

Acute High-Altitude Illness: Updated Principles of Pathophysiology, Prevention, and Treatment

Akute Höhenkrankheit: Ein Update über die Prinzipien der Pathophysiologie, Prävention und Therapie

Summary

- › **The interest** in trekking and mountaineering is increasing, and growing numbers of individuals are travelling to high altitude. Following ascent to high altitude, individuals are at risk of developing one of the three forms of acute high-altitude illness: acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE). The cardinal symptom of AMS is headache that occurs with an increase in altitude. Additional symptoms are anorexia, nausea, vomiting, dizziness, and fatigue.
- › **HACE is characterized** by truncal ataxia and decreased consciousness that generally but not always are preceded by worsening AMS. The typical features of HAPE are a loss of stamina, dyspnea, and dry cough on exertion, followed by dyspnea at rest, rales, cyanosis, cough, and pink, frothy sputum.
- › **These diseases** can develop at any time from several hours to 5 days following ascent to altitudes above 2,500–3,000 m. Whereas AMS is usually self-limited, HACE and HAPE represent life-threatening emergencies that require timely intervention.
- › **For each disease**, we review the clinical features, epidemiology and the current understanding of their pathophysiology. We then review the primary pharmacological and non-pharmacological approaches to the management of each form of acute altitude illness and provide practical recommendations for both prevention and treatment. The essential principles for advising travellers prior to high-altitude exposure are summarized.

KEY WORDS:

Acute Mountain Sickness, High Altitude Cerebral Edema, High Altitude Pulmonary Edema, Hypoxia

Zusammenfassung

- › **Das zunehmende Interesse** am Trekking und Bergsteigen führt zu einer steigenden Anzahl von Touristen, die sich in großen Höhenlagen aufhalten. Nach einem akuten Höhenanstieg besteht das Risiko, eine der drei Formen der akuten Höhenkrankheit zu erleiden: Die akute Bergkrankheit (ABK), das Höhenhirnödem (HHÖ) und das Höhenlungenödem (HLÖ). Das Kardinalsymptom der ABK sind Kopfschmerzen, die durch den Aufstieg in die Höhe entstehen und zunehmen. Zusätzlich kommt es zu mindestens einem der folgenden Symptome: Appetitlosigkeit, Übelkeit, Erbrechen, Schwindel und Abgeschlagenheit.
- › **Das HHÖ** ist durch Ataxie und Bewusstseinsstrübung gekennzeichnet, die in der Regel – aber nicht zwingend – aus einer vorbestehenden ABK hervorgehen. Die typischen Zeichen eines HLÖ sind ein inadäquater Leistungsabfall, Anstrengungsdyspnoe sowie ein trockener Husten unter Belastung.
- › **Im weiteren Verlauf** kommen eine Ruhedyspnoe, pulmonale Rasselgeräusche, Zyanose, Husten in Ruhe und ein pinkfarbenes, schaumiges Sekret hinzu. Die akuten Höhenkrankheiten können innerhalb von Stunden bis zu 5 Tagen nach Aufstieg in Höhen über 2500–3000 m entstehen. Die ABK ist in der Regel selbst-limitierend, wohingegen das HHÖ und HLÖ lebensbedrohliche Erkrankungen darstellen, die einer sofortigen Therapie bedürfen.
- › **In dieser Arbeit** werden die klinischen Erscheinungsbilder, Epidemiologien und das aktuelle Verständnis der pathophysiologischen Konzepte der ABK, des HHÖ und HLÖ dargestellt. Anschließend werden die pharmakologischen und nicht-pharmakologischen Prinzipien dieser drei Krankheitsentitäten beleuchtet. Die Arbeit fasst die Grundlagen für eine kompetente, individuelle Höhenberatung zusammen.

SCHLÜSSELWÖRTER:

Akute Bergkrankheit, Höhenhirnödem, Höhenlungenödem, Hypoxie

Introduction

Exposure to high altitude leads to a fall in barometric pressure and consequently to a decline in the inspired partial pressure of oxygen. In the absence of adaptive mechanisms, the decrease in alveolar oxygen uptake yields a reduction of oxygen delivery to the periphery with the risk of cellular hypoxia and organ dysfunction. The profound effect of altitude on the oxygen cascade is illustrated in figure 1. Main-

taining sufficient oxygenation of organs and tissues in hypoxia presents a significant physiological challenge for the human body. This challenge is further aggravated during exercise due to the additional demand of oxygen resulting from exercising skeletal, respiratory, and cardiac muscles (32). If the adaptive processes fail to compensate sufficiently for the decrease in oxygen availability, acute mountain

REVIEW

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Table 1

Recommended dosages for medications used in the prevention and treatment of acute high-altitude illnesses (adapted from (26)). Of note, since all forms of acute high-altitude illnesses are caused by the lack of oxygen, descent to lower altitudes is the primary and definite treatment. If descent is not possible administration of oxygen provides a suitable treatment alternative to descent for all forms of acute high-altitude illness.

INDICATION		MEDICATION	ROUTE	DOSAGE
AMS	Prevention	Acetazolamide	oral	Moderate risk: 125 mg every 12 h High risk: 250 mg every 12 h
		Dexamethasone	oral	4 mg every 12 h
	Treatment	Ibuprofen	oral	600 mg every 8 h (against headache)
		Metoclopramide	oral	10 mg every 8 h (against nausea)
		Acetazolamide	oral	250 mg every 12 h
		Dexamethasone	oral	4 mg every 6 h (in case of severe AMS)
HACE	Prevention	Acetazolamide	oral	same as for AMS
		Dexamethasone	oral	same as for AMS
	Treatment	Dexamethasone	oral, iv, im	8 mg once, then 4 mg every 6 h
HAPE	Prevention	Nifedipine	oral	30 mg slow release version, every 12 h or 20 mg slow release version every 8 h
		Tadalafil	oral	10 mg every 12 h
	Treatment	Nifedipine	oral	30 mg slow release version, every 12 h or 20 mg slow release version every 8 h

sickness (AMS), high altitude cerebral edema (HACE), or high altitude pulmonary edema (HAPE) may occur. These diseases may develop in non-acclimatized individuals after ascending too fast and too high (21). In this review we summarize the current concepts of the pathophysiology, prevention, and treatment of AMS, HACE, and HAPE.

Acute Mountain Sickness (AMS) and High-Altitude Cerebral edema (HACE)

AMS is a complex of nonspecific symptoms experienced by many within the first days after ascent to an altitude >2,500 m. AMS primarily manifests itself as headache, anorexia, nausea, vomiting, dizziness, and fatigue (37). AMS per se is not life-threatening and in the vast majority of cases the symptoms resolve spontaneously over the next days if no further ascent is made. Very severe AMS, however, may progress to life-threatening HACE, which is characterized by brain swelling and increased intracranial pressure leading to an altered level of consciousness, ataxia, and ultimately death if not treated appropriately (5).

The major determinants of AMS are the absolute altitude reached, the rate of ascent, the extent of pre-acclimatization, and the level of individual susceptibility (42). While the first three factors usually can be controlled, the mechanisms determining the degree of individual susceptibility are obscure. Susceptibility to AMS is not different between males and females, while children and adolescents may be less prone to AMS than adults (24). Whether exercise amplifies AMS or not remains controversial (38, 43). However, it has recently been shown that endurance trained athletes with a high aerobic capacity (>65 ml/kg/min) are at higher risk for developing AMS on the first day following passive and rapid ascent to 3,450 m (40).

The pathophysiology of AMS is still incompletely understood, and no consistent or strong correlations between an overall assessment of AMS and single pathophysiologic factors have been found in a large number of studies over the last 50 years. Also, exceptional high-altitude mountaineers fail to display any remarkable physiological characteristics at sea level (34), and those who cope poorly with high altitude are equally difficult to identify.

Despite the long-lasting search for a test that reliably predicts susceptibility to AMS, currently the best predictor of high-altitude tolerance is the history of performance during previous exposures to a similar altitude with comparable pre-acclimatization (3).

While it is commonly assumed that AMS symptoms peak after the first night spent at a new altitude >2,500 m, we recently described, for the first time, that three different time courses of developing AMS may exist (11). While at a given altitude about 40% of those who suffer from AMS have a peak of their symptoms on day 1, about 40% of those with AMS have a peak in symptom severity on day 2. In about 20% of those who experience AMS, symptom severity increases over time and peaks on day 3 or even later. According to the day at which AMS symptoms are most prominent we suggest that the different time courses of AMS be named type I, type II, and type III. We further hypothesized that these variations of AMS time course are due to the different dominating pathophysiologic factors as summarized in Table 2. Figure 2 summarizes the concepts currently thought to underlie the pathogenesis of AMS and HACE, respectively.

Hypoxemia is an indispensable requirement for the development of AMS and HACE. Usually, at a given altitude arterial oxygen saturation (SaO₂) and tension (PaO₂) are on average slightly lower in individuals with AMS compared to healthy controls (11, 29). Factors that may contribute to the more pronounced hypoxemia in AMS include a lower hypoxic ventilatory drive (36), a higher metabolic demand (40), and an impaired oxygen diffusion caused by interstitial pulmonary edema (14). Once hypoxemia is established, the following pathways may be activated: At high altitude cerebral blood flow (CBF) increases in order to maintain oxygen delivery to the brain (52). The increase in CBF may lead to an increase in hydrostatic vascular pressure, particularly if a limitation in venous outflow exists (53) as it may be the case in supine position. An increased hydrostatic vascular pressure favours the development of HACE, especially if vascular permeability (see below) is also increased (25). The brain itself is an insensate organ except for its meninges and large blood vessels, which contain sensory axons projecting to the trigeminal nerve (39). Brain edema and raised intracranial pressure may cause headache by compressing brain

structures leading to displacement and stretching of pain-sensitive unmyelinated fibres within the trigeminovascular system (1). Connections of afferent fibres of the trigeminal nerve to vegetative centres in the brainstem may also explain accompanying symptoms such as nausea and vomiting (39). A further consequence of hypoxemia may be an increase in vascular permeability through higher levels of oxidative stress, inflammation or upregulation of vascular endothelial growth factor (VEGF) (1, 50), which might be involved in the pathophysiology of HACE. In addition, cytotoxic (intracellular) edema, caused by hypoxic depression of energy-dependent ion transport systems, may contribute to an increase in brain volume and intracranial pressure (23). However, as indicated by lumbar punctures, in AMS the blood-brain barrier seems to be intact for large molecular weight proteins (2) and there are no significant associations between the observed slight increase in brain volume (23) and AMS. Another consequence of hypoxemia in some individuals may be greater activation of the parasympathetic nervous system over that of the sympathetic nervous system, which may typically cause nausea and dizziness (47) and lead, in combination with headache, to the diagnosis of AMS. This may explain why endurance trained athletes, that naturally have a more dominant parasympathetic activity, experience more difficulties to adapt to high altitude on the day of ascent (40).

In HACE visually detectable brain swelling has been demonstrated especially in the splenium of the corpus callosum (22). Susceptibility-weighted MRI also demonstrated a leak of the blood-brain barrier for erythrocytes as evidenced by hemosiderin deposition persisting over years in the corpus callosum and throughout the brain in more severe cases after HACE (44). The clinical features of HACE are truncal ataxia and decreased consciousness that generally but not always are preceded by worsening AMS. Without appropriate treatment HACE can rapidly progress to coma (29).

High Altitude Pulmonary Edema (HAPE)

Investigations over the last 40 years have largely unravelled the pathophysiology of HAPE, which is a pressure-induced, non-cardiac pulmonary edema that occurs within 1-5 days after an acute altitude exposure >3,000 m when acclimatization

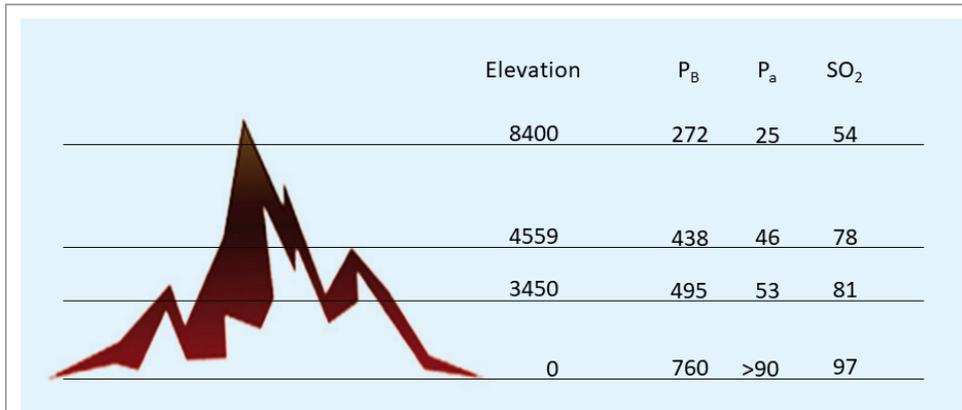


Figure 1

Effect of altitude on arterial oxygenation. The values may vary considerably with weather conditions and between studies. Altitude is given in meters. P_B=barometric pressure [mmHg]; P_a=Arterial partial pressure of oxygen [mmHg]; SO₂=Arterial oxygen saturation [%]. Values are derived from (10, 20, 40).

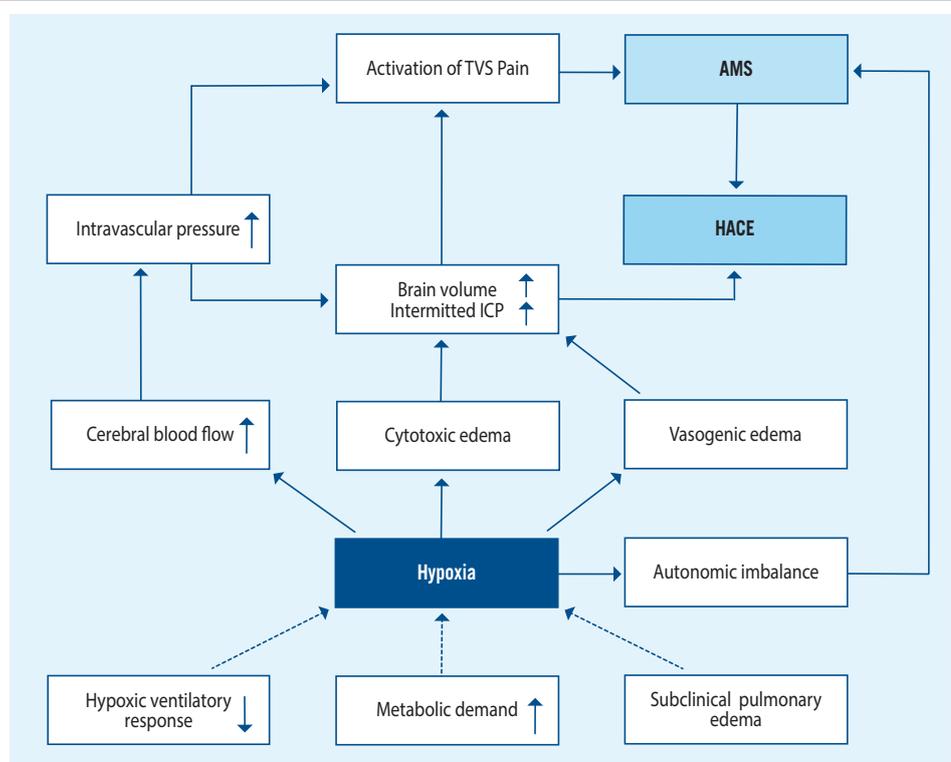


Figure 2

Schematic illustration of pathophysiologic mechanisms thought to underlie AMS and HACE (modified according to (11)). For details see text. AMS=Acute mountain sickness. HACE=High altitude cerebral edema. ICP=Intracranial pressure. TVS=Trigeminovascular system.

is insufficient. If HAPE occurs at lower altitudes (<3,000 m) pre-existing co-morbidities (e.g. left heart failure, pulmonary embolism, abnormalities in pulmonary circulation) must be considered. In about 50-70% of cases HAPE is preceded by symptoms of AMS. Early HAPE symptoms include excessive dyspnoea during exercise and reduced exercise performance. As edema progresses, orthopnoea, gurgling in the chest, and pink frothy sputum will occur. Under these circumstances, arterial SO₂ and PO₂ are dramatically reduced, reflecting the severity of the disease. If untreated, the estimated mortality rate of HAPE is about 50% (5).

As for AMS, the major determinants of HAPE are the absolute altitude reached, the rate of ascent, the extent of pre-acclimatization, and the level of individual susceptibility (5). ➤

Table 2

Factors that may contribute to different time courses of AMS at a given altitude when no further ascent is made (according to (11)).

TIME COURSE OF AMS	CONTRIBUTING FACTORS
Type I	(Over)exertion
	Drug intake ameliorating AMS symptoms
	Autonomic imbalance / parasympathetic overactivity
	Greater metabolic rate leading to higher oxygen consumption
Type II	Pronounced nocturnal desaturations
	Cerebral venous outflow restriction
	Blunted hypoxic ventilatory response
Type III	Slow ventilatory acclimatization
	Subclinical pulmonary edema

A concomitant airway infection may increase the risk for HAPE by increasing permeability of the alveolar-capillary barrier, which favours fluid extravasation into the lung (48). The incidence among persons with an unknown history of HAPE is about 6% if they ascend to 4559 m within one to two days. For individuals with a history of radiographically documented HAPE, i.e. for HAPE-susceptible individuals, this risk increases to about 60% (5).

An important factor in the pathophysiology of HAPE is an excessive hypoxic pulmonary vasoconstriction causing fluid leakage into the lung. The critical role of a high pulmonary artery pressure is confirmed by the fact that descent, oxygen or drugs that lower pulmonary artery pressure are effective for preventing and treating HAPE. Measurements of plasma endothelin (8), of nitric oxide (NO) in exhaled air (12), NO metabolites in broncho-alveolar lavage fluid (49), and NO-dependent endothelial function in the systemic circulation (9) all point to a reduced NO availability and increased endothelin production in hypoxia as main cause of the excessive hypoxic pulmonary vasoconstriction in HAPE-susceptible individuals. Additional factors, e.g. inflammatory-induced increases in the permeability of the alveolar-capillary barrier and/or impaired alveolar fluid clearance, may contribute to the progression of HAPE ((41, 48), Figure 3).

Several mechanisms have been suggested to explain how an exaggerated hypoxic pulmonary vasoconstriction induces pulmonary edema formation (48): First, pulmonary vasoconstriction may cause transarteriolar leakage upstream of the microvasculature. Second, hypoxic pulmonary vasoconstriction may increase hydrostatic pressure at the microvascular level leading to fluid filtration. Third, inhomogeneous regional arterial hypoxic vasoconstriction may yield lung regions with higher flows in areas where the vasoconstriction is weak or not existent. In these areas capillary pressure increases, favouring pre-capillary and capillary fluid filtration. Indeed, MRI studies of lung blood flow at rest have demonstrated that hypoxic pulmonary vasoconstriction is inhomogeneous in HAPE-susceptible individuals, but not in those with HAPE resistance (16). This inhomogeneity in regional blood flow may explain the patchy radiographic appearance of early HAPE that is usually seen on chest radiographs or CT scans.

As described above, a rapid increase in hydrostatic pressure in the pulmonary vasculature leading to increased transvascular fluid filtration is the hallmark of the pathophysiology of HAPE. As an additional factor, a decreased capacity to clear fluid from the alveolar space may also contribute to its progression (41).

The removal of edema fluid from the alveolar space depends on active transport of sodium (Na⁺) and chloride (Cl⁻) across alveolar epithelial type I and II cells (31). Na⁺ enters the cell via various Na⁺ transporters in the apical plasma membrane and is extruded on the basolateral side of the cell by Na⁺/K⁺ pumps. Water follows passively, probably paracellularly and/or through aquaporins, which are water channels that are found predominantly on alveolar epithelial type I cells. From the lung interstitium the fluid is cleared via the lymphatics which may be less developed in HAPE-susceptible persons (13). It is well established that hypoxia decreases transepithelial Na⁺ transport by reducing expression and activity of both the epithelial sodium channel (ENaC) and the Na⁺/K⁺-ATPase. However, if and how much a decreased alveolar fluid clearance and lymphatic transport capacity contribute to the pathophysiology of HAPE is not known.

Prevention of AMS, HACE, and HAPE

There is a variety of non-pharmacologic and pharmacologic options for preventing AMS, HACE, and HAPE. These are largely based on the physiologic and pathophysiologic considerations described above. In general, preventive approaches should take into account the targeted altitude, the history of previous performance at high altitude, the planned rate of ascent, and the extent of pre-acclimatization. Since HACE is considered to be a very severe form of AMS, the preventive measures described for AMS also apply for HACE.

Gradual Ascent

Guidelines for ascents to altitudes >3,000 m recommend that the daily sleeping elevation should not be increased by more than 500 m per day (28). In addition, a day of rest should be included every three to four days. If adherence to this ascent profile is impossible, e.g. due to logistic reasons, terrain, or environmental factors, additional acclimatization days should be considered either before or directly after larger gains in altitude. However, there is a large interindividual difference with respect to high-altitude tolerance, and some persons may tolerate much faster ascent profiles without being compromised in exercise performance or well-being.

Preacclimatization

Exposure to moderate altitudes before ascending to high altitude decreases the risk for AMS, HACE, and HAPE. However, the optimal individual approach of preacclimatization is difficult to predict. In general, preacclimatization should be conducted at an altitude that is high enough to induce adaptive processes and low enough not to cause malaise. Evidence suggests that spending about one week at altitudes between 2,200 to 3,000 m decreases the risk of AMS after subsequent ascent to 4,300 m (6). Also, exposure to altitudes >3,000 m in the weeks preceding a climb to 4,500 m is associated with a reduced incidence of AMS (42). Studies on intermittent normobaric or hypobaric hypoxic exposures preceding the ascent to high altitude exposure have reported conflicting results due to the variability of protocols. In well controlled trials seven sessions in one week or 13 sessions in four weeks of one hour exposures to simulated altitude of 3,700-4,500 m had no effect on AMS after rapid ascent to a real altitude of 4,500 m (45) and in AMS-susceptible individuals to 3,650 m (17). Long and frequent exposures not compatible with regular daily activities reduce the risk of altitude illnesses considerably (7, 35). Sleeping one week in hypoxic tents had no relevant effect on AMS at 4,300 m (19) while two weeks had marginally significant effects at 4,500 m (15).

Pharmacological Approaches

A variety of medications can be used for the prevention of AMS, HACE, and HAPE (Table 1). However, pharmacological prevention of high-altitude illnesses should be based on an assessment of the individual risk for these diseases and should consider other factors such as the ascent profile and the absolute altitudes reached. Pharmacological prophylaxis should be considered for moderate and high-risk ascent profiles, but not for low-risk situations. Of note, if high-altitude illnesses develop even though pharmacological prophylaxis is taken, the therapeutic options are reduced to drugs not yet used and all other measures listed in the guidelines, which are still to be followed.

Acetazolamide is the mainstay in the pharmacological prevention of AMS and HACE (28). The optimal dose is a matter of debate, but several studies suggest that 125 mg twice daily is sufficient for most settings (27). Although doses up to 750 mg daily may be used, they are associated with more side effects and are not recommended as standard prevention of AMS. For children, the recommended dose of acetazolamide is 2.5 mg/kg (up to a maximum of 125 mg) every 12 hours (28). The medication is usually best started on the evening before ascent and should be continued until descent or for 2-3 days at the definite altitude. In case of intolerance or contraindications (e.g. acetazolamide and sulfonamide hypersensitivity, adrenal insufficiency) to acetazolamide, dexamethasone may be taken at a dose of 4 mg twice daily (28). The dose may be increased to 4 mg every 6-8 hours in high-risk settings. Due to the risk of adrenal suppression, dexamethasone should not be stopped abruptly but rather tapered over one week if it was taken for more than 5-7 days. Due to the lack of data for this indication, dexamethasone is not recommended for AMS prevention in children. Of note, acetazolamide and dexamethasone belong to the substances that are prohibited by the World Anti-Doping Agency (WADA), so that competitive athletes are restricted to non-pharmacological approaches for preventing high-altitude illnesses.

The primary method for preventing HAPE is a gradual ascent profile as it is described above. Drugs for HAPE prophylaxis should only be taken by individuals with a prior history of HAPE, if it is not possible to follow the recommended gradual ascent profile (see above). Based on large clinical experience and some smaller studies, the drug of first choice is the calcium-antagonist nifedipine (4, 5). The recommended dose is 30 mg twice daily of the extended-release preparation. It should be started the day

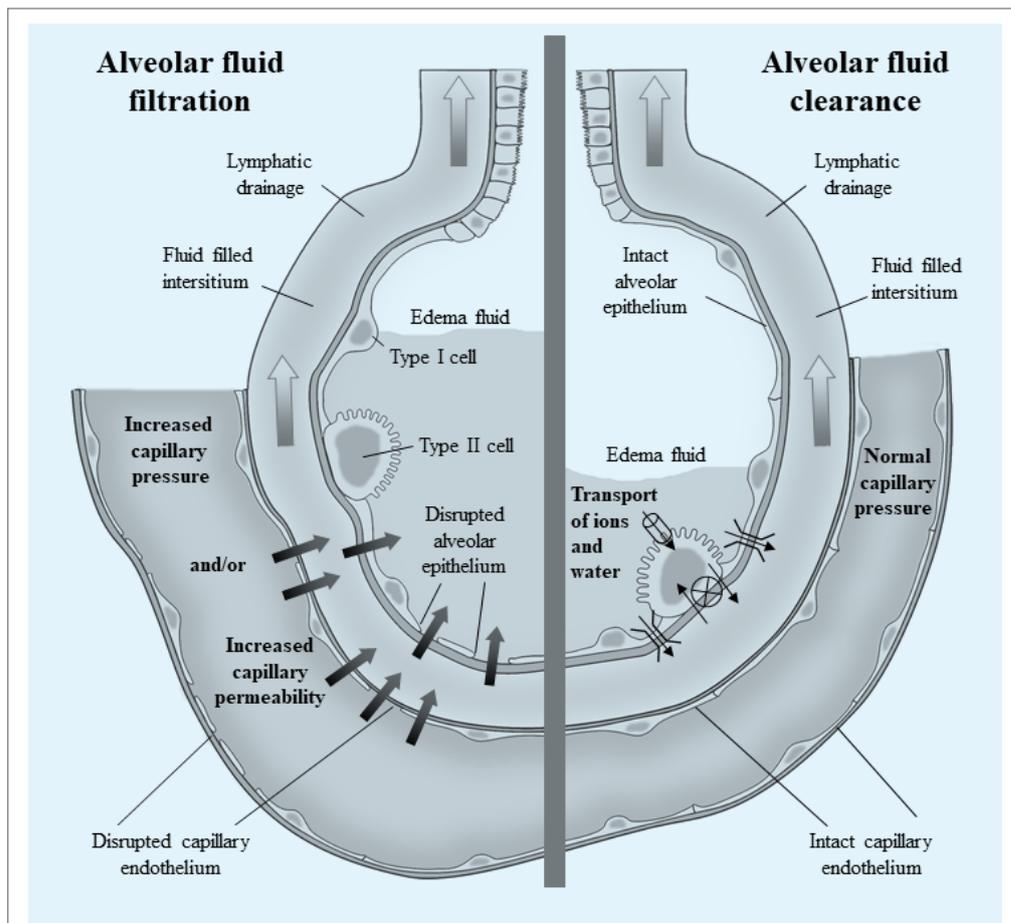


Figure 3

Pulmonary fluid balance (modified according to (50)). Under physiologic conditions the layer of alveolar lining fluid is kept thin to permit efficient gas exchange. Fluid filtration into the lung interstitium is enhanced by an increase in capillary pressure and/or by an increase in capillary permeability (as indicated on the left side of the alveolus). If the quantity of fluid leaving the pulmonary microcirculation exceeds the transport capacity of the lymphatics, interstitial and eventually alveolar edema develops. Once alveolar edema occurs fluid is cleared from the air spaces (as indicated on the right side of the alveolus) by active transport of sodium, chloride, and water across the alveolar epithelial barrier.

before ascent and continued until descent is initiated, or until one has spent 4-5 days at the targeted altitude. Hypotension is not a concern with the extended-release version of the medication and may occur only in a few individuals. Dexamethasone (8 mg twice daily) and tadalafil (10 mg twice daily) taken before ascent are also effective in HAPE prevention (30) and can be taken if contra-indications (e.g. hypotension, hypersensitivity) against nifedipine exist. Pharmacologic consideration suggests that sildenafil (50 mg three times daily) may also be effective (28). However, due to the limited data available these drugs are only recommended as alternatives to nifedipine.

Treatment of AMS, HACE, and HAPE

Since all forms of acute high-altitude illness are caused by the lack of oxygen, descent to lower altitudes is the primary and definitive treatment. If descent is not possible, e.g. due to the terrain or because the patient is too sick, oxygen delivered by nasal cannula or mask at flow rates that relieve symptoms provides a suitable alternative to descent. Usually a peripheral SO_2 of ~90% is sufficient. However, as described below, descent or administration of oxygen is not necessary in all circumstances.

Usually AMS is mild to moderate and can be treated by a day of rest at the same altitude. In case of headache simple analgesics, e.g. paracetamol or ibuprofen, are usually effective, >

and in case of nausea anti-emetics, e.g. metoclopramide, can be taken (5). Dexamethasone (4 mg every 6 hours) alone or in combination with acetazolamide (250 mg twice daily), which is not well documented for treatment, can be administered for those individuals with more severe AMS, or for those who fail to respond to conservative measures (29). Dexamethasone is very effective in treating AMS (18, 26). Individuals who remain ill despite these measures should descend 500-1000 m in altitude or until symptoms resolve. The descent should not be managed alone, particularly in case of severe AMS. In case HACE develops, 8 mg dexamethasone should be administered (intramuscularly, intravenously, or orally) followed by 4 mg every 6 hours (28). Descent or evacuation to low altitude must be initiated as soon as possible. If descent is not feasible, supplemental oxygen or a portable hyperbaric chamber should be used (28). Portable hyperbaric chambers, however, require constant tending by care providers because the devices must be pressurized by hand or foot pumps. The mode of action is a rapid pressurization of the patient (increase of oxygen pressure) which simulates a descent of about 2,000 to 2,500 m. Especially in case of HACE the patient must be closely observed in order not to miss a clinical worsening that requires rapid medical intervention.

As with AMS and HACE, descent remains the single best treatment for HAPE. Individuals should descend at least 1,000 m in altitude (28). If this is not possible, oxygen represents a suitable alternative. Both, descent and oxygen should be combined with nifedipine (30 mg sustained release version every 12 hours) (28). Due to their vasodilating properties, phosphodiesterase inhibitors (e.g. sildenafil, tadalafil) are probably effective in HAPE treatment, but there are no systematic studies examining their efficacy in this situation. Therefore, sildenafil or tadalafil may be used for HAPE treatment if descent, access to supplemental oxygen, or portable hyperbaric therapy are impossible and nifedipine is not available (28). Considering its potential role in HAPE prevention, dexamethasone may be considered for HAPE treatment. Although reports document clinical use in this regard, there are case reports (33) that caution the use of dexamethasone in the treatment of HAPE, because it might have a delayed onset of effects. ■

Conflict of Interest

The authors have no conflict of interest.

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