Key points

- With increasing altitude, barometric pressure falls leading to a progressive fall in the inspired and arterial partial pressures of oxygen.
- Hypoxaemia triggers a series of adaptive physiological responses, termed acclimatisation, which allow humans to tolerate exposure to even very high altitudes.
- The respiratory response to altitude exposure consists of hyperventilation with a periodic breathing pattern typically observed predominantly at rest and during sleep.
- Rapid ascent, inappropriate time for acclimatisation, strenuous physical exertion and individual susceptibility predispose to high-altitude-related illnesses
- Acute mountain sickness (AMS) is characterised by headaches, insomnia, poor appetite and fatigue. It may progress to high-altitude cerebral oedema with altered mental status, loss of consciousness and death if not treated by descent, supplemental oxygen and dexamethasone.
- High-altitude pulmonary oedema (HAPE) is due to exaggerated pulmonary hypertension during hypoxic exposure. It manifests itself within hours to days after rapid ascent to >3,000 m with cough, shortness of breath, cyanosis and pulmonary rales. Treatment includes supplemental oxygen, descent and nifedipine to reduce pulmonary artery pressure.

Lessons from high-altitude physiology

Y. Nussbaumer-Ochsner
K.E. Bloch

Pulmonary Division, University Hospital of Zurich, and Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland.

Educational aims

- To review the physiological response to high-altitude exposure.
- To discuss the three major high-altitude diseases: acute mountain sickness, high-altitude cerebral oedema and high-altitude pulmonary oedema.
- To provide information on prevention and treatment of high-altitude diseases.

Summary

High-altitude exposure causes a series of normal physiological responses, termed acclimatisation, which mitigate the effects of hypobaric hypoxia. Hypoxic ventilatory stimulation results in improved oxygen uptake but is associated with respiratory alkalosis that may trigger periodic breathing, particularly during sleep, thereby impairing sleep quality. As travelling to high altitude is popular, high-altitude related illnesses that affect subjective wellbeing, reduce physical performance and alter mental status are also frequently observed. They encompass acute mountain sickness (AMS), high-altitude cerebral oedema (HACE) and high-altitude pulmonary oedema (HAPE). Depending on ascent rate and individual susceptibility, symptoms usually occur at altitudes above 2,500 m. Therapeutic options include descent accompanied by administration of oxygen and drugs as required. Prevention is based on appropriate acclimatisation, moderate ascent rate, low sleeping altitude and drugs, including acetazolamide, dexamethasone and nifedipine.

Correspondence
K.E. Bloch
Pulmonary Division,
University Hospital of Zurich
Ramistrasse 100, CH-8091 Zurich
Switzerland
Email: konrad.bloch@usz.ch

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A mother, their 14-year-old son and his 14-year-old friend undertook a breathtaking journey. From Interlaken, Switzerland (568 m), they travelled for 2 h by train to the highest railway station in Europe: the Jungfrau Joch, at 3,450 m. They enjoyed the beautiful view but had to hurry to reach the Mönchsjoch hut at 3,650 m that same evening (figure 1). After hiking through the snow for 40 mins with heavy backpacks they arrived at the hut, exhausted but happy. However, 2 h later when the dinner was ready, the son had lost his appetite. He felt dizzy and fatigued and complained of a throbbing headache. He went to bed without food but could not fall asleep. Every few minutes he woke up with shortness of breath. This continued until the next morning when the family decided to return to the lowlands. Upon arrival in Interlaken, the son felt well again.

This vignette illustrates common health problems occurring with oxygen deprivation at high altitude in unacclimatised travellers and mountaineers. With the construction of roads, trains and cable cars, high mountain areas have become easily accessible and popular for recreational activities (skiing, mountaineering) even for those who are unaware of the potential risks of a high-altitude sojourn. Many people also pursue professional work in mountain areas, and in the Americas, Asia and eastern Africa there are permanent settlements at altitudes >2,500 m.

Figure 1
Just before sunset a group of tourists is on the way from the Jungfrau Joch (peak seen in the background at 3,450 m), the highest railway station in Europe, to the Monchsjoch hut (at 3,650 m) where they plan to stay overnight. Easy access by train and other means of transportation entails the risk that people unaware of potential hazards travel to very high mountain areas.

Although humans are able to adapt to quite varying environmental conditions, hypobaric hypoxia associated with rapid ascent to high altitude in unacclimatised subjects, and in particular in patients with pre-existing cardiopulmonary disease, may cause discomfort and even altitude-related illness [1, 2]. The major high-altitude diseases mainly affect the cerebral and cardiopulmonary systems: the cerebral form is AMS, which can progress to HACE, the cardiopulmonary form is HAPE. In its mild form, AMS is quite common. At the Capanna Regina Margherita (Mount Rosa, 4,559 m; figure 2), 22% of climbers have symptoms of AMS requiring a reduction of their physical activity [3]. The development of these conditions is influenced by the rate of the previous ascent, the altitude reached, sleeping altitude and individual susceptibility. Allowing appropriate time for acclimatisation to hypoxia reduces the risk of high-altitude disease. In addition to oxygen deprivation, other factors, such as dehydration and harsh weather conditions, may influence the condition of travellers and mountaineers at high altitude. The impact of these can be reduced with appropriate protection. Apart from the acute forms of altitude-related illnesses, subacute and chronic forms of mountain sickness with pulmonary hypertension may occur in long-term high-altitude residents. The symptoms include polycythemia, hypoxaemia and impaired mental function.

Figure 2
View of the Mount Rosa massif from the south. The Cappanna Regina Margherita is situated on top of a rock at 4,559 m on the Signalkuppe (also called Punta Gnifetti, arrow). The hut has a long-standing tradition as a high altitude medical research facility since 1893. Nowadays, research groups from all over the world perform high-altitude studies during the summer months.

The atmosphere

With increasing altitude, barometric pressure falls. The partial pressures of inspired (P_{I,O_2}) and arterial oxygen (P_{a,O_2}) also decrease, as the partial pressure of a gas is a function of the total pressure. Dry air has an O_2 concentration of 20.9%. When air is inhaled it is warmed and saturated with water vapour. The partial pressure of water vapour at body temperature (37°C) is 47 mmHg. Thus, the P_{I,O_2} at sea level is 149 mmHg, *i.e.* 0.21 times barometric pressure minus water vapour pressure [0.21×(760-47)=149 mmHg]. At an altitude of 3,450 m, corresponding to that of the Jungfrau Joch, the barometric pressure is 497 mmHg and the P_{I,O_2} is [0.21×(497-47)]=94 mmHg, *i.e.* only about two-thirds of that at sea level. Figure 3 shows the relationship between barometric pressure, P_{I,O_2} and altitude.

The normal physiological response to high altitude

With increasing altitude, the human body experiences a progressive oxygen deprivation and hypoxia ensues. Oxygen, essential for normal cellular function can become a limiting factor. Over the course of a prolonged stay at high altitude, a series of adaptive changes to the environment take place. These changes are known as acclimatisation and improve tolerance to high altitude.

Hyperventilation and periodic breathing

One of the first and most important physiological responses to hypoxic exposure is a compensatory

increase in ventilation (figure 4). Hyperventilation augments alveolar ventilation and a further decrease in oxygen tension can be avoided or mitigated. Respiratory stimulation is mediated by hypoxic stimulation of the peripheral chemoreceptors, especially in the carotid body, and by other changes in the chemical control of ventilation. With increasing hyperventilation, alveolar and arterial oxygen tension are augmented but arterial carbon dioxide tension (P_{CO_2}) is reduced. Climbers may recognise hyperventilation by paresthesias in their fingers. The reduction of alveolar and arterial P_{CO_2} due to hyperventilation produces a respiratory alkalosis in arterial blood. The pH gradually returns to normal by renal excretion of bicarbonate. This metabolic compensation is slower and less complete at very high altitudes.

Periodic breathing is characterised by waxing and waning of ventilation with periods of apnoea/hypopnoea alternating with hyperpnoea. CHEYNE [4] and STOKES [5] described the crescendo-decrescendo breathing pattern in patients suffering from severe heart failure. Subsequently, MOSSO [6] and others observed a similar breathing pattern in healthy individuals at high altitude. Periodic breathing is produced by alternating periods of hypoxia that stimulate ventilation thereby inducing hypocapnia. Once the arterial P_{CO_2} falls below a certain level, called the apnoeic threshold, ventilation ceases until arterial P_{CO_2} rises again due to metabolic activity (figures 5 and 6). High-altitude periodic breathing mostly occurs at rest and during sleep, when cortical drives to breathe diminish, but may also prevail during wakefulness and even during physical exercise at higher altitudes. It has been observed that sleep disturbances and periodic breathing are most pronounced during the first few nights after ascent to altitude. There is a tendency towards more regular breathing on the subsequent days, even though persistence of periodic breathing throughout sleep after 10 days to 5 weeks at altitudes >4,500 m have been described.

Spirometry and gas exchange

Vital capacity is slightly reduced at moderate-to-high altitudes (4,559 m) due to a reduced respiratory muscle strength and possibly pulmonary congestion and other factors [7]. Airflow is less affected as the reduced air density lowers the airflow resistance. Using specialised techniques, such as the single-breath nitrogen-washout test or other measurements, an uneven distribution of mechanical properties throughout the lungs and

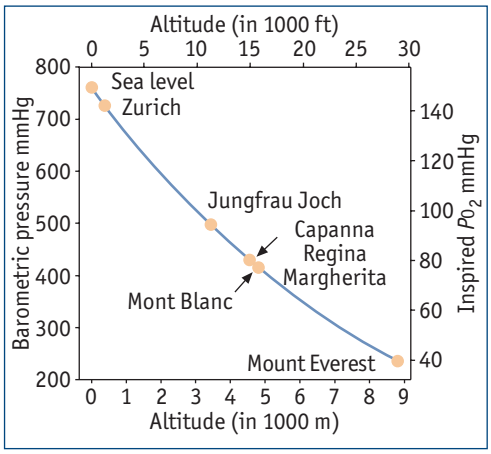


Figure 3
Relationship between altitude, barometric pressure and P_{I,O_2}.

premature closure of peripheral airways during exhalation have been shown and related to subclinical interstitial pulmonary oedema or bronchial obstruction associated with hypocapnia, exercise and cold air [8]. Oxygen uptake through the lungs at high altitude is affected by various factors including a reduced alveolar–capillary oxygen tension (P_{O_2}) driving gradient and a reduced transit time of blood through pulmonary capillaries, due to increased cardiac output. This causes a diffusion limitation of oxygen uptake, which is particularly relevant during exercise; thus, at high altitude, pronounced hypoxia may occur during strenuous physical activities. Acclimatisation to high altitude tends to optimise oxygen transport from the atmosphere to the tissues of various levels of the oxygen cascade as in illustrated in figure 7.

Pulmonary circulation

Hypoxia induces reflex vasoconstriction of the small resistance pulmonary arteries and leads to increased pulmonary artery pressure at high altitude. Since heart rate and cardiac output are also increased, thereby improving oxygen delivery as a compensation for the reduced arterial oxygen saturation, pulmonary artery pressure rises even

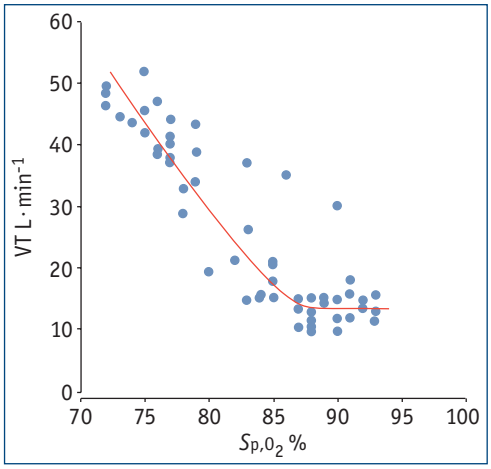


Figure 4
The hypoxic ventilatory response can be tested by letting a subject rebreathe into a spirometer while maintaining a constant P_{CO_2} in the inhaled air by means of a CO_2 absorber. Oxygen saturation (S_{p,O_2}) is measured by a pulse oximeter. Once S_{p,O_2} falls below ~87%, minute ventilation (VE) measured breath by breath increases progressively. The slope of the line fitted to the VE versus S_{p,O_2} values represents the isocapnic hypoxic ventilatory response. It is about 2L per min per % S_{p,O_2} in this case.

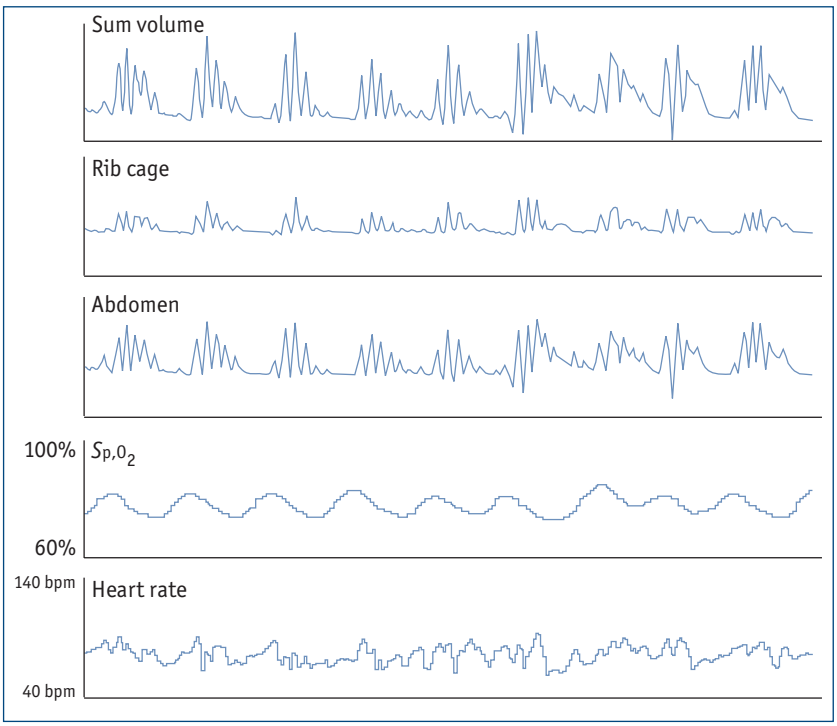


Figure 5
At high altitude, a periodic breathing pattern is typically observed during sleep. The figure shows rib cage and abdominal volume curves and their sum, reflecting lung volume changes recorded by sensors of a respiratory inductive plethysmograph in a sleeping mountaineer at the Capanna Regina Margherita (4,559 m). The S_{p,O_2} oscillates between 72% and 82% and there are pronounced variations in heart rate.

Figure 6
Mechanisms responsible for periodic breathing at high altitude. With increasing altitude, ventilation is stimulated due to hypoxia. Hyperventilation induces hypocapnic alkalosis, which promotes apnoea or hypopnoea in particular during sleep when chemical drives to breathe become more important and cortical drives diminish. During apnoea, pronounced hypoxia with progressive oxygen desaturation and the increasing P_{CO_2} stimulates an arousal and resumption of ventilation. With restoring ventilation, oxygenation is restored and hypocapnic alkalosis returns, thereby perpetuating the oscillatory breathing pattern.

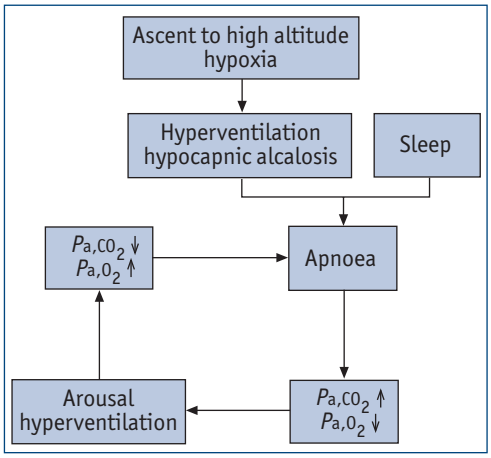
further. This is additionally promoted by heavy physical exercise. If pulmonary artery pressure is excessively elevated, HAPE may occur.

Sleep at high altitudes

Rapid ascent to altitudes >2,500 m is commonly associated with poor sleep quality. Mountaineers may perceive sleep disruption due to repetitive awakenings with a sense of suffocation relieved by a few deep breaths. These sleep disturbances are, at least partly, related to the periodic breathing induced by hypoxia [9], but they may also be promoted by headaches that commonly occur as a symptom of AMS.

Additional acclimatisation mechanisms

Acclimatisation, the physiological adaptation to altitude exposure that takes place over several



days and weeks, affects nearly all organ systems, including the cardiovascular, renal, digestive and musculoskeletal system and the blood. It is well known that high-altitude residents have increased erythrocyte concentrations and therefore have a higher oxygen carrying capacity of the blood compared to lowlanders. Polycythemia at high altitude, however, develops slowly over the course of several days and weeks. The increased erythrocyte concentration of newcomers to high altitude is due to a reduced plasma volume and not a stimulated erythropoiesis. Dehydration is the most important factor.

High-altitude related illness

AMS and HACE

AMS, the most common form of altitude-related illness, affects 10–40% of lowlanders ascending to moderate altitudes (3,000 m) and 40–60% at altitudes between 4,000 m and 5,000 m [2, 3]. The incidence of AMS depends on ascent rate, sleeping altitude, prior acclimatisation and individual susceptibility. There is no physiological measurement that predicts individual susceptibility for AMS and it occurs in both sexes and at all ages. AMS generally starts within 6–12 h after arrival at altitude, manifesting itself with nonspecific symptoms such as headache, loss of appetite, nausea or vomiting, weakness, fatigue and insomnia. The diagnosis of AMS relies on a constellation of typical symptoms in the setting of acute exposure to hypoxia. There are no specific objective signs. Depending on the severity of symptoms the disease can be graded as mild, moderate or severe. Standardised assessment may be performed with the help of the Lake Louise score (table 1) or other questionnaires. In severe forms of AMS, headaches are resistant to analgesics. If additional neurological signs, such as ataxia (detected for example by the heel-to-toe walking test), cognitive deficits and somnolence develop, a potentially life-threatening HACE must be suspected. While mild-to-moderate AMS is mostly self-limiting and disappears with ongoing acclimatisation after 1–2 days, inappropriate or delayed acclimatisation due to further ascent may result in HACE, which is associated with progressive loss of consciousness, coma and finally death within 1–3 days due to brain herniation [1].

Despite a high prevalence, the pathophysiology of AMS and HACE is incompletely understood. The primary cause is hypobaric hypoxia

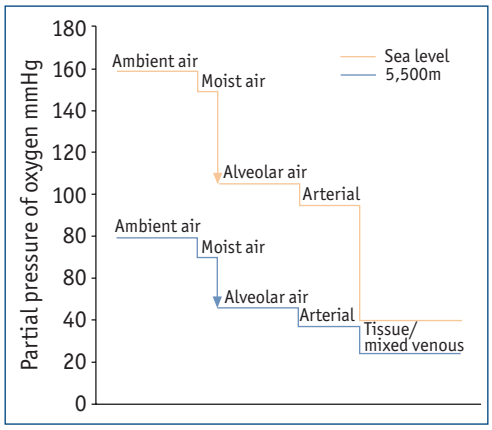


Figure 7

During transport of oxygen from ambient air to the tissues its partial pressure decreases progressively. Altitude exposure and acclimatisation modify several steps of this cascade as illustrated in the diagram. The first step is related to saturation of inhaled air with water vapur. A further drop to the alveolar P02 (arrow) is related to the CO_2 output and oxygen uptake in the alveoli. Hyperventilation at high altitude reduces the alveolar Pco_2 by the increase in alveolar ventilation. Alveolar Po_2 is thereby increased so that the alveolar-capillary driving gradient is partially preserved.

and different hypotheses on the mechanisms leading to brain swelling have been proposed. One possible mechanism could be fluid maldistribution associated with an oversecretion of aldosterone and antidiuretic hormone, as observed in patients with AMS at high altitude compared with suppression in acclimatised persons. Autopsy studies and MRI scans in patients with severe AMS showed vasogenic oedema with perivascular haemorrhages. Thus, hypoxia-triggered increases in cerebral blood flow and impaired autoregulation, and an increased permeability of the blood-brain barrier may contribute to HACE [10]. The clinical course and the rapid recovery of HACE in response to oxygen administration and steroids are consistent with the vasogenic oedema theory. Symptoms and signs of high-altitude related illnesses are summarised in table 2.

Treatment of AMS and HACE

Descent to lower altitudes alleviates AMS symptoms independent of AMS severity. Descending can even be life-saving and is strongly advisable in severe forms of AMS or if there is any sign of HACE. Depending on the severity of AMS, a step-by-step procedure is recommended: symptomatic treatment of mild symptoms and no further ascent until the symptoms have improved; descent to a lower altitude in patients with no response to medical treatment and in those with first signs of HACE. Mild AMS can often be effectively improved by ceasing further ascent, minimising exertion and waiting 1–3 days for acclimatisation.

Headaches in mild forms of AMS respond well to analgesics (acetaminophen, nonsteroidal anti-inflammatory drugs). If AMS progresses from mild-to-moderate or even severe forms, further pharmacological intervention is necessary. The aim of is to stabilise the patient and enable descent by ≥1,000 m. Unless a patient has a known allergy to sulphonamide drugs, standard

Table 1 Lake Louise acute mountain sickness scoring system

Point	Symptom	Score	Severity
Self-reported			
1	Headache	0	No headache
		1	Mild headache
		2	Moderate headache
		3	Severe headache, incapacitating
2	Gastrointestinal symptoms	0	No gastrointestinal symptoms
		1	Poor appetite or nausea
		2	Moderate nausea or vomiting
		3	Severe nausea and vomiting, incapacitating
3	Fatigue and/or weakness	0	Not tired or weak
		1	Mild fatigue or weakness
		2	Moderate fatigue or weakness
		3	Severe fatigue/weakness
4	Dizziness or lightheadness	0	Not dizzy
		1	Mild dizziness
		2	Moderate dizziness
		3	Severe dizziness, incapacitating
5	Difficulty sleeping	0	Slept as well as usual
		1	Did not sleep as well as usual
		2	Woke many times, poor night's sleep
		3	Could not sleep at all
Clinical assessment			
6	Change in mental status	0	No change in mental status
		1	Lethargy or lassitude
		2	Disoriented or confused
		3	Stupor or semiconsciousness
		4	Coma
7	Ataxia (heel-to-toe walking)	0	No ataxia
		1	Manoeuvres to maintain balance
		2	Steps off line
		3	Falls down
		4	Can't stand
8	Peripheral oedema	0	No peripheral oedema
		1	Peripheral oedema at one location
		2	Peripheral oedema at two or more locations
Functional score			
	Overall if you had any symptoms, how did they affect your activity?	0	No reduction in activity
		1	Mild reduction in activity
		2	Moderate reduction in activity
		3	Severe reduction in activity (*e.g.* bed-rest)

The Lake Louise AMS scoring system tries to quantify the severity of disease by scoring typical symptoms of AMS. The sum of the responses to the questions is calculated and a score of ≥3 points on the AMS self-reported questionnaire alone, or >3 in combination with the clinical assessment score, while at altitude >2,500 m constitutes AMS.

Table 2 Acute high-altitude diseases

		Symptoms	Findings
Acute mountain sickness	Mild	Headache, loss of appetite, nausea, insomnia	No specific clinical findings
	Moderate	Headache (sensitive to analgesics), loss of appetite, nausea, insomnia, mild dizziness and fatigue	
	Severe	Headache (resistant to analgesics), severe nausea, vomiting and severe fatigue	
High-altitude cerebral oedema		Headache (resistant to analgesics), vomiting, dizziness, drowsiness	Ataxia, altered consciousness (confusion, impaired mentation, drowsiness, stupor, coma), low-grade fever
High-altitude pulmonary oedema		Decreased performance, dry cough, dyspnoea at rest, orthopnoea, only late in illness pink or bloody sputum, respiratory distress	Resting tachycardia (> 100 beats per min), tachypnoea (> 25 beats per min), low-grade fever, rales on pulmonary auscultation, cyanosis

therapy is 250 mg acetazolamid (Diamox), twice daily. The carbonic anhydrase inhibitor acetazolamide inhibits reabsorption of bicarbonate and sodium in the renal tubules and, thus, causes a bicarbonate diuresis and metabolic acidosis. Compensatory hyperventilation to correct the pH occurs, preventing the arterial oxygen saturation from falling further. Acetazolamide effectively reduces the severity of AMS symptoms within 24 h. A more potent drug is dexamethasone, which has a well-documented effect in all degrees of AMS and in HACE. Although the mechanism of dexamethasone is not clear, it probably acts by improving brain capillary integrity and reducing vasogenic oedema. In severe forms of AMS and HACE, dexamethasone is given initially at 8 mg *i.v.*, followed by 4 mg four times daily *p.o.* If available, low-flow oxygen (2 L per min) relieves symptoms quickly and can be offered until drugs become effective. Because bottled oxygen is heavy and bulky it is rarely carried by trekking or mountaineering parties. The same is also true of inflatable hyperbaric chambers that are sometimes employed by large expeditions or those with good transport links. A person enclosed in such an airtight bag can be exposed to a pressure 140–220 mbar above the ambient pressure by operating foot- or hand-driven pumps, thus simulating a descent of 1,500–2,500 m depending on the altitude and the type of bag used. Hyperbaric bags can be life saving, especially in a remote setting without oxygen or the possibility of descent. The treatment and prevention of AMS and HACE is summarised in table 3.

HAPE

HAPE is a noncardiogenic and noninflammatory type of high-permeability pulmonary oedema caused by elevated pulmonary capillary pressure leading to a red blood cell and protein-rich oedema fluid. HAPE is rare at altitudes <3,500 m but occurs in about 2–4% of mountaineers at 4,559 m within 2–5 days of ascent with initial onset often at night [11]. The prevalence varies depending on the rate of ascent, physical exertion and individual susceptibility. Mountaineers who develop HAPE at altitudes of 3,000–4,500 m have a 60% recurrence rate when ascending rapidly to these altitudes. HAPE can develop independent of AMS or HACE. Initial symptoms include decreased exercise performance due to shortness of breath and a dry cough. With worsening disease, patients develop dyspnoea with minimal activity and a cough productive of pink, frothy sputum. Physical examination often reveals resting tachycardia, cyanosis, crackles on auscultation and low-grade fever. Chest radiograph typically shows perihilar, interstitial or alveolar opacities, increased pulmonary artery diameter but a normal-sized heart (figure 8). The most important differential diagnoses include pneumonia, pulmonary embolism and cardiogenic pulmonary oedema due to myocardial infarction or other heart disease.

The elevated pulmonary capillary pressure in HAPE is probably generated by excessive and heterogeneous hypoxic pulmonary vasoconstriction and consequent over-perfusion of lung areas not protected by hypoxic vasoconstriction. Increased pulmonary capillary pressure results in capillary stress failure and fluid leakage into the alveoli or into the interstitium. Individual susceptibility to HAPE is associated with excessive hypoxic pulmonary vasoconstriction and a constitutively decreased transepithelial Na+ transport in alveolar cells resulting in impaired alveolar water clearance.

Treatment of HAPE

Descent, supplemental oxygen or both are nearly always successful in the treatment of HAPE. If oxygen is not available or descent is not possible, then medication becomes necessary (table 3). Nifedipine lowers pulmonary artery pressure but barely increases the P_{a,O_2}. Hence, for treatment, nifedipine is adjunctive. Mild-to-moderate HAPE can be treated with rest and oxygen. If the individual feels better on the next day and oxygen saturation is >90% without supplemental oxygen they can be discharged. Patients with moderate or severe HAPE, as indicated by the failure

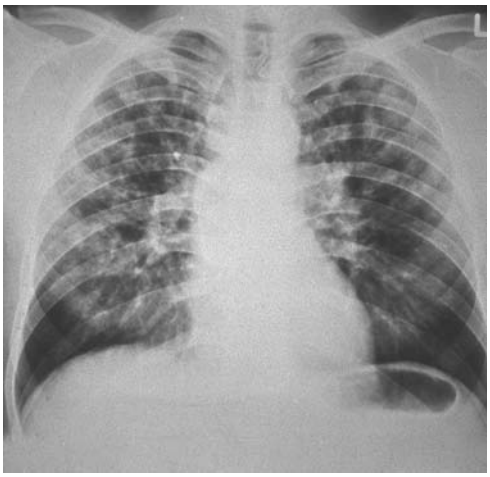


Figure 8
Chest radiograph from a mountaineer with HAPE with bilateral, predominantly perihilar, patchy infiltrates and a normal heart size. (Courtesy of M. Maggiorini, Zurich, Switzerland)

of arterial oxygen saturation to rise to >90% within 5 min of giving high-flow oxygen, should descend to low altitude. If descent is impossible and oxygen unavailable, the hyperbaric bag may be life-saving. Other pulmonary vasodilators, such as inhaled prostaglandins, nitric oxide and phosphodiesterase inhibitors (sildenafil), may be effective but are impractical (inhlaled agents) or afflicted by side effects (headache with sildenafil). In contrast, diuretics (furosemide) and morphine, successfully employed in cardiogenic pulmonary oedema, have not been proven to be effective. These drugs may even have undesirable effects such as dehydration and respiratory depression, respectively.

Prevention of high-altitude related illness

Table 3 contains a summary on the prevention of high-altitude related illnesses. The best and most important strategy to prevent any high-altitude disease is gradual ascent to allow sufficient time for acclimatisation. Above an altitude of 2,500 m, a daily ascent not exceeding 300 m has been recommended although no robust scientific evidence is available to support this advice. An extra day can be added for acclimatisation for every increase of 600–1,200 m at this altitude. If there are signs of high-altitude disease and appropriate acclimatisation is not possible for logistical reasons, preventive pharmacological treatment can be indicated.

In AMS, acetazolamide is the preferred prophylactic drug. It reduces symptoms of AMS and periodic breathing and promotes sleep at high altitude. The recommended daily prophylactic dose is 125 mg twice daily starting the evening before ascent above 2,500 m and continuing for several days or until return to low altitude. Side-effects include paraethesias and gastrointestinal complaints. Like acetazolamide, dexamethasone is effective for both treatment and prevention of AMS. A combination of dexamethasone and acetazolamide has been found to be most effective.

Most important for an effective prophylaxis against HAPE is the avoidance of an excessive hypoxic pulmonary hypertension by keeping a moderate ascent rate and avoiding strenuous exercise. The preferred pulmonary vasodilator is

Table 3 Management and prevention of high-altitude disease.

	Treatment	Prevention
Acute Mountain Sickness		
Mild	Stop ascent, minimise physical exertion, rest and acclimatise at the same altitude. Symptomatic treatment if necessary (analgesics, antiemetics).	Gradual ascent to promote acclimatisation: once above an altitude of 2,500 m, don't ascend more than 300–600 m per day. Spend one night at intermediate altitude. Avoid overexertion.
Moderate	Acclimatise, stay at same altitude for 1–2 days or return to lower altitude. Acetazolamide (Diamox) 250 mg twice daily until descent.	Acetazolamide 125 mg twice daily, starting 24 h before ascent; or dexamethasone 4 mg twice daily
Severe	Immediate descent by ≥500 m. If descent is not possible and oxygen is available, give 2–4 per min of oxygen by face mask or nasal cannula. If descent is not possible and oxygen not available, give dexamethasone (initially 8 mg *i.v.*, followed by 4 mg orally every 6 h), acetazolamide (250 mg twice daily) or both until symptoms resolve. Use a portable hyperbaric chamber if available and clinically required.	
High-altitude cerebral oedema	Immediate descent or evacuation. If descent is not possible, administer oxygen (2–6 L per min) or use a hyperbaric chamber if available. Administer dexamethasone (initially 8 mg *i.v.*, followed by 4 mg orally every 6 h). Check for symptoms and signs of a concomitant HAPE and initiate adequate treatment. Consider acetazolamide if descent is delayed.	As for acute mountain sickness
High-altitude pulmonary oedema	If available, give oxygen 2–6 L per min until oxygen saturation is >90% or use a hyperbaric chamber. Descend as soon as possible. Depending on blood pressure, administer nifedipine. 10–20 mg initially and an extended-release formulation (nifedipine 30/60 mg) subsequently. Treat accompaning acute mountain sickness with dexamethasone 8 mg *i.v.*	Gradual ascent to promote acclimatisation: once >2,500 m, ascend nomore than 300 m per day. Avoid overexertion. Consider taking nifedipine 30–60 mg per day (extended-release formulation).

Most common adverse effects
Acetazolamide: paresthesias, altered taste of carbonated beverages, polyuria.
Dexamethasone: hyperglycaemia, mood changes, rebound effect on withdrawal.
Nifedipine: hypotension, reflex tachycardia.

nifedipine, which effectively lowers pulmonary artery pressure. Nifedipine 30–60 mg per day, in an extend-release formulation, is a well-established prophylactic medication. Dexamethasone and other vasodilators, like tadalafil or sildenafil, also reduce pulmonary artery pressure and have some prophylactic effect against HAPE [12].

The treatment for periodic breathing and sleep disturbances at high altitude is similar to that for control of the daytime symptoms of AMS. Acetazolamide reduces periodic breathing, the mean level and the stability of nocturnal oxygen saturation during sleep. Furthermore, awakenings are reduced and subjective sleep quality is improved.

Benzodiazepines were once thought to be contraindicated for high altitude insomnia due to their potential ventilatory depression. Recent studies show, however, that bezodiazepines in low doses are relatively safe in this setting. Temazepam (10 mg) taken before sleeping resulted in a significant reduction of periodic breathing and had no adverse effect on next-day reaction time, maintenance of wakefulness, cognition or AMS [10]. Temazepam in combination with acetazolamide may effectively improve sleep quality.

Checklist for staying safe during high-altitude treks

- Ascend slowly to allow acclimatisation.
- Build flexibility into trek schedules to allow for the requirements of the slowest in the group to acclimatise.
- Desend urgently in the event of HAPE or HACE even during the night.
- Never leave someone with HAPE or HACE alone.
- Porters and other staff are equally susceptible to altitude illness as other participants but they may be reluctant to report symptoms. Their welfare should be a high priority.

Patients with pre-existing lung disease at high altitude

In contrast to well-documented studies in healthy individuals, little is known about the potential risk of high-altitude exposure in patients with pre-existing lung disease. Counselling these patients is therefore mainly based on expert opinions, anecdotal evidence and extrapolation from studies in normal subjects. The discussion below addresses high-altitude tolerance in selected, common respiratory diseases. For a more extensive review the reader is referred to an article in the *European Respiratory Journal* [14]. An overview of problems of air travel for patients with lung disease has been provided recently in *Breathe* [15].

Chronic obstructive pulmonary disease (COPD)

Many COPD patients are exposed to high altitude by long-term residence or during vacations or flights. Patients with a marginal or reduced P_{a,O_2} at low altitude will drop their P_{a,O_2} to even lower levels during a stay at moderate or high altitude so that the use of supplemental oxygen is advisable to prevent pronounced hypoxaemia, which could lead to excessive pulmonary hypertension and a risk of acute right heart failure or HAPE. The individual need for supplemental oxygen is difficult to predict and recommendations are based on theoretical considerations and small studies in hypobaric chambers or with experimental exposure to a low inspiratory P_{O_2}. From a practical point of view it seems reasonable that patients with severe COPD (forced expiratory volume in one second (FEV1) <50% predicted) with an S_{a,O_2} of <95% at low altitude should have an individual assessment of the potential risks and the necessary precautions before travelling to altitude. Evaluation might include arterial blood gas analysis and spirometry to have a better appreciation of their predicted P_{O_2} at moderate altitude as has been recommended in pre-flight assessment [15]. The intention is to prevent a fall of P_{a,O_2} at altitude to <6.7 kPa (55 mmHg), the level where the steep portion of haemoglobin-oxygen dissociation curve starts and pulmonary artery pressure rises progressively. The P_{a,O_2} at an altitude of 2,438 m (8,000 ft, corresponding to the allowed maximal cabin altitude of commercial airplanes) has been estimated from P_{a,O_2} at sea level based on a regression equation which incorporates the patient's FEV1: predicted P_{a,O_2} [at altitude 2,438 m] = 0.453 (P_{a,O_2} {at sea level}) + 0.386 (FEV1 % pred) + 2.440 [16]. If predicted P_{a,O_2} at altitude is <55 mmHg, supplemental oxygen administration has been suggested, although the clinical significance of temporary hypoxaemia at altitude is not clear. Other factors, such as physical activity, coexisting medical conditions and the experience during previous altitude exposures have to be taken

into account when counselling patients. Baseline medication should be continued and patients instructed regarding the therapy of potential exacerbations (rescue inhalers, oral prednisone, antibiotics). Patients with COPD and pre-existing pulmonary hypertension should be counselled against travelling to high altitude. If absolutely necessary they might take nifedipine slow release 20 mg twice daily to reduce the risk of developing HAPE or acute right heart failure. For patients with very severe airflow obstruction (FEV_1 <25% pred), acetazolamide should be used with caution for AMS prophylaxis since CO_2 retention may lead to worsened dyspnoea or respiratory failure; the dose of acetazolamide should not exceed 125 mg twice daily or an alternative agent such as dexamethasone should be used.

Asthma

Considering the reduced allergen burden with increasing altitude (house-dust mites), improvement in bronchial hyperresponsiveness can be expected. However, inhalation of cold air may worsen asthma symptoms, especially in combination with exercise or hypoxia-induced hyperventilation. A survey in adventure travellers with known asthma revealed that 88 of 203 subjects had asthma attacks during their journey, 40 reported asthma worsening, 32 experienced the worst asthma attack of their life and 11 suffered from a life-threatening asthma attack during travel [17]. Frequent use of inhaled bronchodilators (more than twice weekly) before travel, suggesting poorly controlled asthma, and participation in intense physical exercise during treks were associated with attacks during travel. Based on this experience, patients with uncontrolled, severe asthma should be cautioned against trekking and travelling to high altitude, in particular to remote areas. Asthma patients with controlled disease should continue to take their usual medications when travelling to high altitude, avoid strenuous exercise in a cold environment and take a supply of rescue inhalers, oral prednisone and an antibiotic to treat any asthma exacerbation and infections.

Obstructive sleep apnoea syndrome

As the prevalence of obstructive sleep apnoea syndrome (OSA) is quite high, the number of patients with the disorder is also expected to be large among high-altitude sojourners. Whether travelling to, and staying at, high altitude exposes OSA patients to particular health risks that differ from those described above for healthy subjects has not been appropriately investigated. Studies in OSA patients dwelling near sea level exposed to a hypoxic air mixture corresponding to a simulated altitude of 2,750 m (inspiratory oxygen fraction of 0.16) revealed a reduction of obstructive apnoea/hypopnoea but a high number of central apnoea/hypopnoea events [18]. In another study, OSA patients living at an altitude >2,400 m in Colorado were referred for sleep studies to laboratories at sea level and at 1,370 m [19]. These investigations revealed a significant reduction in the number of apnoea/hypopnoea events at lower compared with higher altitudes, which was predominantly related to a reduction in central events. These data have led to the hypothesis that patients with OSA predominantly have central sleep apnoea when sleeping at high altitude. Further studies are required to corroborate the preliminary observations in OSA patients at altitude and to evaluate whether they require adaptation of their CPAP therapy or another treatment such as acetazolamide.

Diseases associated with pulmonary hypertension

Pulmonary arterial pressure in patients with pre-existing pulmonary hypertension is further increased at high altitude. Several case reports suggest that pre-existing pulmonary hypertension may exacerbate the pathophysiology of HAPE and, therefore, predispose to HAPE. In general, patients with pre-existing pulmonary hypertension should be counselled against high-altitude travel. If high-altitude travel cannot be avoided, patients must be informed about signs and symptoms of HAPE and for patients not on medical therapy, prophylaxis with nifedipine can be given (nifedipine 20 mg SR) for the duration of their stay. Supplemental oxygen should be recommended, if available, to avoid hypoxic pulmonary vasoconstriction.

Future perspectives

Although the lessons learned from high altitude physiology over the past few years have been exciting and extensive, there are still areas of uncertainty [20]. The mechanisms underlying high-altitude diseases, including genetic factors, remain to be investigated in further detail. The physiological effects of high-altitude exposure on patients with cardiac and pulmonary diseases and the prophylaxis and treatment of high-altitude related illness in such patients are

Educational questions

1. What does the 14-year-old boy, described in the vignette, suffer from?
a) Migraine.
b) Acute mountain sickness.
c) Dehydration.
d) Flu-like illness.
2. What should be done in this case?
a) Immediate evacuation by helicopter.
b) Acetaminophen to treat the headaches and further ascent the next day if symptoms have improved.
c) Acetazolamide, acclimatisation at lower altitude for 1–2 days and then further ascent.
d) Acetazolamide and dexamethasone followed by the same procedure as in answer c.
3. What do you recommend to this young mountaineer for his next alpine tour?
a) Taking acetazolamide 500 mg the evening before ascent.
b) Ascending slowly, a maximum of 300 m per day once above 2,500 m.
c) Flying by helicopter to this altitude to minimise physical exertion.
d) Performing endurance training at least three times a week.

Suggested answers

1: b

Migraine, dehydration and exhaustion are all important differential diagnoses of acute mountain sickness. The rapid ascent from 568–3,450 m in <24 h, headache and loss of appetite together with the poor sleeping quality suggest AMS.

2: b

Immediate descent in mild forms of AMS is not necessary. Symptomatic treatment with acetaminophen when headaches develop can be attempted. If headaches do not respond to analgesics, dexamethasone, 4 mg orally should be taken. Poor sleep quality due to AMS may be improved with acetazolamide. If nausea and vomiting occur, dexamethasone can be given intravenously. Further ascent should be delayed and more time for acclimatisation allowed.

3: b

Physical fitness does not protect against high-altitude related illness. Drug prophylaxis can be helpful. The dose of acetazolamide would be 125 mg twice daily starting one day before ascent.

Suggested further reading

West JB, Schoene RB, Milledge JS. High altitude medicine and physiology. London, Hodder Education, 2007.

largely unknown. Many of these unanswered questions are evaluated worldwide by various groups through laboratory and field studies. This research is of increasing importance as the number of subjects affected with high-altitude related illness is growing related to the popularity of outdoor and mountaineering activities and the continuing progress in transport means that facilitate the access to remote and high mountain areas.

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