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Review

High-altitude illnesses: Old stories and new insights into the pathophysiology, treatment and prevention

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ABSTRACT

Areas at high-altitude, annually attract millions of tourists, skiers, trekkers, and climbers. If not adequately prepared and not considering certain ascent rules, a considerable proportion of those people will suffer from acute mountain sickness (AMS) or even from life-threatening high-altitude cerebral (HACE) or/and pulmonary edema (HAPE). Reduced inspired oxygen partial pressure with gain in altitude and consequently reduced oxygen availability is primarily responsible for getting sick in this setting. Appropriate acclimatization by slowly raising the hypoxic stimulus (e.g., slow ascent to high altitude) and/or repeated exposures to altitude or artificial, normobaric hypoxia will largely prevent those illnesses. Understanding physiological mechanisms of acclimatization and pathophysiological mechanisms of high-altitude diseases, knowledge of symptoms and signs, treatment and prevention strategies will largely contribute to the risk reduction and increased safety, success and enjoyment at high altitude. Thus, this review is intended to provide a sound basis for both physicians counseling high-altitude visitors and high-altitude visitors themselves.

Introduction

Millions of international tourists, trekkers, mountaineers and skiers are attracted to mountainous areas all over the world. This was at least true until spring 2020 before the lockdown due to the COVID-19 pandemic that severely affected travel activities but will very likely return to a similar level when the pandemic has been overcome.[1–3] To give some examples, in 2019 nearly 1.2 million tourists visited Nepal, 197,786 for pilgrimage and 171,937 for trekking and mountaineering.[4] The latest figures (2018) reporting the yearly numbers of climbers on the various routes of Kilimanjaro amount to more than 47,000.[5] Annually, over 40 million hikers and skiers visit the mountainous regions of Alps[6] and about 400 million skier days (primarily downhill skiers and snowboarders) have been estimated from 2,000 ski areas across 80 countries worldwide.[7] A large proportion of those people is acutely exposed to altitudes above 2,000 m (about 6,560 ft) where the risk to suffer from mountain illnesses starts and becomes more prevalent with further increasing altitude.[8,9] Altitude regions are usually defined as high altitude (1,500–3,500 m; ~5,000–11,500 ft), very high altitude (3,500–5,500 m; ~11,500–18,000 ft), and extreme altitude (>5,500 m; >18,000 ft).[10] Acute mountain sickness (AMS) is the most frequently observed and usually benign and self-limited high-altitude illness.[8,10] In contrast, high-altitude cerebral (HACE) and pulmonary edema (HAPE) occurs rather rarely but are life-threatening diseases.[11,12]

It is long known that the increasing level of hypoxemia due to the reduced inspired oxygen partial pressure with gain in altitude is the primary reason for developing acute mountain sicknesses. Appropriate acclimatization is able to prevent altitude (hypoxia) related illnesses.[8,13,14] The effectiveness of various pre-acclimatization strategies, including continuous and intermittent exposures to hypobaric and/or normobaric hypoxia is well documented.[15,16] Rapid ascent to high altitude represents one of the most important risk factors for AMS development and staging for some days at even moderate altitude, i.e., 2,200 m, will considerably reduce the AMS incidence.[17,18] Bloch and colleagues convincingly demonstrated that slower ascent rates to the highest camp (6,865 m) on Muztagh Ata were associated with lesser AMS symptoms and enhanced summit success compared to climbers ascending faster.[19] Generally, lowlanders can ascend and fully acclimatize to altitudes of about 5,000 m for continuous residence.[20] Acclimatization to altitudes even higher than 7,000 m for rather

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Abbreviation list

AQP-4	Aquaporin-4
AMS	Acute mountain sickness
ARNT	Aryl hydrocarbon nuclear translocator
BBB	Blood-brain barrier
COVID-19	Corona virus disease 2019
ECG	Electrocardiogramme
EPO	Erythropoietin
ESQ	Environmental Symptoms Questionnaire
HAPE	High-altitude pulmonary edema
HACE	High-altitude cerebral edema
HIF	Hypoxia-inducible factor
HVR	Hypoxic ventilatory response
LLS	Lake Louise Scoring system
MRI	Magnetic resonance imaging
NO	Nitric oxide
P_ACO_2	Alveolar carbon dioxide partial pressure
P_AO_2	Alveolar oxygen partial pressure
PO_2	Oxygen partial pressure
PDE	Phosphodieseterase
PFO	Patent foramen ovale
ROS	Reactive oxygen species
UIAA	Union Internationale des Associations d'Alpinisme Medical Commission
VEGF	Vascular endothelial growth factor
$\dot{V}O_{2max}$	Maximum oxygen consumption

short-term stays (days) was demonstrated in mountaineers, while acclimatization over 8,000 m seems not to be possible for human beings.[21]

There are commonly accepted rules for safe acclimatization at altitudes above 2,500 m, recommending not to exceed sleeping altitude by 300–500 m per day and having a rest day for every 1,000 m altitude gain (and also prior to or following a greater ascent rate).[22] Considering these rules would largely prevent severe high-altitude illnesses, but their implementation is often hampered by given logistic conditions. Underestimating the risk of getting sick, mostly based on incomplete understanding of both the physiology and the individual management of acclimatization, favors violation of the acclimatization rules as well. Thus, this review is aimed at discussing mechanisms, diagnosis, and therapeutic options of high-altitude illnesses as the underlying rationale for the development and application of individually tailored prevention strategies.

Acute mountain sickness and high-altitude cerebral edema

AMS and HACE constitute cerebral forms of high-altitude illnesses because associated symptoms indicate pathophysiological effects of hypobaric hypoxia primarily originating in the brain. Whereas AMS is the most frequent and benign illness developing at high altitude, HACE occurs rather rarely but represents a potentially life-threatening disease requiring rapid intervention. HACE is considered as the end stage of progressing AMS.[8]

AMS

Epidemiology and diagnosis

AMS typically affects individuals rapidly ascending from low to high altitudes (>2,000 m).[9] Symptoms are predominantly headaches, but also include nausea, lack of appetite, vomiting, insomnia, dizziness, and/or fatigue. Symptoms will steeply increase during the first 6–12 h at altitude depending on the individual's susceptibility to AMS, with faster progressing nausea in those most susceptible to AMS.[23] At the moderate and high altitudes of the Eastern Alps, the AMS prevalence was shown to increase from 7% at 2,200 m to 38% at 3,500 m[9] and was as high as 52% at 4,559 m (very high altitude) in the Western Alps.[24] Richalet and colleagues reported a 23.7% incidence of severe AMS, derived from a cohort of 1,326 subjects sojourning to 4,000 m.[25] Females seem to be slightly more affected than males[26], and younger individuals are slightly more affected than older ones.[27] Children suffer similarly from AMS as do adults.[28]

Diagnosis of AMS is commonly based on the use of the Lake Louise Scoring system (LLS) or the shortened (11-item) version (ESQ-C) of the 67-item Environmental Symptoms Questionnaire (ESQ-III). The LLS is a self-assessment questionnaire including five main symptoms (headache, nausea, dizziness, fatigue, and difficulty sleeping), each rated with a score from 0 to 3 (0 for no discomfort, 1 for mild, 2 for moderate, and 3 for severe symptoms).[29] Recently, the consensus group has revised the LLS and eliminated difficulty sleeping as a questionnaire item.[30] A score of 3 or higher is classified as AMS. The questions of the ESQ-C are scored on a scale of 0–5, with 0 reported as "not at all" and 5 as "extreme." Each response score is multiplied by the factorial weight of its symptom and a score of 0.70 or greater is classified as AMS-C. It has to be noted that diagnostic results of different AMS scoring systems, i.e., LLS, ESQ-III, and the visual analog scale (VAS), should not be interchanged. For instance, Wagner and colleagues found an AMS prevalence of 63% when defined as LLS $\geq$3, which was 49% when defined as either LLS $\geq$5 or ESQ-III $\geq$0.7. Although there was agreement in prevalence between the LLS $\geq$5 and ESQ-III $\geq$0.7, the authors found a discrepancy in AMS classification in 16% of the cases.[31] Nevertheless, based on these findings and practical/clinical observations in the field, a LLS $\geq$5 or ESQ-III $\geq$0.7 are considered to be clinically relevant.

Pathophysiology

Although low-pressure environment per se might slightly increase AMS development, acute hypoxia associated with rapid gain in altitude constitutes the primary cause.[14,32–34] At the cellular level, hypoxia leads to activation of the hypoxia-inducible factor (HIF) pathway.[35] HIF-1 (as also for HIF-2) is a heterodimeric transcription factor consisting of a constitutively expressed β-subunit (HIF-1β, also known as aryl hydrocarbon nuclear translocator, ARNT) and an oxygen-regulated α-subunit (HIF-1α or its isoform HIF-2α which is expressed in a cell restricted manner).[35] Under normoxic conditions, the oxygen-dependent α-subunit is hydroxylated making it vulnerable to proteasomal degradation. In hypoxic conditions, hydroxylation is blocked and the α-subunit accumulates in cells. HIFs promote the expression of many hundreds of genes to support the maintenance of tissue oxygen supply. For instance, stabilization of the α-subunit in hypoxia/at altitude results in up-regulation of erythropoietin (EPO) and vascular endothelial growth factor (VEGF) transcription, promoting erythropoiesis and angiogenesis.[36,37] HIFs are also involved in the regulation of glycolytic metabolism and reducing mitochondrial oxygen consumption in hypoxia.[38]

At a systemic level, acute exposure to hypoxia also initiates several physiological responses to counteract hypoxia and improving oxygen delivery to tissues.[13,39] The most important include hyperventilation, triggered by the hypoxic ventilatory response (HVR),[39] hemoconcentration due to diuresis, and elevation of heart rate and cardiac output due to sympathetic activation.[40,41] Resting ventilation steadily increases during the first few days at high altitude, typically reaching a plateau after 4–8 days up to an altitude of about 4,300 m.[42,43] This progressive increase (ventilatory acclimatization) is associated with an increase in the alveolar oxygen partial pressure (P_AO_2) and a decrease in the alveolar partial pressure of carbon dioxide (P_ACO_2).[13] The resulting hypocapnia with

respiratory alkalosis is at least partly compensated by renal bicarbonate excretion.[44] Characteristically, cerebral blood flow increases during the first 12 h at high altitude and declines with acclimatization over 3–5 days to near baseline values.[45] Cerebral blood flow is primarily regulated by hypoxic vasodilation and hypocapnic/hypercapnic vasoconstriction/vasodilation.

Moreover, exposure to high altitude provokes, mostly HIF-dependent, a variety of (patho-)physiological responses, including the production of reactive oxygen species (ROS),[46,47] eicosanoids,[48] and cytokines (markers of inflammation).[49] It becomes apparent that those immediate and subacute responses to hypobaric hypoxia are extremely complex, and appropriate acclimatization will depend on the severity of hypoxia (speed of ascent) and individual's responsiveness (susceptibility) to hypoxia. Failure to acclimatize adequately will result in the development of acute mountain sickness.

Based on the obviously multi-factorial genesis of AMS, pathophysiological mechanisms included are still a matter of debate. What is certain is that acute exposure to hypoxia represents the primary cause initiating the development of AMS in certain individuals under particular conditions.[14] However, effects of hypobaria may also contribute as McGuire et al. showed that exposure to nonhypoxic hypobaria was associated with subcortical white matter hyperintensities,[50] supported by the observation of more severe or at least different AMS development in hypobaric compared to normobaric hypoxia.[51,52] Most subjects showed an early increase of the cerebral blood flow and brain parenchyma volume during the first 40 min at high altitude, which was then compensated by a decrease in the intracranial cerebrospinal fluid. However, these early changes seem not to be related to AMS severity.[53] Thus, persisting intravascular pressure, edema formation and brain swelling might lead to AMS development. Kallenberg et al. demonstrated mild extracellular vasogenic edema in magnetic resonance imaging (MRI) contributing to generalized brain swelling, which was independent of AMS.[54] In that study, intracellular cytotoxic edema was associated with AMS severity, likely related to anatomic predisposition ('tight-fit' brain); the brain volume was increased by only 0.5%.[54] Similar results were reported by Schoonman et al. who demonstrated that mild vasogenic edema had developed after 6 h in normobaric hypoxia, again unrelated to AMS, but found also mild cytotoxic edema in those with severe AMS.[55] It seems likely that the increase in cerebral blood flow does not fully provide sufficient oxygen delivery, and consequently, compromised cellular energy and associated interruption of the Na^+/K^+-pump can explain cytotoxic edema formation. The comprehensive study performed by Sagoo et al. who took sequential MRI scans during a 22-h exposure to normobaric hypoxia with an F_IO_2 of 0.12 revealed an increase of total brain parenchymal volume (including the grey and white matter as well), but only white matter edema (indicating vasogenic edema) was correlated with AMS scores.[56] Interestingly, these researchers also detected veno-compression of the small and deep cerebral veins, which is likely to contribute to brain swelling and increased intracranial pressure especially in subjects with anatomical characteristics.[56] Some brain swelling and elevation of intracranial pressure seem to be involved at least in severe headache and AMS development.

Headache at high altitude, the cardinal symptom of AMS, may be a consequence of activation and sensitization of the trigeminovascular system by mechanical (e.g., increased cranial and/or intravascular pressure) and/or chemical (e.g., nitric oxide, prostaglandins, inflammatory parameters, ROS) stimulation.[57–59] Connections of these pain fibers to vegetative centers in the brainstem could explain additional AMS symptoms like nausea and vomiting.[60] Thus, besides mechanical stimuli related to elevated cerebral blood flow and/or brain swelling, AMS symptoms may be primarily caused by activation of the trigeminovascular system. Importantly, hypoxia and other altitude-related stresses are known to trigger migraine or cluster headache, which is not easily distinguished from AMS in subjects not suffering from primary headache disorders.[58,61] Moreover, exercise, dehydration, alcohol consumption, etc. are known modulators of AMS severity.[62–64] Taken together, all these findings suggest that AMS results from heterogeneous pathophysiologic processes and the large variability of responses depending on the individual's susceptibility.[23] For instance, resistance to AMS was shown to be associated with a large anti-inflammatory and/or anti-permeability response during hypoxia exposure likely preventing downstream pathophysiological events leading to AMS.[65]

Treatment

Hypoxia, and to a small extent also the low barometric pressure, are the primary causes for the development of high-altitude illnesses, and slow ascent rates represent the most important measure to prevent those illnesses.[8,32] Individuals suffering from headache and only moderate AMS (Lake Louise score between 6 and 9)[30] can stay at altitude in general. None or only light exercises are recommended, paralleled by appropriate fluid intake and, if necessary, intake of pain relievers (plus antiemetics) (see Fig. 1). It is strictly advised against ascending to higher altitudes before symptoms have disappeared.[8,10,66] In the case, if symptoms persist or become even aggravated, descent is the necessary consequence. In severe AMS, descent should be performed passively (if possible), administering low-flow oxygen (2–4 L/min; if available) or using a hyperbaric bag (if available). Unfortunately, the evidence level for the effectiveness of non-pharmacological treatment strategies is low.[67]

Pharmacological treatment of AMS includes acetazolamide (a carbonic anhydrase inhibitor) and/or dexamethasone, particularly in more severe AMS. Information on administration, doses, and potential side effects are shown in Figs. 1.[8,10,66,67] Recently, both metoclopramide (10 mg) and ibuprofen (400 mg) have been suggested as effective alternative treatment options to treat high-altitude headache and AMS as well.[68]

HACE

Epidemiology and diagnosis

It is generally suggested that (severe) AMS in some cases may progress to life-threatening HACE. Whether and why this is really the case is still unknown. Usually, but not necessarily, HACE is preceded by AMS and rarely occurs at altitudes lower than 3,000 m. HACE prevalence data vary considerably depending on the population studied but may roughly amount to about 1%. In Nepal trekkers, a HACE prevalence of 1% has been reported between altitudes of 4,243 and 5,500 m, but the prevalence increased to 3.4% in subjects suffering from AMS.[69] Richalet et al. recorded a HACE prevalence of 0.98% in a cohort of 1,326 individuals sojourning to 4,000 m,[25] and Wu et al. reported a prevalence of 0.28% among 14,000 railroad workers who travelled from lowland China to Tibet (3,500–5,000 m).[70] Most prevalent symptoms in subjects suffering from HACE include altered mental status and ataxia.[11] Especially ataxia represents an early warning symptom indicating potential HACE development.[71] Other accompanying symptoms to be mentioned are headache, anorexia, nausea, vomiting, and retinal hemorrhages.[71,72] Moreover, concurrent HAPE is not unusual in HACE.[72] Proper diagnosis would require MRI, which is usually not available at the site of occurrence but may confirm the HACE diagnosis after empirical therapy and clinical improvement.[72,73] Rapid suspected HACE diagnosis and treatment in the field (based on symptoms mentioned above) is of utmost importance because an initially alert mountaineer suffering from HACE may rapidly deteriorate to coma and even death. Differential diagnosis to be considered in cases with atypical presentation primarily include intracranial hemorrhage, stroke, hypoglycemia, hyponatremia, hypothermia.[72]

Pathophysiology

Preceding pathophysiological mechanisms in HACE seem identical to those of severe AMS. Why some individuals do not recover and AMS progresses to HACE remains to be elucidated. Again, specific conditions and individual's susceptibility may play important roles. MRI findings

High-Altitude Illness	Medication	Prevention *Administration Dose*	Therapy *Administration Dose*	Side Effects
High-Altitude Headache	Acetaminophen Ibuprofen	oral: 1 g/6 h oral: 400 mg/8 h	oral: 1 g/6 h oral: 400 mg/8 h	gastrointestinal bleeding
Acute Mountain Sickness	Acetazolamide	oral: 125 mg/12 h *Pediatrics:* 2.5 mg/kg/12 h	oral: 250 mg/12 h *Pediatrics:* 2.5 mg/kg/12 h	diuresis, nausea, paresthesias, taste disturbances, myopia
	Dexamethasone	oral: 2 mg/6 h or 4 mg/12 h	oral, im, or iv: 4 mg/6 h	hyperglycemia and psychiatric alterations
HACE	Dexamethasone	oral: 2 mg/6 h or 4 mg/12 h	oral, im, or iv: 8 mg loading dose then 4 mg/6 h	hyperglycemia and psychiatric alterations

Fig. 1. Medications for the prevention and treatment of high-altitude headache (HAH), acute mountain sickness (AMS) and high-altitude cerebral edema (HACE).

typically demonstrate vasogenic edema formation in white matter areas preferentially in the splenium of the corpus callosum.[73] This indicates dysfunction/disruption of the blood-brain barrier (BBB). For instance, BBB dysfunction at high altitude may result from ROS-associated membrane destabilization and inflammation, but also from local HIF and VEGF activation.[74] A recent study points to a potential role for the glymphatic system of the brain in the pathogenesis of HACE.[75] Increased expression of aquaporin-4 (AQP-4) water channels (the main component of the lymphatic system) in astrocytes was associated with HACE development in animals exposed to hypobaric hypoxia.[75] MRI scans even months after recovery from HACE confirm previous brain edema with brain-barrier disruption by hemosiderin deposition following microhemorrhage especially in the splenium of the corpus callosum.[76] Interestingly, Pichler Hefti et al. found such microhemorrhages also in the cerebellar peduncles of a high-altitude climber indicating a reasonable connection between the anatomical site of the lesion and ataxia.[77,78]

Treatment

As HACE is usually fatal within 24 h if untreated, early diagnosis and immediate treatment are of utmost importance. If HACE is the likely diagnosis, rapid passive descent (if possible) to the lowest possible altitude is strongly recommended, administering oxygen (2–4 L/min; if available) or using a hyperbaric bag (if available).

Dexamethasone represents the pharmacological treatment of choice. Information on administration, doses, and potential side effects are shown in Figs. 1.[10,11,66]

High altitude pulmonary edema

Epidemiology and diagnosis

HAPE rarely occurs at altitudes lower than 3,000 m,[41,79] but has been reported at elevations as low as 1,400 m in vacationing skiers in the French Alps.[80] In a prospective cohort study, including 1,326 individuals ascending to about 4,000 m, a HAPE incidence of 1.7% was recorded; in comparison, the HACE incidence was 0.98% and that for severe AMS was 23.7%.[25] The prevalence for HAPE may broadly vary depending, e.g., on the acclimatization status and susceptibility of the individual, the speed of ascent, and the absolute altitude reached. The HAPE incidence was 0.2% in people with unknown HAPE history when ascending within 4 days to 4,500 m, but increased to 6% when reaching this altitude in only 1–2 days.[66] Interestingly, high-altitude visitors suffering from HAPE are mostly young males, while reascent HAPE in high-altitude residents affects both males and females.[81] Remarkably, under rapid ascent conditions, the risk of HAPE recurrence increases to 60% among individuals with a HAPE history.[82] In contrast to AMS, mortality of untreated HAPE amounts to 50%.[66]

Initial symptoms include inappropriate dyspnea during exercise associated with strikingly reduced exercise performance, followed by orthopnea, drowsiness, cough and pink frothy sputum.[66,83,84] Signs comprise central cyanosis and low peripheral oxygen saturation, crackles/wheezing in at least one lung field, tachypnea and tachycardia.[10,66,84] As these symptoms and signs are commonly accompanied by mild fever, HAPE is often misdiagnosed as pneumonia. Hyperventilation syndrome and pulmonary embolism may be considered as differential diagnosis.[10,66] Due to the high risk of mortality, rapid diagnosis and appropriate treatment in the field (see below) is pivotal.

Pathophysiology

HAPE represents non-cardiogenic pulmonary edema provoked by excessive hypoxic pulmonary vasoconstriction and exaggerated increase in pulmonary-artery and capillary pressure.[12,85] As a consequence of the high pressure, a noninflammatory and hemorrhagic alveolar capillary leak develops, which induces secondarily an inflammatory response.[86] Although an unusually high pulmonary-artery pressure is a hallmark in HAPE, an exaggerated hypoxic pulmonary vasoconstriction per se was demonstrated not to be highly predictive for HAPE-susceptibility.[87] Thus, a presently not well-defined genetic predisposition may cause the exceptionally high pulmonary vascular response to hypoxia in HAPE-susceptible subjects,[88,89] likely associated with insufficient synthesis/bioavailability of nitric oxide, potentially related to high oxidative stress levels.[89] In addition, a defect of the transepithelial sodium transport was demonstrated in HAPE-susceptible individuals, supporting the view that the combination of a constitutive and an acquired defect in the mechanism of sodium transport will facilitate HAPE development.[90] Also, a large patent foramen ovale (PFO) in the heart has been suggested as a contributing factor to HAPE by exaggerated arterial hypoxemia.[91] However, the critical PO_2 initiating hypoxic pulmonary vasoconstriction primarily depends on the P_AO_2, with some contribution also from the bronchial arterial PO_2 and mixed venous PO_2 in an additive manner.[92,93] Last but not least, extreme cold and severe physical exertion may represent predisposing factors.[94,95]

Treatment

Mortality is also high for HAPE (about 50%) without option for descent or appropriate treatment.[84] If HAPE is the likely diagnosis, rapid passive descent (if possible) to the lowest possible altitude is strongly recommended, administering oxygen (2–4 L/min via mask; if available) or using a hyperbaric bag (if available).

Nifedipine represents the pharmacological treatment of choice. Information on administration, doses, and potential side effects are shown in Fig. 2[10,11,66,84] Potential benefits of phosphodiesterase inhibitors for the treatment of high-altitude pulmonary edema are only provided by anecdotal reports.[66]

A simplified overview on the treatment regimen of various high-altitude illnesses is depicted in Fig. 3.

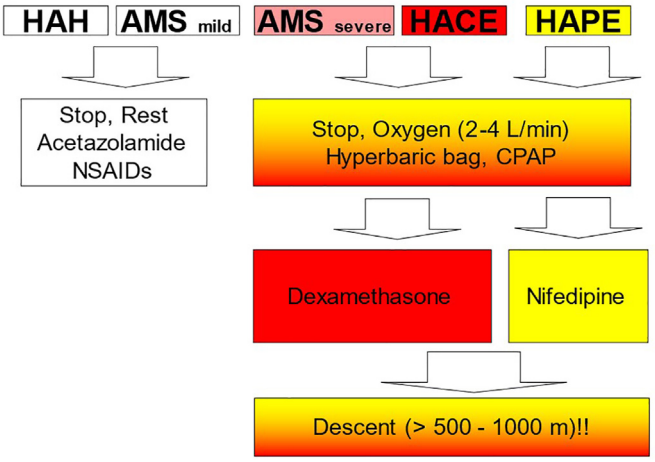

Fig. 3. Simplified treatment regimen for various high-altitude illnesses. HAH, high-altitude headache; AMS, acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema; NSAIDs, non-steroidal anti-inflammatory drugs, CPAP, continuous positive airway pressure.

How to prevent high-altitude illnesses?

Physical preparation and medical pre-examination

It should be mentioned beforehand that individuals with pre-existing cardiopulmonary diseases such as coronary heart disease, pulmonary hypertension, chronic pulmonary disease or obstructive sleep apnea should be assessed specifically by an expert before undergoing travel to high altitude.

It is essential to prepare physically in order to optimize aerobic capacity and endurance performance in the setting of high-altitude travel/climbing where maximum oxygen consumption ($\dot{V}o_{2max}$) declines substantially due to the lower oxygen availability.[96] For the majority visiting high altitudes, specific exercise is also needed to achieve adaptation of the musculoskeletal system especially when planning strenuous trekking or mountaineering trip. Thus, the amount, intensity and type of physical exercise depend on the kind of travel planned and the individual health status and fitness level. Although preparation is crucial for success and safety,[97,98] especially at extreme altitude, evidence-based recommendations are scarce. Therefore, the following part is primarily based on expert opinion.

In general, poly-sportive endurance training combined with core strengthening is recommended. For the adaptation of the musculoskeletal system, subjects should be used to hike for several hours. Physical preparation should also include walking downhill since this is associated with the highest power load for the lower limb muscles (quadriceps muscle).[99] It is often disregarded that most of high-altitude mountaineers/trekkers will carry a backpack for several hours daily and have to sleep in a tent or very basic accommodation. Those aspects must also be considered in the preparation phase. It is a general rule, to slowly approach high altitudes in terms of ascent duration and maximal height reached.[8,10] This rule is of utmost importance in older subjects who (re-) start travelling to higher altitudes and in those with pre-existing comorbidities, e.g., cardiovascular and/or metabolic diseases.[22,100,101] In practical terms, this means that for high altitude-naive subjects, it is advisable to begin with journeys to 2,500–3,000 m, and then increase the maximal altitude destinations up to 4,000 to 5,500 m before travelling to and/or mountaineering at extreme altitudes (>5,500 m).

High-Altitude Illness	Medication	Prevention *Administration Dose*	Therapy *Administration Dose*	Side Effects
HAPE	Nifedipine, *slow release*	oral: 30 mg/12 h or: 20 mg/8 h	oral: 30 mg/12 h or: 20 mg/8 h	dizziness, headache, hypotension
	Dexamethasone	oral: 2 mg/6 h or 4 mg/12 h		hyperglycemia and psychiatric alterations
	Tadalafil	oral: 10 mg/12 h		dizziness, headache, hypotension
	Sildenafil	oral: 50 mg/8 h		dizziness, headache, hypotension
	Salmeterol	inhaled: 125 µg/12 h		tremor, tachycardia, hypokalemia

Fig. 2. Medications for the prevention and treatment of high-altitude pulmonary edema (HAPE).

Nowadays commercial travelling, trekking and expedition agencies usually request a medical check-up before participation in high-altitude sojourns. There is no clear evidence of which type and modality of pre-examination are useful in terms of safety and success at high altitude. Usually, a thorough medical history, including the risk for cardiovascular events and thrombophilia is performed combined with vaccination advice. We would like to emphasize the importance to obtain a detailed travel history and history of previous high-altitude illness since this is one of the most important predictors for future risk of developing high-altitude illnesses.[9,102] In addition, a resting electrocardiogramme (ECG) is often performed, analogous to sports medical testing, although no data support the usefulness of this examination when it comes to adverse events during high altitude exposure. Of course, this is part of pre-examinations in those suffering from cardiovascular diseases.[101] Moreover, it is not advised to perform echocardiography assessing potential structural abnormalities, specifically PFO (except in individuals with susceptible to HAPE),[91] or hypoxic challenge test to evaluate for the extent of hypoxic pulmonary vasoconstriction in altitude-naïve subjects or subjects with no clear history of high-altitude illness.

For mountaineers going to extreme altitudes above 7,000 m, comprehensive cardiopulmonary exercise testing is recommended during the preparation phase as a general cardiopulmonary checkup and as a basis to optimize training recommendation. The additional costs for such tests are reasonable and negligible for the mountaineer considering the usually high costs for high-altitude expeditions.

Acclimatization

Acclimatization refers to several adaptive processes in the body including, e.g., increased ventilation with an immediate onset, metabolic compensation of respiratory alkalosis and erythropoiesis with a slower onset. Several publications have elaborately discussed this topic.[8,13,66,103] All acclimatization concepts described here reduce the risk of developing AMS, HACE and HAPE by giving the necessary time for multiple adaptations of the organ systems.[104]

The effectiveness of different strategies in the prevention of high-altitude illnesses in a specific setting is not entirely clear, due to several reasons. On the one hand, it is difficult to perform field studies in a blinded and controlled fashion. On the other hand, strategies may be carried out very variably, besides various confounding factors, the target altitude, the ascent rate and route during the sojourn may vary even more. A summary of the most important concepts is described below.

Complete acclimatization is believed to occur up to altitudes around 5,500 m, though this threshold is likely variable depending on inter-individual factors, susceptibility and external factors, e.g., latitude, time of the year, and weather conditions).[105] Above this altitude, deterioration with catabolism and organ dysfunctions seem to limit complete adaptation and permanent or long-lasting residence.[106–108] It is to be noted that the above-mentioned statements and limitations are not intended to distract from the fact that acclimatization is the most important determinant in the preparation and execution of a safe, successful and joyful journey to high altitudes.

Slow ascent and staging

Slow and graded ascent is the most common strategy used to prevent high altitude illness though only very few studies investigated the effect of ascent rate on AMS in a controlled fashion.[19] It is commonly recommended not to exceed an ascent rate of 500 m per day (altitude refers to the sleeping altitude) at altitudes above 2,500 m.[10,66] Additional rest days are scheduled in this strategy for every additional ascent of 1,000–1,500 m (example in Fig. 4). Richalet and colleagues have specified conditions for optimized acclimatization (including the 400 m-rule) in their recently presented clinico-physiological score.[109]

Staging refers to the concept of staying several days at the moderate altitude of 2,000–3,000 m to allow for sufficient acclimatization, enabling a more rapid ascent afterwards.[17] Considering the above-mentioned ascending rates and intermittent rest days, slow ascent can be seen as a form of staging. Both types have been traditionally used in high-altitude mountaineering and trekking and are efficient in reducing the risk of AMS and might even improve exercise performance.[17,110] However, these acclimatization rules are often violated because they are time-consuming and often incompatible with most

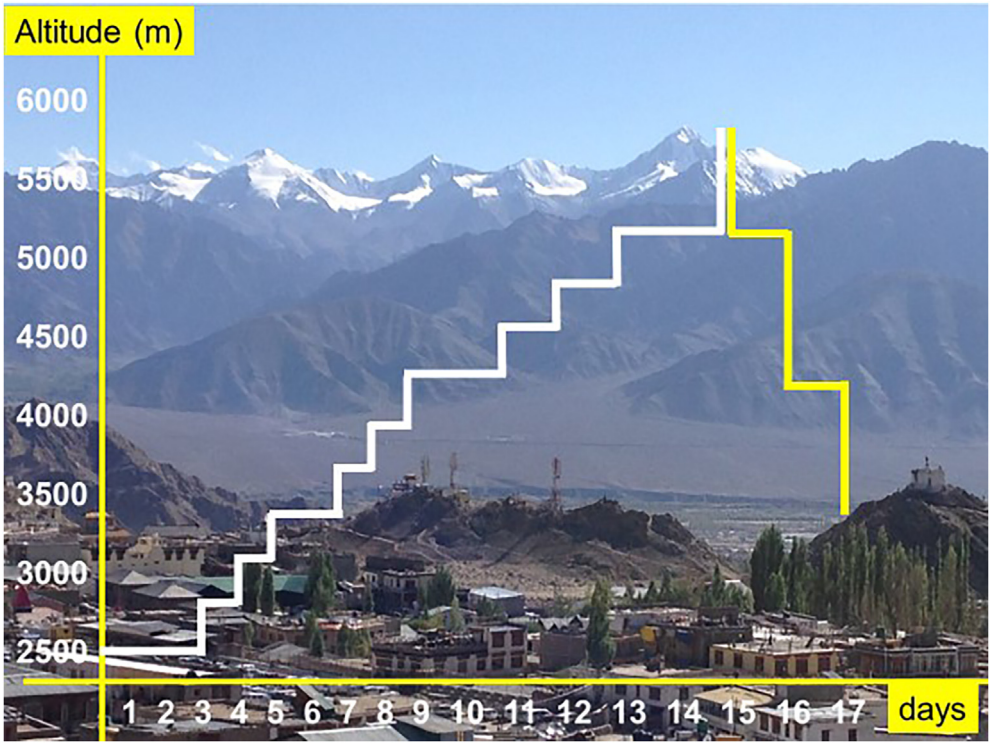

Fig. 4. Example of a safe (traditional) ascent from 2,500 m to 6,121 m (Stok Kangri, Ladakh). 300–500 m per day and one rest day for every 1,000 m gain in altitude.

current travel practices or the implementation is not possible due to the given environment.

Pre-acclimatization

Sufficient acclimatization is sometimes hampered due to rapid passive ascents to high-altitude locations by airplane, helicopter, car or cable car, but also due to the necessity to reach a high-altitude camp or hut without the opportunity to have an additional overnight stay. On the other hand, proper acclimatization may be limited simply because of time restrictions. Whereas short-term sojourns to high altitude, i.e., 1–3 h, are usually well-tolerated, longer stays are associated with an increased risk to develop AMS and reduced exercise tolerance. In such cases, the use of appropriate pre-acclimatization strategies, and in certain cases also pharmacological support (see below) may be considered.

Pre-acclimatization strategies, independent of whether performed in a natural or artificial environment, aim to induce ventilatory, metabolic, hematological, neurophysiological, and hormonal changes needed for an adequate adaptation to high altitude before the actual sojourn.[15,111–114] Short-term stay at moderate altitude before the planned trip is a natural form of pre-acclimatization, which is probably as effective as a slow ascent.[115] In this study from Schneider and colleagues a lower prevalence of AMS was found in subjects exposed to 4,559 m at the Capanna Margherita who spent more time above 3,000 m than the other subjects. According to the authors, ≥5 days of pre-exposure above 3,000 m are efficient in reducing the risk of developing AMS, with an odds ratio of 3.2 for AMS in subjects without the corresponding pre-exposition.[115] Although this is still not fully elucidated, it is supposed that a pre-exposure as close as possible to the high-altitude journey is favorable, however, a time gap until two months was shown to be effective.

A recent opinion position by members of the Union Internationale des Associations d'Alpinisme Medical Commission (UIAA MedCom) suggests that exposures to intermittent normobaric hypoxia prior to high-altitude climbing may reduce AMS symptoms and enhance the chance to succeed in high-altitude expeditions.[116] However, the authors also referred to the lack of robust evidence for those effects and the necessity to pay particular attention to safety issues.

The application of normobaric hypoxia for potential pre-acclimatization, even with the use of a mobile device (altitude-conditioning apparatus), has already been evaluated more than 3 decades ago.[117] Although these authors did not report significant effects on AMS development between the experimental and the control group, based on effect size calculation, there was a beneficial effect of pre-acclimatization by repeated normobaric hypoxia exposures (AMS-C 1.60 vs. 2.61 in controls, ES 0.7).[117] Subsequently, several experiments were performed in order to evaluate the effectiveness of normobaric and hypobaric hypoxia exposures on the prevention of AMS and exercise reduction.[118–124] Unfortunately, large variations in the hypoxia levels, exposure durations, and differences between the simulated altitude of pre-acclimatization and the following prolonged altitude exposure for determination of AMS development hinder the evaluation of efficacy. Although the findings are controversial, most studies indicate some beneficial consequences on AMS development and exercise performance and importantly, no adverse events associated with pre-acclimatization. It may be carefully concluded that longer periods of pre-acclimatization are more effective.[16] This is confirmed from observations of prolonged (up to 6 weeks) and progressive (2,000 to about 5,500 m simulated altitude) hypoxia exposures in individuals before climbing Mount Everest rapidly (within 3 weeks using bottled oxygen) (Everest Flash, commercial offer). Of course, comprehensive future studies are needed to evaluate individual responses to various pre-acclimatization strategies including effects of age, sex, exercise, diet, and sleep.

Pharmacological support

Knowledge on the preventive effects of drugs may help to better understand physiological mechanisms of the acclimatization process. The use of drugs to speed up acclimatization allowing a more rapid ascent cannot be generally recommended but may represent an option for individuals susceptible to rather severe high-altitude illness, and/or in cases where a rapid ascent is unavoidable, e.g., in rescue operations, high airport destinations, etc. Information on the administration and doses of medications for the prevention of high-altitude illnesses are given in Figs. 1 and 2.

Acetazolamide

Acetazolamide belongs to the group of sulfonamides and inhibits carbonic anhydrase, which leads to a reduction in renal bicarbonate reabsorption. Increased diuresis of bicarbonate compensates for respiratory alkalosis at altitude and shifts towards metabolic acidosis. This in turn optimizes respiratory drive and adaptation to high altitude. Several randomized trials and reviews showed acetazolamide to be effective in reducing the risk of developing AMS in subjects with a known history of AMS and rapid ascent to altitudes above 2,500 m.[125–131] It is recommended to apply a lower dose treatment regimen with 125 mg acetazolamide orally twice a day.[126,132,133] Practically, prophylaxis should be initiated 8–24 h before ascent and continued for 48 h up to the highest altitude reached,[134] but administering acetazolamide on the day of ascent was shown to be similarly effective.[135] If staging is used as the primary acclimatization strategy acetazolamide could safely be used in an on-and-off strategy, taking the before mentioned rules into account.

In addition, acetazolamide is efficient in ameliorating altitude-related sleep disorders, mainly excessive periodic breathing.[136] By improving sleep quality acetazolamide also optimizes adaptation to hypobaric hypoxia.

The main side effect arises from the increased diuresis, however, dizziness, lightheadedness, nausea, vomiting, diarrhea, change in taste particularly for carbonated drinks, kidney stones, and myopia have been reported. By using the low dosage regimen some of these adverse events can be minimized. Caution must be taken in subjects with known or suspected sulfonamide intolerance. When pharmacological prophylaxis is needed, acetazolamide is the first choice. Recent studies suggest that methazolamide may represent an alternative for acetazolamide when taken for the prevention and treatment of high-altitude illnesses, maybe even associated with fewer side effects.[137] However, more large-scale studies are needed. Finally, non-steroidal anti-inflammatory drugs like ibuprofen may represent an alternative or an add on to acetazolamide for AMS prevention.[138]

Dexamethasone

Dexamethasone is an efficient drug in preventing severe AMS, HACE, and HAPE.[8,11,104,125,139] With regard to HACE, concerns have been raised whether dexamethasone treatment of severe and life-threatening HACE is still effective with preexisting dexamethasone prophylaxis and therefore represents a second-line strategy. In our opinion, dexamethasone should only be prescribed for prophylaxis by an experienced high-altitude and expedition doctor after having thoroughly considered and optimized all other factors, e.g., when acetazolamide is contraindicated due to sulfonamide allergy or the previous experience of adverse effects and an appropriate ascent protocol is not feasible.

Calcium antagonists and phosphodiesterase inhibitors

Nifedipine is the most investigated calcium antagonist in subjects susceptible to HAPE. Nifedipine 30 mg orally every 12 h is used for both treatment and prophylaxis[6,10] (Fig. 2).

Phosphodieseterase-5 (PDE5) inhibitors are used in subjects with pulmonary arterial hypertension and are a reasonable option for preventing and treating HAPE. Maggiorini et al. could show that twice-daily ingestion of tadalafil 10 mg prevented HAPE in susceptible subjects.[139] Although only tadalafil has been investigated in this setting, it may be assumed that sildenafil is similarly effective. A combined therapy or prophylaxis of nifedipine and PDE5-inhibitor should be avoided due to possibly severe hypotension. The limitation of PDE5-inhibitor in

prophylaxis is the side effect profile with frequently occurring headache (Fig. 2).

Oxygen

Supplementation of oxygen via nasal cannula or mask is a safe and effective option in the prevention of high-altitude illness. Usually, low-flow oxygen with 1–2 L/min is applied during sleep, although higher flow rates and permanent supplementations are used in commercial expeditions, e.g., to Mt. Everest (Everest Flash) as well. This prophylactic strategy is mainly limited due to logistical restraints and high costs.

Salmeterol

Beta-adrenergic agonist salmeterol 125 μg inhaled twice daily was associated with a significant reduction of HAPE incidence in susceptible subjects in one study[140] (Table 2). One mechanism of action involved is probably the improved alveolar fluid clearance due to stimulated transepithelial sodium transport.[140,141] Since this therapy is less effective than calcium antagonists and PDE5-inhibitors, salmeterol is regarded as an add-on only.

Ginkgo biloba

This herbal supplement has also been investigated for prophylaxis of AMS with conflicting results.[103,142,143] Two placebo-controlled trials could not show any beneficial effect of ginkgo biloba in reducing the incidence of AMS.[144,145] Thus, current knowledge does not support the recommendation of this supplement for effective AMS prevention.

Conclusions

Although knowledge on the physiology of acclimatization to high altitude and the pathophysiology of high-altitude illnesses, and on effective prevention and treatment strategies has considerably increased during the past decades, there are still outstanding issues and challenges to be met by future research. For example, modern pre-acclimatization strategies using normobaric hypoxia chambers/tents before rapidly ascending to extreme altitudes represent such challenges. Nonetheless, considering the “old” rule of slow ascent to allow appropriate acclimatization, “listening” to the individual physiological responses during the ascent, and knowledge on adequate treatment in the case of disease development remain the mainstays for safe and enjoyable high-altitude sojourns.

Submission statement

The manuscript has not been published and is not under consideration for publication elsewhere.

Authors’ contributions

MB provided the conceptual basis for this review and the first draft. UH and JPH added content, editing, and formatting in the drafting of this manuscript.

Conflict of interest

The authors have no conflict of interest.

References

[1]. Brugger H, Basnyat B, Ellerton J, Hefti U, Strapazzon G, Zafren K. *Letter to the editor:* COVID-19 lung injury is different from high altitude pulmonary edema. *High Alt. Med. Biol.* 2020;21(2):204–205. https://doi.org/10.1089/ham.2020.0061.

[2]. Grannemann JJ, Röper A. Aufenthalte in großen Höhen nach COVID-19-Infektion – neue Aspekte der höhenmedizinischen Beratung [Travelling to High Altitude Destinations after Recovery from COVID-19-infection: new Aspects of Medical Advice in Altitude Medicine]. *Pneumologie*. 2021;75(3):214–220. https://doi.org/10.1055/a-1239-0334.

[3]. Millet GP, Debevec T, Brocherie F, Burtscher M, Burtscher J. Altitude and COVID-19: friend or foe? A narrative review. *Physiol Rep*. 2021;8(24), e14615. https://doi.org/10.14814/phy2.14615.

[4]. Government of Nepal. *Nepal tourism facts*. https://www.tourism.gov.np//files/statistics/21.pdf; 2019. Accessed September 2, 2020.

[5]. The most popular trekking routes on Kilimanjaro - the latest figures | CMK. Climb Mount Kilimanjaro. https://www.climbmountkilimanjaro.com/popular-trekking-routes-kilimanjaro-latest-figures/; 2018. Accessed September 2, 2020.

[6]. Burtscher M, Ponchia A. The risk of cardiovascular events during leisure time activities at altitude. *Prog. Cardiovasc. Dis.* 2010;52(6):507–511. https://doi.org/10.1016/j.pcad.2010.02.008.

[7]. Niedermeier M, Gatterer H, Pocecco E, et al. Mortality in different mountain sports activities primarily practiced in the winter season-A narrative review. *Int. J. Environ. Res. Publ. Health*. 2019;17(1):259. https://doi.org/10.3390/ijerph17010259. Published 2019 Dec 30.

[8]. Hackett PH, Roach RC. High-altitude illness. *N. Engl. J. Med.* 2001;345(2):107–114. https://doi.org/10.1056/NEJM200107123450206.

[9]. Mairer K, Wille M, Bucher T, Burtscher M. Prevalence of acute mountain sickness in the Eastern Alps. *High Alt. Med. Biol.* 2009;10(3):239–245. https://doi.org/10.1089/ham.2008.1091.

[10]. Netzer N, Strohl K, Faulhaber M, Gatterer H, Burtscher M. Hypoxia-related altitude illnesses. *J. Trav. Med.* 2013;20(4):247–255. https://doi.org/10.1111/jtm.12017.

[11]. Hackett PH, Roach RC. High altitude cerebral edema. *High Alt. Med. Biol.* 2004;5(2):136–146. https://doi.org/10.1089/1527029041352054.

[12]. Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O. Prevention of high-altitude pulmonary edema by nifedipine. *N. Engl. J. Med.* 1991;325(18):1284–1289. https://doi.org/10.1056/NEJM199110313251805.

[13]. Lenfant C, Sullivan K. Adaptation to high altitude. *N. Engl. J. Med.* 1971;284(23):1298–1309. https://doi.org/10.1056/NEJM197106102842305.

[14]. West JB, Richalet JP. Denis Jourdanet (1815-1892) and the early recognition of the role of hypoxia at high altitude. *Am. J. Physiol. Lung Cell Mol. Physiol.* 2013;305(5):L333–L340. https://doi.org/10.1152/ajplung.00128.2013.

[15]. Muza SR, Beidleman BA, Fulco CS. Altitude preexposure recommendations for inducing acclimatization. *High Alt. Med. Biol.* 2010;11(2):87–92. https://doi.org/10.1089/ham.2010.1006.

[16]. Fulco CS, Beidleman BA, Muza SR. Effectiveness of preacclimatization strategies for high-altitude exposure. *Exerc. Sport Sci. Rev.* 2013;41(1):55–63. https://doi.org/10.1097/JES.0b013e31825eaa33.

[17]. Beidleman BA, Fulco CS, Muza SR, et al. Effect of six days of staging on physiologic adjustments and acute mountain sickness during ascent to 4300 meters. *High Alt. Med. Biol.* 2009;10(3):253–260. https://doi.org/10.1089/ham.2009.1004.

[18]. Mairer K, Wille M, Burtscher M. The prevalence of and risk factors for acute mountain sickness in the Eastern and Western Alps. *High Alt. Med. Biol.* 2010;11(4):343–348. https://doi.org/10.1089/ham.2010.1039.

[19]. Bloch KE, Turk AJ, Maggiorini M, et al. Effect of ascent protocol on acute mountain sickness and success at Muztagh Ata, 7546 m. *High Alt. Med. Biol.* 2009;10(1):25–32. https://doi.org/10.1089/ham.2008.1043.

[20]. West JB. Human responses to extreme altitudes. *Integr. Comp. Biol.* 2006;46(1):25–34. https://doi.org/10.1093/icb/icj005.

[21]. West JB. Acclimatization and tolerance to extreme altitude. *J. Wilderness Med.* 1993;4(1):17–26. https://doi.org/10.1580/0953-9859-4.1.17.

[22]. Luks AM. Clinician's corner: what do we know about safe ascent rates at high altitude? *High Alt. Med. Biol.* 2012;13(3):147–152. https://doi.org/10.1089/ham.2012.1055.

[23]. Burtscher M, Wille M, Menz V, Faulhaber M, Gatterer H. Symptom progression in acute mountain sickness during a 12-hour exposure to normobaric hypoxia equivalent to 4500 m. *High Alt. Med. Biol.* 2014;15(4):446–451. https://doi.org/10.1089/ham.2014.1039.

[24]. Maggiorini M, Bühler B, Walter M, Oelz O. Prevalence of acute mountain sickness in the Swiss Alps. *BMJ*. 1990;301(6756):853–855. https://doi.org/10.1136/bmj.301.6756.853.

[25]. Richalet JP, Larmignat P, Poitrine E, Letournel M, Canouï-Poitrine F. Physiological risk factors for severe high-altitude illness: a prospective cohort study. *Am. J. Respir. Crit. Care Med.* 2012;185(2):192–198. https://doi.org/10.1164/rccm.201108-1396OC.

[26]. Hou YP, Wu JL, Tan C, Chen Y, Guo R, Luo YJ. Sex-based differences in the prevalence of acute mountain sickness: a meta-analysis. *Mil Med Res*. 2019;6(1):38. https://doi.org/10.1186/s40779-019-0228-3. Published 2019 Dec 9.

[27]. Gianfredi V, Albano L, Basnyat B, Ferrara P. Does age have an impact on acute mountain sickness? A systematic review. *J. Trav. Med.* 2020;27(6). https://doi.org/10.1093/jtm/taz104. taz104.

[28]. Villca N, Asturizaga A, Heath-Freudenthal A. High-altitude illnesses and air travel: pediatric considerations. *Pediatr Clin North Am*. 2021;68(1):305–319. https://doi.org/10.1016/j.pcl.2020.09.015.

[29]. Roach RC, Bärtsch P, Hackett PH, Oelz O. The Lake Louise acute mountain sickness scoring system. In: Sutton JRHC, Coates G, eds. *Hypoxia and Molecular Medicine*. Queen City Press; 1993:272–274 (Conference preceding).

[30]. Roach RC, Hackett PH, Oelz O, et al. The 2018 lake louise acute mountain sickness score. *High Alt. Med. Biol.* 2018;19(1):4–6. https://doi.org/10.1089/ham.2017.0164.

[31]. Wagner DR, Teramoto M, Knott JR, Fry JP. Comparison of scoring systems for assessment of acute mountain sickness. *High Alt. Med. Biol.* 2012;13(4):245–251. https://doi.org/10.1089/ham.2012.1030.

[32]. Millet GP, Debevec T. CrossTalk proposal: barometric pressure, independent of PO2 , is the forgotten parameter in altitude physiology and mountain medicine. *J Physiol*. 2020;598(5):893–896. https://doi.org/10.1113/JP278673.

[33]. Richalet JP. CrossTalk opposing view: barometric pressure, independent of PO2 , is not the forgotten parameter in altitude physiology and mountain medicine. *J Physiol*. 2020;598(5):897–899. https://doi.org/10.1113/JP279160.

[34]. Pun M. The physiologic basis of high-altitude diseases. *Ann. Intern. Med.* 2005; 142(7):591–592. https://doi.org/10.7326/0003-4819-142-7-200504050-00023.

[35]. Semenza GL. Hypoxia-inducible factors in physiology and medicine. *Cell*. 2012; 148(3):399–408. https://doi.org/10.1016/j.cell.2012.01.021.

[36]. Haase VH. Regulation of erythropoiesis by hypoxia-inducible factors. *Blood Rev.* 2013;27(1):41–53. https://doi.org/10.1016/j.blre.2012.12.003.

[37]. Weidemann A, Johnson RS. Biology of HIF-1 alpha. *Cell Death Differ.* 2008;15(4): 621–627. https://doi.org/10.1038/cdd.2008.12.

[38]. Taylor CT. Mitochondria and cellular oxygen sensing in the HIF pathway. *Biochem. J.* 2008;409(1):19–26. https://doi.org/10.1042/BJ20071249.

[39]. Weil JV, Byrne-Quinn E, Sodal IE, et al. Hypoxic ventilatory drive in normal man. *J. Clin. Invest.* 1970;49(6):1061–1072. https://doi.org/10.1172/JCI106322.

[40]. Reeves JT. In: *Sympathetics and hypoxia: a brief overview. In: Hypoxia and Molecular Medicine, edited by , Sutton J.R., Houston C., Coates G. Burlington, VT. Queen City.* 1993:1–6.

[41]. Bärtsch P, Gibbs JS. Effect of altitude on the heart and the lungs. *Circulation*. 2007;116(19):2191–2202. https://doi.org/10.1161/CIRCULATIONAHA.106.650796.

[42]. Bender PR, McCullough RE, McCullough RG, et al. Increased exercise SaO 2 independent of ventilatory acclimatization at 4,300 m (1985) *J. Appl. Physiol.* 1989;66(6):2733–2738. https://doi.org/10.1152/jappl.1989.66.6.2733.

[43]. Sato M, Severinghaus JW, Bickler P. Time course of augmentation and depression of hypoxic ventilatory responses at altitude (1985) *J. Appl. Physiol.* 1994;77(1): 313–316. https://doi.org/10.1152/jappl.1994.77.1.313.

[44]. Zouboules SM, Lafave HC, O'Halloran KD, et al. Renal reactivity: acid-base compensation during incremental ascent to high altitude. *J Physiol*. 2018; 596(24):6191–6203. https://doi.org/10.1113/JP276973.

[45]. Ainslie PN, Subudhi AW. Cerebral blood flow at high altitude. *High Alt. Med. Biol.* 2014;15(2):133–140. https://doi.org/10.1089/ham.2013.1138.

[46]. Bailey DM, Taudorf S, Berg RM, et al. Increased cerebral output of free radicals during hypoxia: implications for acute mountain sickness? *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2009;297(5):R1283–R1292. https://doi.org/10.1152/ajpregu.00366.2009.

[47]. Strapazzon G, Malacrida S, Vezzoli A, et al. Oxidative stress response to acute hypobaric hypoxia and its association with indirect measurement of increased intracranial pressure: a field study. *Sci. Rep.* 2016;6:32426. https://doi.org/10.1038/srep32426. Published 2016 Aug 31.

[48]. Richalet JP, Hornych A, Rathat C, Aumont J, Larmignat P, Rémy P. Plasma prostaglandins, leukotrienes and thromboxane in acute high altitude hypoxia. *Respir. Physiol.* 1991;85(2):205–215. https://doi.org/10.1016/0034-5687(91)90062-n.

[49]. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N. Engl. J. Med.* 2011; 364(7):656–665. https://doi.org/10.1056/NEJMra0910283.

[50]. McGuire SA, Sherman PM, Wijtenburg SA, et al. White matter hyperintensities and hypobaric exposure. *Ann. Neurol.* 2014;76(5):719–726. https://doi:10.1002/ana.24264.

[51]. Roach RC, Loeppky JA, Icenogle MV. Acute mountain sickness: increased severity during simulated altitude compared with normobaric hypoxia. *J. Appl. Physiol.* 1996;81(5):1908–1910. https://doi.org/10.1152/jappl.1996.81.5.1908 (1985).

[52]. DiPasquale DM, Strangman GE, Harris NS, Muza SR. Acute mountain sickness symptoms depend on normobaric versus hypobaric hypoxia. *BioMed Res. Int.* 2016;2016:6245609. https://doi.org/10.1155/2016/6245609.

[53]. Dubowitz DJ, Dyer EA, Theilmann RJ, Buxton RB, Hopkins SR. Early brain swelling in acute hypoxia (1985) *J. Appl. Physiol.* 2009;107(1):244–252. https://doi.org/10.1152/japplphysiol.90349.2008.

[54]. Kallenberg K, Bailey DM, Christ S, et al. Magnetic resonance imaging evidence of cytotoxic cerebral edema in acute mountain sickness. *J. Cerebr. Blood Flow Metabol.* 2007;27(5):1064–1071. https://doi.org/10.1038/sj.jcbfm.9600404.

[55]. Schoonman GG, Sándor PS, Nirkko AC, et al. Hypoxia-induced acute mountain sickness is associated with intracellular cerebral edema: a 3 T magnetic resonance imaging study. *J. Cerebr. Blood Flow Metabol.* 2008;28(1):198–206. https://doi.org/10.1038/sj.jcbfm.9600513.

[56]. Sagoo RS, Hutchinson CE, Wright A, et al. Magnetic Resonance investigation into the mechanisms involved in the development of high-altitude cerebral edema. *J. Cerebr. Blood Flow Metabol.* 2017;37(1):319–331. https://doi.org/10.1177/0271678X15625350.

[57]. Sanchez del Rio M, Moskowitz MA. High altitude headache. Lessons from headaches at sea level. *Adv. Exp. Med. Biol.* 1999;474:145–153.

[58]. Serrano-Dueñas M. High-altitude headache. *Expert Rev. Neurother.* 2007;7(3): 245–248. https://doi.org/10.1586/14737175.7.3.245.

[59]. Burtscher M, Likar R, Nachbauer W, Philadelphy M. Aspirin for prophylaxis against headache at high altitudes: randomised, double blind, placebo controlled trial. *BMJ*. 1998;316(7137):1057–1058. https://doi.org/10.1136/bmj.316.7137.1057.

[60]. Luks AM, Swenson ER, Bärtsch P. Acute high-altitude sickness. *Eur. Respir. Rev.* 2017;26(143):160096. https://doi.org/10.1183/16000617.0096-2016. Published 2017 Jan 31.

[61]. Kudrow L. The pathogenesis of cluster headache. *Curr. Opin. Neurol.* 1994;7(3): 278–282. https://doi.org/10.1097/00019052-199406000-00017.

[62]. Roach RC, Maes D, Sandoval D, et al. Exercise exacerbates acute mountain sickness at simulated high altitude (1985) *J. Appl. Physiol.* 2000;88(2):581–585. https://doi.org/10.1152/jappl.2000.88.2.581.

[63]. Castellani JW, Muza SR, Cheuvront SN, et al. Effect of hypohydration and altitude exposure on aerobic exercise performance and acute mountain sickness (1985) *J. Appl. Physiol.* 2010;109(6):1792–1800. https://doi.org/10.1152/japplphysiol.00517.2010.

[64]. Burtscher M, Mairer K, Wille M, Broessner G. Risk factors for high-altitude headache in mountaineers. *Cephalalgia*. 2011;31(6):706–711. https://doi.org/10.1177/0333102410394678.

[65]. Julian CG, Subudhi AW, Wilson MJ, Dimmen AC, Pecha T, Roach RC. Acute mountain sickness, inflammation, and permeability: new insights from a blood biomarker study (1985) *J. Appl. Physiol.* 2011;111(2):392–399. https://doi.org/10.1152/japplphysiol.00391.2011.

[66]. Bärtsch P, Swenson ER. Clinical practice: acute high-altitude illnesses. *N. Engl. J. Med.* 2013;368(24):2294–2302. https://doi.org/10.1056/NEJMcp1214870.

[67]. Simancas-Racines D, Arevalo-Rodriguez I, Osorio D, Franco JV, Xu Y, Hidalgo R. Interventions for treating acute high altitude illness. *Cochrane Database Syst. Rev.* 2018;6(6). https://doi.org/10.1002/14651858.CD009567.pub2. CD009567. Published 2018 Jun 30.

[68]. Irons HR, Salas RN, Bhai SF, Gregorie WD, Harris NS. Prospective double-blinded randomized field-based clinical trial of metoclopramide and ibuprofen for the treatment of high altitude headache and acute mountain sickness. *Wilderness Environ. Med.* 2020;31(1):38–43. https://doi.org/10.1016/j.wem.2019.11.005.

[69]. Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet*. 1976;2(7996):1149–1155. https://doi.org/10.1016/s0140-6736(76)91677-9.

[70]. Wu TY, Ding SQ, Liu JL, et al. Who should not go high: chronic disease and work at altitude during construction of the Qinghai-Tibet railroad. *High Alt. Med. Biol.* 2007;8(2):88–107. https://doi.org/10.1089/ham.2007.1015.

[71]. Wu T, Ding S, Liu J, et al. Ataxia: an early indicator in high altitude cerebral edema. *High Alt. Med. Biol.* 2006;7(4):275–280. https://doi.org/10.1089/ham.2006.7.275.

[72]. Davis C, Hackett P. Advances in the prevention and treatment of high altitude illness. *Emerg Med Clin North Am*. 2017;35(2):241–260. https://doi.org/10.1016/j.emc.2017.01.002.

[73]. Hackett PH, Yarnell PR, Hill R, Reynard K, Heit J, McCormick J. High-altitude cerebral edema evaluated with magnetic resonance imaging: clinical correlation and pathophysiology. *J. Am. Med. Assoc.* 1998;280(22):1920–1925. https://doi.org/10.1001/jama.280.22.1920.

[74]. Lafuente JV, Bermudez G, Camargo-Arce L, Bulnes S. Blood-Brain barrier changes in high altitude. *CNS Neurol. Disord. - Drug Targets*. 2016;15(9):1188–1197. https://doi.org/10.2174/1871527315666160920123911.

[75]. Simka M, Latacz P, Czaja J. Possible role of glymphatic system of the brain in the pathogenesis of high-altitude cerebral edema. *High Alt. Med. Biol.* 2018;19(4): 394–397. https://doi.org/10.1089/ham.2018.0066.

[76]. Schommer K, Kallenberg K, Lutz K, Bärtsch P, Knauth M. Hemosiderin deposition in the brain as footprint of high-altitude cerebral edema. *Neurology*. 2013;81(20): 1776–1779. https://doi.org/10.1212/01.wnl.0000435563.84986.78.

[77]. Pichler Hefti J, Hoigné-Perret P, Kottke R. Extensive microhemorrhages of the cerebellar peduncles after high-altitude cerebral edema. *High Alt. Med. Biol.* 2017; 18(2):182–184. https://doi.org/10.1089/ham.2016.0103.

[78]. Kottke R, Pichler Hefti J, Rummel C, Hauf M, Hefti U, Merz TM. Morphological brain changes after climbing to extreme altitudes–A prospective cohort study. *PloS One*. 2015;10(10), e0141097. https://doi.org/10.1371/journal.pone.0141097. Published 2015 Oct 28.

[79]. Schoene RB. Illnesses at high altitude. *Chest*. 2008;134(2):402–416. https://doi.org/10.1378/chest.07-0561.

[80]. Gabry AL, Ledoux X, Mozziconacci M, Martin C. High-altitude pulmonary edema at moderate altitude (< 2,400 m; 7,870 feet): a series of 52 patients. *Chest*. 2003; 123(1):49–53. https://doi.org/10.1378/chest.123.1.49.

[81]. Sophocles Jr AM, Bachman J. High-altitude pulmonary edema among visitors to Summit County, Colorado. *J. Fam. Pract.* 1983;17(6):1015–1017.

[82]. Bärtsch P, Maggiorini M, Mairbäurl H, Vock P, Swenson ER. Pulmonary extravascular fluid accumulation in climbers. *Lancet*. 2002;360(9332):571–572. https://doi.org/10.1016/S0140-6736(02)09723-4.

[83]. Schoene RB. Pulmonary edema at high altitude. Review, pathophysiology, and update. *Clin. Chest Med.* 1985;6(3):491–507.

[84]. Swenson ER, Bärtsch P. High-altitude pulmonary edema. *Comp. Physiol.* 2012; 2(4):2753–2773. https://doi.org/10.1002/cphy.c100029.

[85]. Oelz O, Maggiorini M, Ritter M, et al. Prevention and treatment of high altitude pulmonary edema by a calcium channel blocker. *Int. J. Sports Med.* 1992;13(Suppl 1):S65–S68. https://doi.org/10.1055/s-2007-1024598.

[86]. Swenson ER, Maggiorini M, Mongovin S, et al. Pathogenesis of high-altitude pulmonary edema: inflammation is not an etiologic factor [published correction appears in JAMA 2002 Sep 4;288(9):1064] *J. Am. Med. Assoc.* 2002;287(17): 2228–2235. https://doi.org/10.1001/jama.287.17.2228.

[87]. Dehnert C, Mereles D, Greiner S, et al. Exaggerated hypoxic pulmonary vasoconstriction without susceptibility to high altitude pulmonary edema. *High Alt. Med. Biol.* 2015;16(1):11–17. https://doi.org/10.1089/ham.2014.1117.

[88]. Eichstaedt CA, Mairbäurl H, Song J, et al. Genetic predisposition to high-altitude pulmonary edema. *High Alt. Med. Biol.* 2020;21(1):28–36. https://doi.org/10.1089/ham.2019.0083.

[89]. Scherrer U, Turini P, Thalmann S, et al. Pulmonary hypertension in high-altitude dwellers: novel mechanisms, unsuspected predisposing factors. *Adv. Exp. Med. Biol.* 2006;588:277–291. https://doi.org/10.1007/978-0-387-34817-9_23.

[90]. Sartori C, Duplain H, Lepori M, et al. High altitude impairs nasal transepithelial sodium transport in HAPE-prone subjects. *Eur. Respir. J.* 2004;23(6):916–920. https://doi.org/10.1183/09031936.04.00115304.

[91]. Allemann Y, Hutter D, Lipp E, et al. Patent foramen ovale and high-altitude pulmonary edema. *J. Am. Med. Assoc.* 2006;296(24):2954–2958. https://doi.org/10.1001/jama.296.24.2954.

[92]. Marshall BE, Marshall C, Magno M, Lilagan P, Pietra GG. Influence of bronchial arterial PO2 on pulmonary vascular resistance (1985) *J. Appl. Physiol.* 1991;70(1):405–415. https://doi.org/10.1152/jappl.1991.70.1.405.

[93]. Swenson ER. Hypoxic pulmonary vasoconstriction. *High Alt. Med. Biol.* 2013;14(2):101–110. https://doi.org/10.1089/ham.2013.1010.

[94]. Schoene RB, Roach RC, Hackett PH, Harrison G, Mills Jr WJ. High altitude pulmonary edema and exercise at 4,400 meters on Mount McKinley. Effect of expiratory positive airway pressure. *Chest.* 1985;87(3):330–333. https://doi.org/10.1378/chest.87.3.330.

[95]. Swenson ER. Early hours in the development of high-altitude pulmonary edema: time course and mechanisms (1985) *J. Appl. Physiol.* 2020;128(6):1539–1546. https://doi.org/10.1152/japplphysiol.00824.2019.

[96]. West JB. Climbing Mt. Everest without oxygen: an analysis of maximal exercise during extreme hypoxia. *Respir. Physiol.* 1983;52(3):265–279. https://doi.org/10.1016/0034-5687(83)90085-3.

[97]. Burtscher M, Gatterer H, Kleinsasser A. Cardiorespiratory fitness of high altitude mountaineers: the underestimated prerequisite. *High Alt. Med. Biol.* 2015;16(2):169–170. https://doi.org/10.1089/ham.2015.0021.

[98]. Rossetti GMK, Macdonald JH, Smith M, et al. MEDEX2015: greater sea-level fitness is associated with lower sense of effort during Himalayan trekking without worse acute mountain sickness. *High Alt. Med. Biol.* 2017;18(2):152–162. https://doi.org/10.1089/ham.2016.0088.

[99]. Minetti AE, Formenti F, Ardigò LP. Himalayan porter's specialization: metabolic power, economy, efficiency and skill. *Proc. Biol. Sci.* 2006;273(1602):2791–2797. https://doi.org/10.1098/rspb.2006.3653.

[100]. Mohajeri S, Perkins BA, Brubaker PL, Riddell MC. Diabetes, trekking and high altitude: recognizing and preparing for the risks. *Diabet. Med.* 2015;32(11):1425–1437. https://doi.org/10.1111/dme.12795.

[101]. Parati G, Agostoni P, Basnyat B, et al. Clinical recommendations for high altitude exposure of individuals with pre-existing cardiovascular conditions: a joint statement by the European Society of Cardiology, the Council on hypertension of the European Society of Cardiology, the European Society of hypertension, the international Society of mountain medicine, the Italian Society of hypertension and the Italian Society of mountain medicine. *Eur. Heart J.* 2018;39(17):1546–1554. https://doi.org/10.1093/eurheartj/ehx720.

[102]. Bärtsch P, Grünig E, Hohenhaus E, Dehnert C. Assessment of high altitude tolerance in healthy individuals. *High Alt. Med. Biol.* 2001;2(2):287–296. https://doi.org/10.1089/152702901750265378.

[103]. Basnyat B, Murdoch DR. High-altitude illness. *Lancet.* 2003;361(9373):1967–1974. https://doi.org/10.1016/S0140-6736(03)13591-X.

[104]. Luks AM. Physiology in Medicine: a physiologic approach to prevention and treatment of acute high-altitude illnesses (1985) *J. Appl. Physiol.* 2015;118(5):509–519. https://doi.org/10.1152/japplphysiol.00955.2014.

[105]. West JB. Highest inhabitants in the world. *Nature*. 1986;324(6097):517. https://doi.org/10.1038/324517a0.

[106]. Pugh LG. Man at high altitude: studies carried out in the Himalaya. *Sci. Basis Med. Annu. Rev.*. 1964:32–54.

[107]. Ward M. High altitude deterioration. *Proc. R. Soc. Lond. B Biol. Sci.* 1954;143(910):40–42. https://doi.org/10.1098/rspb.1954.0052.

[108]. Cerretelli P. Muscle energetics and ultrastructure in chronic hypoxia. *Respiration.* 1992;59(Suppl 2):24–29. https://doi.org/10.1159/000196117.

[109]. Richalet JP, Pillard F, Le Moal D, et al. Validation of a score for the detection of subjects with high risk for severe high-altitude illness [published online ahead of print, 2020 Dec 29] *Med. Sci. Sports Exerc.*. 2020 https://doi.org/10.1249/MSS.0000000000002586. Publish Ahead of Print:10.1249/MSS.0000000000002586.

[110]. Fulco CS, Muza SR, Beidleman B, et al. Exercise performance of sea-level residents at 4300 m after 6 days at 2200 m. *Aviat Space Environ. Med.* 2009;80(11):955–961. https://doi.org/10.3357/asem.2540.2009.

[111]. Benoit H, Germain M, Barthélémy JC, et al. Pre-acclimatization to high altitude using exercise with normobaric hypoxic gas mixtures. *Int. J. Sports Med.* 1992;13(Suppl 1):S213–S216. https://doi.org/10.1055/s-2007-1024643.

[112]. Ponchia A, Noventa D, Bertaglia M, et al. Cardiovascular neural regulation during and after prolonged high altitude exposure. *Eur. Heart J.* 1994;15(11):1463–1469. https://doi.org/10.1093/oxfordjournals.eurheartj.a060415.

[113]. Savourey G, Garcia N, Besnard Y, Hanniquet AM, Fine MO, Bittel J. Physiological changes induced by pre-adaptation to high altitude. *Eur. J. Appl. Physiol. Occup. Physiol.* 1994;69(3):221–227. https://doi.org/10.1007/BF01094792.

[114]. Staab JE, Beidleman BA, Muza SR, Fulco CS, Rock PB, Cymerman A. Efficacy of residence at moderate versus low altitude on reducing acute mountain sickness in men following rapid ascent to 4300 m. *High Alt. Med. Biol.* 2013;14(1):13–18. https://doi.org/10.1089/ham.2012.1065.

[115]. Schneider M, Bernasch D, Weymann J, Holle R, Bartsch P. Acute mountain sickness: influence of susceptibility, preexposure, and ascent rate. *Med. Sci. Sports Exerc.* 2002;34(12):1886–1891. https://doi.org/10.1097/00005768-200212000-00005.

[116]. Hilty MP, Hefti U, Brugger H, Bouzat P. Letter to the Editor: preacclimatization for Expeditions to Extreme Altitude: an Opinion Position from the Union Internationale des Associations d'Alpinisme Medical Commission. *High Alt. Med. Biol.* 2020;21(3):303–304. https://doi.org/10.1089/ham.2020.0029.

[117]. Burse RL, Forte Jr VA. Acute mountain sickness at 4500 m is not altered by repeated eight-hour exposures to 3200-3550 m normobaric hypoxic equivalent. *Aviat Space Environ. Med.* 1988;59(10):942–949.

[118]. Ricart A, Casas H, Casas M, et al. Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. *Wilderness Environ. Med.* 2000;11(2):84–88. https://doi.org/10.1580/1080-6032(2000)011[0084:anherc]2.3.co;2.

[119]. Casas M, Casas H, Pagés T, et al. Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. *Aviat Space Environ. Med.* 2000;71(2):125–130.

[120]. Fulco CS, Muza SR, Beidleman BA, et al. Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2011;300(2):R428–R436. https://doi.org/10.1152/ajpregu.00633.2010.

[121]. Wille M, Gatterer H, Mairer K, et al. Short-term intermittent hypoxia reduces the severity of acute mountain sickness. *Scand. J. Med. Sci. Sports*. 2012;22(5):e79–e85. https://doi.org/10.1111/j.1600-0838.2012.01499.x.

[122]. Faulhaber M, Pocecco E, Gatterer H, et al. Seven passive 1-h hypoxia exposures do not prevent AMS in susceptible individuals. *Med. Sci. Sports Exerc.* 2016;48(12):2563–2570. https://doi.org/10.1249/MSS.0000000000001036.

[123]. Dehnert C, Böhm A, Grigoriev I, Menold E, Bärtsch P. Sleeping in moderate hypoxia at home for prevention of acute mountain sickness (AMS): a placebo-controlled, randomized double-blind study. *Wilderness Environ. Med.* 2014;25(3):263–271. https://doi.org/10.1016/j.wem.2014.04.004.

[124]. Treml B, Kleinsasser A, Hell T, Knotzer H, Wille M, Burtscher M. Carry-over quality of pre-acclimatization to altitude elicited by intermittent hypoxia: a participant-blinded, randomized controlled trial on antedated acclimatization to altitude. *Front. Physiol.* 2020;11:531. https://doi.org/10.3389/fphys.2020.00531. Published 2020 May 29.

[125]. Ellsworth AJ, Larson EB, Strickland D. A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. *Am. J. Med.* 1987;83(6):1024–1030. https://doi.org/10.1016/0002-9343(87)90937-5.

[126]. Basnyat B, Gertsch JH, Johnson EW, Castro-Marin F, Inoue Y, Yeh C. Efficacy of low-dose acetazolamide (125 mg BID) for the prophylaxis of acute mountain sickness: a prospective, double-blind, randomized, placebo-controlled trial. *High Alt. Med. Biol.* 2003;4(1):45–52. https://doi.org/10.1089/152702903321488979.

[127]. Gertsch JH, Lipman GS, Holck PS, et al. Prospective, double-blind, randomized, placebo-controlled comparison of acetazolamide versus ibuprofen for prophylaxis against high altitude headache: the Headache Evaluation at Altitude Trial (HEAT). *Wilderness Environ. Med.* 2010;21(3):236–243. https://doi.org/10.1016/j.wem.2010.06.009.

[128]. Swenson ER. Carbonic anhydrase inhibitors and hypoxic pulmonary vasoconstriction. *Respir. Physiol. Neurobiol.* 2006;151(2–3):209–216. https://doi.org/10.1016/j.resp.2005.10.011.

[129]. Swenson ER, Teppema LJ. Prevention of acute mountain sickness by acetazolamide: as yet an unfinished story. *J. Appl. Physiol.* 2007;102(4):1305–1307. https://doi.org/10.1152/japplphysiol.01407.2006 (1985).

[130]. Swenson ER. Carbonic anhydrase inhibitors and high altitude illnesses. *Subcell. Biochem.* 2014;75:361–386. https://doi.org/10.1007/978-94-007-7359-2_18.

[131]. Kayser B, Dumont L, Lysakowski C, Combescure C, Haller G, Tramèr MR. Reappraisal of acetazolamide for the prevention of acute mountain sickness: a systematic review and meta-analysis. *High Alt. Med. Biol.* 2012;13(2):82–92. https://doi.org/10.1089/ham.2011.1084.

[132]. Basnyat B, Gertsch JH, Holck PS, et al. Acetazolamide 125 mg BD is not significantly different from 375 mg BD in the prevention of acute mountain sickness: the prophylactic acetazolamide dosage comparison for efficacy (PACE) trial. *High Alt. Med. Biol.* 2006;7(1):17–27. https://doi.org/10.1089/ham.2006.7.17.

[133]. McIntosh SE, Hemphill M, McDevitt MC, et al. Reduced acetazolamide dosing in countering altitude illness: a comparison of 62.5 vs 125 mg (the RADICAL trial). *Wilderness Environ. Med.* 2019;30(1):12–21. https://doi.org/10.1016/j.wem.2018.09.002.

[134]. Burtscher M, Gatterer H, Faulhaber M, Burtscher J. Acetazolamide pre-treatment before ascending to high altitudes: when to start? *Int. J. Clin. Exp. Med.* 2014;7(11):4378–4383. Published 2014 Nov 15.

[135]. Lipman GS, Jurkiewicz C, Winstead-Derlega C, et al. Day of ascent dosing of acetazolamide for prevention of acute mountain sickness. *High Alt. Med. Biol.* 2019;20(3):271–278. https://doi.org/10.1089/ham.2019.0007.

[136]. Liu HM, Chiang IJ, Kuo KN, Liou CM, Chen C. The effect of acetazolamide on sleep apnea at high altitude: a systematic review and meta-analysis. *Ther. Adv. Respir. Dis.* 2017;11(1):20–29. https://doi.org/10.1177/1753465816677006.

[137]. Lu H, Zhang H, Jiang Y. Methazolamide in high-altitude illnesses. *Eur. J. Pharmaceut. Sci.* 2020;148:105326. https://doi.org/10.1016/j.ejps.2020.105326.

[138]. Schilling M, Irarrázaval S. Ibuprofen versus acetazolamide for prevention of acute mountain sickness. Ibuprofeno comparado con acetazolamida para prevención de mal agudo de montaña. *Medwave*. 2020;20(5), e7733. https://doi.org/10.5867/medwave.2020.05.7732. Published 2020 Jun 11.

[139]. Maggiorini M, Brunner-La Rocca HP, Peth S, et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. *Ann. Intern. Med.* 2006;145(7):497–506. https://doi.org/10.7326/0003-4819-145-7-200610030-00007.

[140]. Sartori C, Allemann Y, Duplain H, et al. Salmeterol for the prevention of high-altitude pulmonary edema. *N. Engl. J. Med.* 2002;346(21):1631–1636. https://doi.org/10.1056/NEJMoa013183.

[141]. Matthay MA, Flori HR, Conner ER, Ware LB. Alveolar epithelial fluid transport: basic mechanisms and clinical relevance. *Proc. Assoc. Am. Phys.* 1998;110(6):496–505.
[142]. Gertsch JH, Seto TB, Mor J, Onopa J. Ginkgo biloba for the prevention of severe acute mountain sickness (AMS) starting one day before rapid ascent. *High Alt. Med. Biol.* 2002;3(1):29–37. https://doi.org/10.1089/152702902753639522.
[143]. Dumont L, Mardirosoff C, Tramèr MR. Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ*. 2000;321(7256):267–272. https://doi.org/10.1136/bmj.321.7256.267.
[144]. Gertsch JH, Basnyat B, Johnson EW, Onopa J, Holck PS. Randomised, double blind, placebo controlled comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT). *BMJ*. 2004;328(7443):797. https://doi.org/10.1136/bmj.38043.501690.7C.
[145]. Chow T, Browne V, Heileson HL, Wallace D, Anholm J, Green SM. Ginkgo biloba and acetazolamide prophylaxis for acute mountain sickness: a randomized, placebo-controlled trial. *Arch. Intern. Med.* 2005;165(3):296–301. https://doi.org/10.1001/archinte.165.3.296.