some hydration, depending on how much is consumed. The effect of chewing coca leaves on preventing or treating HAI has not been well studied, but there is no convincing evidence of benefit, while the harms of coca are well described [83,85]. We do not recommend chewing coca leaves as a means for preventing HAI. (See "Cocaine use disorder in adults: Epidemiology, clinical features, and diagnosis".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5$^{th}$ to 6$^{th}$ grade reading level, and they answer the four or five key questions a patient might have

about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Altitude sickness (including mountain sickness) (The Basics)")
- Beyond the Basics topic (see "Patient education: High-altitude illness (including mountain sickness) (Beyond the Basics)")

## SUMMARY AND RECOMMENDATIONS

- **High altitude physiology** – The arterial partial pressure of oxygen ($PaO_2$) decreases with altitude, resulting in progressive tissue hypoxia. The normal compensatory response to hypobaric hypoxia is termed acclimatization. Its main feature is increased ventilation. The capacity to acclimatize varies greatly among individuals and is dependent upon many factors, including the degree of hypoxic stress (rate of ascent, altitude attained), the intrinsic capacity of the individual to compensate for diminished $PaO_2$, and extrinsic factors. The process begins within minutes of ascent but requires three to five days for protection from high-altitude illness (HAI) and several weeks to complete. (See 'High altitude physiology' above.)
- **Terminology** – HAI is the collective term for the pathologic syndromes that can develop following an initial ascent to high altitude or following a further ascent while already at high altitude. HAI includes acute mountain sickness (AMS) and high altitude cerebral edema (HACE), which afflict the brain, and high altitude pulmonary edema (HAPE), which afflicts the lungs. (See 'Definitions' above.)
- **Risk factors** – Individual factors associated with an increased risk for HAI include (table 5) (see 'Risk factors' above):
  - Past history of HAI (strongly predictive if conditions are similar)

- Rate of ascent
- Altitude attained, especially sleeping altitude
- Vigorous exertion at altitude before adequate acclimatization
- Substances (eg, alcohol) or conditions that interfere with acclimatization
- Comorbidities that interfere with respiration (eg, neuromuscular disease) or circulation (eg, pulmonary hypertension)

- **Altitude as physiologic stress** – High altitude is commonly categorized according to the physiologic stress it produces (table 2 and table 3). Progressive ascent results in increased hypoxic stress, requiring greater degrees of physiologic and behavioral adaptations in order to preserve function. The more rapid the ascent and the higher the altitude, the greater the stress. (See 'Environmental' above.)

  - Less than 1500 m (5000 feet): HAI symptoms generally do not manifest.

  - From about 1500 to 2500 m (5000 to 8200 feet): Symptoms are generally mild, if experienced at all.

  - Starting at about 2500 m (8200 feet): Symptoms of mild to moderate AMS become quite common among unacclimatized visitors after rapid ascent, and HAPE may also occur, but it is more common above 3000 m (9800 feet).

  - Above 3000 to 4000 m (9800 to 13,100 feet): AMS is common among people who have not properly acclimatized, and the risk of severe HAI, including life-threatening HAPE and HACE, is substantial.

- **Risk stratification of the traveler to high altitude** – Strategies for determining the risk of developing HAI in the traveler to altitude are reviewed in the text. During such evaluations, it is important to distinguish between the risk of developing HAI and the risk that high altitude may exacerbate a specific comorbidity (eg, coronary heart disease). A useful exercise for determining the risk of HAI is to make a graph, with the patient, of the proposed ascent profile for the trip. Other important factors to consider when planning a trip include the ease with which the traveler can descend to lower altitude and the availability of oxygen or medical care. (See 'Risk stratification of the traveler to high altitude' above.)

- **Prevention of HAI** – Gradual ascent is the surest and safest method of preventing or ameliorating HAI. Most individuals ascend to high altitude without complications by allowing sufficient time to acclimatize. As a general guideline, individuals who normally

reside below 1500 m (5000 feet) elevation should avoid an abrupt ascent to sleeping altitudes above 2800 m (9200 feet). Sedative-hypnotics should be avoided during acclimatization. Abstinence from alcohol is safest, but a single drink is unlikely to cause problems. Vigorous exertion at altitude contributes to the development of both AMS and HAPE, and should also be avoided during acclimatization. Additional preventive strategies are discussed in the text. (See 'Prevention of high-altitude illness' above.)

- **Pharmacologic prophylaxis** – Patients with a known predilection for HAI despite gradual ascent, and others who must ascend rapidly for convenience (eg, tourists traveling to mountain resort) or work (eg, rescue personnel) may benefit from pharmacologic prophylaxis. These are summarized in the table (table 6) and discussed in greater detail separately. (See 'Pharmacologic prophylaxis' above and "High-altitude pulmonary edema", section on 'Prophylactic medications' and "Acute mountain sickness and high-altitude cerebral edema", section on 'Pharmacologic prevention of AMS/HACE'.)

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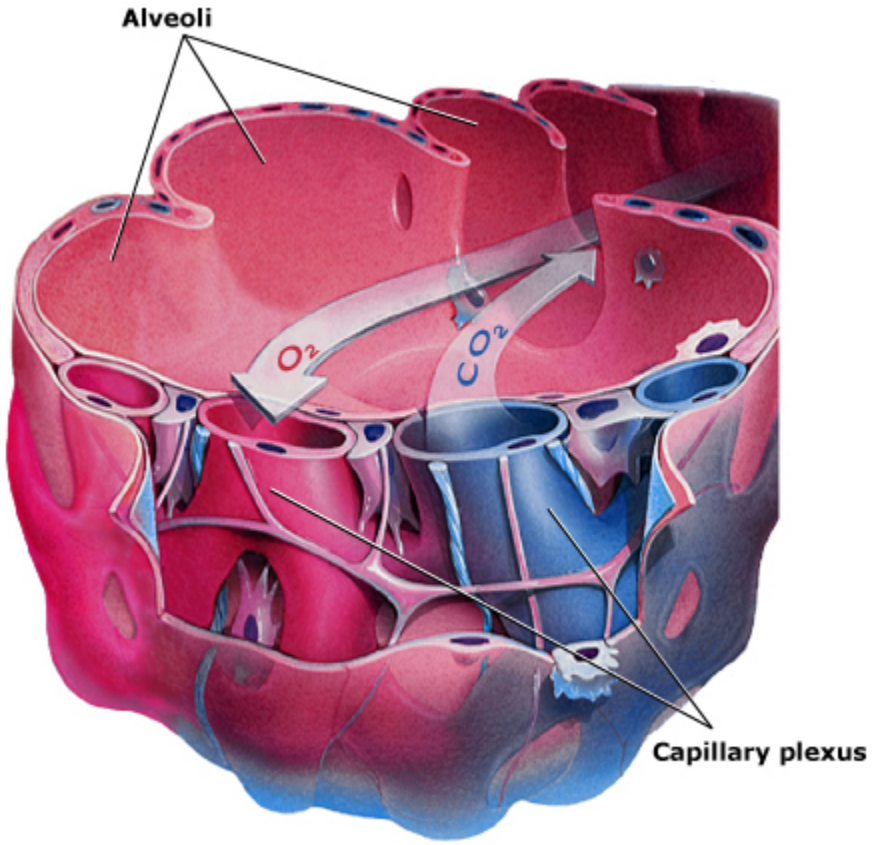
Topic 181 Version 30.0

## GRAPHICS

### How air is exchanged in the lungs




This figure depicts how oxygen ($O_2$) and carbon dioxide ($CO_2$) pass between the alveloi (inside the lung) and the capillaries (the blood stream).

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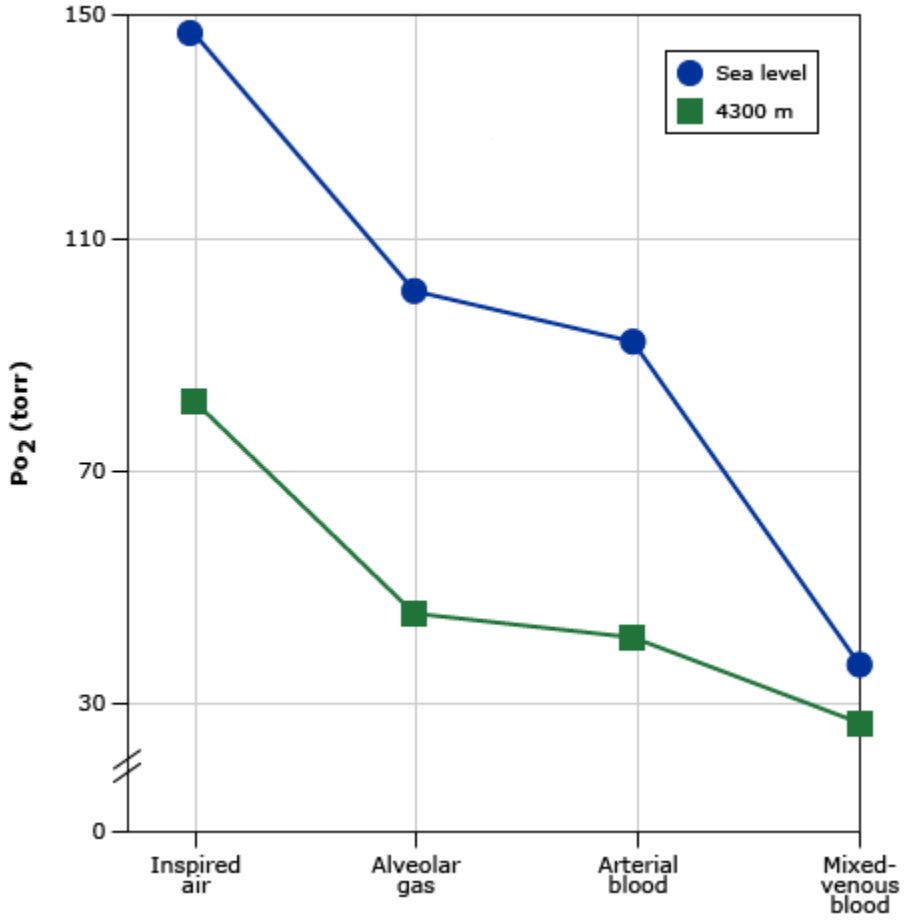
Graphic 58392 Version 2.0

## Oxygen cascade at sea level and 4300 meters

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Graphic 97579 Version 4.0

## Acute effect of altitude on oxygen saturation and arterial blood gas values

| Population | Altitude (meters) | Altitude (feet) | $P_B$ (mm Hg) | $PaO_2$ (mm Hg) | $SaO_2$ (%) | $PaCO_2$ (mm Hg) |
|---|---|---|---|---|---|---|
| Altitude residents | 1646 | 5400 | 630 | 73 (65-83) | 95.1 (93-97) | 35.6 (30.7-41.8) |
| Acute exposure | 2810 | 9219 | 543 | 60 (47.4-73.6) | 91 (86.6-95.2) | 33.9 (31.3-36.5) |
| | 3660 | 12,008 | 489 | 47.6 (42.2-53) | 84.5 (80.5-89) | 29.5 (23.5-34.3) |
| | 4700 | 15,420 | 429 | 44.6 (36.5-47.5) | 78 (70.8-85) | 27.1 (22.9-34) |
| | 5340 | 17,520 | 401 | 43.1 (37.6-50.4) | 76.2 (65.4-81.6) | 25.7 (21.7-29.7) |
| | 6140 | 20,144 | 356 | 35 (26.9-40.1) | 65.6 (55.5-73) | 22 (19.2-24.8) |
| Subacute exposure | 6500 | 21,325 | 346 | 41.1 ± 3.3 | 75.2 ± 6 | 20 ± 2.8 |
| | 7000 | 22,966 | 324 | – | – | – |
| | 8000 | 26,247 | 284 | 36.6 ± 2.2 | 67.8 ± 5 | 12.5 ± 1.1 |
| | 8400 | 27,559 | 272 | 24.6 ± 5.3 | 54 | 13.3 |
| | 8848 | 29,029 | 253 | 30.3 ± 2.1 | 58 ± 4.5 | 11.2 ± 1.7 |
| | 8848 | 29,029 | 253 | 30.6 ± 1.4 | – | 11.9 ± 1.4 |

$P_B$: barometric pressure; $PaCO_2$: arterial partial pressure of carbon dioxide; $PaO_2$: arterial partial pressure of oxygen; $SaO_2$: arterial oxygen saturation.

* Data are mean values and (range) and were obtained in subjects 20 to 40 years of age during the first one to two days of arriving at altitude (acute exposure) and associated with good acclimatization (subacute exposure).

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*Data from:*

1. *Loeppky JA, Caprihan A, Luft UC. VA/Q inequality during clinical hypoxemia and its alterations. In: Shiraki K, Yousef, MK (Eds). Man in Stressful Environments, CC Thomas, Springfield, Il, 1987, p. 199.*
2. *McFarland RA, Dill DB. A comparative study of the effects of reduced oxygen pressure on man during acclimatization. J Aviat Med 1938; 9:18.*

*Reproduced from: Hackett PH, Roach RC. High-altitude medicine and physiology. In: Auerbach PS (Ed). Wilderness Medicine, 6th edition, Elsevier Mosby, Philadelphia, 2012. Table used with the permission of Elsevier Inc. All rights reserved.*

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Graphic 98575 Version 3.0

## Physiologic effects of high altitude

| **High altitude: 1500 to 3500 m (4921-11,483 ft)** |
|---|
| High-altitude illness common with abrupt ascent to above 2500 m (8202 ft) |
| Decreased exercise performance and increased ventilation |
| Minor impairment in $SpO_2$, usually at least 90 percent; $PaO_2$ significantly diminished 55 to 75 mmHg |
| **Very high altitude: 3500 to 5500 m (11,483-18,045 ft)** |
| Most common range for severe high-altitude illness |
| Abrupt ascent may be dangerous; requires a period of acclimatization |
| $SpO_2$ 75 to 85 percent; $PaO_2$ 40 to 60 mmHg |
| Extreme hypoxia may occur during sleep, exercise and high-altitude illness |
| **Extreme altitude: 5500 to 8850 m (18,045-29,035 ft)** |
| Progressive deterioration of physiologic function eventually outstrips acclimatization |
| Above the highest permanent human habitation |
| Abrupt ascent almost always precipitates severe high-altitude illness |
| A period of acclimatization necessary to ascend to extreme altitude |
| Severe hypoxia and hypocapnia; $SpO_2$ 58 to 75 percent, $PaO_2$ 28 to 40 mmHg |

$SaO_2$: arterial oxygen saturation; $PaO_2$: arterial $PO_2$; $PO_2$: partial pressure of oxygen.

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*Data from: Hackett, PH, Roach, RC. High-Altitude Medicine. In: Wilderness Medicine, 5th ed, Auerbach, PS (Ed), Mosby, Philadelphia 2007.*

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Graphic 63999 Version 3.0

## Elevations for high altitude cities, peaks, and resorts

| Location | Altitude |
|---|---|
| **Cities** | |
| **The 10 highest cities in the world** | |
| 1. Lhasa, Tibet, China | 12,002 ft/3658 m |
| 2. La Paz, Bolivia | 11,910 ft/3630 m |
| 3. Cuzco, Peru | 11,152 ft/3399 m |
| 4. Sucre, Bolivia | 9331 ft/2844 m |
| 5. Quito, Ecuador | 9249 ft/2819 m |
| 6. Toluca, Mexico | 8793 ft/2680 m |
| 7. Bogotá, Colombia | 8675 ft/2644 m |
| 8. Cochabamba, Bolivia | 8390 ft/2557 m |
| 9. Addis Ababa, Ethiopia | 7900 ft/2408 m |
| 10. Asmara, Eritrea | 7789 ft/2374 m |
| **Some large cities at high altitude** | |
| Mexico City | 7350 ft/2240 m |
| Johannesburg | 5740 ft/1750 m |
| Nairobi | 5446 ft/1660 m |
| Denver | 5280 ft/1610 m |
| Guatemala City | 5020 ft/1530 m |
| **Some ski resorts at high altitude (lodging >8000 ft/2400 m)*** | |
| **Asia** | |
| Lijiang, Yunnan, China | 14,816 ft/4516 m |
| Gulmarg, Kashmir, India | 8500 ft/2600 m |
| Other resorts in Yunnan and Sichuan, China; Iran; Kyrgyzstan | |
| **North America** | |
| Breckenridge, Colorado | 9600 ft/2926 m |

| | |
|---|---|
| Crested Butte, Colorado | 9375 ft/2858 m |
| Telluride, Colorado | 8750 ft/2668 m |
| Vail, Colorado | 8120 ft/ 2476 m |
| Aspen, Colorado | 8000 ft/2439 m |
| **South America** | |
| Valle Nevado, Chile | 9383 ft/2860 m |
| Portillo, Chile | 8360 ft/2548 m |
| **Europe and Japan** | |
| None | |
| **Peaks** | |
| **The Seven Summits** | |
| Mount Everest, Asia | 29,035 ft/8850 m |
| Aconcagua, South America | 22,841 ft/6962 m |
| Denali, North America | 20,320 ft/6194 m |
| Mount Kilimanjaro, Africa | 19,563 ft/5963 m |
| Mount Elbrus, Europe | 18,510 ft/5642 m |
| Vinson Massif, Antarctica | 16,066 ft/4897 m |
| Puncak Jaya, Australia/Oceania | 16,023 ft/4884 m |
| **8000 m peaks** | |
| Mount Everest, Nepal | 29,035 ft/8850 m |
| K2, Pakistan | 28,253 ft/8612 m |
| Kangchenjunga, Nepal | 28,169 ft/8586 m |
| Lhotse, Nepal | 27,940 ft/8516 m |
| Makalu, Nepal | 27,765 ft/8462 m |
| Cho Oyu, Nepal | 26,906 ft/8201 m |
| Dhaulagiri, Nepal | 26,794 ft/8167 m |
| Manaslu, Nepal | 26,758 ft/8156 m |
| Nanga Parbat, Pakistan | 26,658 ft/8125 m |
| Annapurna, Nepal | 26,545 ft/8091 m |
| Gasherbrum, Pakistan | 26,470 ft/8068 m |
| Broad Peak, Pakistan | 26,400 ft/8047 m |

| | |
|---|---|
| Gasherbrum II, Pakistan | 26,360 ft/8035 m |
| Shisha Pangma, Tibet | 26,289 ft/8013 m |

ft: feet; m: meters.

* Elevations given are for lodging locations, not for ski trails or summits.

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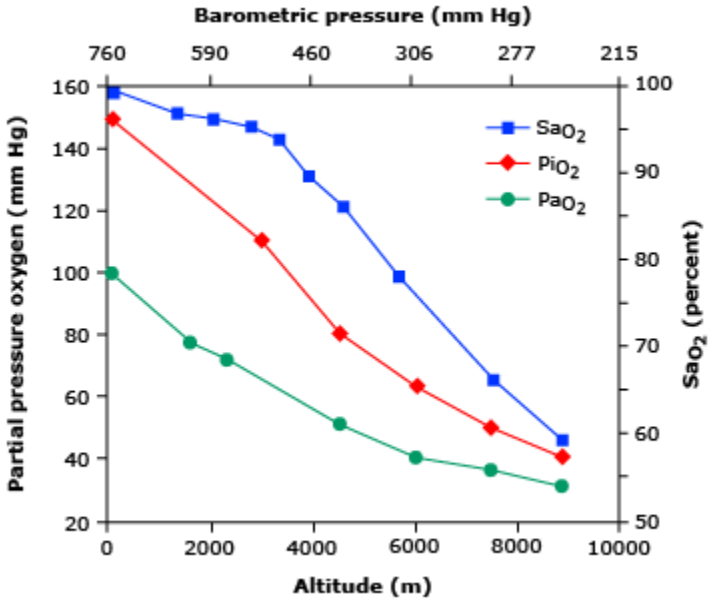
Graphic 50199 Version 6.0

## Oxygenation at different altitudes




Increasing altitude results in a decrease in inspired oxygen ($PiO_2$), arterial oxygen$_2$ ($PaO_2$), and arterial oxygen saturation ($SaO_2$). Note that the difference between $PiO_2$ and $PaO_2$ narrows at high altitudes because of increased ventilation, and that $SaO_2$ is well maintained while awake until over 3000 meters.

---

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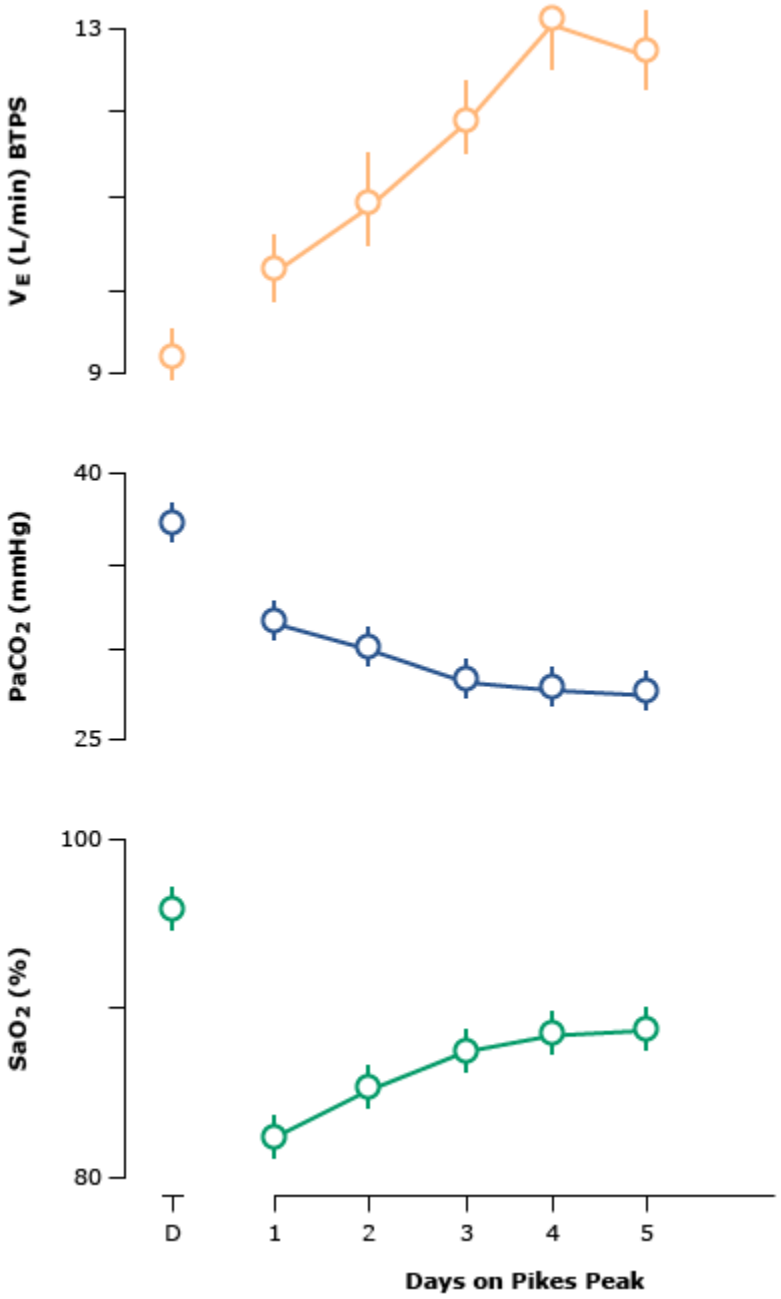
Graphic 56808 Version 2.0

## Ventilatory acclimatization at altitude




The graphs above show the changes that occur in minute ventilation, end-tidal carbon dioxide, and oxygen saturation as climbers adapt to high altitude; in this case, 4300 meters at Pikes Peak.

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$SaO_2$: arterial oxygen saturation; $V_E$: minute ventilation; BTPS: body temperature pressure saturated; $PaCO_2$: partial pressure of carbon dioxide; D: day.

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*Adapted with permission from: Huang SY, Alexander JK, Grover RF, et al. Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. J Appl Physiol Respir Environ Exerc Physiol 1984; 56:602. Copyright © 1984 The American Physiological Society. All rights reserved.*

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Graphic 122647 Version 4.0

## Medical conditions caused or exacerbated by high altitude

| |
|---|
| **High-altitude illness** |
| Acute mountain sickness/High-altitude cerebral edema (AMS/HACE) |
| High-altitude pulmonary edema (HAPE) |
| **Altitude-related illness (partial list)** |
| **Acute** |
| High-altitude headache |
| High-altitude pharyngitis and bronchitis |
| High-altitude syncope |
| Acute hypoxia |
| Organic brain syndrome |
| Peripheral edema |
| Sleep periodic breathing (central sleep apnea) |
| Ultraviolet keratitis (snow blindness) |
| High-altitude retinopathy |
| Hypothermia and frostbite |
| High-altitude deterioration |
| Reentry pulmonary edema |
| **Chronic** |
| Chronic mountain sickness (Monge's disease, chronic mountain polycythemia) |
| High-altitude pulmonary hypertension, with or without right heart failure |
| Reentry pulmonary edema |
| Problems of pregnancy: preeclampsia, hypertension, and low-birth-weight infants |
| **Problems potentially exacerbated by high altitude (partial list)** |
| Various congenital and valvular heart diseases |
| Hypertension |
| Primary and secondary pulmonary hypertension |
| Symptomatic coronary artery disease |
| Poorly compensated heart failure |
| Chronic obstructive pulmonary disease |

| |
|---|
| Sickle cell disease and trait |
| Sleep disordered breathing (including central sleep apnea) |
| Urinary retention from BPH |
| High-risk pregnancy |
| Radial keratotomy |

ADHF: Acute decompensated heart failure; BPH: Benign prostatic hyperplasia; COPD: Chronic obstructive pulmonary disease

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Graphic 75758 Version 4.0

## Risk for high altitude illness

| Risk of HAI | Description |
|---|---|
| Low | No prior history of altitude illness and planning ascent to <2800 m |
| | Taking two days or more to arrive at 2500 to 3000 m from low altitude |
| | Ascending no more than 500 m/day (sleeping altitude) once over 2500 m **and** taking one extra day to acclimatize for every additional 1000 m of ascent |
| Moderate | Prior history of AMS and ascending to 2500 to 2800 m in less than two days |
| | No history of AMS and ascending to 2800 m or higher in less than two days |
| | Ascending >500 m/day (increase in sleeping elevation) at altitudes above 3000 m **with** one extra day for acclimatization for every additional 1000 m of ascent |
| High | History of severe altitude illness (HACE, HAPE) |
| | History of AMS and ascending to 2800 m or higher in less than two days |
| | Ascending over 3500 m in less than two days |
| | Ascending >500 m/day (increase in sleeping elevation) above 3000 m without extra days for acclimatization; rapid guided ascents (eg, Mt. Kilimanjaro in <7 days) |
| | Persons with medical conditions predisposing to altitude illness |

Notes:

Altitudes listed refer to the altitude at which the person sleeps.

Ascent is assumed to begin at low altitude (<1200m).

Risk categories are for unacclimatized persons.

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AMS: acute mountain sickness; HACE: high altitude cerebral edema; HAPE: high altitude pulmonary edema; m: meters.

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*Adapted from: Luks AM, McIntosh SE, Grissom CK, et al. Wilderness Medical Society practice guidelines for the prevention and treatment of acute altitude illness: 2014 Update. Wilderness Environ Med 25, S4–S14 (2014).*

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Graphic 65647 Version 6.0

## Pharmacologic treatment and prevention of high altitude illness (HAI)

| Condition | | Preferred agent | Alternatives |
|---|---|---|---|
| **AMS/HACE** | Prevention* | **Acetazolamide:** 125 mg orally every 12 hours<br>Children: 2.5 mg/kg (maximum single dose: 125 mg) orally every 12 hours[¥]<br>Duration: Start day before ascent and continue 2 to 3 days at maximum altitude; may use once at night thereafter to improve sleep | **Dexamethasone:** 2 mg orally every 6 hours or 4 mg orally every 12 hours<br>Children: Acetazolamide preferred; do not use for prophylaxis<br>Duration: Start day of ascent and continue 2 to 3 days at maximum altitude but for no more than 7 days total |
| | Treatment of mild AMS[¶] | **Acetazolamide:** 125 to 250 mg orally every 12 hours<br>Children: 2.5 mg/kg (maximum single dose: 250 mg) orally every 12 hours[¥]<br>Duration: Continue for 24 hours after symptoms resolve or descent completed | **Dexamethasone:** 2 to 4 mg orally every 6 hours<br>Children: 0.15 mg/kg (maximum single dose: 4 mg) orally every 6 hours<br>Duration: Continue until 24 hours after symptoms resolve or descent completed but for no more than 7 days total |
| | Treatment of moderate to severe AMS | **Dexamethasone:**[Δ] 4 mg orally every 6 hours<br>Children: 0.15 mg/kg (maximum single dose: 4 mg) orally every 6 hours<br>Duration: Continue for 24 hours after symptoms resolve or descent completed but for no more than 7 days total | **Acetazolamide:** 125 to 250 mg orally every 12 hours<br>Children: 2.5 mg/kg (maximum single dose: 250 mg) orally every 12 hours[¥]<br>Duration: Continue for 24 hours after symptoms resolve or descent completed |

| | | | |
|---|---|---|---|
| | Treatment of HACE | **Dexamethasone:**[Δ] 8 to 10 mg orally /IM/IV once, then 4 mg orally/IM/IV every 6 hours<br>Children: 0.15 mg/kg (maximum single dose: 4 mg) every 6 hours<br>Duration: Continue until 24 hours after symptoms resolve or descent completed but for no more than 7 days total | **Acetazolamide:** 250 mg orally every 12 hours; may use as adjunct with dexamethasone; **not** for monotherapy<br>Children: 2.5 mg/kg (maximum single dose: 250 mg) orally every 12 hours[¥]<br>Duration: Continue until 24 hours after symptoms resolve or descent completed |
| **HAPE** | Prevention* | **Nifedipine:** 60 mg extended-release orally divided daily (30 mg orally every 12 hrs; or 20 mg orally every 8 hours)[◇]<br>Children: 0.5 mg/kg (maximum single dose: 20 mg) extended-release orally every 8 hours[◇]<br>Duration: Start day before ascent and continue for 5 days at maximum altitude | Further research is needed before the medications listed below can be recommended for routine use in HAPE prevention:<br>**Tadalafil:** 10 mg orally every 12 hours; start day of ascent and continue 3 to 5 days at maximum altitude<br>**Sildenafil:** 50 mg orally every 8 hours; start day of ascent and continue 3 to 5 days at maximum altitude<br>**Dexamethasone:** 8 mg orally every 12 hours; start day of ascent and continue 48 to 72 hours at maximum altitude<br>**Acetazolamide:** 125 to 250 mg orally every 12 hours; start day before ascent and continue 48 to 72 hours at maximum altitude |
| | Treatment[§] | **Nifedipine:** 60 mg extended-release orally divided daily (30 mg orally every 12 hours or 20 mg orally every 8 hours)[◇]<br>Children: 0.5 mg/kg (maximum single dose: 20 mg) extended-release orally every 8 hours[◇]<br>Duration: Continue until descent completed, symptoms resolved, and $SpO_2$ normal for altitude | Further research is needed before the medications listed below can be recommended for routine use in HAPE treatment:<br>**Tadalafil:** 10 mg orally every 12 hours<br>**Sildenafil:** 50 mg orally every 8 hours<br>Duration: Continue until descent completed, symptoms resolved, |

| | | | |
|---|---|---|---|
| | | | and $SpO_2$ normal for altitude |

AMS: acute mountain sickness; HACE: high altitude cerebral edema; HAPE: high altitude pulmonary edema; IM: intramuscular; NSAID: nonsteroidal antiinflammatory drug; HAI: high-altitude illness; $SpO_2$: oxygen saturation.

* Gradual ascent is the best strategy for prevention of HAI. Early recognition of symptoms and prompt treatment are critical to reduce risk of progression to serious HAI (such as HAPE and HACE). Reserve pharmacologic prophylaxis for patients who have a history of HAPE or recurrent AMS and patients at high risk (as well as selected patients at moderate risk) of developing AMS/HACE according to criteria listed in the separate UpToDate content. Provision of these medications for "rescue" treatment is also reasonable.

¶ May not require pharmacologic treatment. Rest, halt ascent, and symptomatic treatment (eg, acetaminophen or NSAID for headache and ondansetron for nausea/vomiting) may be sufficient. Refer to accompanying UpToDate text.

Δ Treatment with dexamethasone alleviates symptoms of AMS/HACE but does not improve acclimatization. Dexamethasone is not a substitute for immediate descent in HACE.

◇ In United States the lowest strength extended-release nifedipine oral preparation available is 30 mg. In some other countries, 10 and 20 mg extended-release preparations are available.

§ May not require any pharmacologic intervention. In proper setting, rest and supplemental oxygen may be sufficient. Refer to accompanying UpToDate text.

¥ For immediate administration in children, a liquid acetazolamide solution can be made by crushing a 125 mg or 250 mg tablet and suspending it in cherry, chocolate, or other flavored syrup to hide the bitter taste. A flavored oral suspension useful in patients who cannot swallow pills or for measurement of doses used in smaller children (eg <125 mg) can also be compounded by a pharmacy. Detail is available in the acetazolamide pediatric drug monograph.

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*Courtesy of Scott Gallagher, MD and Peter Hackett, MD, with additional data from:*

1. *Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society Consensus Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med 2019; 30:S3.*
2. *Pollard A, Niermeyer S, Barry P, et al. Children at high altitude: an international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, March 12, 2001. High Alt Med Biol 2001; 2:389.*

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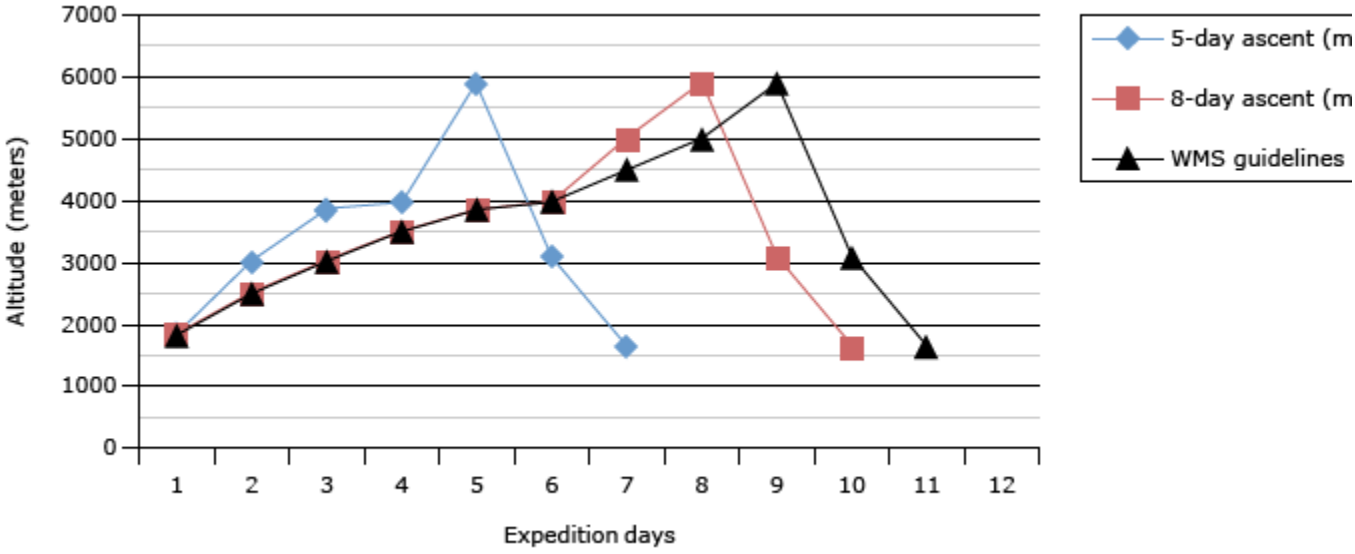
Graphic 76719 Version 15.0

# Ascent profile graph to identify and mitigate risk of high altitude illness




Comparison of different ascent profiles on a Kilimanjaro, Tanzania, showing a high-risk 5-day ascent vers moderate-risk 8-day ascent versus a low-risk schedule that follows the WMS Altitude Guidelines.

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*Reproduced from: Campbell AD, McIntosh SE, Nyberg A, et al. Risk stratification for athletes and adventurers in high-altitude envi Recommendations for preparticipation evaluation wilderness. Wilderness & Environ Med 2015; 26:S30. Illustration used with the of Elsevier Inc. All rights reserved.*

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Graphic 115963 Version 1.0

## Contributor Disclosures

**Scott A Gallagher, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Peter Hackett, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Jonathan M Rosen, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Daniel F Danzl, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Michael Ganetsky, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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