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REVIEW

A practical approach to high-altitude illness

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Summary

At high altitudes, the human body is exposed to low partial pressure of inhaled oxygen, the condition known as hypobaric hypoxia. When the ability of the human body to adapt to these conditions is exceeded, Acute Altitude Illness (AAI) develops. In the AAI spectrum, Acute Mountain Sickness (AMS), High Altitude Pulmonary Edema (HAPE) and High-Altitude Cerebral Edema (HACE) are usually described. Due to the high incidence of AAI and potentially high mortality in HAPE and HACE patients, a series of prophylactic and therapeutic measures are introduced as proposed by the current guidelines. The most important prevention of AAI is the low speed of ascent. The treatment of choice for HAPE and HACE is quick descent, supplemental oxygen if available, and medications such as acetazolamide, dexamethasone, nifedipine, and phosphodiesterase inhibitors.

Keywords: Acute Altitude Illness, Acute Mountain Sickness, High Altitude Cerebral Edema, High Altitude Pulmonary Edema, hypoxia.

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INTRODUCTION

A vast majority of the global human population resides at altitudes close to the sea level. Only about 1% is permanently settled above 2500 m. (1)However, every year tens of millions of people travel to high-altitude areas of the Alps, the Rockies, the Himalayas or the Andes for work or leisure. Areas that only world-class professional mountaineers visited a few decades ago are nowadays sites of blooming mass tourism and the supporting industry. The importance of better education of medical professionals on altitude-related medical conditions cannot be more emphasized in the current climate of rapidly developing high-altitude tourism. Even so, formal medical education still fails to address this subject adequately. (2)

The most important feature of a high-altitude environment is low barometric pressure. With ascending altitude, barometric pressure drops exponentially. However, the composition of the lower atmospheric layers is surprisingly uniform, up to 100 km above the sea level, with approximately 21% oxygen content. Therefore, although the inspired air always contains 21% oxygen, the partial pressure of oxygen in the inspired air *will decrease* with ascending altitude. Such a condition is called *hypobaric hypoxia*. In contrast, almost all cases of hypoxia at the sea level are classified as *normobaric hypoxia*. Low partial pressure of inhaled oxygen results in low partial pressure throughout the oxygen cascade, thus impeding all oxygen-dependent cellular processes.

Luckily, the human body can adapt to altitude and hypobaric hypoxia in the process called acclimatization. When these adaptation mechanisms are overwhelmed, Acute Altitude Illness (AAI) develops. Acute Altitude Illness is didactically and clinically divided into Acute Mountain Sickness (AMS), High Altitude Pulmonary Edema (HAPE) and High Altitude Cerebral Edema (HACE). However, the effects of high altitude expand beyond these three manifestations.

ACUTE MOUNTAIN SICKNESS

Acute Mountain Sickness is the mildest form of AAI. It affects an increasing number of people with ascending altitude, with the reported incidence of up to 75% at altitudes over 5 000 m. (3) It is generally accepted that AMS occurs at altitudes of ≥ 2500 m in unacclimatized individuals with the usual delay of 4–12 h upon the arrival at the new altitude. However, in susceptive individuals, symptoms of AMS can manifest at lower altitudes as well. (4)

The clinical diagnosis of AMS is made per exclusion, but in real-world conditions scoring systems (otherwise developed for research purposes) are used to identify individuals with AMS. The most frequently used one is Lake Louise AMS Score **(Table1)**. It should be emphasized that the assessment of symptoms should be performed at least 6 h after the ascent has been completed to allow enough time for AMS to present and avoid misinterpretation of the symptoms of exhaustion, dehydration or environmental exposure. (5) Based on the latest revision of the Lake Louise criteria, a score of 3 or more points with at least one point for headache suggests AMS. (6) However, some authors have challenged headache as a mandatory criterion for AMS diagnosis, arguing that some cases of AMS could be overlooked because patients were not presenting with headache. (7)

Table 1. Lake Louise Acute Mountain Sickness Score.

Headache	0—None at all 1—A mild headache 2—Moderate headache 3—Severe headache, incapacitating
Gastrointestinal symptoms	0—Good appetite 1 - Poor appetite or nausea 2 - Moderate nausea or vomiting 3 - Severe nausea and vomiting, incapacitating
Fatigue and/or weakness	0 - Not tired or weak 1 - Mild fatigue/weakness 2 - Moderate fatigue/weakness 3 - Severe fatigue/weakness, incapacitating
Dizziness/ light-headedness	0 - No dizziness/light-headedness 1 - Mild dizziness/light-headedness 2 - Moderate dizziness/light-headedness 3 - Severe dizziness/light-headedness, incapacitating

(Modified from: Roach RC, Hackett PH, Oelz O, Bärtsch P, Luks AM, MacInnis MJ, et al. The 2018 Lake Louise Acute Mountain Sickness Score. High Alt Med Biol. 2018;19(1):4-6.)

Several risk factors for developing AMS have been proposed, with conflicting evidence for some of them. They include a history of previous AMS, younger age, obesity, preexisting lung disease, increased exertion, rapid ascent, ascent >400 m per day, altitude attained, preacclimatisation, altitude of residence and a more controversial gender and resting SpO2. (8-11)There is no evidence that chronic underlying medical problems such as asthma, coronary artery disease, or diabetes mellitus increase the risk of becoming ill following an ascent. (4) Current guidelines of the Wilderness Medical Society differentiate three risk categories of altitude ascents based on the speed of ascent and the individual's suspected or known susceptibility to AAI **(Table 2)**. (12)

Prophylactic measures include both non-pharmacological and pharmacological interventions. Non-pharmacological actions are far more beneficial to patients than pharmacological ones. They include preacclimatization and an adjusted speed of ascent. Decision on the speed of ascent depends on multiple environmental and personal factors, including terrain, weather, logistical issues, but also the fitness and competence of the expedition members. For ascents to altitudes over 3000 m, most guidelines recommend the daily increase of sleeping el-

Table 2. Risk categories for Acute Altitude Ilness.

Risk category	Description
Low	• Individuals with no history of altitude illness and ascending to ≤ 2800 m • Individuals taking ≥ 2 days to arrive at 2500 - 3000 m with subsequent increases in sleeping elevation < 500 m/day and an extra day for acclimatization every 1000 m
Moderate	• Individuals with a history of AMS and ascending to 2500 - 2800 m in 1 day • No history of AMS and ascending to >2800 m in 1 day • All individuals ascending >500 m/day (increase in sleeping elevation) at altitudes above 3000 m but with an extra day for acclimatization every 1000 m
High	• Individuals with a history of AMS and ascending to >2800 m in 1 day • All individuals with a history of HACE or HAPE • All individuals ascending to > 3500 m in 1 day • All individuals ascending > 500 m/day (increase in sleeping elevation) above >3000 m without extra days for acclimatization • Very rapid ascents (e.g., < 7 days ascents of Mt. Kilimanjaro)

AMS - Acute Mountain Sickness; HACE - High Altitude Cerebral Edema; HAPE - High Altitude Pulmonary Edema. The altitudes listed in the table refer to the altitude at which the person sleeps. Ascent is assumed to start from elevations < 1200 m. The risk categories described pertain to unacclimatized individuals.
(Luks AM, Auerbach PS, Freer L, Grissom CK, Keyes LE, McIntosh SE, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med. 2019;30(4s):S3-s18.)

evation should not exceed 300-600 m, with at least one day for rest after every 1000 m of altitude gained. Sleeping altitude is considered more significant than maximal altitude achieved during waking hours. (12) So far, there is only one actual randomized controlled trial to evaluate the influence of the speed of ascent on AMS, and this study provided strong evidence for the fact that slower ascent is associated with lower incidence and severity of AMS as well as a higher ascent success rate. (13)

Preacclimatization refers to repeated exposure to hypobaric or normobaric hypoxia in the days and weeks before the high-altitude travel. Although recommended and employed by many experienced high-altitude mountaineers, current guidelines do not endorse particular protocols of preacclimatization. Still, they only suggest that some preacclimatization should be considered due to a lack of evidence to support a specific practice. (12) However, it is recognized that exposure to hypobaric hypoxia is more effective than exposure to normobaric hypoxia and more prolonged exposure to hypoxic conditions compared to shorter ones. (14)

Table 3. Recommended medications used for prevention of AMS, HAPE and HACE in adults.

Medication	Indication	Dosage
Acetazolamide	AMS, HACE	125 mg every 12 h
Dexamethasone	AMS, HACE	2 mg every 6 h or 4 mg every 12 h
Ibuprofen	AMS	600 mg every 8 h
Nifedipine	HAPE	30 mg ER every 12 h or 20 mg ER every 8 h
Tadalafil	HAPE	10 mg every 12 h
Sildenafil	HAPE	50 mg every 8 h

All medications are taken via the oral route. AMS - Acute Mountain Sickness; HACE - High Altitude Cerebral Edema; HAPE - High Altitude Pulmonary Edema; ER - extended-release.
(Modified from: Luks AM, Auerbach PS, Freer L, Grissom CK, Keyes LE, McIntosh SE, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med. 2019;30(4s)S3-s18.)

Adequate hydration is mandatory at high altitudes to avoid dehydration which can mimic the symptoms of AMS. It is important to note that overhydration can be as dangerous as AMS due to dilutional hyponatremia. (15) Coca plant is traditionally used in the Andes to alleviate or prevent symptoms of AMS, but current evidence does not support its use. (16) Short-term oxygen therapy from small volume canisters (2 – 10 L/canister) does not bring any benefit to AMS prevention or treatment. (12)

Prophylactic medications **(Table 3)** are recommended in moderate and high-risk situations **(Table 2)**. (12) Acetazolamide and dexamethasone are the most frequently used prophylactic drugs. Due to fewer side effects, acetazolamide is preferred to dexamethasone, but dexamethasone should be used in cases of severe adverse effects to acetazolamide. The concurrent use of these drugs for prophylactic purposes is not advised except in emergencies that mandate very rapid ascent, such as search & rescue or military missions. The timing of prevention is essential. Both medications should be started on the day before the ascent, but they still have beneficial effects if started on the first day of the ascent. For individuals ascending to and staying at the same elevation for more than several days, prophylaxis may be stopped after two days spent at the highest altitude. For individuals ascending to a mountain top and then descending significantly on the same day, medications should be stopped in the absence of AMS/HACE symptoms. (12) There are indications that ibuprofen (17-19), metoclopramide (20) or budesonide (21, 22) could be used to prevent AMS, but more robust evidence is still needed (23). Weak recommendation exists, however, for ibuprofen to be used for AMS prevention in individuals who do not wish to take acetazolamide or dexamethasone or who have ad-

verse reactions to these medications. (12) Paracetamol, Gingko Biloba and inhaled budesonide are not currently recommended for AMS prophylaxis. (12)

By far the most effective treatment option for AMS is descent. Descent is indicated in severe AMS and treatment-resistant AMS. (12) Symptoms usually resolve after 300 to 1000 m of descent, but the descent is not always necessary, and it sometimes is not possible either.

Using supplemental oxygen therapy is highly recommended for treating AMS. However, oxygen supplementation should be reserved for severe AMS or high-altitude medical facilities since bottled oxygen or oxygen concentrators are scarce. The way of oxygen administration and inspired fractional concentration of oxygen (FiO2) should be targeted to raise SpO2to >90% to relieve symptoms or if descent is not possible. (12)

Recommended medications for the treatment of AMS are listed in Table 4. Both acetazolamide and dexamethasone should be considered for the treatment of AMS. Acetazolamide is the preferred prophylactic option that is seldom sufficient in treating severe AMS. At the same time, dexamethasone is the preferred treatment option used for prophylaxis in high-risk situations. Paracetamol and ibuprofen are recommended for treating high-altitude headaches but not for AMS treatment. (12)

If AMS symptoms do not progress to HAPE or HACE, they usually resolve spontaneously or after pharmacological or non-pharmacological treatment. Most frequently, the patients who no longer have AMS symptoms will decide to undertake further ascent. However, if symptoms do not fully resolve after the descent, the ascent to previously attained altitude is not advised. (12)

More severe forms of AAI are HAPE and HACE. The mortality rate from HAPE and HACE is approaching 50% without adequate medical care. (24) Patients can develop HAPE and HACE simultaneously in up to 10 % of cases. (25)

HIGH-ALTITUDE PULMONARY EDEMA

High-altitude pulmonary edema (HAPE) is non-cardiogenic pulmonary edema associated with the exposure to hypobaric hypoxia. The incidence of HAPE rises with altitude to 6% at 4500 m and up to 15% at 5500 m. Sporadic cases have been described at altitudes as low as 2000 m. In individuals with a history of HAPE, the recurrence rate is as high as 60%. It is likely fatal if left untreated. The mortality rate depends on multiple factors, including early recognition and treatment, but it is still very high, approximately 50% in untreated patients. Although AMS and HAPE are considered parts of the AAI spectrum, only half of the patients with HAPE have predeceasing or concomitant AMS. (26)

Risk factors are similar to those for AMS but also include individual susceptibility due to low hypoxic ventilatory response, the use of sleep medication, excessive salt ingestion, pulmonary hypertension, increased pulmonary vascular reactivity, and genetic susceptibility. (27-30)

The current understanding of HAPE pathophysiology suggests hypoxia is a primary cause. Hypoxia causes widespread hypoxic pulmonary arterial vasoconstriction, leading to increased pressure in pulmonary circulation. That, in addition tohypoxia-induced increase in capillary permeability, causes fluid to move into the alveoli resulting in noncardiogenic pulmonary edema. (31)

Typically, the initial presentation of HAPE is unspecific with a decreased exercise tolerance, exertional dyspnea, chest pain and non-productive cough. It can quickly progress to dyspnea at rest and productive cough with frothy pink sputum of pure blood. Objectively, SpO2 is at least 10% lower than expected for a particular altitude, usually between 40% and 70%. Patients are typically tachypneic, tachycardiac, sometimes with central cyanosis, rales and wheezes. (26, 32) Chest X-ray patterns of HAPE are also non-specific and encompass bilateral symmetrical perihilar opacities, bilateral symmetrical diffuse opacities, unilateral diffuse opacities, bilateral asymmetrical focal opacities, and even lobar consolidation with lower zone or, less commonly, upper zonal predilection but with the normal-sized heart and mediastinum. (33) EKG sometimes shows a right axis deviation and/or myocardial ischemia. Laboratory investigations are of limited use. In a patient with pulmonary infiltrates on chest radiography, rapid correction of clini-

Table 4. Recommended doses of the medications used for treating AMS, HAPE and HACE in adults.

Medication	Indication	Route	Dosage
Acetazolamide	AMS, HACE	PO	250 mg every 12 h
Dexamethasone	AMS,	PO, IV, IM	4 mg every 6 h
Dexamethasone	HACE	PO, IV, IM	8 mg once, then 4 mg every 6 h
Nifedipine	HAPE	PO	30 mg ER every 12 h or 20 mg ER every 8 h

AMS - Acute Mountain Sickness; HACE - High Altitude Cerebral Edema; HAPE - High Altitude Pulmonary Edema; ER - extended release; PO - oral route; IV - intravenous route; IM - intramuscular route.
(Modified from: Luks AM, Auerbach PS, Freer L, Grissom CK, Keyes LE, McIntosh SE, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med. 2019;30(4s):S3-s18.)

cal status and SpO2 with supplemental oxygen is pathognomonic of HAPE. (26)

Crucial prophylactic measure for HAPE includes gradual ascent since there is a clear relationship between the rate of ascent and disease incidence. Preacclimatisation should also be considered. Pharmacological prophylaxis (Table 3) should be used only in individuals with a history of HAPE. Nifedipine is the medication of choice and should be started on the day before the ascent and continued either until descent is initiated or the individual has spent four days at the highest elevation, perhaps up to 7 days if the individual's rate of ascent was faster than recommended. Acetazolamide can be considered to prevent the reentry HAPE in people with a history of this disorder. Phosphodiesterase inhibitors should be considered in HAPE-susceptible individuals who are not candidates for nifedipine and dexamethasone in individuals who are not candidates for either nifedipine or phosphodiesterase inhibitors. Salmeterol is not recommended for HAPE prevention. (12)

Given the life-threatening nature of HAPE, the primary therapeutic option is descent. The patient should descend at least 1000 m with the least possible effort. If available, supplemental oxygen should be provided to target SpO2 >90% or to relieve symptoms. A portable hypobaric chamber could be used if descent is not feasible,is delayed or supplemental oxygen is not available. Continuous positive airway pressure (CPAP) devices should be considered when another therapeutic approach is unavailable or as an adjunct therapy in patients not responding to supplemental oxygen. (12)

Recommended pharmacological treatment is listed in Table 4. Nifedipine is the medication of choice. Tadalafil or sildenafil can be used if nifedipine is not available, but concomitant use with nifedipine should be avoided due to possible hypotension. Acetazolamide and diuretics should not be used to treat HAPE. Due to insufficient evidence, no recommendation can be made regarding dexamethasone. (12)

HIGH-ALTITUDE CEREBRAL EDEMA (HACE)

HACE is the rearrest but the most severe and the most dangerous form of AAI. If not recognized and managed correctly, it can lead to death within 24 h due to brain herniation. It is generally considered an extreme or end-stage form of AMS. Incidence if HACE is up to 12% at altitudes of 6000 m. (34, 35) The risk factors for HACE are identical to those for AMS.

Two prevailing theories identify hypoxia as the primary etiological factor of HACE. Hypoxia evokes hemodynamic responses leading to cerebral overperfusion of microvascular cerebral blood vessels. This translates to elevated capillary pressure and capillary leakage resulting in vasogenic edema. (36)However, cytotoxic edema, also observed in HACE, is likely a consequence of Na+/K+ ATPase dysfunction due to diminished oxygen supply. (37) Both vasogenic and cytotoxic components are likely to contribute to intracranial hypertension.

Unlike HAPE, most HACE cases present a clear progression of AMS symptoms to decline in cognitive functions, the level of consciousness, slurred speech, papilledema and truncal ataxia. (38) Truncal ataxia, often described as "drunken sailor gait," can be frequently overlooked or misinterpreted as muscle fatigue. One must keep a full vigilance of truncal ataxia since it is the earliest sign of HACE (4). Other symptoms can also overlap with dehydration, hypothermia, hypoglycemia or hyponatremia, so laboratory testing is essential for differential diagnosis. Imaging techniques are usually not readily available in remote areas but, just like lumbar punction (39), only show elevated intracranial pressure with cerebral edema. There is no correlation between the severity of edema with HACE clinical presentation or the outcome (34, 40), and neither imaging nor lumbar punction are necessary for diagnosis.

Prevention of HACE should be prioritized over treatment. Appropriate acclimatization by gradual ascent as described in AMS prevention and/or repeated preacclimatisation will likely prevent this illness. (25) Medications can and should be used in moderate and high-risk situations (Table 2) to prevent HACE (Table 3). Dexamethasone is most frequently used. As for AMS prevention, medication should be started on the day before the ascent. For individuals ascending to and remaining at a given elevation, upon the arrival at the target elevation, the medication should be continued for four days in individuals adhering to the recommended ascent rate and 4 to 7 days in individuals ascending faster than recommended rates. Individuals who ascend to a target elevation and immediately descend can stop the medication once the descent is initiated (12)

HACE is, by definition, a true medical emergency with a very high mortality rate. It is essential to initiate the treatment as soon as possible, which can be challenging, if not impossible, in remote areas without endangering the lives of other expedition members. Descent and supplemental oxygen are recommended non-pharmacological treatment options for HACE. A portable hyperbaric chamber should be used if they are not feasible or available. There is no recommendation concerning CPAP use due to a lack of evidence. Pharmacological treatment should be initiated immediately (Table 4), especially if descent is not possible at the time or other non-pharmacological treatment options are unavailable. Dexamethasone is the primary treatment of choice for HACE, but acetazolamide can be used as an adjunct. (12) To our knowledge, studies on diuretic use in treating HACE were not published to date.

Conclusion

When the ability of the human body to adapt to high altitude is exceeded, an AAI develops. In the AAI spectrum, AMS, HAPE and HACE are usually described. Due to the high incidence of AAI and potentially high mortality in HAPE and HACE patients, a series of prophylactic and therapeutic measures are introduced. The most important prevention of AAI includes acclimatization and low speed of ascent, but pharmacological prophylaxis is available and recommended in some cases. The treatment of choice for HAPE and HACE is quick descent with oxygen and a portable hyperbaric bag if available, as well as the use of supplemental oxygen, acetazolamide, nifedipine, dexamethasone, and phosphodiesterase inhibitors.

Conflict of interest

None to declare.

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Sažetak

Ljudsko telo je na velikim nadmorskim visinama izloženo niskom parcijalnom pritisku kiseonika. Ovo stanje je poznato kao hipobarna hipoksija. Kada je sposobnost organizma da se prilagodi ovim uslovima prekoračena, dolazi do razvoja akutne visinske bolesti (AVB). U okviru spektra ABV opisuju se tri entiteta: akutna planinska bolest, visinski edem pluća i visinski edem mozga. Zbog velike učestalosti AVB i potencijalno visokog mortaliteta kod pacijenata sa visinskim edemom pluća ili mozga, preporučuje se niz profilaktičkih i terapijskih mera u skladu sa aktuelnim smernicama. Najvažnija mera prevencije AVB je malabrzina uspona i lekovi acetazolamid, deksametazon i ibuprofen. Terapija izbora za visinski edem pluća i mozga je brzo spuštanje na značajno nižu nadmorsku visinu, oksigenoterapija i lekovi acetazolamid, deksametazon, nifedipin i inhibitori fosfodiesteraze.

Ključne reči: akutna visinska bolest, akutna planinska bolest, edem mozga, edem pluća, hipoksija.

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