REVIEW ARTICLE

Altitude Sickness

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ABSTRACT

Altitude sickness encompasses conditions such as acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE), affecting individuals ascending to high altitudes without proper acclimatization. The fundamental cause is decreased barometric pressure, leading to reduced oxygen availability. Acclimatization is the body's adaptive response, involving respiratory, cardiovascular, pulmonary, hematopoietic, and cerebral circulatory adjustments. Key factors influencing acclimatization include the rate of ascent, altitude, individual susceptibility, and physical fitness.

AMS, the most common altitude illness, typically occurs above 2500 meters. Symptoms include headache, anorexia, nausea, fatigue, and lightheadedness. Diagnosis relies on reported symptoms. Prevention involves gradual ascent, limiting sleeping elevation gains, and prophylactic medications. Treatment includes descent, oxygen, acetazolamide, or dexamethasone.

HAPE is a potentially fatal condition with fluid leakage into the alveoli. Symptoms include dyspnea at rest, dry cough, and cyanosis. Diagnosis involves clinical assessment and pulse oximetry. Prevention includes gradual ascent and nifedipine for those with a history. Treatment requires immediate descent and oxygen therapy.

HACE, the most severe form, is progression from AMS, characterized by ataxia, severe headache, nausea, vomiting, and altered mental status. Diagnosis is based on clinical assessment. Treatment prioritizes rapid descent, high-flow oxygen, and dexamethasone.

Chronic mountain sickness (CMS) affects long-term high-altitude residents, marked by excessive erythrocytosis. Treatment involves descent, oxygen therapy, and medications like acetazolamide.

Awareness, effective prevention strategies, and prompt treatment are crucial to mitigate life-threatening complications associated with altitude sickness.

INTRODUCTION

Altitude sickness encompasses a range of conditions that can affect individuals ascending to high altitudes without proper acclimatization. This manuscript explores the pathophysiology, prevention, diagnosis, and treatment of these conditions, including acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE).

Altitude sickness impacts millions of individuals annually, particularly trekkers, climbers, and military personnel. Over 81 million humans reside at elevations above 2500 meters.[1] The increasing popularity of high-altitude destinations necessitates updated protocols to mitigate associated risks. It is estimated that up to 20%-25% of travelers to altitudes above 2500 meters develop AMS, underscoring the importance of prevention and timely intervention.[2]

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Altitude and Hypoxia

The fundamental cause of altitude sickness is decrease in barometric pressure that accompanies increasing altitude, leading to reduction in the partial pressure of oxygen in inspired air and, consequently, reduced oxygen availability to the body. This reduced oxygen availability, known as hypoxia, sets off a series of physiologic adaptations that can result in altitude sickness if the ascent is too rapid for the body to adjust.[2-4]

Most healthy individuals tolerate elevations up to 3658 meters (12,000 feet) without significant oxygen desaturation.[2,4] At higher elevations, however, noticeable physiologic effects typically occur when arterial oxygen saturation falls below 90%.[2,4] This highlights the variability in individual responses to altitude, with some individuals experiencing symptoms at lower elevations, particularly those with underlying medical conditions.[5]

Acclimatization

Acclimatization is a complex physiologic process that enables the body to adapt to high-altitude environments, minimizing the consequences of hypoxia. Multiple organ systems contribute to these adaptations.[2,4]

Respiratory System

A key initial response to altitude is increased tidal volume and respiratory rate, known as hypoxic ventilatory response (HVR).2,4 This hyperventilation elevates the alveolar partial pressure of oxygen (PaO_2) but induces respiratory alkalosis. Renal compensation via bicarbonate excretion begins after 24-48 hours, causing metabolic acidosis to restore acid-base balance and allowing continued hyperventilation for improved oxygen uptake.[2,4] Individuals who acclimatize may develop increased sensitivity to hypoxia, possibly due to adaptations mediated by hypoxia-inducible factor 1 alpha (HIF-1α).[2,4,6,7]

Alveolar hypoxia triggers hypoxic pulmonary vasoconstriction (HPV), raises pulmonary arterial pressure, and can enhance ventilation-perfusion matching. However, uneven HPV can predispose to HAPE.[4,8,9] Hypoxia can increase microvascular permeability in the lungs and contribute to edema formation, exacerbating pulmonary edema.[2,3,10,11] Several mechanisms might be involved including the role of HIF-1α , upregulation of vascular endothelial growth factor (VEGF), and release of inflammatory mediators.[2,3,7]

Cardiovascular System

Initially, sympathetic activation involving epinephrine and norepinephrine release elevates heart rate, blood pressure, and pulmonary perfusion.[2,4] Over time, plasma volume reduction through diuresis lowers cardiac output, with heart rate returning closer to baseline, and sensitivity to catecholamines decreasing.[2,4]

Hematopoietic System

Diuresis and plasma volume contraction cause hemoconcentration, rapidly boosting the blood's oxygen content.[2,4] Hypoxia stimulates erythropoietin production, increasing red blood cell mass over several weeks, thereby enhancing oxygen-carrying capacity.[2,5,6] However, excessive erythrocytosis can contribute to chronic mountain sickness (CMS).[2,4]

Cerebral Circulation

At rest, the brain is responsible for 20% of the body's total oxygen consumption. In response to hypoxia, cerebral blood flow slightly increases, especially when PaO_2 falls below 60 mmHg.[2,4] This helps maintain adequate oxygen delivery to the brain.

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- It is important to note that acclimatization is gradual and varies among individuals. Factors influencing acclimatization include:
- Rate of ascent: A slow ascent rate reduces the risk of altitude sickness.[2,12]
- Altitude: Acclimatization capacity declines with increasing altitude.[2,4,8]Individual susceptibility: Genetics, age, gender, and history of altitude illness.[2,4,5,8]
- Physical fitness: Fitness does not prevent altitude sickness but may help individuals tolerate physical exertion at altitude.[2]

It is important to note that even with proper training and acclimatization, the body has limits in adapting to extreme altitudes. At altitudes above 5500 meters, physiologic impairment often surpasses adaptive mechanisms.[2,4]

ACUTE MOUNTAIN SICKNESS

Acute mountain sickness (AMS) is the most common form of altitude illness, characterized by a constellation of symptoms that typically emerge within hours to days of ascending above 2500 meters.[4,10,12] Hypoxia is a central cause, although the "tight-fit" hypothesis posits that individuals with reduced intracranial and intraspinal cerebrospinal fluid (CSF) capacity are more susceptible to AMS because there is less capacity to accommodate brain swelling.[4,8,10]

As brain volume increases at altitude, CSF volume must decrease to maintain intracranial volume, but these compensatory measures are finite. Once exhausted,

intracranial pressure (ICP) rises.[2,4,8] Certain activities such as lifting, valsalva maneuvers, or turning the head can transiently increase ICP, exacerbating symptoms.[8] This supports the tight-fit hypothesis, as these actions further increase intracranial blood volume. While ICP might not be elevated at rest in individuals with mild AMS, it can rise sharply during exertion.[8] Thus, fluctuating ICP may explain the headache that is a primary symptom of AMS, similar to patients with idiopathic intracranial hypertension without papilledema.[8] In moderate to severe AMS and HACE, ICP is definitively elevated.[2,8,12] Hypoxia-induced intracranial venous hypertension may also play a role, although its significance remains controversial.[8]

Diagnosis of AMS relies solely on reported symptoms, as there are no specific physical examination findings or laboratory tests.[2,5,8] The Lake Louise AMS score is a tool for assessing altitude illness, with points assigned for headache, gastrointestinal upset, and functional impairment, but it is not typically used for definitive clinical diagnosis.[12] The hallmark symptom is headache, often throbbing and frontal or global.[12] However, some debate exists about whether headache is mandatory, with some experts emphasizing an individual's overall functional status.[5,8,12] Additional symptoms include anorexia, nausea, fatigue, and lightheadedness or dizziness. Dehydration can also exacerbate or mimic AMS symptoms, complicating diagnosis.[5,8] It is important to consider the traveler's well-being and functional status when diagnosing AMS, given the lack of a definitive diagnostic gold standard. If an individual feels ill and must curtail daily activities soon after ascending above 2500 meters, AMS is highly likely.[5]

Prevention of AMS

A gradual or staged ascent is the most effective preventive measure.[5] Current guidelines suggest limiting sleeping elevation gains to ≤500 meters per day and adding a rest day every 3-4 days above 3000 meters.[5] This "climb high, sleep low" strategy reduces nighttime hypoxic stress when respiratory drive diminishes.[4,8] Acetazolamide aids acclimatization by promoting bicarbonate excretion (compensating for respiratory alkalosis) and stimulating ventilation.[2,5,8] Typical preventive dosing is 125 mg twice daily, beginning 24 hours before ascent and continuing during high-altitude exposure. Dexamethasone is a corticosteroid with anti-inflammatory and anti-edema effects, making it another prophylactic option, though long-term use is discouraged due to potential adverse effects.[2,5,8] While dehydration does not directly influence AMS susceptibility, adequate hydration is crucial for overall well-being at high altitude. Avoiding alcohol and sedatives, which can suppress respiratory drive and worsen hypoxemia, is also recommended.[2,4,5,8]

Treatment of AMS

The cornerstone of AMS management is descent—even 500-1000 meters can be sufficient.[5] In more severe cases, supplementary oxygen may be given to maintain arterial oxygen saturation (SaO_2) above 90%.2,5,8 Mild AMS often improves with acetazolamide, while more severe presentations benefit from dexamethasone to reduce cerebral edema.[5] Portable hyperbaric chambers (e.g., Gamow bags) can simulate descent by increasing barometric pressure and effectively raising local oxygen availability—though they should not replace an actual descent to a safer elevation.[2,4,5,8]

HIGH-ALTITUDE PULMONARY EDEMA

High-altitude pulmonary edema (HAPE) is a potentially fatal condition caused by fluid leakage from pulmonary capillaries into the alveoli, compromising gas exchange. It typically appears within the first 2-4 days at altitudes above 2500 meters.[2-4,9] Excessive pulmonary hypertension driven by HPV is central to HAPE pathogenesis, especially among individuals with an exaggerated HPV response, likely an inherent trait.[3,9] The severity of edema directly correlates with increase in pulmonary arterial pressure (PAP), as evidenced by the presence of protein and red blood cells in the lung fluid of individuals experiencing the highest PAP increases.[4,8]

The hallmark symptom of HAPE is dyspnea at rest, differentiating it from AMS. Early symptoms often mimic fatigue and decreased exercise tolerance, which can be mistakenly attributed to other causes.[2,5,8] A persistent dry cough develops, followed by cyanosis and progressively worsening shortness of breath, particularly at night. Tachycardia and tachypnea ensue as the condition advances.[2,5,8] In field settings with limited resources, the diagnosis of HAPE often relies on history and clinical assessment.[2,5,8] However, pulse oximetry, if available, can confirm hypoxemia disproportionate to the altitude, helping to distinguish HAPE from other causes of dyspnea like anxiety or poor physical conditioning.

Additional contributors include impaired alveolar fluid clearance, blunted HVR, and extreme nocturnal hypoxemia, forming a multifactorial pathophysiology.[2,5] HAPE often presents with dyspnea at rest, fatigue, dry cough, and cyanosis.[2,5,8] In field settings, diagnosis typically hinges on clinical presentation; in well-equipped medical facilities, pulse oximetry, chest radiography, and electrocardiography are recommended for HAPE evaluation.[2,5,8] Pulse oximetry can detect disproportionate hypoxemia, while portable ultrasound may show B-lines, a nonspecific sign of pulmonary edema.[5,8]

Prevention of HAPE

To prevent HAPE when traveling to higher altitudes, a gradual ascent profile remains key.[5,9] Nifedipine, a calcium channel blocker, is a recommended prophylactic agent for those with prior history of HAPE, generally started one day before ascent and continued until descent or after a few days at the highest sleeping altitude.[2,5] However, systematic studies are needed to determine optimal duration of nifedipine prophylaxis, with recommendations ranging from 4-7 days.[5] Tadalafil and dexamethasone show potential for HAPE prophylaxis, but current evidence is insufficient to supersede nifedipine.[5]

Treatment of HAPE

Immediate descent to lower elevation is the most crucial treatment for HAPE. Another essential component of HAPE management is to supplement with oxygen therapy to maintain SaO_2 above 90%.[2,5,8] While nifedipine lowers PAP, it offers no definitive outcome benefit when added to oxygen, rest, and descent.[2,5,9] Tadalafil or sildenafil (phosphodiesterase 5 [PDE-5] inhibitors) may help by enhancing oxygenation and reducing PAP, but further data are needed.[3,5,9] Temporary use of a portable hyperbaric chamber can be life-saving if descent or oxygen supplementation is unavailable, but descent is the primary intervention.[5]

HIGH-ALTITUDE CEREBRAL EDEMA

High-altitude cerebral edema (HACE) is the least frequent but most severe form of altitude sickness, manifesting usually within 1-3 days after arrival at high altitude; however, symptoms may appear later, even around 5-9 days for some individuals.[2,4,12] HACE represents a life-threatening progression from AMS, characterized by cerebral edema that can be vasogenic (fluid leakage from vessels) or cytotoxic (intracellular swelling).[2,4] Studies using lumbar puncture demonstrate that elevated CSF (pressure of >300 mmH^2O) is commonly observed in HACE.[8] Cerebral edema is also evident on imaging studies (computed tomography [CT], magnetic resonance imaging [MRI]), or confirmed during autopsy.[8] Small petechial hemorrhages were consistently observed in autopsies, with occasional findings of venous sinus thrombosis.[8]

Many individuals with HACE also have pulmonary edema, although it may be subclinical.[2,8] Early stages of HACE might be partially reversible, but untreated, progression leads to cytotoxic edema developing in gray matter, culminating in brain herniation and death.[2,4] Focal neurologic signs, such as third and sixth cranial nerve palsies, may develop due to brainstem distortion and extra-axial compression. These focal signs can make it difficult to differentiate cerebral edema from primary cerebrovascular events.[2,4,8]

Ataxia, especially truncal ataxia, is the defining clinical feature that helps differentiate HACE from AMS and HAPE.[2,5,8,12] It often precedes development of altered mental status, making it an early warning sign. Other symptoms include severe headache, nausea and vomiting, and progressive encephalopathy, which can culminate in seizures and coma. Similar to AMS, HACE diagnosis primarily relies on clinical assessment, particularly in the field.[2,5,8,12] The presence of ataxia and altered mental status in the context of recent altitude exposure strongly suggests HACE.[2,5,8,12] Exaggerated hypoxemia may be evident on arterial blood gas analysis or pulse oximetry. Additionally, clinical examination and chest radiography may reveal concurrent pulmonary edema, as HACE often coexists with HAPE.[5,8] In settings with advanced imaging capabilities, brain CT may reveal nonspecific findings such as compressed sulci and flattened gyri, along with white matter attenuation.[5,8] MRI provides more specific findings, characteristically showing high T2 signal in the white matter, particularly in the splenium of the corpus callosum, which is most prominent on diffusion-weighted images.[5,8] While these imaging findings are helpful in confirming the diagnosis, particularly retrospectively, initial diagnosis in the field necessitates reliance on clinical judgment alone.[5,8]

Treatment of HACE

As with other altitude illnesses, rapid descent is the priority.[5] High-flow oxygen improves cerebral oxygenation, while dexamethasone reduces intracranial swelling to reduce cerebral edema.[2,8] Portable hyperbaric chambers offer a temporary measure when immediate descent is difficult.[2,5,8] However, any delay in evacuation can lead to prolonged coma or permanent neurologic deficits and even death.[2,5,8] Even with prompt and appropriate treatment, some individuals may experience lasting cognitive or motor impairments.[2,5,8]

CHRONIC MOUNTAIN SICKNESS

Chronic mountain sickness (CMS) predominantly affects those living at high altitudes long term.[4,8] CMS is characterized by excessive erythrocytosis (elevated red blood cell count), leading to increased blood viscosity and symptoms such as headache, fatigue, dyspnea, and cyanosis.[2,4]

Definitive treatment is descent, after which symptoms often improve—though they recur with return to altitude.[4,8] Oxygen therapy (especially during sleep) can help, and phlebotomy may offer subjective relief, although objective benefits are limited.[4,8] Certain medications (e.g., medroxyprogesterone acetate, acetazolamide) can reduce hematocrit by enhancing oxygenation.[8] Acetazolamide, in particular, can improve nocturnal oxygen saturation, reduce heart rate and sleep apnea events, and decrease

hematocrit, underscoring the role of hypoventilation and nighttime desaturation in CMS pathophysiology.[2,8]

CONCLUSION

Altitude sickness poses significant risks to travelers who ascend to elevations above 2500-3000 meters. It can present in various forms, including AMS, HAPE, and HACE. Prevention is critical and involves gradual ascent, proper acclimatization, and use of prophylactic medications. Treatment typically includes descent to lower altitudes, supplemental oxygen, and pharmacologic therapy. Recent Wilderness Medical Society guidelines emphasize individualized risk assessment, slower ascent profiles, and prophylactic use of medications like acetazolamide and dexamethasone to ensure safety. Prompt recognition and intervention remain the best strategies for avoiding life-threatening complications.

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