BMJ Best Practice

High altitude illness

Straight to the point of care

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Summary

High-altitude illness (HAI) encompasses acute mountain sickness, high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). These diseases typically occur in lowland residents following an ascent to high altitude.

Although acute mountain sickness is normally a self-limiting disease, it is associated with the development of HACE.

HAPE and cerebral oedema are often fatal if left untreated.

Descent is the most effective form of treatment for all three conditions.

The diagnosis is usually clinical. However, the combination of a remote and hostile environment together with the potential for other medical conditions sometimes makes confirmation of the diagnosis difficult to achieve.

New symptoms at altitude should be assumed to be those of a high-altitude illness until proven otherwise.

Definition

HAI encompasses acute mountain sickness, HAPE, and HACE.[1] These diseases typically occur in lowland residents following an ascent to high altitude.

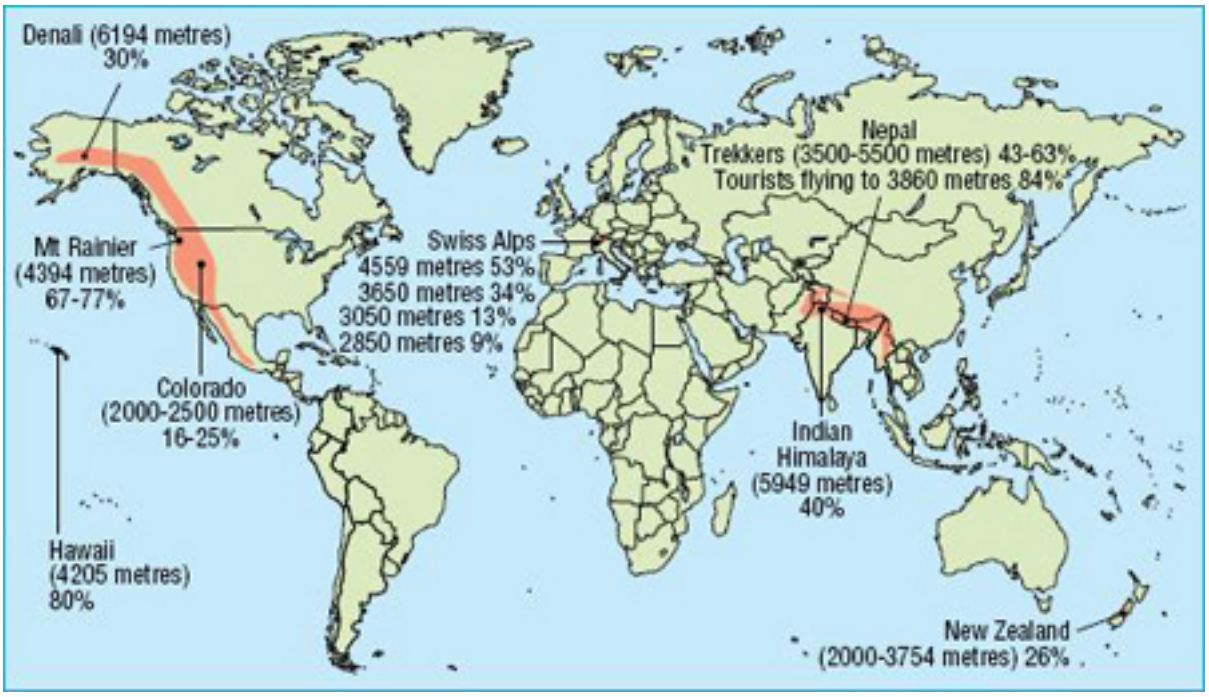
Epidemiology

High-altitude illness (HAI) typically occurs within hours or days of ascending to altitudes above 2000 m.[5] It typically occurs in lowland residents and sometimes in those from high altitude who have spent considerable time at low altitude. The development of acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE) depend upon a number of human and environmental risk factors. These include: height reached, rate of ascent, age, awareness of high-altitude illness before travel, location of long-term residence, exertion, underlying medical conditions, and history of previous high-altitude illness.[6]

There appears to be little difference in incidence between men and women, or adults and children.[7] The exact incidence is difficult to determine, as the combination of different risk factors and inaccuracies with field diagnosis impact upon the results of epidemiological studies. However, it is clear from a large number of studies that AMS is the most common high-altitude illness.[6] In those staying at alpine huts in Western Europe, the incidence of AMS has been shown to approximate 9% at 2850 m, 13% at 3050 m, and 34% at 3650 m.[8] At higher altitudes in the Himalayas, the incidence of AMS has been shown to range between 10% (3000 to 4000 m), 15% (4000 to 4500 m), and 51% (4500 to 5000 m), depending upon the altitude reached.[9] HAPE is more common than HACE, although both diseases often coincide. HAPE can still occur in up to 3%, and HACE in 1%, of those individuals who ascend slowly to altitudes above 3000 m.[7]

In those ascending more rapidly, the incidence of AMS, HAPE, and HACE increases. In one study, in the Mount Everest region of Nepal, 84% of those who flew directly to nearby Shayangboche (3740 m) complained of symptoms of AMS the following day.[10] Indian soldiers transported to 3600 m were more likely to contract HAPE following a rapid (15.5%) ascent, rather than a much slower (2.3%) ascent profile.[11] Similarly, 31% of Vedic pilgrims at a high-altitude lake in Nepal were diagnosed with HACE following a very rapid 2-day ascent from low altitude to 4300 m.[12]

Between 13% and 20% of those who present with HAPE show signs of HACE, and up to 50% of those who die from HAPE also have evidence of HACE on autopsy.[13] [14]



Global incidence of acute mountain sickness

From: Barry PW, Pollard AJ. BMJ. 2003;326:915-919

Aetiology

The cause is hypoxia; an ascent to altitude is accompanied by a fall in barometric pressure that results in a reduction in the partial pressure of inspired oxygen (PIO2).[1]

On the summit of Kilimanjaro (5895 m) the PIO2 is approximately one half of that found at sea level, and on the summit of Mount Everest (8850 m) it is just one third. Although the human body tries to acclimatise to this change in PIO2, in cases of acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE), this process is incomplete.

Pathophysiology

Despite acute mountain sickness (AMS) being by far the most common of illnesses to occur in new arrivals to altitude, less is known about the pathophysiology of this condition than its fatal complications high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE). The leading explanation suggests that AMS may be due to an increase in cerebral volume that is due to either an increase in cerebral blood flow or the presence of cerebral oedema.[7] [15] While vasodilation itself may be enough to stimulate the trigeminovascular system and cause headache and other AMS symptoms, the presence of oedema has been suggested by a number of high-altitude clinicians to explain the pathophysiology of the condition.[16] Many argue that AMS is a mild form of HACE and is therefore caused by oedema, either directly or by the effect of oedema on intracranial pressure (ICP). Unfortunately, little evidence is available to support this conclusion, with studies being unable to show a consistent pattern of oedema or ICP elevation in AMS.[17] [18] [19]

On ascending to altitude, falling levels of PIO2 trigger hypoxic pulmonary vasoconstriction (HPVR) in the pulmonary vasculature. HPVR directs blood flow away from hypoxic areas of the lung, and towards areas that are well oxygenated.[7] This results in a rise in mean pulmonary artery pressure and a heterogeneous blood flow to different parts of the lung. In areas that receive high blood flow the capillary transmural pressure rises and the walls of the capillary and alveolus are exposed to stress failure. In the majority of those who ascend to altitude, this remains no more than a threat. However, in cases of HAPE, these changes are more pronounced and the alveolar capillary membrane becomes extensively damaged. This allows oedema, rich in high molecular weight proteins and red blood cells, to pass freely into the alveoli and impair oxygenation.[20] [21] [22]

In HACE, hypoxia triggers a rise in cerebral blood flow that increases shear forces directed towards the blood-brain barrier (BBB). Breakdown of the BBB results in the formation of 'vasogenic oedema' that tends to accumulate in the white matter of the corpus callosum.[14] This area is particularly prone to oedema as it has a rich supply of blood vessels and, more importantly, an orderly network of extracellular channels that encourage the accumulation of fluid. T2-weighted MRI scans of those with HACE often demonstrate this clearly.[23] Eventually, large quantities of vasogenic oedema interfere with the metabolism of the cells and affect oxygen-dependent ion pumps in the cell membrane. Ion pump failure results in an increase in sodium ions inside the cell and the absorption of water in order to maintain normal cell osmolarity. The accumulation of this fluid or 'cytotoxic oedema' has been postulated as a contributing factor to the later stages of HACE.

Damage to the alveolar capillary membrane and BBB not only encourages the formation of oedema, but it also exposes the basement membranes of injured cells to the circulation. This results in (1) the activation of platelets resulting in the formation of thrombi and (2) the release of neutrophils triggering an inflammatory response. It is reasonable to assume that these processes contribute to the rapid deterioration that is often seen in cases of untreated HAPE and HACE.

All those who ascend to altitude are exposed to hypoxia and therefore experience an increase in cerebral blood flow and the effects of hypoxic pulmonary vasoconstriction. Although these changes may be more pronounced in HACE and HAPE, it may be that differences in the tissues of the brain and lung are largely responsible for the formation and clearance of oedema. In those susceptible to HAPE, concentrations of epithelial sodium channel proteins are reduced, preventing the clearance of oedema from alveoli.[24] [25] In HACE, a number of different molecules have been implicated in weakening the BBB during hypoxia. These include bradykinin, histamine, arachidonic acid, oxygen and hydroxyl free-radicals, nitric oxide, noradrenaline, and vascular endothelial growth factor.[14]

Classification

Clinical entities

Acute mountain sickness (AMS)

- A syndrome of non-specific symptoms that occurs following arrival at altitudes above 2500 m. It is defined by the Lake Louise Consensus Group as the presence of headache, together with 1 or more of the following: gastrointestinal symptoms (anorexia, nausea, or vomiting), fatigue, dizziness, and lightheadedness.[2]

High-altitude pulmonary edema (HAPE)

- A non-cardiogenic form of pulmonary oedema characterised by the presence of fatigue, breathlessness, cough, productive sputum, and chest pain.[3] [4]

High-altitude cerebral edema (HACE)

- An encephalopathy that results in changes in consciousness, abnormalities in motor function, and visual disturbances.[3] [4]

Case history

Case history #1

Four young men aged between 15 and 18 were attempting the Marangu route on the Tanzanian mountain Kilimanjaro (5895 m). The team set off late from the park entrance (1600 m) and took only 3 hours to jog to the Mandara Hut (2740 m) in order to avoid travelling in the dark. After a poor night's sleep, all 4 complained of a throbbing headache the following morning, together with loss of appetite, nausea, and tiredness.

Case history #2

On descending from the summit of the Argentinean mountain Cerro Aconcagua (6962 m), a 24-year-old female climber became increasingly tired and breathless. On arrival back at camp (5700 m) she began to cough up pink blood-stained sputum, and complained of pain in her chest. On examination she was found to have a respiratory rate of 44, a heart rate of 122, and an arterial oxygen saturation of 55%.

Other presentations

In addition to acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE), high-altitude cerebral edema (HACE) is an important clinical entity of high-altitude illness.

In the majority of HACE cases there will be a history of AMS that fails to respond to rest, fluids, and appropriate treatment. In some cases AMS is simply ignored. Unsteadiness and weakness tends to develop earliest, with visual disturbances becoming increasingly common as the condition progresses. Simple physical activities such as dressing, washing, and eating take longer to perform and are eventually neglected. The sufferer prefers to sleep. Subtle changes in behaviour and personality are sometimes noted by teammates during the early stages of the disease. Sufferers often deny the presence of symptoms and have little recollection of their experience following recovery. Occasionally, symptoms of AMS may be absent early in HACE and lead to a misdiagnosis such as dehydration, exhaustion, or even a hangover being made.

Approach

The appearance of new symptoms at altitude should be assumed to be due to high-altitude illness until proved otherwise. An accurate history and an appropriate physical examination are often all that is required to diagnose acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE) in the field. Anyone with AMS presenting with abnormal neurological findings must be assumed to have HACE.

History

AMS

AMS tends to present within 24 hours of an ascent to a new altitude. Symptoms usually resolve on descent or within 7 days at altitude where the condition first presented.[5] The symptoms of AMS include headache, anorexia, nausea, vomiting, lightheadedness, fatigue and dizziness.[1] [2] [6] The headache seen in AMS tends to be diffuse and constant, often worsening with straining, lifting, or coughing. In young children, AMS is also characterised by fussy behaviour that often presents as crying, restlessness, or muscular tension.[46]

HAPE and HACE often take longer to develop than AMS. In many cases HAPE and HACE are preceded by AMS.[47] [48]

HAPE

In HAPE, the most common symptoms are breathlessness, cough, and fatigue.[6] [48] At first the cough tends to be dry before becoming loose and productive as the patient deteriorates.[48] Sputum is usually frothy and either white or pink, turning to frank blood in only the most severe of cases. Most sufferers prefer to lie with their head elevated as the cough is often worse on lying flat. Chest pain can occur, and this is often precordial and rarely pleuritic in nature. Mild HAPE can have a pronounced effect upon exercise intensity, with the sufferer finding even the simplest task exhausting.

HACE

In the majority of HACE cases there will be a history of AMS that fails to respond to rest, fluids, and appropriate treatment. In some cases AMS is simply ignored. Unlike AMS and HAPE, HACE presents with neurological findings.[1] Unsteadiness and weakness tend to develop earliest with visual disturbances becoming increasingly common as the condition progresses. Simple physical activities such as dressing, washing, and eating take longer to perform and are eventually neglected. The sufferer prefers to sleep. Subtle changes in behaviour and personality are sometimes noted by teammates during the early stages of the disease.[48] Sufferers often deny the presence of symptoms and have little recollection of their experience following recovery. Occasionally, symptoms of AMS may be absent early in HACE and lead to a misdiagnosis such as dehydration, exhaustion, or even a hangover being made.[48]

HAPE and HACE often coincide. Physicians should have a low threshold for treating both conditions; if left untreated, HAPE and HACE are rapidly fatal.

Examination

AMS

As clinical signs are often absent in AMS, the condition is usually diagnosed from an appropriate history.

Nevertheless, the following changes have been seen in AMS.

- Peripheral oedema: this tends to occur in the periorbital area after sleep and around the ankles and wrists following exertion.[8]
- Rales: isolated occasional rales are sometimes audible on chest auscultation.[26]
- Pyrexia: a mild pyrexia may be present in AMS. A mean rise of 0.5°C (0.9°F) has been demonstrated in mild AMS (Lake Louise score = 3) and 1.2°C (2.2°F) in more severe cases (Lake Louise score >3).[49]
- A low arterial oxygen saturation (SaO2) and elevated heart rate: while a single resting SaO2 or heart rate recording may be of little use, a series of measurements showing a large difference between the patient and those who share the same ascent profile may help identify individuals who are acclimatising poorly and are therefore prone to AMS.[50] [51] [52]

HAPE

- Respiratory rate (RR): although HAPE can occasionally present without evidence of shortness of breath, an elevated resting respiratory rate is often a very useful early indication of the condition. In severe cases, the RR can exceed 40 breaths per minute at rest, making even the mildest exertion impossible.[53]
- Heart rate (HR): the resting HR is increased in those with HAPE. In severe cases, the resting HR can exceed 140 beats per minute; however, in most cases the HR is much lower, varying between 90 and 120 beats per minute.[53]
- Cyanosis: in the majority of cases there is clear evidence of cyanosis. This tends to affect extremities such as the fingers, toes, and facial features.[54]
- Pyrexia: low-grade pyrexia (38°C, 100.4°F) is a common feature of HAPE. This is usually higher than that seen in AMS.[49]
- Rales on auscultation: typically audible in both lung fields. These tend to be concentrated in mid and lower zones.
- Accentuated pulmonary second sound: on auscultation of the heart, an accentuated pulmonary second sound may be heard, indicating the presence of pulmonary hypertension.[55]
- Low arterial oxygen saturation (SaO2): SaO2 measurements are low in HAPE. At 4559 m, HAPE patients have been shown to have a mean SaO2 of 48% compared with 78% in healthy individuals.[56] It is essential that SaO2 measurements of healthy, well-acclimatised individuals are used as a benchmark when interpreting these results. SaO2 measurements are often lower than expected in even the healthiest of individuals at altitude.

HACE

- Mental state assessment: in the early stages of HACE, signs can often be subtle and are therefore easily missed. At first HACE patients may appear tired, irritable, confused, forgetful, or prone to bouts of irrational behaviour. Completing simple tasks may be problematic: tying shoe laces, using cutlery, or writing a diary may be a lengthy process. On questioning, sufferers may be unable to recall the time, day, date, or location. Conventional tests that assess basic arithmetic (subtracting 7 from 100) and memory (being given a name, age, and address and asked to recall at a later stage of the examination) are often useful in identifying the early stages of HACE.
- Neurological assessment[4]

- Ataxia is common. This can be identified by observing the individual walk heel-to-toe for a short distance and complete a 180-degree turn. In severe cases, ataxia may prevent individuals from standing up or even sitting upright.
- Abnormalities in tone and power can also occur. There may be neck stiffness. Rarely, cranial nerve palsies are present and tend to involve those nerves controlling eye movement (III, IV, and VI).
- Reflexes are usually brisk and clonus is sometimes present. Extensor plantar reflexes are common.
- Evidence of urinary incontinence or retention is sometimes seen.
- Visual and auditory hallucinations, seizures, tinnitus, vertigo, tremors, speech disturbance, and deafness have been reported; however, these features are rare.[4]
- Fundoscopy: retinal haemorrhages and papilloedema are common.[55]

Assessment of disease severity

AMS can be assessed using either the Lake Louise score or the AMS-C score of the Environmental Symptom Questionnaire (ESQ). Both scoring systems can also be used to assess HACE; the presence of ataxia and changes in mental state signify the presence of HACE. The ESQ takes much longer to complete, and calculating the AMS-C score is difficult in the field setting. It consists of 67 questions, of which 11 are used to calculate the AMS-C score. An AMS-C score of 0.7 or more is accepted as a cut-off for AMS.

The Lake Louise score tends to be preferred as it is not only easier to use but it is also capable of recognising milder disease at an earlier stage. According to the Lake Louise scoring system, a score of 3 or more in the presence of a headache fulfils the diagnosis of AMS.[2]

Details of the scoring system are as follows:

- Headache: 0 = none, 1 = mild, 2 = moderate, 3 = severe and incapacitating
- Gastrointestinal symptoms: 0 = good appetite, 1 = poor appetite or nausea, 2 = moderate nausea or vomiting, 3 = severe, incapacitating nausea and vomiting
- Fatigue and/or weakness: 0 = none, 1 = mild, 2 = moderate, 3 = severe
- Dizziness or light-headedness: 0 = none, 1 = mild, 2 = moderate, 3 = severe

In children <4 years old, the Children's Lake Louise Score (CLLS) is used.[46] According to the CLLS, AMS is present if there has been a recent gain in altitude and the CLLS is ≥7. Details of the scoring system are as follows:

- Amount of unexplained fussiness: 0 (no fussiness) to 6 (constant fussiness when awake)
- Intensity of fussiness: 0 (no fussiness) to 6 (severe fussiness when awake)
- Appetite: 0 = normal, 1 = slightly less than normal, 2 = much less than normal, 3 = vomiting or not eating
- Playfulness: 0 = normal, 1 = playing slightly less, 2 = playing much less than normal, 3 = not playing
- Ability to sleep: 0 = normal, 1 = slightly less or more than normal, 2 = much less or more than normal, 3 = not able to sleep.

HAPE is graded as follows.[53] [57]

- Grade1 (mild): minor symptoms with limitation of heavy effort only. Slight resting tachycardia and increased respiratory rate. No limitation of normal activities.
- Grade 2 (moderate): patient is ambulatory, but normal activities are reduced. Tachycardia and tachypnoea are present. Weakness, dyspnoea, and cough are evident to others. Rales may be present.
- Grade 3 (serious): symptoms are present at rest. The patient may be unable to walk and may prefer to rest. Simple tasks may be impossible. Senses may be dulled. Confusion and disorientation may be present. Tachycardia and tachypnoea are present. Rales are easily heard.
- Grade 4 (severe): patient is obtunded or comatose and cannot respond logically to questions or commands. Patient is unable to sit or stand. Exhibits noisy breathing with sounds of fluid in the airways. There is marked tachycardia and tachypnoea.

Investigations

An accurate history and an appropriate physical examination are often all that is required or available to diagnose AMS, HAPE, and HACE in the field.

HAPE

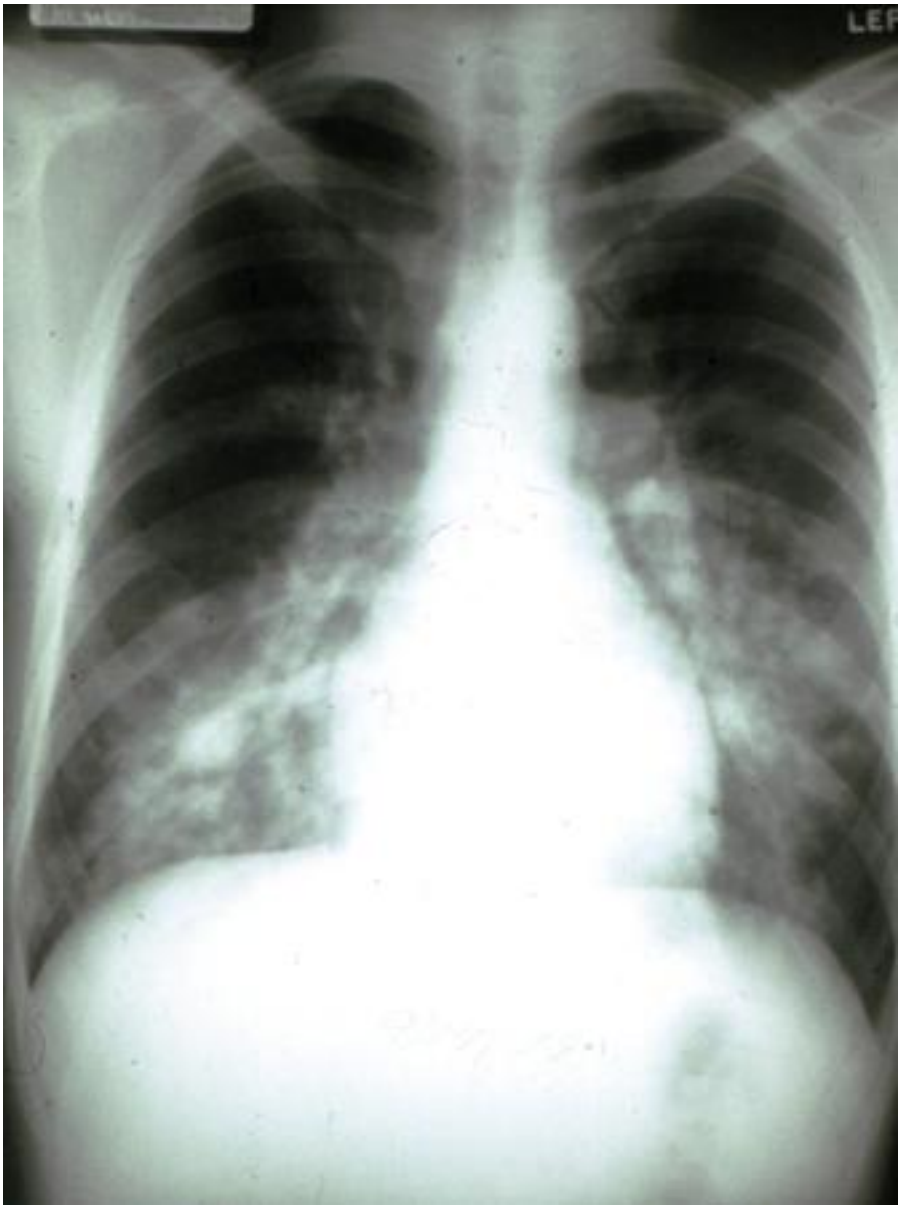
Patients with HAPE may be admitted to hospital, but this is only likely to happen if the patient is on holiday in a developed tourist resort (such as ski resorts), if flying direct into a high-altitude city (such as La Paz), or if rescued rapidly by helicopter. Most patients will have improved with descent prior to any admission. If they are admitted, the following tests can be considered:

Arterial blood gases (ABG)

- Typically reduced PaO2 and reduced or normal PaCO2
- May show respiratory alkalosis.

Radiography

- The onset of radiographic changes in HAPE can be highly variable.[55] However, most cases eventually develop asymmetrical areas of 'cotton wool' infiltrates in the mid and lower zones of the lung fields.[56]
- Changes tend to begin in the right mid zone and eventually spread across to the left. The apices and costophrenic angles are usually spared. Although prominent pulmonary vasculature may be present, this is a common finding in anyone ascending to altitude.[58] Signs of cardiogenic pulmonary oedema are usually absent. Complete resolution of pulmonary infiltrates occurs quickly following recovery.[59]



CXR of high-altitude pulmonary oedema

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ECG

- Typically shows a sinus tachycardia and changes compatible with acute pulmonary hypertension. These include: right axis deviation and bundle branch block; peaked P waves in leads II, III, and aVF; and an increase in the depth of precordial S waves.[55]

Chest ultrasound and echocardiography

- In HAPE, the presence of oedema can result in the formation of 'comet-tail artefacts' that are visible on ultrasound scanning. These, when assessed over 28 separate lung fields, can provide an objective assessment of pulmonary oedema, and can be used to monitor the course of the disease.[57] [60] The presence of a patent foramen ovale (present in 25% of the general population) may be associated with an increasing susceptibility to HAPE.[61]

Laboratory investigations

- The majority of laboratory investigations are normal in HAPE.
- In some cases a small rise in the white blood count occurs; this is due to a mild neutrophil leukocytosis.[55]

HACE

Patients with HACE may be admitted to hospital, but again this may well not happen due to complexities of rapid evacuation. If admitted with residual symptoms after descent, they should undergo the following tests:

CT brain

- In keeping with an increase in intracranial pressure, CT scanning can reveal compression of the ventricles and changes to the gyri and sulci present on the surface of the cerebral hemispheres.

MRI brain

- Performed in addition to CT brain
- Shows formation of oedema in the white matter. This is often concentrated in the splenium of the corpus callosum. Grey matter is largely unaffected by HACE. Changes seen on CT and MRI may take weeks or even months to resolve after clinical recovery.[14] [23]

Lumbar puncture

- Performed following imaging
- An increase in intracranial pressure is often seen in HACE; in advanced cases of HACE, this can exceed normal values by up to 300 mm H2O[62]
- Cerebrospinal fluid (CSF) analysis may reveal the presence of red blood cells in severe cases, but in the vast majority of HACE patients CSF will be normal.[4]

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include high altitude, rapid ascent, resident at low altitude and recurrence due to individual susceptibility.[31]

headache (common)

- The headache tends to be diffuse and constant, often worsening with straining, lifting, or coughing.[2] [6] [29]

ataxia (common)

- Common in high-altitude cerebral edema (HACE).[48]
- Identified by observing the individual walk heel-to-toe for a short distance and complete a 180-degree turn.
- In severe cases ataxia may prevent individuals from standing up or even sitting upright.
- Has also been found to be present in up to 60% of patients with high-altitude pulmonary edema (HAPE).[4]

change in mental state: for example, tired, irritable, confused, forgetful, irrational (common)

- In the early stages of HACE, signs can often be subtle and are therefore easily missed.
- At first, HACE patients may appear tired, irritable, confused, forgetful, or prone to bouts of irrational behaviour. Completing simple tasks may be problematic: tying shoe laces, using cutlery, or writing a diary may be a lengthy process. On questioning, patients may be unable to recall the time, day, date, or location. Conventional tests that assess basic arithmetic (subtracting 7 from 100) and memory (being given a name, age, and address and asked to recall at a later stage of the examination) are often useful in identifying the early stages of HACE.
- A mental state assessment should be normal in AMS.

abnormal tone, power, and reflexes (common)

- Abnormalities in tone and power can also occur in patients with high-altitude cerebral edema.
- There may be neck stiffness.
- Reflexes are usually brisk and clonus is sometimes present. Extensor plantar reflexes are common.[4]

Other diagnostic factors

nausea, vomiting, and loss of appetite (common)

- Nausea, vomiting, and loss of appetite are most common, while abdominal pain and change in bowel habit tends not to occur.

fatigue and weakness (common)

- Inability to perform simple tasks; reduced exercise capacity.

dizziness or lightheadedness (common)

- Early symptom of acute mountain sickness (AMS).

difficulty sleeping (common)

- On ascending to altitude, unacclimatised lowlanders typically complain that they take longer to get to sleep, wake frequently, often have unpleasant dreams, and do not feel refreshed in the morning.[63]

visual disturbance (common)

- Increasingly common as the condition progresses.

shortness of breath (common)

- Dyspnoea (50% to 77%) and, to a lesser extent, orthopnoea (8% to 16%) are common in high-altitude pulmonary edema (HAPE).[4] [64]
- In mild cases of HAPE, this may only be seen during exertion. However, in more advanced cases this can occur at rest.

cough with or without sputum (common)

- In the early stages of HAPE the cough is often dry before becoming loose and productive as the patient deteriorates.
- Sputum is usually frothy and either white or pink, turning to frank blood in only the most severe of cases.
- Most sufferers prefer to lie with their head elevated as the cough is often worse when lying flat. Occurs in 52% to 70% of those with HAPE.[4] [64]

rales (common)

- Audible in those with AMS, HAPE, and HACE.
- In HAPE, they are usually audible in both lung fields and tend to be concentrated in mid and lower zones.[55]

peripheral oedema (common)

- This tends to occur in the periorbital area after sleep and around the ankles and wrists following exertion.[8]

accentuated pulmonary second sound (common)

- In patients with HAPE an accentuated pulmonary second sound may be heard, indicating the presence of pulmonary hypertension.[55]

pyrexia (common)

- Mild pyrexia may be present in AMS and HAPE.
- A mean rise of 0.5°C (0.9°F) has been demonstrated in mild AMS (Lake Louise score = 3) and 1.2°C (2.2°F) in more severe cases (Lake Louise score >3).[49]
- A temperature of 38°C (100.4°F) or more is commonly seen in HAPE.[49]

elevated respiratory rate (common)

- Rarely, HAPE can present without any evidence of shortness of breath. However, an elevated resting respiratory rate is often a very useful early indication of the condition. In severe cases respiratory rate can exceed 40 breaths per minute at rest, making even the mildest exertion impossible.[53]

elevated heart rate (common)

- Resting heart rate (HR) can be increased in high-altitude illness. In severe cases of high-altitude pulmonary edema, resting HR can exceed 140 beats per minute. However, in most cases HR is much lower, varying between 90 and 120 beats per minute.[53]

low arterial oxygen saturation (common)

- It is essential that arterial oxygen saturation (SaO2) measurements of healthy well-acclimatised individuals are used as a benchmark when interpreting these results; SaO2 measurements are often lower than expected in even the healthiest of individuals at altitude.
- While a single resting SaO2 recording may be of little use in the diagnosis, a series of measurements showing a large difference between the patient and those who share the same ascent profile may help identify individuals who are acclimatising poorly and are therefore prone to acute mountain sickness.[50] [51] [52]
- In HAPE, SaO2 measurements are low. At 4559 m, HAPE patients have been shown to have a mean SaO2 of 48% compared with 78% in healthy individuals.[56]

cyanosis (common)

- In the majority of cases of HAPE there is clear evidence of cyanosis. This tends to affect extremities such as the fingers, toes, and facial features.[54]

urinary incontinence or retention (common)

- Upper motor neuron sign in patients with HACE.[4]

retinal haemorrhages and papilloedema on fundoscopy (common)

- Common finding in HACE.[55]

chest pain (uncommon)

- Precordial chest pain occurs in up to 21% of HAPE. The pain does not radiate and is not pleuritic in nature.[4] [64]

cranial nerve palsies (III, IV, and VI) (uncommon)

- Rarely, cranial nerve palsies are present in patients with HACE and tend to involve those nerves controlling eye movement (III, IV, and VI).[4]

visual and auditory hallucinations, seizures, tinnitus, vertigo, tremors, speech disturbance, and deafness (uncommon)

- Have all been reported in HACE. However, these features are rare.[4]

Risk factors

Strong

high altitude

- As height is gained, the partial pressure of inspired oxygen (PIO2) falls. In those arriving at alpine huts in Western Europe, the incidence of acute mountain sickness (AMS) has been found to be 9% at 2850 m, 13% at 3050 m, and 34% at 3650 m.[8] In the Himalayas, the incidence of AMS among 150 trekkers ranged between 10% (3000 to 4000 m), 15% (4000 to 4500 m), and 51% (4500 to 5000 m).[9] The incidence of high-altitude pulmonary edema (HAPE) follows a similar pattern with an incidence of 0.1% at 3063 m rising to 5.3% at 4486 m.[4]

rapid ascent

- A gradual ascent to altitude allows the body time to acclimatise.[1] During a trek from Lukla (2900 m) to Everest base camp (5400 m) those taking 6 days were 26% less likely to develop AMS than those taking just 4 days.[26] Ascending to an altitude of 3500 m over the course of 4 days reduces the incidence and severity of AMS by 41% when compared with those taking a 1-hour flight to the same altitude.[11] The incidence of HAPE in Indian soldiers transported by air to 3500 m or higher has been shown to be 5.7%; however, if this journey is completed by road the incidence falls to only 0.3%.[27]
- Research shows that periods of hypoxic exposure or 'pre-acclimatisation' prior to ascending to altitude may be able to reduce the incidence of AMS. However, the duration and degree of hypoxic exposure are not yet clear.[28] [29]

low-altitude residence

- Residents at low altitude have been found to be at least 3 times more likely to suffer from AMS (27% versus 8%) following a rapid ascent to 3000 m than those who live permanently above 900 m. This incidence can be reduced by a 1-week stay at 1600 m, and eliminated completely by spending at least 2 months at 1800 m before ascending to 3000 m.[11]
- Alternatively, frequent exposures to altitude combined with a slow ascent can lead to a 5-fold reduction in AMS.[5] [30]
- By allowing the body long periods of time to acclimatise, it is possible to dramatically reduce the risk of high-altitude illness.[29]

history of previous altitude illness

- Although the cause of this is unclear, high-altitude illness tends to recur. A study of mountaineers climbing to 4559 m showed that those with a history of AMS were more likely to develop the condition than those without. The difference in AMS incidence was most noticeable in those who took <3 days to climb from 2000 m to 4559 m (59% versus 32%).[17] [31]

Weak

younger age

- A limited number of studies appear to suggest that advanced age is protective against AMS. Of visitors to resorts in Colorado, 16% of those aged older than 60 developed AMS compared with 25% of the general population.[5]
- Unfortunately, conflicting data are also available and so the connection with age is unclear.[32]
- Although age may have an intrinsic advantage at altitude, older climbers may simply ascend more slowly, avoid excessive amounts of exercise, or attribute their symptoms to other comorbidities.[33]

exertion

- Working at altitude (e.g., mining) has been associated with altitude sickness.[34] Traditionally, new arrivals to high-altitude communities have been encouraged to rest. The benefits of this have only been confirmed in a single small hypobaric chamber study where 7 participants spent a total of 20 hours at an equivalent altitude of 4572 m over 2 different days. On the first day, the participants undertook 2 hours of moderate exercise, while the next day was spent resting. The incidence and severity of AMS was considerably lower following rest compared with the exercising session.[35]

poor awareness of high-altitude illness prior to travel

- A study published in 2004 demonstrated that trekkers travelling to Nepal had a greater awareness of high-altitude illness when compared with an earlier group assessed 12 years earlier (95% versus 80%). This resulted in a slower ascent to altitude, better use of medicines, and a fall in the incidence of AMS from 45% to 29% above 4000 m.[36]

existing medical condition

- Individuals with specific medical conditions meeting one or more particular criteria face an elevated risk of encountering issues at high altitude.[6] These criteria include factors such as the individual's susceptibility to hypoxemia at high altitudes, for instance if they suffer from a lung disease of considerable severity like chronic obstructive pulmonary disease. Their vulnerability to impaired ventilatory responses and potential complications arising from pulmonary vascular responses to hypoxia, such as in pulmonary hypertension, must also be considered. Hypoxia might pose a risk of

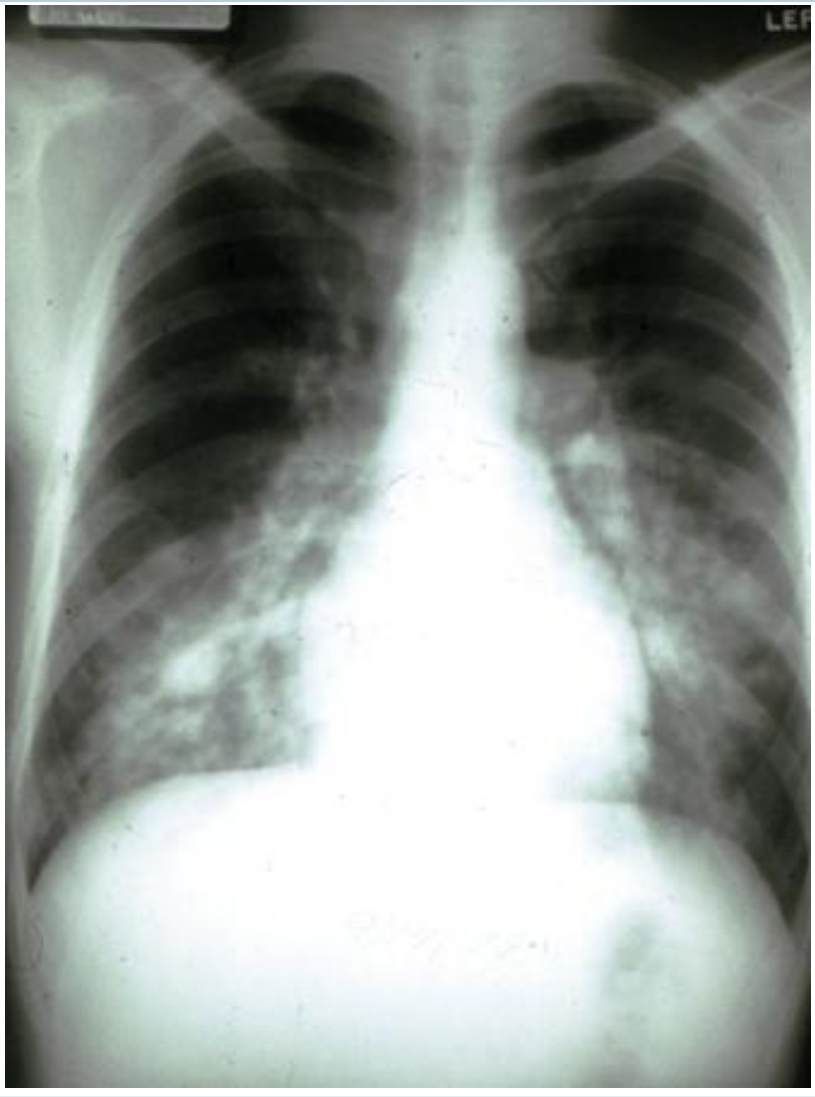
complications due to the underlying medical condition, for instance rapid deterioration in those with sickle cell disease. These individuals may develop high-altitude illness at lower elevations.[6]

Investigations

1st test to order

Test	Result
clinical diagnosis • High-altitude illness is primarily a clinical diagnosis, where patients present with typical findings in association with high-altitude travel.	**features of high-altitude illness**

Other tests to consider

Test	Result
arterial blood gases • High-altitude pulmonary edema (HAPE) may demonstrate respiratory alkalosis.	**HAPE: reduced PaO2 and low to normal PaCO2**
chest radiography • The onset of radiographic changes in HAPE can be highly variable.[55] However, most cases eventually develop asymmetrical areas of 'cotton wool' infiltrates in the mid and lower zones of the lung fields.[56]  *CXR of high-altitude pulmonary oedema* *Published with the kind permission of the Wilderness Medical Society* • Changes tend to begin in the right mid zone and eventually spread across to the left. The apices and costophrenic angles are usually spared. • Although prominent pulmonary vasculature may be present, this is a common finding in anyone ascending to altitude.[58] • Signs of cardiogenic pulmonary oedema are usually absent. Complete resolution of pulmonary infiltrates occurs quickly following recovery.[59]	**HAPE: asymmetrical areas of 'cotton wool' infiltrates in the mid and lower zones of the lung fields**

Test	Result
ECG • In HAPE, the ECG usually shows a sinus tachycardia and changes compatible with acute pulmonary hypertension. These include right axis deviation and bundle branch block; peaked P waves in leads II, III, and aVF; and an increase in the depth of precordial S waves.[55]	**HAPE: sinus tachycardia and changes compatible with acute pulmonary hypertension**
chest ultrasound and echocardiography • In HAPE, the presence of oedema can result in the formation of 'comet-tail artefacts' that are visible on ultrasound scanning. These, when assessed over 28 separate lung fields, can provide an objective assessment of pulmonary oedema and can be used to monitor the course of the disease.[57] [60] • The presence of a patent foramen ovale (present in 25% of the general population) may be associated with an increasing susceptibility to HAPE.[61]	**HAPE: 'comet-tail artefacts'**
WBC count • The majority of laboratory investigations are normal in high-altitude illness. • In some cases of HAPE a small elevation in the WBC count occurs; this is due to a mild neutrophil leukocytosis.[55]	**elevated**
lumbar puncture • An increase in intracranial pressure is often seen in high-altitude cerebral edema (HACE). In advanced cases of HACE this can exceed normal values by up to 300 mm H2O.[62] • Cerebrospinal fluid (CSF) analysis may reveal the presence of red blood cells in severe cases, but in the vast majority CSF will be normal.[4]	**HACE: elevated intracranial pressure, RBCs**
CT head • In keeping with an increase in intracranial pressure, CT scanning can reveal compression of the ventricles and changes to the gyri and sulci present on the surface of the cerebral hemispheres. • Changes seen on CT may take weeks or even months to resolve after clinical recovery.[14] [23]	**compression of ventricles**
MRI head • MRI scanning shows formation of oedema in the white matter. This is often concentrated in the splenium of the corpus callosum. Grey matter is largely unaffected by HACE. Changes seen on MRI may take weeks or even months to resolve after clinical recovery.[14] [23]	**oedema in white matter**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Acute exacerbation asthma	• Although the absence of common triggers such as house dust mites, pollution, and pollen may improve the symptoms of some sufferers, exercise, low humidity, and cold exposure may exacerbate the condition in others.[65] • The presence of wheeze and diurnal variation of symptoms is rare in high-altitude pulmonary edema (HAPE).	• Therapeutic trial with short acting beta-2-agonists should significantly improve symptoms.[25]
Community-acquired pneumonia	• May be difficult to clinically differentiate. • The presence of green or yellow sputum, rigors, and a high fever that do not resolve on descent are suggestive of pneumonia.	• Elevated WBC and positive sputum cultures. • Chest x-ray may demonstrate infiltration, consolidation, effusions, and cavitation.
Acute exacerbation of chronic heart failure (CHF)	• While significant numbers of individuals with cardiac risk factors head to altitude, the vast majority do not.[66] It is therefore far more likely that those presenting with peripheral oedema, cyanosis, tachypnoea, cough, and blood-stained sputum are suffering from HAPE and should be treated accordingly. • Pronounced right-sided heart failure (ascites, hepatomegaly, and an elevated jugular venous pressure) may help distinguish the condition from HAPE. • Presence of a gallop rhythm or a heart murmur (will be absent in HAPE).	• Cardiomegaly on CXR. • ECG may demonstrate arrhythmia, ischaemic ST- and T-wave changes. • Echocardiography shows abnormal systolic and diastolic function.
Hyperventilation syndrome	• May be triggered by the demands of the high-altitude environment; therefore is often difficult to distinguish clinically from HAPE.	• Diagnosis is clinical.

Condition	Differentiating signs / symptoms	Differentiating tests
	• Those with HAPE predominantly suffer from the effects of hypoxia; those with hyperventilation will be affected by hypocapnia, dizziness, paraesthesia, and perceptual disturbances.	
Myocardial infarction	• Unlike the chest pain in HAPE, MI pain is often described as a crushing pain radiating into the neck, jaw, and arms. While this may be eased with oxygen and rest similar to HAPE, descent may have little effect upon such symptoms. • The presence of acute mountain sickness symptoms and evidence of cough and abnormalities on chest auscultation makes a diagnosis of HAPE more likely.	• ECG demonstrates arrhythmia or acute ischaemic ST- and T-wave changes. • Cardiac catheterisation will demonstrate abnormal coronary flow.
Pulmonary embolism	• In the absence of clinical signs of deep vein thrombosis (pain, swelling, and redness in an affected limb) distinguishing pulmonary embolism (PE) from HAPE is difficult in the field setting. • In the absence of any improvement on descent or HAPE treatment, the diagnosis of HAPE will be unlikely.	• Positive D-dimer. • ECG changes suggestive (but not diagnostic) of PE include tachycardia, new right axis deviation, new right bundle branch block and the classical S wave in lead I, Q wave with T-wave inversion in lead III. • Ventilation-perfusion scan demonstrates abnormality in perfusion. • CT pulmonary angiography demonstrates the presence of thrombus in the pulmonary vessels.
Acute psychosis	• Thought disorder, delusions, and sensory hallucinations are features consistent with a diagnosis of acute psychosis. • Although high-altitude cerebral edema (HACE) tends to present with motor symptoms, visual disturbance, and changes in the level of consciousness, in some cases the condition can be confused with psychotic behaviour	• Diagnosis is clinical.

Condition	Differentiating signs / symptoms	Differentiating tests
	(personality changes and episodes of bizarre behaviour). • Unlike HACE, symptoms may resolve spontaneously at altitude or persist for long periods without any evidence of physical deterioration typically seen in HACE. • In acute psychosis treatment with dexamethasone and supplemental oxygen will be ineffective.	
Carbon monoxide poisoning	• Difficult to differentiate clinically. • Carbon monoxide poisoning has been found to occur at altitude following prolonged exposure to gas stoves in confined areas such as snow holes or small tents.[67] • Typically, individuals present with flu-like symptoms before eventually developing ataxia, confusion, and loss of consciousness.	• Carboxyhaemoglobin level is elevated.
Dehydration	• Warm temperatures, prolonged periods of exertion, and limited access to clean water make dehydration a common problem at altitude. Like acute mountain sickness, headache, nausea, dizziness, and tiredness may all occur. However, these symptoms tend to respond quickly to 1 to 2 litres of isotonic fluid. In addition, thirst, orthostatic hypotension, reduced urine output, and the presence of dry skin and mucous membranes may all help distinguish dehydration from high-altitude illness.	• Diagnosis is clinical.
Diabetic ketoacidosis (DKA)	• Known history of insulin-dependent diabetes. Recent infection or change in insulin therapy. • The presence of polyuria, thirst, and acetone on the breath supports the	• Elevated glucose level. • Ketonuria.

Condition	Differentiating signs / symptoms	Differentiating tests
	diagnosis of DKA. May be precipitated by high altitude.[68]	
Exhaustion	• While exhaustion may follow a prolonged period of exertion at altitude, difficulties in sleeping, nausea, headache, and dizziness should be absent. • Importantly, in exhausted individuals abnormal neurological signs are absent and they should still be able to perform basic tasks such as eating, drinking, and going to the toilet.	• Diagnosis is clinical.
Hangover	• Headache, nausea, and malaise of a hangover can mirror the symptoms of acute mountain sickness. • A history of excess alcohol use, an absence of sleep disturbance, and improvement with fluids and simple analgesics supports hangover as a cause of symptoms.	• Diagnosis is clinical.
Hypoglycaemia	• Neurological changes seen following prolonged periods of hypoglycaemia are easily confused with illness at high altitude. • In the absence of blood glucose measurement, a history of palpitations, shakiness, and cold extremities may be associated with the early manifestations of a hypoglycaemic attack. • Clinical improvement following the administration of sugary foods makes acute mountain sickness unlikely.	• Low glucose level.
Hyponatraemia	• Symptoms are similar to acute mountain sickness and HACE; however, cramps and a raised body temperature (>39°C, 102.2°F) may distinguish these from	• Electrolytes abnormal, although diagnosis is clinical in field.

Condition	Differentiating signs / symptoms	Differentiating tests
	heat exhaustion and salt depletion.[69] [70] • Those with heat exhaustion respond to salt replacement and appropriate fluid resuscitation. • In cases of hyponatraemia caused by the intake of excessive amounts of water, fluid restriction is necessary.	
Hypothermia	• Difficult to differentiate clinically. • Core temperature low. • Warming measures (hot water bottles, additional layers of dry clothing, and the consumption of warm drinks and food) will correct symptoms. • Hypothermia can often occur in those with HAPE or HACE.	• Diagnosis is clinical.
Ingestion of hallucinogenic agents	• A wide range of hallucinogenic agents are now available in popular high-altitude destinations. • While psychiatric symptoms predominate, changes in neurology can make it difficult to distinguish their use from HACE. • Supplemental oxygen and other HACE treatments will have no effect. • A thorough history from teammates and onlookers is essential.	• Diagnosis is clinical.
Migraine	• Ascent to high altitude is a recognised trigger for migraine. • The presence of a prodrome and aura may help distinguish migraine from acute mountain sickness (AMS). Similarly, migraine headaches tend to be unilateral and pulsating and unlike AMS can be accompanied by nasal stuffiness, scalp tenderness, and changes in bowel and bladder habits.	• Diagnosis is clinical.

Condition	Differentiating signs / symptoms	Differentiating tests
	• While migraines typically last for up to 72 hours, AMS symptoms may persist for longer and sometimes only resolve with descent. • Unlike some migraines, AMS is not associated with menstruation and does not cause visual disturbances or unilateral motor weakness.	
Generalised seizures	• In HACE, seizures tend to occur in the final stages of the condition and will have been preceded by other symptoms. • At altitude, seizure activity in those with epilepsy varies between individuals. The combination of poor sleep, hypoxia, and hypocapnia has been postulated as a cause for increasing activity in some cases.[71] • A thorough history is useful in these cases and may identify changes in the patient's medicine compliance; or, in those presenting with unexpected seizures, there may be evidence of unexplained events several years before.[71]	• MRI and EEG are confirmatory and will demonstrate epileptiform activity, and focal or localising abnormality.
Stroke	• Most commonly present with amaurosis fugax, dysphasia, and unilateral disturbances in sensory and motor function; in some cases changes in consciousness can occur that may be clinically difficult to differentiate from HACE. • HACE is often preceded by symptoms of acute mountain sickness and improves with descent and appropriate treatment; symptoms of transient ischaemic attack or stroke often persist.	• CT head will demonstrate ischaemia or haemorrhage.

Criteria

The Lake Louise Acute Mountain Sickness Scoring System[2]

Acute mountain sickness (AMS) can be assessed using either the Lake Louise score or the AMS-C score of the Environmental Symptom Questionnaire (ESQ).[2] [72] The ESQ can also be used to assess high-altitude cerebral edema (HACE); the presence of ataxia and changes in mental state signify the presence of HACE.

The ESQ takes much longer to complete, and calculating the AMS-C score is difficult in the field setting. It consists of 67 questions, of which 11 are used to calculate the AMS-C score. An AMS-C score of 0.7 or more is accepted as a cut-off for AMS.

The Lake Louise score tends to be preferred as it is not only easier to use but it is also capable of recognising milder disease at an earlier stage. According to the Lake Louise scoring system, a score of 3 or more in the presence of a headache fulfils the diagnosis of AMS.[2]

Symptoms:

- Headache
  - 0 = none
  - 1 = mild
  - 2 = moderate
  - 3 = severe and incapacitating
- Gastrointestinal symptoms
  - 0 = good appetite
  - 1 = poor appetite or nausea
  - 2 = moderate nausea or vomiting
  - 3 = severe, incapacitating nausea and vomiting
- Fatigue and/or weakness
  - 0 = none
  - 1 = mild
  - 2 = moderate
  - 3 = severe
- Dizziness or light-headedness
  - 0 = none
  - 1 = mild
  - 2 = moderate
  - 3 = severe

No neurological findings are exhibited in AMS alone, and the condition is self-limited. However, a change in mental status and ataxia are the classic findings in HACE, which can onset following AMS.[2] [29]

Children's Lake Louise Score (CLLS)[46]

Used for assessing children <4 years old. According to the CLLS, AMS is present if there has been a recent gain in altitude and the CLLS is ≥7. Details of the scoring system are as follows:

- Amount of unexplained fussiness: 0 (no fussiness) to 6 (constant fussiness when awake)
- Intensity of fussiness: 0 (no fussiness) to 6 (severe fussiness when awake)
- Appetite: 0 = normal, 1 = slightly less than normal, 2 = much less than normal, 3 = vomiting or not eating
- Playfulness: 0 = normal, 1 = playing slightly less, 2 = playing much less than normal, 3 = not playing
- Ability to sleep: 0 = normal, 1 = slightly less or more than normal, 2 = much less or more than normal, 3 = not able to sleep.

High-altitude pulmonary edema[53] [57]

Grade 1: Mild

- Minor symptoms with limitation of heavy effort only. Slight resting tachycardia and increased respiratory rate. No limitation of normal activities.

Grade 2: Moderate

- Patient is ambulatory, but normal activities are reduced. Tachycardia and tachypnoea are present. Weakness, dyspnoea, and cough are evident to others. Rales may be present.

Grade 3: Serious

- Symptoms are present at rest. The patient may be unable to walk and may prefer to rest. Simple tasks may be impossible. Senses may be dulled. Confusion and disorientation may be present. Tachycardia and tachypnoea are present. Rales are easily heard.

Grade 4: Severe

- Patient is obtunded or comatose and cannot respond logically to questions or commands. Patient is unable to sit or stand. Exhibits noisy breathing with sounds of fluid in the airways. There is marked tachycardia and tachypnoea.

Approach

In the vast majority of cases, acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE) can be prevented by ascending slowly once above altitudes of >2500 m.[29] In those patients who are prone to AMS or have to ascend quickly, acetazolamide or dexamethasone may be given prophylactically.[37] [38] [39] Although both have been shown to be effective in preventing AMS, acetazolamide is preferred because the side effects of dexamethasone are considerable.[12] [17] [40] [73] [74] [75] Regular doses of acetazolamide have been shown to be effective; however, higher doses are associated with side effects such as paraesthesias, commonly experienced in the hands and feet.[41] [76] [77] [78]

Prophylactic agents such as nifedipine and dexamethasone reduce the incidence of HAPE in individuals with a previous history of radiographically documented disease.[45] [79] Nifedipine is preferred because its effectiveness and safety profile are well understood.[29] The use of these agents in combination has not been studied. There is no evidence to support the use of prophylactic agents in the prevention of HACE.

In patients who develop high-altitude illness the STOP, REST, TREAT, and DESCEND approach should be followed. This involves stopping and resting once symptoms arise, instigating treatment once a diagnosis has been made, and descending whenever necessary. Patients with AMS can resume their ascent once symptoms resolve, and it is advisable to use pharmacological prophylaxis before continuing. Further ascent or re-ascent to a previously attained altitude must not be attempted in the presence of continuing symptoms.[29]

In cases where the diagnosis is uncertain, the STOP, REST, TREAT, and DESCEND approach should still be followed. In these cases either rest or descent depending upon the nature of the symptoms is advised.

In HAPE and HACE the effectiveness of medical treatment is very limited and can only slow down the onset of the condition. Rapid descent is the only reliable treatment option. It can often be life-saving.

Wherever possible, those with HAPE and HACE should be treated in a hospital environment if they reach such facilities prior to making a full recovery.

Acute mountain sickness (AMS)

Headaches are treated with fluids and simple analgesics such as paracetamol. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen should be used with caution because there is anecdotal evidence that there is a significant risk of gastrointestinal bleeding at high altitude.[80] [81] Anti-emetics may be used if the patient complains of nausea and vomiting.

One Cochrane review found that acetazolamide or dexamethasone may reduce symptom severity compared with placebo (low quality evidence).[82] In patients refractory to rest and symptomatic therapy, acetazolamide, dexamethasone, and oxygen may be used under medical supervision. However, these may take several hours to work and can initially worsen symptoms.[79] [83] [84] If symptoms persist descent is the treatment of choice.[6]

Sleep disturbance can be treated with either acetazolamide or a hypnotic.

High-altitude pulmonary edema (HAPE)

The mainstay of treatment is descent to a lower altitude. When descent is delayed a simulated descent using supplemental oxygen or a portable hyperbaric chamber may be used. Patients should be kept warm

and, if clinically dehydrated, should be given replacement fluids of a type, route, and volume appropriate to their overall clinical condition and that avoids fluid overload.

The calcium-channel blocker nifedipine inhibits hypoxic pulmonary vasoconstriction and reduces pulmonary artery pressure; therefore, it can be used in both prophylaxis and treatment of HAPE.[3][38] [57] Other agents such as dexamethasone have only been shown to be effective in prophylaxis.

It should be noted that in confirmed cases of HAPE where drugs, oxygen, or a hyperbaric bag have been used, their role is purely to buy time for the vital descent. Further ascent should not be considered.

High-altitude cerebral edema (HACE)

The mainstay of treatment is descent or simulated descent using supplemental oxygen or a portable hyperbaric chamber. In HACE, dexamethasone often improves the clinical situation and makes evacuation easier. Although the duration of the treatment is not clear, once a course of dexamethasone has been started this should be continued until the person has reached low altitude.[3] [14]

As with HAPE, if drugs, oxygen or a hyperbaric bag are used, their role is purely to buy time to arrange the vital descent. Further ascent should not be considered.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial (summary)		
high-altitude ascent planned		
	1st	**prophylactic non-pharmacological measures**
with rapid ascent planned or known AMS susceptibility	**plus**	**acetazolamide or dexamethasone**
with previous HAPE episode	**plus**	**nifedipine**

Acute		(summary)
AMS		
	1st	rest ± descent or simulated descent
	adjunct	analgesia
	adjunct	anti-emetic
	adjunct	acetazolamide or hypnotic
	2nd	acetazolamide or dexamethasone
	plus	descent or simulated descent
HAPE only		
	1st	descent or simulated descent
	plus	nifedipine
HACE only		
	1st	descent or simulated descent
	plus	dexamethasone
concurrent HAPE and HACE		
	1st	descent or simulated descent
	plus	nifedipine + dexamethasone

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial

high-altitude ascent planned

high-altitude ascent planned — **1st** — **prophylactic non-pharmacological measures**

» Once above 3000 m, individuals should ascend no more than 500 m in any 24-hour period, and undertake a rest day every 3-4 days of ascent.[7] [29]

» Avoiding strenuous activity on arrival and maintaining adequate hydration are also thought to limit the incidence of high-altitude illness.[3] [85]

with rapid ascent planned or known AMS susceptibility — **plus** — **acetazolamide or dexamethasone**

Treatment recommended for ALL patients in selected patient group

Primary options

» acetazolamide: children: 2.5 mg/kg orally (immediate-release) every 12 hours, maximum 125 mg/dose; adults: 125 mg orally (immediate-release) twice daily, or 500 mg orally (extended-release) once or twice daily

Secondary options

» dexamethasone: adults: 2 mg orally every 6 hours, or 4 mg every 6-12 hours

» If a rapid ascent is planned, or the patient has known susceptibility to acute mountain sickness (AMS), acetazolamide is the preferred prophylactic agent.[37] [38] [39] [40]

» Dexamethasone is an alternative choice for those who are allergic to or intolerant of acetazolamide.[29] [40] [41] Both have been shown to prevent the symptoms of AMS.[17] [37] [73] [74]

» Medicines are usually started at least 1 day prior to ascent and continued until acclimatisation is deemed to be complete. If dexamethasone is used for longer than 10 days, medication should be tapered over one week rather than stopped abruptly to avoid risk of adrenal suppression.[29]

» Dexamethasone should also not be used for prophylaxis in children due to the potential for

Initial

side effects unique to this population and the availability of other safe alternatives: namely, graded ascent and acetazolamide.[29]

» Regular doses of acetazolamide have been shown to be effective; however, higher doses are associated with side effects such as paraesthesias, commonly experienced in the hands and feet.[41] [76] [77] [78]

with previous HAPE episode **plus** **nifedipine**

Treatment recommended for ALL patients in selected patient group

Primary options

» nifedipine: children: consult specialist for guidance on dose; adults: 30 mg orally (extended-release) every 12 hours

» Nifedipine has been shown to reduce the incidence of high-altitude pulmonary edema (HAPE) in individuals with a previous history of radiographically documented disease.[45] Extended-release preparations are preferred and should be started 24 hours prior to ascent and continued until return to a low altitude.[7] [29]

Acute

AMS

1st **rest ± descent or simulated descent**

» In the event of acute mountain sickness (AMS), sufferers need to stop, rest, treat their symptoms, and descend if improvements do not occur (the STOP, REST, TREAT, DESCEND approach). In mild cases it may be enough to rest for a few days and treat symptoms with simple analgesia and anti-emetics.

» Patients with AMS can resume their ascent once symptoms resolve, and it is advisable to use pharmacological prophylaxis before continuing. Further ascent or re-ascent to a previously attained altitude must not be attempted in the presence of continuing symptoms.

» However, in those who fail to improve within 12-24 hours, descent is usually necessary and any further ascent should be made with the utmost caution. Often a descent of only a few hundred metres can improve symptoms.

» AMS can also be treated with supplemental oxygen (2-4 L/min) and portable hyperbaric therapy. Unfortunately, their effects are short-lived and symptoms tend to return within a few hours of stopping treatment.[86]

adjunct **analgesia**

Treatment recommended for SOME patients in selected patient group

Primary options

» paracetamol: children: 10-15 mg/kg orally every 4-6 hours when required, maximum 75 mg/kg/day; adults: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

Secondary options

» ibuprofen: children ≥6 months of age: 5-10 mg/kg orally every 6-8 hours when required, maximum 40 mg/kg/day; adults: 400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

» aspirin: children: 10-15 mg/kg orally every 4-6 hours when required, maximum 60-80 mg/kg/day; adults: 300-600 mg orally every

Acute

4-6 hours when required, maximum 4000 mg/day

» Headache should be treated with analgesics. There is anecdotal evidence to suggest that a significant risk of gastrointestinal bleeding exists at altitude.[80] It is therefore recommended that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are used with caution at altitude.

» In a prospective randomised clinical trial with a field-based, double-blinded design, ibuprofen effectively reduced symptoms such as headaches and nausea.[87]

adjunct **anti-emetic**

Treatment recommended for SOME patients in selected patient group

Primary options

» prochlorperazine: children: ≥2 years of age and 9-13 kg body weight: 2.5 mg orally every 12-24 hours when required, maximum 7.5 mg/day; children: ≥2 years of age and 14-17 kg body weight: 2.5 mg orally every 8-12 hours when required, maximum 10 mg/day; children: ≥2 years of age and 18-39 kg body weight: 2.5 mg orally every 8 hours or 5 mg every 12 hours when required, maximum 15 mg/day; children: ≥2 years of age and >39 kg body weight: 5 mg orally every 6-8 hours when required, maximum 20 mg/day; adults: 5-10 mg orally every 6-8 hours when required, maximum 40 mg/day

OR

» promethazine: children ≥2 years of age: 0.25 to 1 mg/kg orally/intramuscularly/intravenously every 4-6 hours when required, maximum 25 mg/dose and 100 mg/day; adults: 12.5 to 25 mg orally/intramuscularly/intravenously, every 4-6 hours when required, maximum 100 mg/day

OR

» ondansetron: children: consult specialist for guidance on dose; adults: 4-8 mg orally/intravenously every 8 hours when required, maximum 24 mg/day

OR

Acute

» metoclopramide: children: consult specialist for guidance on dose; adults: 5-10 mg orally/intramuscularly/intravenously every 8 hours when required for a maximum of 5 days, maximum 30 mg/day

» Anti-emetics can be used to treat symptoms of nausea and vomiting.

» Metoclopramide was found to be effective at reducing symptoms, including headache and nausea, in a prospective, double-blinded, randomised, field-based clinical trial.[87]

» Metoclopramide should be used for up to 5 days only in order to minimise the risk of neurological and other adverse effects.[88]

adjunct **acetazolamide or hypnotic**

Treatment recommended for SOME patients in selected patient group

Primary options

» acetazolamide: children: 2.5 mg/kg orally (immediate-release) every 12 hours, maximum 250 mg/dose; adults: 250 mg orally (immediate-release) every 12 hours

OR

» temazepam: adults: 10 mg orally once daily at night

OR

» zolpidem: adults: 5 mg orally (immediate-release) once daily at bedtime when required; 6.25 mg orally (extended-release) once daily at bedtime when required; higher doses may cause next-morning drowsiness and are not recommended, especially in women

» Acetazolamide or a hypnotic may be used to treat sleep disturbances.

» Acetazolamide is often used to successfully treat episodes of periodic breathing that are commonly seen during sleep at altitude.[89]

» In cases of intolerance or allergy to acetazolamide, hypnotics such as temazepam and zolpidem have been used successfully at altitude without causing respiratory depression.[90] [91] Hypnotics are not approved for use in children.

Acute

» Regular doses of acetazolamide have been shown to be effective; however, higher doses are associated with side effects such as paraesthesias, commonly experienced in the hands and feet.[41] [76] [77] [78]

2nd **acetazolamide or dexamethasone**

Primary options

» acetazolamide: children: 2.5 mg/kg orally (immediate-release) every 12 hours, maximum 250 mg/dose; adults: 250 mg orally (immediate-release) every 12 hours

OR

» dexamethasone: children: 0.15 mg/kg/orally/intramuscularly/intravenously every 6 hours, maximum 4 mg/dose; adults: 8 mg orally/intramuscularly/intravenously initially, followed by 4 mg every 6 hours

» Acetazolamide or dexamethasone may be used to treat acute mountain sickness (AMS) if patients are refractory to rest and symptomatic treatment; however, these may take several hours to work and can initially worsen symptoms.[79] [83] [84]

» Regular doses of acetazolamide have been shown to be effective; however, higher doses are associated with side effects such as paraesthesias, commonly experienced in the hands and feet.[41] [76] [77] [78]

plus **descent or simulated descent**

Treatment recommended for ALL patients in selected patient group

» In those who fail to improve within 12-24 hours, descent is usually necessary. Often a descent of only a few hundred metres can improve symptoms.

» AMS can also be treated with supplemental oxygen (2-4 L/min) and portable hyperbaric therapy. Unfortunately, their effects are short-lived and symptoms tend to return within a few hours of stopping treatment.[86]

HAPE only

1st **descent or simulated descent**

» Ideally, those with high-altitude pulmonary edema (HAPE) should descend quickly to low altitude.

Acute

» In the event of any delay, the partial pressure of inspired oxygen (PIO2) can be increased by using supplemental oxygen (face mask or nasal prongs 2-4 L/minute), or a portable hyperbaric chamber (2 psi - 13.8 KPa).[7]

» A combination of supplemental oxygen and portable hyperbaric treatment can be used in severe cases.[92]

plus **nifedipine**

Treatment recommended for ALL patients in selected patient group

Primary options

» nifedipine: children: consult specialist for guidance on dose; adults: 30 mg orally (extended-release) every 12 hours

» Nifedipine is able to inhibit hypoxic pulmonary vasoconstriction and reduce pulmonary artery pressure.[3] It can therefore be used in both prophylaxis and treatment of high-altitude pulmonary edema (HAPE).[57] [93]

HACE only

1st **descent or simulated descent**

» Ideally, those with high-altitude cerebral edema (HACE) should descend quickly to low altitude.

» In the event of any delay, the partial pressure of inspired oxygen (PIO2) can be increased by using supplemental oxygen (face mask or nasal prongs 2-4 L/minute), or a portable hyperbaric chamber (2 psi - 13.8 KPa).[7]

» A combination of supplemental oxygen and portable hyperbaric treatment can be used in severe cases.[92]

plus **dexamethasone**

Treatment recommended for ALL patients in selected patient group

Primary options

» dexamethasone: children: 0.15 mg/kg/ orally/intramuscularly/intravenously every 6 hours, maximum 4 mg/dose; adults: 8 mg orally/intramuscularly/intravenously initially, followed by 4 mg every 6 hours

» In high-altitude cerebral edema (HACE), dexamethasone often improves the clinical situation and makes evacuation easier.

Acute

» Although the duration of the treatment is not clear, once a course of dexamethasone has been started this should be continued until the person has reached low altitude.[3] [14]

concurrent HAPE and HACE

1st **descent or simulated descent**

» Those with concurrent high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) should descend quickly to low altitude.

» In the event of any delay, the partial pressure of inspired oxygen (PIO2) can be increased by using supplemental oxygen (face mask or nasal prongs 2-4 L/minute), or a portable hyperbaric chamber (2 psi - 13.8 KPa).[7]

» A combination of supplemental oxygen and portable hyperbaric treatment can be used in severe cases.[92]

plus **nifedipine + dexamethasone**

Treatment recommended for ALL patients in selected patient group

Primary options

» nifedipine: children: consult specialist for guidance on dose; adults: 30 mg orally (extended-release) every 12 hours
-and-
» dexamethasone: children: 0.15 mg/kg orally/intramuscularly/intravenously every 6 hours, maximum 4 mg/dose; adults: 8 mg orally/intramuscularly/intravenously initially, followed by 4 mg every 6 hours

» Patients require treatment with both nifedipine and dexamethasone.

» Nifedipine is able to inhibit hypoxic pulmonary vasoconstriction and reduce pulmonary artery pressure.[3] It can therefore be used in both prophylaxis and treatment of high-altitude pulmonary edema (HAPE).[57] [93] Care should be taken to avoid excessively large decreases in systemic pressure as this may decrease cerebral perfusion pressure and cause cerebral ischaemia.

» In high-altitude cerebral edema (HACE), dexamethasone often improves the clinical situation and makes evacuation easier.

» Although the duration of the treatment is not clear, once a course of dexamethasone has

Acute

been started this should be continued until the person has reached low altitude.[3] [14]

Emerging

Phosphodiesterase-5 inhibitors for HAPE prophylaxis

Orally administered phosphodiesterase-5 inhibitors have been shown to improve oxygenation and exercise capacity in well-acclimatised individuals exposed to hypoxia.[94] This has been thought to be due to an increase in the availability of nitric oxide, a powerful vacillator present in the lungs that is capable of reducing pulmonary artery pressure and improving gas exchange.[94] [95] Sildenafil has been used safely in the treatment of HAPE; however, clinical trials into its use have not yet been performed.[57] Nifedipine remains the preferred agent for the prophylaxis of HAPE.

Dexamethasone for HAPE prophylaxis

Dexamethasone is believed to act in a similar way to the phosphodiesterase-5 inhibitors by stimulating alveolar fluid re-absorption and reducing hypoxic pulmonary vasoconstriction. A course of dexamethasone resulted in 0 out of 10 HAPE-susceptible mountaineers developing the condition on arrival at 4559 m compared with 7 out of 9 taking placebo.[96] Until further evidence and experience with dexamethasone is obtained, nifedipine will remain the preferred agent for the prophylaxis of HAPE.

Ginkgo biloba for acute mountain sickness (AMS) prophylaxis

Ginkgo biloba has been shown in some studies to reduce the incidence and severity of AMS, but other studies have shown no effect.[44] [97] The discrepancy may be due to differences in the source and composition of ginkgo used. Acetazolamide and dexamethasone have been found to be considerably more effective.[7] [29]

Primary prevention

In the vast majority of cases, acute mountain sickness, high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE) can be prevented by ascending slowly once above altitudes >2500 m. Once above 3000 m, the altitude at which one sleeps should not be increased by more than 500 m in 24 hours. In addition, a rest day should be taken every 3-4 days.[29]

In those patients who are prone to acute mountain sickness (AMS) or intend to ascend quickly, acetazolamide or dexamethasone may be given prophylactically.[37] [38] [39] Acetazolamide is preferred, but if a patient is intolerant or allergic, dexamethasone may be given.[29] [40] [41]

Systematic reviews assessing the effectiveness of less commonly-used prophylactic medications (e.g., selective serotonin receptor agonists, N-methyl-D-aspartate receptor antagonists, endothelin-1 receptor antagonists, anticonvulsants and spironolactone), and miscellaneous or non-pharmacological interventions (including ginkgo biloba), have been unable to determine efficacy or safety, because of the small number of studies available and their limited quality.[29] [42] [43] [44]

Nifedipine has been shown to reduce the incidence of HAPE in individuals with a previous history of radiographically documented HAPE.[45]

Individuals with existing medical conditions should consult a physician to discuss pre-travel planning in order to decrease risk of high-altitude illness. Discussions should cover whether their conditions are stable, whether any dose adjustments are necessary, and whether the destination has available medical resources.[1] [6]

Patient discussions

In the vast majority of cases, acute mountain sickness, high-altitude pulmonary edema, and high-altitude cerebral edema can be prevented by ascending slowly once above altitudes of >2500 m. Once above 3000 m, the altitude at which one sleeps should not be increased by more than 500 m in 24 hours. A rest day should be taken every 3-4 days.[29]

Patients are advised to ascend slowly in future ascents to high altitude and should take extra caution. Education should be provided about the appropriate course of action if symptoms appear, and when to seek help.

Monitoring

Monitoring

Long-term monitoring is not required.

Complications

Complications	Timeframe	Likelihood
coma	**short term**	**low**
Severe cases of high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) may result in coma. These patients require immediate intubation and ventilation as well as all of the supportive measures typically needed in a comatose patient.		
generalised seizures	**short term**	**low**
Rarely occurs with HACE. Must be differentiated from epilepsy. Treated with anticonvulsant drugs in addition to typical HACE management.		
permanent neurological deficits	**short term**	**low**
Rarely, patients may have long-term neurological deficits if HACE is severe or prolonged.		

Prognosis

In mild cases of acute mountain sickness (AMS), symptoms tend to resolve quickly with rest and treatment. However, further ascent may see the return of AMS and the development of high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE).

Left untreated, cases of HAPE and HACE are often fatal.

In HAPE, recovery tends to occur within a few days of returning to low altitude, while the neurological features of HACE may take several weeks to disappear.

Although individuals with a history of AMS, HAPE, and HACE seem prone to having further episodes of high-altitude illness, many cases of HAPE and HACE are sporadic. Following a life-threatening episode of high-altitude illness, a return to altitude should not be excluded. However, a cautious approach with advice from an experienced altitude physician and possible use of prophylaxis with a slow-ascent profile is vital.

Diagnostic guidelines

North America

CDC Yellow Book: health information for international travel - high elevation travel & altitude illness (https://wwwnc.cdc.gov/travel/page/yellowbook-home)

Published by: Centers for Disease Control and Prevention **Last published:** 2023

Treatment guidelines

North America

CDC Yellow Book: health information for international travel - high elevation travel & altitude illness (https://wwwnc.cdc.gov/travel/page/yellowbook-home)

Published by: Centers for Disease Control and Prevention **Last published:** 2023

Wilderness Medical Society practice guidelines for the prevention and treatment of acute altitude illness: 2019 update (https://www.wemjournal.org/content/collection_practice_guidelines)

Published by: Wilderness Medical Society **Last published:** 2019

Key articles

- Centers for Disease Control and Prevention. CDC Yellow Book 2024: health information for international travel. Section 4: environmental hazards & risks - high elevation travel & altitude illness. May 2023 [internet publication]. Full text (https://wwwnc.cdc.gov/travel/yellowbook/2024/environmental-hazards-risks/high-elevation-travel-and-altitude-illness)
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Images

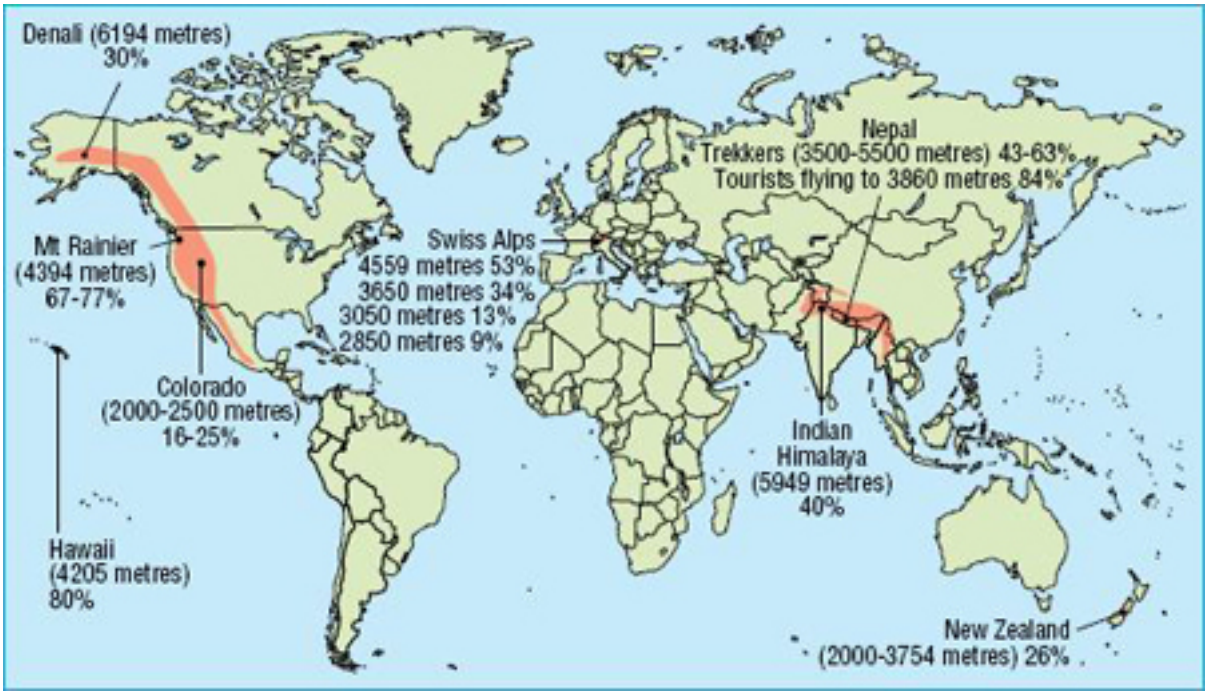

Figure 1: Global incidence of acute mountain sickness

From: Barry PW, Pollard AJ. BMJ. 2003;326:915-919

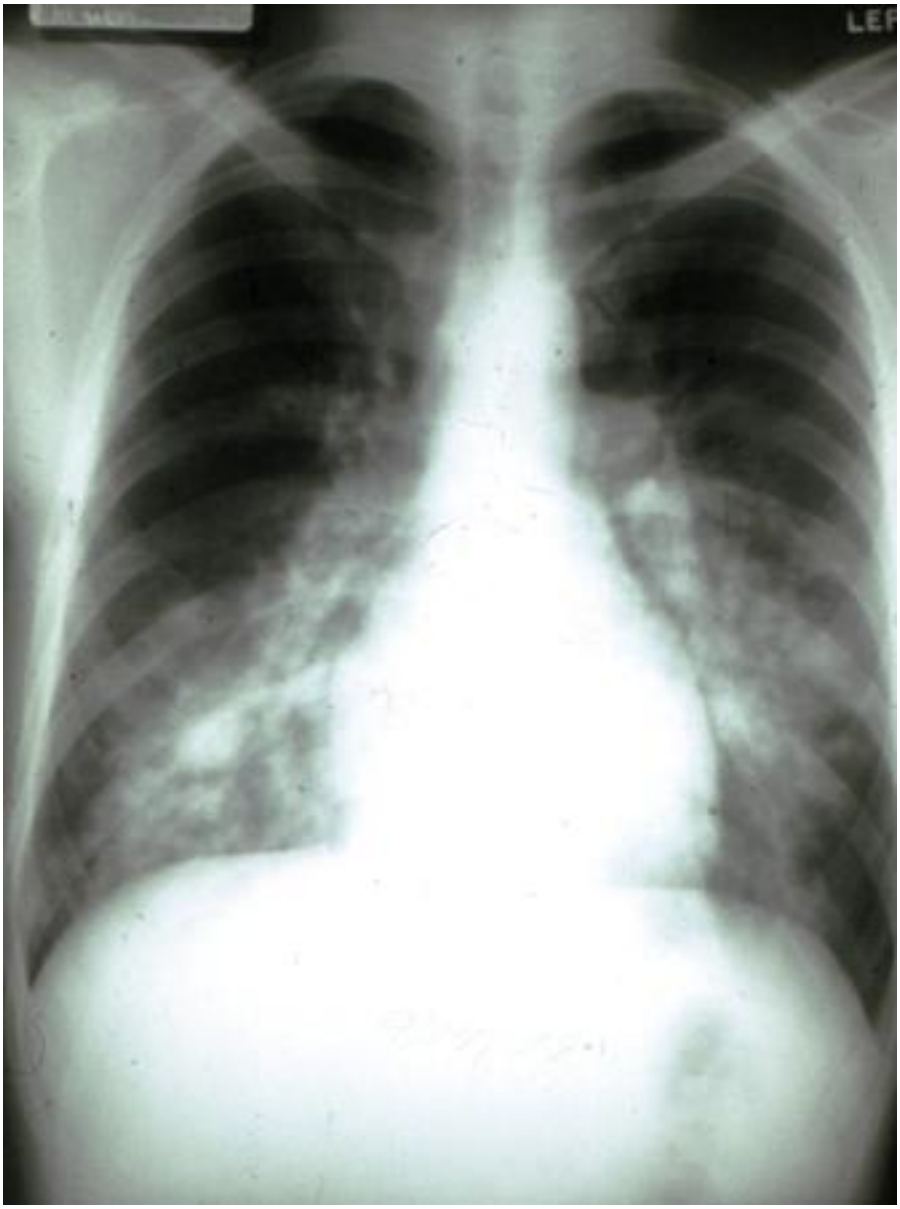

Figure 2: CXR of high-altitude pulmonary oedema

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Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

Contributors:

// Authors:

Jeremy S. Windsor, MBChB, DCH, FCARCSI

Specialist Registrar
Anaesthetics and Intensive Care Medicine, University College Hospital, London, UK
DISCLOSURES: JSW is an author of a number of references cited in this topic.

// Peer Reviewers:

James S. Milledge, MBBS

Honorary Professor
Department of Physiology, University College London, London, UK
DISCLOSURES: JSM declares that he has no competing interests.

Mike Grocott, MD

Senior Lecturer
Intensive Care Medicine, University College Hospital, London, UK
DISCLOSURES: MG declares that he has no competing interests.

Haibo Wang, MD, PhD

Assistant Professor
LSU Health Sciences Center, Shreveport, LA
DISCLOSURES: HW declares that he has no competing interests.