Wolters Kluwer

High-altitude pulmonary edema

Authors: Scott A Gallagher, MD, Peter Hackett, MD
Section Editor: Daniel F Danzl, MD
Deputy Editor: Michael Ganetsky, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2023. | **This topic last updated:** Oct 04, 2022.

Please read the Disclaimer at the end of this page.

INTRODUCTION

Anyone who travels to high altitude, whether a recreational hiker, skier, mountain climber, soldier, or worker, is at risk of developing high-altitude illness. High-altitude pulmonary edema (HAPE) is a life-threatening non-cardiogenic pulmonary edema and the most common fatal manifestation of severe high-altitude illness [1].

The pathophysiology, clinical presentation, treatment, and prevention of HAPE are reviewed here. Other forms of high-altitude illness are discussed separately. (See "Acute mountain sickness and high-altitude cerebral edema" and "High-altitude illness: Physiology, risk factors, and general prevention" and "High-altitude disease: Unique pediatric considerations".)

PATHOPHYSIOLOGY

HAPE is the abnormal accumulation of plasma and some red blood cells in the lung air sacs due to a breakdown in the pulmonary blood-gas barrier, triggered by hypobaric hypoxia. This breakdown develops from a number of maladaptive responses to the hypoxia encountered at higher altitudes, including poor ventilatory response, increased sympathetic tone, exaggerated and uneven pulmonary vasoconstriction (pulmonary hypertension), inadequate production of endothelial nitric oxide, overproduction of endothelin, and inadequate alveolar

fluid clearance, many of which are genetically determined [2,3]. The end result is a patchy accumulation of extravascular fluid in the alveolar spaces that impairs gas exchange and can, in severe cases, prove fatal.

Genetics clearly play an important role in the risk of HAPE, as suggested by the marked variability in individual susceptibility, the higher rates of recurrence among some individuals, familial groupings, and the pathophysiologic factors mentioned above. However, HAPE genetic studies are conflicting, and clear conclusions are elusive. Genes associated with HAPE have included those in the pathways for nitric oxide, renin-angiotensin-aldosterone, hypoxia-inducible factor (HIF), heat shock protein (HSP 70), pulmonary surfactant proteins A1 and A2, aquaporin-5, and the BMPR2 gene that is associated with pulmonary arterial hypertension [2,4,5].

High mean pulmonary artery pressure, in excess of 35 to 40 mmHg, appears to be the initiating event. However, while elevated pulmonary artery pressure is essential for HAPE, this by itself is insufficient. The other essential factor is uneven vasoconstriction. Specific segmental and subsegmental capillary beds with relatively less vasoconstriction are disproportionately exposed to elevated microvascular pressures (>20 mmHg) that arise from the elevated mean pulmonary artery pressure. This uneven vasoconstriction and regional overperfusion result in failure of the alveolar-capillary barrier and patchy pulmonary edema [6].

As disruption of the alveolar-capillary barrier progresses, high molecular weight proteins, cells, and fluid leak into the alveolar space. Eventually, basement endothelial and epithelial cell membranes are disrupted, leading to alveolar hemorrhage.

A striking feature of HAPE is the rapid reversibility of this process with descent or simply the administration of oxygen. Pulmonary vascular resistance and pulmonary artery pressure drop immediately and return to normal within days after treatment or descent to low altitude.

EPIDEMIOLOGY AND RISK FACTORS

HAPE is divided into two types:

- Classic HAPE, involving acute ascent of those normally residing at low altitude
- Re-entry HAPE, involving re-ascent of those normally residing at high altitude after a stay at low altitude

Another category has been suggested for children living at high altitude who develop pulmonary edema with respiratory infection but without a change in altitude [7].

HAPE generally occurs above 2500 meters (8000 feet) and is uncommon below 3000 meters (10,000 feet) (table 1 and table 2) [8,9]. The risk depends upon individual susceptibility, altitude attained, rate of ascent, and time spent at high altitude. In those without a history of HAPE, the incidence is 0.2 percent with ascent to 4500 meters (14,800 feet) over four days but 6 percent when ascent occurs over one to two days. In those with a history of HAPE, recurrence is 60 percent with an ascent to 4500 meters over two days. At 5500 meters (18,000 feet), the incidence ranges between 2 and 15 percent, again depending upon rate of ascent.

Symptoms of acute mountain sickness develop in a high percentage of those with HAPE [10,11]. HAPE and high-altitude cerebral edema (HACE) may also occur concomitantly due to the severe hypoxemia of HAPE. (See "Acute mountain sickness and high-altitude cerebral edema".)

Factors associated with an increased incidence of HAPE include male sex, cold ambient temperatures, pre-existing respiratory infection, and vigorous exertion [10]. Pre-existing conditions or anatomic abnormalities that lead to increased pulmonary blood flow, pulmonary hypertension, or increased pulmonary vascular reactivity may predispose to HAPE, even at altitudes below 2500 meters. These include pulmonary hypertension of any etiology, congenital absence of one pulmonary artery, and intracardiac shunts, such as atrial septal defects and ventricular septal defects.

A patent foramen ovale (PFO), in the setting of rising pulmonary vascular resistance during hypoxic pulmonary vasoconstriction, may reverse the direction of blood flow, shunting blood from right to left and further exacerbating hypoxemia. PFO is four times more common among HAPE-susceptible individuals. Larger PFOs correlate directly with increased arterial hypoxemia and a trend toward an increased risk of developing HAPE. However, PFO does not cause a greater rise in pulmonary artery pressure [12]. Whether PFO contributes to HAPE or is merely a marker of increased vascular reactivity and susceptibility remains unknown. There is currently no indication for closing PFO in susceptible persons in hopes of preventing HAPE.

CLINICAL PRESENTATION

Presentation in adults

Symptoms and signs — HAPE generally begins with a subtle, nonproductive cough, and shortness of breath with exertion, often when walking uphill [9,13]. Such nonspecific symptoms are easily mistaken for a benign upper respiratory tract infection or attributed to normal breathlessness at high altitude or exhaustion. Initial symptoms typically appear two to four days after arrival at a new altitude. Occasionally, HAPE develops precipitously. This occurs more often at night or after severe exertion. HAPE almost never develops after a week at the same altitude.

As HAPE progresses, dyspnea becomes noticeable at rest and severe with any attempt at exertion. Even walking on a level surface becomes an effort. A cardinal clinical feature of HAPE is the early progression from dyspnea with exertion to dyspnea at rest. In about 50 percent of cases, HAPE is accompanied by acute mountain sickness [10]. (See "Acute mountain sickness and high-altitude cerebral edema".)

As symptoms progress, the cough can become productive of pink, frothy sputum and may produce frank blood. Severely restricted exercise tolerance becomes debilitating, and severe hypoxemia may become life threatening without prompt descent or supplemental oxygen. Severe hypoxemia may cause drowsiness or concomitant high-altitude cerebral edema (HACE).

On physical examination, tachycardia, tachypnea, and low-grade fever (up to 38°C) are common. Inspiratory crackles may be more prominent in the right middle lobe initially but become bilateral and diffuse as HAPE progresses. Auscultation of the right middle lobe is best performed at the mid-lateral chest wall. Persons with blunted carotid body function, genetic or acquired (eg, carotid endarterectomy, neck radiation), may present without respiratory symptoms and instead with drowsiness, confusion, and other central nervous system symptoms and findings that might more commonly be associated with HACE.

Oxygen saturation — Pulse oximetry reveals saturation values (SpO_2) at least 10 points lower than expected for the altitude, and absolute values may be as low as 40 to 50 percent. Typically, the patient appears better than expected given the severity of hypoxemia, and the oxygen saturation improves promptly (usually within 10 to 15 minutes) in response to supplemental oxygen. This rapid correction of the SpO_2 and clinical status with supplemental oxygen in the setting of a severe infiltrative lung process seen on radiograph are virtually pathognomonic for HAPE, as this does not occur with other pulmonary processes (eg, pneumonia, acute decompensated heart failure) capable of causing such severe hypoxemia and associated with diffuse crackles or rhonchi.

Thus, pulse oximetry is often a useful tool for distinguishing HAPE from other conditions. However, expected SpO_2 values vary with a number of factors, including the altitude, degree and rate of acclimatization, patient's hypoxic ventilatory drive, and method of measurement (eg, variation among pulse oximeters); and therefore should be interpreted carefully. SpO_2 is lowest on the first day at high altitude and rises over four days to a near-maximum value, usually 3 to 5 points higher than day one. Although expected values can vary widely in normal individuals at any given altitude, comparing SpO_2 measurements with others in the same travel group who arrived at high altitude together can help to establish a relative "normal" range. The following figures provide approximate average values for SpO_2 and other parameters at a range of altitudes (figure 1 and table 3).

Presentation in children — In children, HAPE typically presents as increasing respiratory distress over one to two days but may develop more precipitously. Young children may manifest only pallor or cyanosis and depressed consciousness, though most will have tachypnea, hypoxemia, and crackles [14]. In infants, increased pulmonary artery pressure and fetal shunting, without HAPE, can cause severe hypoxemia. (See 'Pathophysiology' above and "High-altitude disease: Unique pediatric considerations".)

HAPE alone does **not** cause an elevation in body temperature over 38.3°C (101°F), and young children with a higher temperature should be assessed for other causes of fever. Respiratory infection and HAPE can coexist. (See "Fever without a source in children 3 to 36 months of age: Evaluation and management".)

The differential diagnosis in children includes pneumonia, undetected intracardiac shunts, and (in infants) opening of fetal shunts in response to high-altitude pulmonary hypertension. Some authors suggest that children who develop HAPE should be evaluated for structural heart problems [14,15]. (See "Pathophysiology of left-to-right shunts" and "Isolated ventricular septal defects (VSDs) in infants and children: Anatomy, clinical features, and diagnosis" and "Isolated atrial septal defects (ASDs) in children: Classification, clinical features, and diagnosis" and "Community-acquired pneumonia in children: Clinical features and diagnosis", section on 'Clinical presentation'.)

IMAGING STUDIES

Plain radiograph, computed tomography, and echocardiography — As with acute mountain sickness and high-altitude cerebral edema (HACE), the diagnosis of HAPE is based upon the history and physical examination. However, chest radiography is useful and reveals

characteristic patchy alveolar infiltrates, predominantly in the right central hemithorax, which become more confluent and bilateral as the illness progresses (image 1). However, in some cases, the infiltrates may start in the left lung [16]. Rarely, the edema is entirely unilateral even when severe, which suggests a pulmonary artery agenesis or obstruction [17].

Although the radiographic appearance of HAPE may mimic that of infectious infiltrates, we often find a significant discrepancy between the extensive infiltrates on radiograph and the patient's clinical status. The patient with HAPE often does not appear as severely ill as one would expect based on the radiograph findings and steadily improves with oxygen therapy. In contrast, a patient with a comparable chest radiograph due to pneumonia typically appears critically ill and often requires tracheal intubation and mechanical ventilation.

Computed tomography (CT) of the chest, while rarely indicated, reveals a patchy lobular ground-glass appearance and consolidative opacities, reflecting heterogeneous alveolar filling (image 2). Echocardiography reveals increased pulmonary artery pressure and sometimes right heart dysfunction and paradoxical septal motion [1,2].

Ultrasound — Observational studies suggest that ultrasonography is a highly sensitive and semi-quantitative means of detecting increased extravascular lung water [18-20]. If traditional chest radiography is unavailable (eg, at a remote clinic or in the field), chest sonography is a practical and useful tool for identifying HAPE.

In the appropriate clinical setting, namely ascent to high altitude by an unacclimatized person who develops typical signs and symptoms and an abnormally low oxygen saturation (SpO_2), HAPE can be confirmed by the presence of ultrasound lung comets (ULCs) (image 3 and movie 1). ULCs are sonographic artifacts originating from water-thickened interlobular septa fanning out from the lung surface. They are caused by the air-fluid interface in the presence of increased extravascular lung water. ULCs may be referred to as B-lines or "comet tails" and are the sonographic equivalent of radiographic Kerley B-lines, which are described separately. (See "Evaluation of diffuse lung disease by conventional chest radiography", section on 'Linear'.)

While the quantity of ULCs corresponds closely to clinical and oximetry findings, it is not yet known what number of ULCs is an appropriate diagnostic threshold for HAPE, as opposed to subclinical pulmonary edema. Nevertheless, the technique for identifying ULCs is easily performed and may be useful in the proper clinical setting, such as when the cause of dyspnea is unclear despite a careful history and physical examination [21,22].

Drawbacks to using ultrasound to diagnose HAPE include a lack of specificity and questions about its utility. Ultrasound cannot differentiate HAPE from cardiogenic pulmonary edema and other causes of increased extravascular lung water. In addition, ultrasound findings may not be clinically relevant at high altitude, as clinically insignificant ULCs are commonly seen in recreational climbers who are asymptomatic and do not develop HAPE [22-24]. Finally, ultrasound findings may not add to what is already known from examination findings and oximetry.

LABORATORY TESTS

No laboratory test demonstrates adequate specificity to aid in the diagnosis of HAPE. In patients with HAPE, the white blood cell count may be modestly elevated. Brain natriuretic peptide (BNP) and related tests (eg, pro-BNP) may be slightly elevated at high altitudes, and troponin may be elevated in the setting of HAPE associated with right heart strain. However, such results are not helpful in distinguishing among potential diagnoses (eg, acute coronary syndrome, acute decompensated heart failure) and may not be elevated in the patient with HAPE. The results of other readily available tests are also nonspecific and unhelpful in diagnosing HAPE. (See "Heart failure: Clinical manifestations and diagnosis in adults", section on 'Natriuretic peptide'.)

DIAGNOSIS

HAPE is typically diagnosed clinically on the basis of the history and examination findings. The initial symptoms typically begin two to four days after arrival at high altitude and include a subtle nonproductive cough, shortness of breath on exertion, and difficulty walking uphill. Symptoms can develop more precipitously in children. Over one to two days, the cough often becomes productive. Early progression from dyspnea with exertion to dyspnea at rest is a cardinal feature. Prominent examination findings include tachycardia, tachypnea, low-grade fever (up to 38°C), and pulmonary crackles. Oxygen saturation is lower than expected for a given altitude. Treatment with supplemental oxygen and rest can lead to rapid improvement. Characteristic findings on imaging studies, when available and indicated, help to confirm the diagnosis.

DIFFERENTIAL DIAGNOSIS

Diagnoses confused with HAPE — Pneumonia heads the list of differential diagnoses that can be confused with HAPE, but others to consider include pulmonary embolism, acute decompensated heart failure, acute coronary syndrome, bronchitis, reactive airway disease, and exercise-associated hyponatremia [25,26]. Of note, HAPE and infection can coexist. (See "Clinical evaluation and diagnostic testing for community-acquired pneumonia in adults" and "Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism" and "Approach to diagnosis and evaluation of acute decompensated heart failure in adults" and "Diagnosis of acute myocardial infarction" and "Exercise-associated hyponatremia".)

Differentiating HAPE from such ailments as pneumonia or acute decompensated heart failure can be difficult, particularly in older patients with comorbid conditions. In such patients, HAPE is a diagnosis of exclusion, and alternative diagnoses should be worked up in standard fashion. HAPE is associated with marked weakness and often severe hypoxemia (oxygen saturation [SpO_2] of 50 to 75 percent; partial pressure of oxygen [PaO_2] of 25 to 40 mmHg). While ill appearing, such patients with HAPE generally look better than would be expected given their extreme hypoxemia and improve rapidly with supplemental oxygen therapy.

More commonly, the diagnosis of HAPE is entertained in otherwise healthy patients with a characteristic history and examination findings. Rapid response over one to two hours of oxygen therapy strongly suggests the diagnosis of HAPE in this setting. Rapid improvement with descent is another important clue to the diagnosis of HAPE.

There is **no** pathophysiologic or clinical relationship between HAPE and severe acute respiratory syndrome coronavirus 2, as has been suggested by some [27-29].

Distinguishing HAPE and pneumonia — The non-specific symptoms and signs associated with pneumonia, including cough, dyspnea, low-grade fever, pulmonary infiltrates, and hypoxemia; and laboratory abnormalities such as a modestly elevated white blood cell count are also common features of HAPE.

HAPE may be precipitated by or co-exist with pneumonia, and distinguishing between these diagnoses can be challenging. The presence of marked hypoxemia (common with HAPE), extensive infiltrates on chest radiograph, and modest elevations of the white blood cell count (10,000 to 15,000/microL) frequently influence clinicians treating HAPE to administer empiric antibiotics for the possibility of concomitant bacterial pneumonia. While the decision to treat HAPE with empiric antibiotics based on such concerns remains clinical and subjective, many

cases of pneumonia (when in fact present) in this setting are of viral etiology and do **not** warrant antibiotic administration.

There is little published, high-quality evidence that can help to distinguish reliably between isolated HAPE and HAPE with concomitant pneumonia, but a number of clinical findings can provide some insight. Purulent sputum (particularly if a properly performed gram stain is positive for bacteria), temperature >38°C (100.5°F), elevated white blood cell count (>15,000/microL with a left shift, ie, predominately bands), elevated procalcitonin (>0.25 mcg/L) or highly elevated C-reactive protein, positive polymerase chain reaction respiratory panel, and a history of respiratory tract infection in the two to three days preceding the development of HAPE are consistent with an infectious process, and the authors believe that treatment with empiric antibiotics is appropriate in this setting.

Conversely, in otherwise healthy patients with a characteristic history of HAPE and examination findings consistent with the diagnosis, antibiotics are typically not necessary. In such cases, a rapid response over several hours to oxygen therapy strongly suggests the diagnosis of HAPE. In contrast, symptoms and signs of pneumonia require several days before clinical improvement. Rapid improvement with descent to lower altitude is another important diagnostic clue suggesting the diagnosis of HAPE without pneumonia.

TREATMENT

General approach to treatment — Early recognition of HAPE and prompt intervention are critical to assuring a favorable outcome [30]. Unlike high-altitude cerebral edema (HACE), immediate descent is not mandatory in all treatment settings. Instead, treatment of HAPE varies depending upon a number of factors, including severity of illness, available treatments, setting, clinician experience, and patient preference. As examples, management of a resort skier at 2500 meters may consist solely of supplemental oxygen and rest, while management of a mountaineer camping in a remote location at 5500 meters and without access to supplemental oxygen requires immediate descent.

The key principle in successful treatment of HAPE, regardless of the setting or patient age, is prompt reduction of pulmonary artery pressure. Means to achieve this end include limiting physical exertion and cold exposure, providing supplemental oxygen via tank or concentrator, and, when indicated, evacuation to a lower altitude or simulating descent using hyperbaric therapy. Descent (simulated or actual), supplemental oxygen, or the two combined are effective and appear to be superior to any pharmacologic therapy.

Because of ethical considerations, no trials have been performed in patients with HAPE that directly compare treatment with oxygen and descent versus pharmacologic therapy alone. In the one uncontrolled study in which nifedipine alone was used for treatment, clinical outcomes were poor relative to those reported in studies where treatment consisted of oxygen and descent without medications [31]. Nevertheless, if supplemental oxygen is unavailable and descent difficult or impossible, medication could be lifesaving [2,30].

When oxygen and/or descent are employed, the addition of medication may not be necessary. In a trial with 113 HAPE patients, adding nifedipine to descent and oxygen provided no additional benefit [32]. In a trial performed with the Indian military, 153 HAPE patients showed no additional benefit from either dexamethasone or nifedipine given with oxygen compared with those treated with oxygen alone [33].

Nonpharmacologic interventions

Oxygen — Supplemental oxygen is first-line therapy for HAPE and should be provided in all treatment settings when available [34-37]. It can be lifesaving. Relieving hypoxemia is the most effective method of reducing pulmonary artery pressure, reversing capillary leak, and protecting the brain and other organs. Supplemental oxygen immediately increases partial pressure of oxygen (PaO_2) and reduces both the heart and respiratory rates.

Based on the authors' field experience, when supplies are limited, low-flow oxygen given for a longer duration is preferable to high flow and short duration. Supplemental oxygen combined with descent (or hyperbaric therapy) is the ideal treatment.

In the hospital setting, supplemental oxygen and rest are generally sufficient therapy [34,37]. A common regimen in North American hospitals near ski resorts (elevation approximately 2500 to 3000 meters) is to treat with high-flow supplemental oxygen by nasal cannula or face mask for several hours until the patient's oxygen requirement is ≤3 L/min, with the oxygen saturation (SpO_2) maintained at 90 percent or higher. If the patient is clinically improved and appropriate for outpatient therapy, they may be sent home with an oxygen concentrator to be used continuously and strict instructions to rest. The patient's condition and SpO_2 are rechecked daily until an ambulatory SpO_2, measured while the patient breathes room air, is ≥90 percent. The usual duration of oxygen therapy is two to three days. At this point, supplemental oxygen can be discontinued. The patient is advised to return to activity **gradually** over the following one to three days. Descent is not mandatory but is always an option in this setting.

Rest and warmth — Strenuous physical exertion and cold stress both elevate pulmonary

artery pressure and can exacerbate HAPE. Thus, limiting exertion and avoiding exposure to cold are fundamental aspects of treatment. A patient with HAPE, for example, should not carry a pack while descending. The role of bedrest is unclear. A study with 36 patients with mild to moderate re-entry HAPE at 3750 meters in Peru showed that while bedrest alone resulted in complete recovery, bedrest with oxygen was more effective [35]. Most subsequent studies have used the combination of bedrest and oxygen [32,33,36]. In the Colorado ski resorts, we generally do not recommend strict bedrest during oxygen therapy in the patient's domicile.

Descent — In remote high-altitude settings where supplemental oxygen is unavailable, descent should begin as soon as HAPE is suspected [2,30]. HAPE can progress rapidly, and the opportunity for evacuation may be lost if there is delay. At higher elevations (>4000 meters), descent is mandatory, in part because of the risk of developing HACE. Ideally, immediate evacuation is undertaken to a hospital below 3000 meters that is capable of providing high-flow oxygen.

Nevertheless, in practice, scores of HAPE patients are treated successfully in remote clinics or base camps with modest descent and rest, sometimes in combination with portable hyperbaric therapy, low-flow supplemental oxygen, and medication. Many remote clinics are located only 500 to 1000 meters below the elevation of HAPE onset. When HAPE is diagnosed early and treated in the manner described, many climbers go on to reascend slowly after three days or more of recovery [38]. Recurrence of HAPE in such circumstances has not been reported. Severe cases require evacuation to a medical facility at lower elevation.

Hyperbaric therapy — In remote settings, lightweight portable hyperbaric chambers may be lifesaving, particularly when supplemental oxygen is unavailable or in short supply [39]. These devices, although costly, are well-suited to mountaineering and trekking expeditions at high altitude, where compressed oxygen cylinders are too heavy and bulky to transport and are difficult to maintain.

In isolated mountain settings, hyperbaric therapy is commonly combined with pharmacotherapy and supplemental oxygen, if available. In the hospital setting, elevation is generally lower, and high-flow oxygen is readily available. Hyperbaric therapy is not practical or necessary in such hospitals or clinics. (See "Acute mountain sickness and high-altitude cerebral edema", section on 'AMS treatment' and "Acute mountain sickness and high-altitude cerebral edema", section on 'HACE treatment'.)

Positive airway pressure and other therapies — The use of a breathing mask providing

pressure on expiration (EPAP) has been shown to improve gas exchange in HAPE and may be useful as a temporizing measure [40]. A similar effect may be achievable by having the patient breathe through pursed lips.

Continuous positive airway pressure (CPAP) is used in some ski resort clinics with anecdotal success. Nevertheless, no controlled study has established that CPAP improves clinical outcome in patients with HAPE, and in published case reports, CPAP has only been used in combination with other therapies [41]. A CPAP helmet has been used in the field [42].

High-flow nasal canula for the management of HAPE has not been studied, although theoretically, this intervention would be useful for all forms of type 1 (hypoxemic) respiratory failure.

Pharmacologic interventions — A summary of medications used to treat HAPE is provided (table 4). More thorough discussions of these treatments are found below.

Nifedipine — In the field setting, oxygen and descent remain the most important treatments for HAPE. Nifedipine may be considered adjunctive therapy when oxygen is unavailable and descent is difficult or impossible, although little clinical evidence supports the practice. (See 'General approach to treatment' above.)

Nifedipine is a nonspecific calcium channel blocker that acts by reducing pulmonary vascular resistance and pulmonary artery pressure, as well as systemic resistance and blood pressure. It also slightly improves PaO_2.

Recommended doses vary, but a common regimen is to give 30 mg of a slow-release formulation every 12 hours. Nifedipine is well tolerated by most patients and is unlikely to cause significant hypotension in previously healthy persons. Clinicians should give or be prepared to give isotonic intravenous fluid (eg, normal saline) to any critically ill HAPE patient who may be intravascularly depleted and is receiving nifedipine.

One unblinded, uncontrolled study of six patients with HAPE found that nifedipine treatment led to clinical improvement. However, another observational study involving 133 patients with HAPE reported that nifedipine offered no advantage when used as an adjunct to oxygen and descent [32].

Tadalafil and sildenafil — Tadalafil and sildenafil are phosphodiesterase-5 (PDE-5) inhibitors that augment the pulmonary vasodilatory effects of nitric oxide by blocking the degradation of cyclic guanosine monophosphate (cGMP), the intracellular mediator of nitric oxide. Nitric oxide is a potent pulmonary vasodilator and reduces hypoxic pulmonary

vasoconstriction and pulmonary hypertension in HAPE [2]. Both tadalafil and sildenafil have been shown to be effective as prophylaxis for HAPE, but neither has been studied as treatment [43-45]. (See 'Prophylactic medications' below.)

Nevertheless, based upon their mechanism of action, both tadalafil and sildenafil may be effective adjunct treatments for established HAPE when neither oxygen nor descent is an available option. These drugs may have advantages over nifedipine because they lower pulmonary artery pressure with less risk of lowering systemic blood pressure. However, tadalafil caused a marked headache in 2 of 10 subjects in one small randomized trial, a well-known side effect of this class of medications [43]. The appropriate dose for treatment is unknown but might be similar to that used for prophylaxis (tadalafil 10 mg by mouth every 12 hours; sildenafil 50 mg by mouth every eight hours).

Dexamethasone — Although glucocorticoids may have a role in prophylaxis, they have not been studied as treatment for HAPE. Nonetheless, some experts have recommended their use based on the mechanism of action [46], while others disagree [47]. We reserve glucocorticoids for treatment of HACE or severe acute mountain sickness, which may co-exist with HAPE. (See 'Prophylactic medications' below.)

Beta agonist — Salmeterol may be useful in the treatment of HAPE as it enhances removal of alveolar fluid, but this use remains unstudied. (See 'Prophylactic medications' below.)

Ineffective or contraindicated therapies — Diuretic therapy, nitrates, and morphine are no longer recommended in the treatment of HAPE and could be harmful.

PREVENTION

Suggested approach to prophylaxis — Gradual ascent remains the primary method for preventing all forms of high-altitude illness, including HAPE. For those with a history of HAPE, we recommend an ascent rate of no more than 400 meters per day in sleeping altitude. For patients with no history of medical problems at high altitude or of pulmonary hypertension, the risk of HAPE is low, and routine pharmacologic prophylaxis is not warranted.

In individuals at high risk, particularly those with a history of HAPE, pharmacologic prophylaxis may be prudent, especially when time does not allow for adequate acclimatization. Nifedipine is the drug of choice for prophylaxis against HAPE. It should be started the day prior to ascent if possible and continued for five days at a fixed altitude, or continued with progressive altitude gain (up to seven days after reaching the destination

altitude in individuals who ascend faster than recommended) until the start of descent.

While the results of initial small studies are promising, further research is needed to determine whether dexamethasone or phosphodiesterase 5 (PDE-5) inhibitors such as tadalafil are effective prophylactic medications. Based upon mechanism and clinical experience, acetazolamide is a reasonable medication for HAPE prophylaxis, but formal studies are lacking. Salmeterol should be considered only an adjunct prophylactic medication to nifedipine in high-risk individuals with a clear history of recurrent HAPE.

Prophylactic medications — A summary of medications used for the prophylaxis and treatment of HAPE is provided (table 4). More thorough discussions of the drugs used for prophylaxis are found below.

Nifedipine — Nifedipine is the preferred drug for the prevention of HAPE but is used only in high-risk individuals and only when acclimatization is not possible. Ideally, treatment is started 24 hours prior to ascent and continued for five days at the destination altitude. In higher-risk scenarios, treatment may be continued for up to seven days at the destination altitude or until the start of descent. We give 30 mg of the extended-release formulation every 12 hours.

In a small randomized trial, 20 mg of a slow-release formulation taken by mouth every eight hours while the participants performed a steep ascent prevented HAPE in 9 of 10 subjects with a history of repeated episodes documented by chest radiograph [48]. Seven of the 11 subjects given placebo developed radiographically proven HAPE. Note that 20 mg extended-release formulations are not available in the United States.

Dexamethasone — Further study is needed to determine whether dexamethasone is an appropriate medication for prophylaxis against HAPE. In one randomized trial of 29 individuals with a history of HAPE, none of the 10 participants given dexamethasone prophylaxis (8 mg every 12 hours) developed HAPE during a rapid ascent from 490 to 4559 meters with an overnight stay [43]. Prophylaxis with dexamethasone has the added advantage of preventing acute mountain sickness/high-altitude cerebral edema (HACE), whereas nifedipine and the PDE-5 inhibitors have no such effect.

Dexamethasone's mechanism of action remains unclear. It may involve upregulation of nitric oxide production and upregulation of alveolar epithelial membrane sodium channels and sodium-potassium ATPase.

Tadalafil and sildenafil — In small studies, the PDE-5 inhibitors sildenafil and tadalafil

prevented hypoxic pulmonary hypertension and the development of HAPE [49-51]. Optimal doses have not been established. Regimens for sildenafil have varied from a single dose of 50 or 100 mg just prior to exposure for acute ascent, to 40 mg three times per day for individuals who spend two to six days at high altitude; we give 50 mg every eight hours. For tadalafil, 10 mg every 12 hours is the usual dose. These drugs are potentially safer than nifedipine because there is less risk of hypotension, but they are more expensive and carry the risk of severe headaches. Sildenafil has shorter dosing intervals because its half-life is four to five hours; tadalafil's half-life is 17 hours. These drugs can be started the day of ascent and continued for three to five days after reaching maximal altitude; they can be extended for up to seven days or until start of descent in individuals who ascend faster than recommended.

Beta agonist — Salmeterol prevented HAPE in 50 percent of subjects in one small study and thus appears less effective than other agents [52]. However, it is safe and can be used in combination with acetazolamide or other medications. Salmeterol was chosen for prophylactic studies because of its relatively longer duration of action. Albuterol is less expensive and may be effective prophylaxis, but this has not been studied.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Management of environmental emergencies".)

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 5th to 6th 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

- **Epidemiology and risk factors** – High-altitude pulmonary edema (HAPE) generally occurs above 2500 meters (8000 feet). The incidence depends upon individual susceptibility, altitude attained, rate of ascent, and time spent at high altitude. Symptoms of acute mountain sickness develop in approximately 50 percent of those with HAPE. High-altitude cerebral edema (HACE) may occur concomitantly. (See 'Pathophysiology' above and 'Epidemiology and risk factors' above and "Acute mountain sickness and high-altitude cerebral edema".)

  Pre-existing conditions or anatomic abnormalities that lead to increased pulmonary blood flow, pulmonary hypertension, or increased pulmonary vascular reactivity may predispose to HAPE, even at altitudes below 2500 meters. Such conditions include pulmonary hypertension of any etiology and intracardiac shunts, such as atrial septal defects and ventricular septal defects. Additional risk factors are described in the text. (See 'Epidemiology and risk factors' above.)

- **Clinical presentation in adults** – HAPE generally begins with a subtle, nonproductive cough, shortness of breath with exercise, and difficulty walking uphill. Symptoms typically appear two to four days after arrival at higher altitude. As HAPE progresses, dyspnea becomes noticeable at rest and severe with any attempt at exertion. Tachycardia, tachypnea, and low-grade fever are common. A cardinal clinical feature of HAPE is the progression from dyspnea with exertion to dyspnea at rest over a relatively brief period. Oxygen saturation values are at least 10 points below normal for altitude and usually range from 50 to 75 percent. (See 'Clinical presentation' above.)

- **Clinical presentation in children** – In children, HAPE presents as increasing respiratory distress over one to two days but may develop more precipitously. Young children may manifest only pallor and depressed consciousness or other nonspecific symptoms. It

can be difficult to differentiate between HAPE and viral respiratory infection, and the two may coexist. (See 'Presentation in children' above.)

- **Diagnostic imaging** – Chest radiography usually reveals characteristic patchy alveolar infiltrates, predominantly in the right central hemithorax, which become more confluent and bilateral as the illness progresses. A significant discrepancy often exists between the extensive infiltrates on radiograph and the clinical status of the patient, who often does not appear severely ill and steadily improves with oxygen therapy. Ultrasound can detect increased extravascular lung water, which can help to confirm the diagnosis of HAPE. Other commonly available tests are nonspecific. (See 'Imaging studies' above.)

- **Distinguishing HAPE from heart failure or pneumonia** – Differentiating HAPE from such ailments as acute decompensated heart failure or pneumonia can be difficult, particularly in older patients with comorbid conditions. In such patients, HAPE is a diagnosis of exclusion. In general, HAPE is associated with marked weakness and hypoxemia that is more severe than that associated with most cases of pneumonia. Rapid improvement over hours in response to oxygen therapy or descent strongly suggests the diagnosis of HAPE. In otherwise healthy patients with a characteristic history of HAPE and examination findings consistent with the diagnosis, antibiotics are typically not necessary. (See 'Diagnoses confused with HAPE' above and 'Distinguishing HAPE and pneumonia' above.)

- **Management** – Early recognition of HAPE and prompt intervention are critical to assuring a favorable outcome. Immediate descent is not mandatory in all cases, if oxygen is available; treatment varies depending upon the severity of illness, available treatments, setting, and clinician experience. (See 'Treatment' above.)

  We recommend that supplemental oxygen be given as first-line treatment, rather than any pharmacologic therapy, to all patients with HAPE whenever it is available (**Grade 1B**). Descent to lower altitude may be needed in addition to supplemental oxygen depending on the circumstances. At higher elevations (>4000 meters), descent is mandatory.

  Oxygen and descent (actual or simulated using a hyperbaric enclosure) are often effective alone and appear to be superior to any pharmacologic therapy. In the hospital setting, supplemental oxygen and rest are generally sufficient treatment. In remote high-altitude settings, descent should begin as soon as HAPE is suspected. Adjunctive

medical therapies may be helpful and are discussed in the text. (See 'Pharmacologic interventions' above.)

- **Prophylaxis** – For patients with no history of medical problems at high altitude, the risk of HAPE is low, and routine prophylaxis is not warranted. We suggest prophylaxis with nifedipine, rather than other pharmacologic therapy (eg, dexamethasone), for individuals with a history of HAPE or with known predisposing factors who must ascend to altitudes above 2500 meters without adequate time for acclimatization (**Grade 2C**). In such circumstances, we give nifedipine (30 mg of a slow-release formulation every 12 hours). Additional adjunct medications for prophylaxis are discussed in the text. (See 'Prevention' above.)

REFERENCES

1. Luks AM, Swenson ER, Bärtsch P. Acute high-altitude sickness. Eur Respir Rev 2017; 26.
2. Hackett PH, Luks, AM, et al. High altitude medicine and pathophysiology. In: Wilderness Medicine, 7th ed, Auerbach PS (Ed), Elsevier, Philadelphia 2016. p.8.
3. Swenson ER, Bärtsch P. High-altitude pulmonary edema. Compr Physiol 2012; 2:2753.
4. Eichstaedt CA, Mairbäurl H, Song J, et al. Genetic Predisposition to High-Altitude Pulmonary Edema. High Alt Med Biol 2020; 21:28.
5. Eichstaedt CA, Benjamin N, Grünig E. Genetics of pulmonary hypertension and high-altitude pulmonary edema. J Appl Physiol (1985) 2020; 128:1432.
6. Swenson ER. Early hours in the development of high-altitude pulmonary edema: time course and mechanisms. J Appl Physiol (1985) 2020; 128:1539.
7. Ebert-Santos C. High-Altitude Pulmonary Edema in Mountain Community Residents. High Alt Med Biol 2017; 18:278.
8. Bärtsch P, Mairbäurl H, Maggiorini M, Swenson ER. Physiological aspects of high-altitude pulmonary edema. J Appl Physiol (1985) 2005; 98:1101.
9. Bärtsch P, Swenson ER. Acute high-altitude illnesses. N Engl J Med 2013; 369:1666.
10. Hultgren HN, Honigman B, Theis K, Nicholas D. High-altitude pulmonary edema at a ski resort. West J Med 1996; 164:222.
11. Jones BE, Stokes S, McKenzie S, et al. Management of high altitude pulmonary edema in the Himalaya: a review of 56 cases presenting at Pheriche medical aid post (4240 m). Wilderness Environ Med 2013; 24:32.
12. Duke JW, Beasley KM, Speros JP, et al. Impaired pulmonary gas exchange efficiency, but normal pulmonary artery pressure increases, with hypoxia in men and women with a

patent foramen ovale. Exp Physiol 2020; 105:1648.

13. Hackett PH, Roach RC. High-altitude illness. N Engl J Med 2001; 345:107.
14. Giesenhagen AM, Ivy DD, Brinton JT, et al. High Altitude Pulmonary Edema in Children: A Single Referral Center Evaluation. J Pediatr 2019; 210:106.
15. Liptzin DR, Abman SH, Giesenhagen A, Ivy DD. An Approach to Children with Pulmonary Edema at High Altitude. High Alt Med Biol 2018; 19:91.
16. Vock P, Brutsche MH, Nanzer A, Bärtsch P. Variable radiomorphologic data of high altitude pulmonary edema. Features from 60 patients. Chest 1991; 100:1306.
17. Fiorenzano G, Dottorini M. Unilateral High-Altitude Pulmonary Edema. Ann Am Thorac Soc 2017; 14:1492.
18. Yang W, Wang Y, Qiu Z, et al. Lung Ultrasound Is Accurate for the Diagnosis of High-Altitude Pulmonary Edema: A Prospective Study. Can Respir J 2018; 2018:5804942.
19. Canepa CA, Harris NS. Ultrasound in Austere Environments. High Alt Med Biol 2019; 20:103.
20. Alsup C, Lipman GS, Pomeranz D, et al. Interstitial Pulmonary Edema Assessed by Lung Ultrasound on Ascent to High Altitude and Slight Association with Acute Mountain Sickness: A Prospective Observational Study. High Alt Med Biol 2019; 20:150.
21. Ma D, Bao H, Zhang H, et al. [Application of lung ultrasound examination in severe high altitude pulmonary edema]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2017; 29:815.
22. Lim R, Ma IWY, Brutsaert TD, et al. Transthoracic sonographic assessment of B-line scores during ascent to altitude among healthy trekkers. Respir Physiol Neurobiol 2019; 263:14.
23. Pratali L, Cavana M, Sicari R, Picano E. Frequent subclinical high-altitude pulmonary edema detected by chest sonography as ultrasound lung comets in recreational climbers. Crit Care Med 2010; 38:1818.
24. Coffman KE, Stewart GM, Carlson AR, et al. Effect of age on the presence of comet tails at high altitude. Respir Physiol Neurobiol 2019; 259:166.
25. Hew-Butler T, Rosner MH, Fowkes-Godek S, et al. Statement of the Third International Exercise-Associated Hyponatremia Consensus Development Conference, Carlsbad, California, 2015. Clin J Sport Med 2015; 25:303.
26. Bennett BL, Hew-Butler T, Rosner MH, et al. Wilderness Medical Society Clinical Practice Guidelines for the Management of Exercise-Associated Hyponatremia: 2019 Update. Wilderness Environ Med 2020; 31:50.

27. Luks AM, Swenson ER. COVID-19 Lung Injury and High-Altitude Pulmonary Edema. A False Equation with Dangerous Implications. Ann Am Thorac Soc 2020; 17:918.
28. Archer SL, Sharp WW, Weir EK. Differentiating COVID-19 Pneumonia From Acute Respiratory Distress Syndrome and High Altitude Pulmonary Edema: Therapeutic Implications. Circulation 2020; 142:101.
29. Luks AM, Freer L, Grissom CK, et al. COVID-19 Lung Injury is Not High Altitude Pulmonary Edema. High Alt Med Biol 2020; 21:192.
30. Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med 2019; 30:S3.
31. Oelz O, Maggiorini M, Ritter M, et al. Nifedipine for high altitude pulmonary oedema. Lancet 1989; 2:1241.
32. Deshwal R, Iqbal M, Basnet S. Nifedipine for the treatment of high altitude pulmonary edema. Wilderness Environ Med 2012; 23:7.
33. Yanamandra U, Nair V, Singh S, et al. Managing High-Altitude Pulmonary Edema with Oxygen Alone: Results of a Randomized Controlled Trial. High Alt Med Biol 2016; 17:294.
34. Pollard AJ, 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.
35. Marticorena E, Hultgren HN. Evaluation of therapeutic methods in high altitude pulmonary edema. Am J Cardiol 1979; 43:307.
36. Zafren K, Reeves JT, Schoene R. Treatment of high-altitude pulmonary edema by bed rest and supplemental oxygen. Wilderness Environ Med 1996; 7:127.
37. Luks AM. Do we have a "best practice" for treating high altitude pulmonary edema? High Alt Med Biol 2008; 9:111.
38. Dawadi S, Adhikari S. Successful Summit of Two 8000 m Peaks After Recent High Altitude Pulmonary Edema. Wilderness Environ Med 2019; 30:195.
39. Freeman K, Shalit M, Stroh G. Use of the Gamow Bag by EMT-basic park rangers for treatment of high-altitude pulmonary edema and high-altitude cerebral edema. Wilderness Environ Med 2004; 15:198.
40. Schoene RB, Roach RC, Hackett PH, et al. High altitude pulmonary edema and exercise at 4,400 meters on Mount McKinley. Effect of expiratory positive airway pressure. Chest 1985; 87:330.

41. Walmsley M. Continuous positive airway pressure as adjunct treatment of acute altitude illness. High Alt Med Biol 2013; 14:405.
42. Koch RO, Hinterhuber L, Faulhaber M, et al. A successful therapy of high-altitude pulmonary edema with a CPAP helmet on Lenin Peak. Clin J Sport Med 2009; 19:72.
43. Maggiorini M, Brunner-La Rocca HP, Peth S, et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. Ann Intern Med 2006; 145:497.
44. Bates MG, Thompson AA, Baillie JK. Phosphodiesterase type 5 inhibitors in the treatment and prevention of high altitude pulmonary edema. Curr Opin Investig Drugs 2007; 8:226.
45. Bärtsch P, Swenson ER, Maggiorini M. Update: High altitude pulmonary edema. Adv Exp Med Biol 2001; 502:89.
46. Richalet JP. Pro: Corticosteroids Are Useful in the Management of HAPE. High Alt Med Biol 2015; 16:186.
47. Mairbäurl H, Baloglu E. Con: Corticosteroids Are Useful in the Management of HAPE. High Alt Med Biol 2015; 16:190.
48. Bärtsch P, Maggiorini M, Ritter M, et al. Prevention of high-altitude pulmonary edema by nifedipine. N Engl J Med 1991; 325:1284.
49. Richalet JP, Gratadour P, Robach P, et al. Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. Am J Respir Crit Care Med 2005; 171:275.
50. Ghofrani HA, Reichenberger F, Kohstall MG, et al. Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest base camp: a randomized, double-blind, placebo-controlled crossover trial. Ann Intern Med 2004; 141:169.
51. Baquero H, Soliz A, Neira F, et al. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study. Pediatrics 2006; 117:1077.
52. Sartori C, Allemann Y, Duplain H, et al. Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med 2002; 346:1631.

Topic 183 Version 28.0

GRAPHICS

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.

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

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

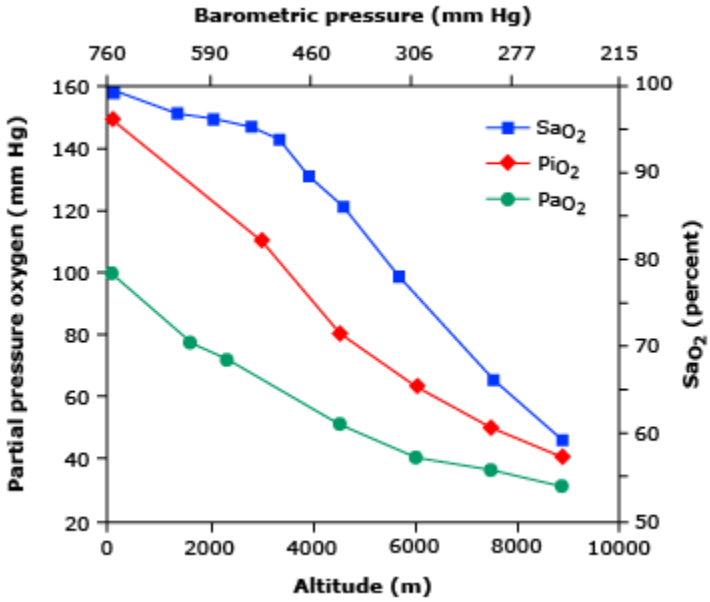
Gasherbrum II, Pakistan	26,360 ft/8035 m
Shisha Pangma, Tibet	26,289 ft/8013 m

ft: feet; m: meters.

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

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.

Graphic 56808 Version 2.0

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.

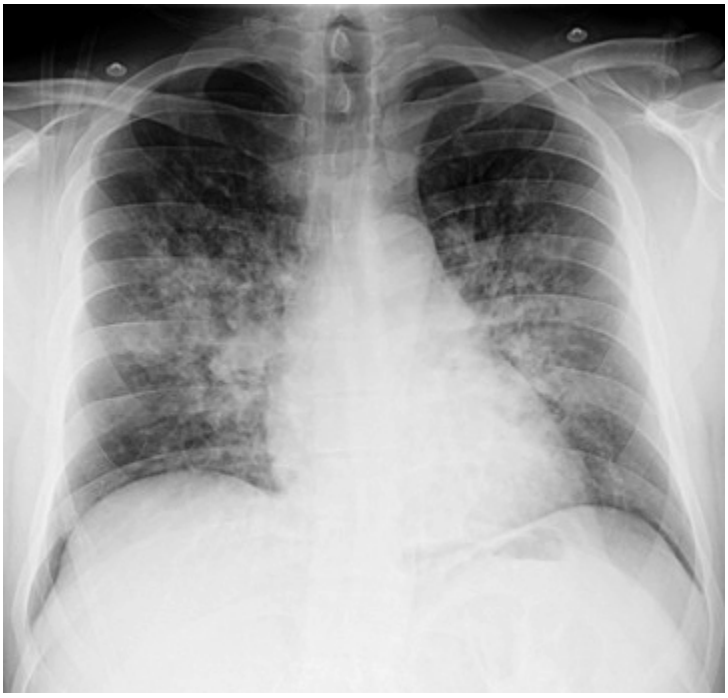
* Data are mean values and (range) and were obtained in subjects 20 to 40 years of age during the first one to two days of arriving at altitude (acute exposure) and associated with good acclimatization (subacute exposure).

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.*

Graphic 98575 Version 3.0

Plain chest radiograph of HAPE



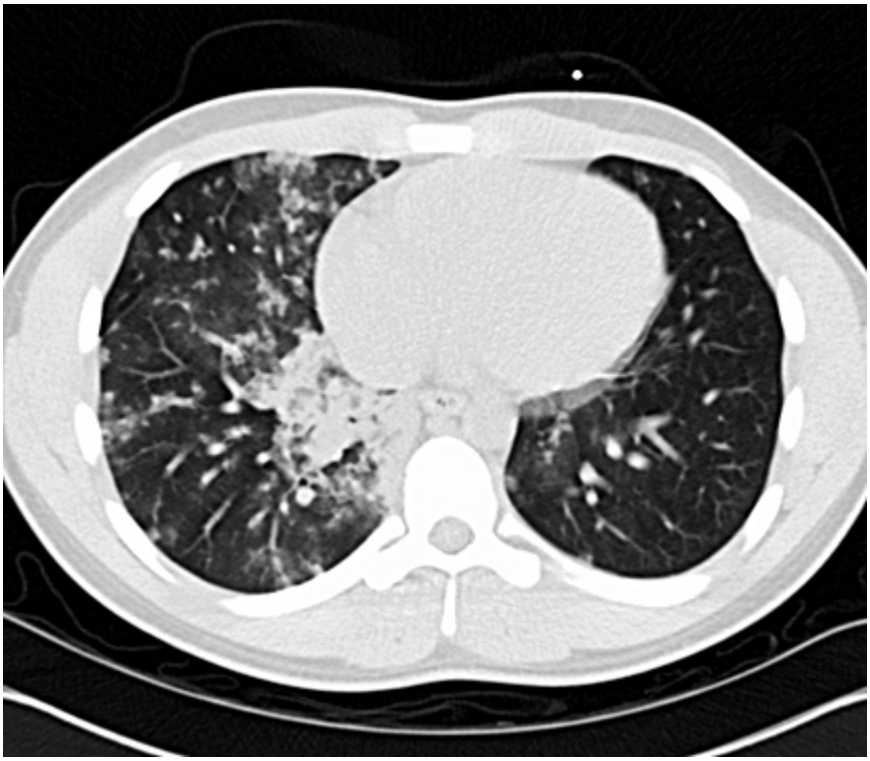
Plain chest radiography is useful in HAPE and reveals characteristic patchy alveolar infiltrates, predominantly in the right central hemithorax, which become more confluent and bilateral as the illness progresses. In a few cases, HAPE may not take this classic radiographic appearance.

HAPE: High altitude pulmonary edema.

Courtesy of Scott A Gallagher, MD.

Graphic 80267 Version 3.0

HAPE CT



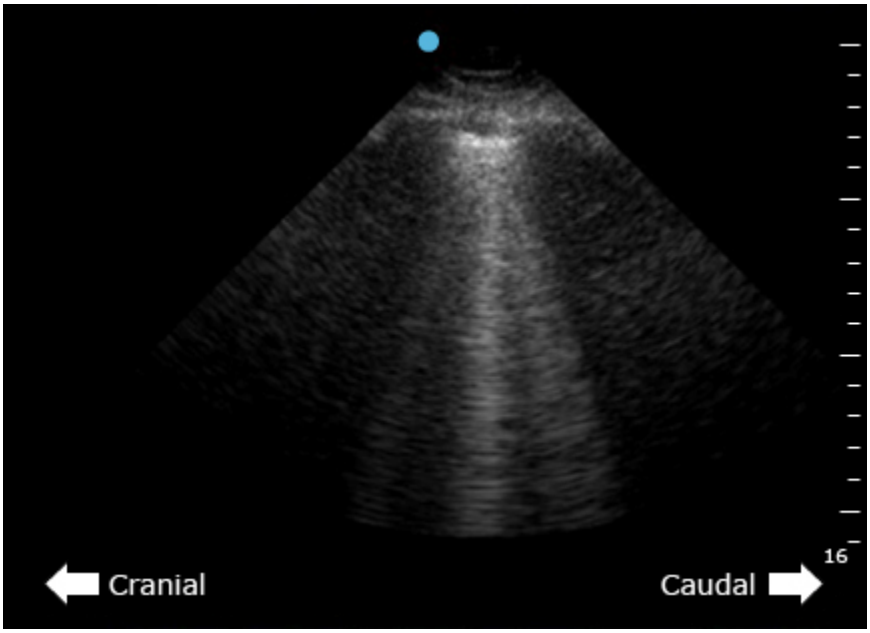
With HAPE, chest CT often reveals patchy alveolar infiltrates, predominantly in the right central hemithorax, which become more confluent and bilateral as the illness progresses.

HAPE: high altitude pulmonary edema; CT: computed tomography.

Courtesy of Scott A Gallagher, MD.

Graphic 67452 Version 3.0

B lines on thoracic ultrasound



Pleural ultrasound image depicting B lines ("comet tail artifact"), which are seen in acute pulmonary edema and acute respiratory distress syndrome. The presence of B lines would provide an alternate explanation for increased density seen on the chest radiograph, other than pleural fluid.

Graphic 71143 Version 3.0

Pharmacologic treatment and prevention of high altitude illness (HAI)

Condition		Preferred agent	Alternatives
AMS/HACE	Prevention*	**Acetazolamide:** 125 mg orally every 12 hours Children: 2.5 mg/kg (maximum single dose: 125 mg) orally every 12 hours[¥] 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 Children: Acetazolamide preferred; do not use for prophylaxis 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 Children: 2.5 mg/kg (maximum single dose: 250 mg) orally every 12 hours[¥] Duration: Continue for 24 hours after symptoms resolve or descent completed	**Dexamethasone:** 2 to 4 mg orally every 6 hours Children: 0.15 mg/kg (maximum single dose: 4 mg) orally every 6 hours 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 Children: 0.15 mg/kg (maximum single dose: 4 mg) orally every 6 hours 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 Children: 2.5 mg/kg (maximum single dose: 250 mg) orally every 12 hours[¥] 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 Children: 0.15 mg/kg (maximum single dose: 4 mg) every 6 hours 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 Children: 2.5 mg/kg (maximum single dose: 250 mg) orally every 12 hours[¥] 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)[◇] Children: 0.5 mg/kg (maximum single dose: 20 mg) extended-release orally every 8 hours[◇] 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: **Tadalafil:** 10 mg orally every 12 hours; start day of ascent and continue 3 to 5 days at maximum altitude **Sildenafil:** 50 mg orally every 8 hours; start day of ascent and continue 3 to 5 days at maximum altitude **Dexamethasone:** 8 mg orally every 12 hours; start day of ascent and continue 48 to 72 hours at maximum altitude **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)[◇] Children: 0.5 mg/kg (maximum single dose: 20 mg) extended-release orally every 8 hours[◇] 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: **Tadalafil:** 10 mg orally every 12 hours **Sildenafil:** 50 mg orally every 8 hours 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.

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.*

Graphic 76719 Version 15.0

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. **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.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy