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High Altitude Sickness - Epidemiology, Pathophysiology, Symptoms, Prevention and Treatment

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Abstract

High altitude sickness encompasses three overlapping syndromes—acute mountain sickness (AMS), high altitude cerebral edema (HACE), and high altitude pulmonary edema (HAPE)—triggered when ascent outpaces acclimatization to hypobaric hypoxia. With more than 100 million people ascending above 2,500 m annually, these conditions represent a significant yet largely preventable burden in travel medicine. This narrative review synthesizes current evidence on the epidemiology, pathophysiology, clinical presentation, prevention, and treatment of acute altitude illness. Relevant literature was identified through PubMed/MEDLINE and Google Scholar, prioritizing recent authoritative syntheses, Cochrane systematic reviews of preventive interventions, consensus diagnostic statements, and primary mechanistic studies. No formal quality scoring or meta-analysis was performed. AMS is the most common form, with prevalence ranging from 15% to 80% depending on absolute altitude, ascent rate, and individual susceptibility; prior history is the strongest predictor. HACE and HAPE are rarer but potentially fatal, the latter being the leading cause of altitude-related death. All forms originate from hypobaric hypoxia: the cerebral syndromes reflect hypoxic vasodilation and blood-brain barrier disruption with vasogenic edema, whereas HAPE arises from exaggerated, heterogeneous hypoxic pulmonary vasoconstriction causing capillary stress failure. Emerging research highlights roles for HIF and VEGF signaling, oxidative stress, and microglial activation. Prevention rests on graded ascent—particularly controlling nightly gains in sleeping altitude—supplemented by acetazolamide, dexamethasone, or nifedipine in higher-risk individuals. Treatment is anchored by descent, complemented by oxygen and targeted pharmacotherapy. Early recognition of ataxia and resting dyspnea remains the single most important determinant of survival.

Keywords: acute mountain sickness, high altitude illness, high altitude pulmonary edema, high-altitude cerebral edema

1. Introduction

Travel to high altitudes has become an everyday phenomenon. Each year, more than 100 million people ascend above 2,500 m for recreation, work, or military duty, and tens of millions live permanently at such elevations (Sydykov et al., 2021; Zidan et al., 2025). The defining environmental stressor in these regions is hypobaric hypoxia: as barometric pressure falls with increasing altitude, the partial pressure of inspired oxygen declines proportionally, reducing the driving pressure for oxygen across the alveolar-capillary membrane and ultimately lowering arterial and tissue oxygen content (Luks & Hackett, 2022). When the rate of ascent outpaces the body's capacity to acclimatize, a spectrum of acute illnesses may follow.

The term "high altitude sickness" (acute altitude illness) classically encompasses three overlapping clinical syndromes: acute mountain sickness (AMS), the common and usually self-limited form; high altitude cerebral edema (HACE), a rare but potentially fatal encephalopathy generally regarded as the severe end of the AMS continuum; and high altitude pulmonary edema (HAPE), a noncardiogenic pulmonary edema that is the leading cause of altitude-related death (Basnyat & Murdoch, 2003; Gatterer et al., 2024). AMS and HACE share a neurological basis and frequently coexist, whereas HAPE may occur alone or together with the cerebral syndromes (Luks et al., 2017).

These conditions matter clinically because they are largely preventable and, when recognized early, highly treatable, yet they continue to cause disability or deaths in otherwise healthy travelers. Their epidemiology is shaped by behavior (rate of ascent) and physiology, which allows clinicians to influence outcomes through patient education and chemoprophylaxis (Zafren, 2014; Luks et al., 2024). The purpose of this narrative review is to synthesize current evidence on the epidemiology, pathophysiology, clinical presentation, prevention, and treatment of acute altitude illness, integrating classical descriptions with recent mechanistic

and guideline developments.

2. Methodology

This is a narrative (non-systematic) review. Relevant literature was identified through PubMed/MEDLINE and Google Scholar using combinations of the terms: acute mountain sickness, high-altitude cerebral edema, high-altitude pulmonary edema, altitude illness, hypobaric hypoxia, acclimatization, acetazolamide, dexamethasone, and nifedipine. No formal quality scoring or meta-analysis was performed; the synthesis is interpretive rather than quantitative**.**

3. Epidemiology

AMS is the most frequent of the altitude illnesses, and its incidence rises with the absolute elevation reached, the rapidity of ascent and individual susceptibility. Reported prevalence ranges widely, from roughly 15% to as high as 80%, depending primarily on these three variables (Luks et al., 2017; Gatterer et al., 2024). Illness is rarely occurs below about 2,500 m but becomes increasingly common above this threshold; in field studies in the Alps, AMS prevalence rose from a few percent at intermediate huts to roughly one in five mountaineers above 4,500 m, and increased further after the first night spent at altitude (Gatterer et al., 2024). In a classic study of recreational travelers to moderate-elevation Colorado resorts (from 2,000 m to 3,000 m), about 25% developed AMS, most within the first 12 hours of arrival, with symptoms commonly reducing physical activity (McGowan, Thurman, & Huecker, 2025). Symptoms typically appear within 6 to 12 hours of ascent, and most resolve within 1 to 3 days if no further ascent occurs (McGowan, Thurman, & Huecker, 2025).

Identified risk factors include a prior history of AMS - the single strongest predictor, together with higher target altitude, faster ascent rate, lack of pre-acclimatization, younger age and

strenuous exertion (Luks et al., 2017; Gatterer et al., 2024). Physical fitness is not protective, and the influence of sex is inconsistent across studies. Permanent residence at low altitude and certain genetic predispositions further modulate risk (Khodaee et al., 2016).

HACE and HAPE are considerably less common but far more dangerous. HACE most often develops above 4,000 m and is the least frequent of the three syndromes, with an incidence of roughly 0.5-1% among those ascending to such elevations; it carries a high fatality rate if not promptly recognized and treated (McGowan, Huecker, & Vincent, 2025). HAPE incidence varies from well under 1% during slow ascents to several percent or higher with rapid ascent to extreme altitude, and untreated mortality has historically approached 50% (Basnyat & Murdoch, 2003; Sydykov et al., 2021). Because these severe forms can evolve from initially mild AMS, epidemiological surveillance and individual risk stratification remain important to prevention (Luks et al., 2024).

4. Pathophysiology

The unifying initiating event in all altitude illnesses is hypobaric hypoxia and the cascade of physiological responses it provokes. Reduced arterial oxygen content triggers the hypoxic ventilatory response and sympathetic activation. At molecular level, it stabilizes hypoxia-inducible factors (HIFs), master transcriptional regulators that reprogram cellular metabolism, erythropoiesis, and vascular tone (Zidan et al., 2025; Cai et al., 2026). Hypoxia also generates oxidative stress, which contributes to endothelial dysfunction and increased vascular permeability across multiple organs (Pena et al., 2022). The clinical syndromes diverge according to whether the brain or the lung bears the brunt of these changes.

4.1 AMS and HACE

AMS and HACE are best understood as a neurological continuum driven by the brain's

response to hypoxia (Turner et al., 2021). Hypoxia causes cerebral vasodilation and increased cerebral blood flow, raising intracranial blood volume; this, combined with mild interstitial fluid accumulation, is thought to underlie the headache and constitutional symptoms of AMS (McGowan, Thurman, & Huecker, 2025; Van Osta et al., 2005). Whether AMS represents incipient cerebral edema or a distinct, milder phenomenon remains debated, since measurable brain edema is not consistently demonstrable in mild AMS (Turner et al., 2021).

HACE, by contrast, is characterized by frank cerebral edema. The prevailing view is that HACE is predominantly a vasogenic edema arising from disruption of the blood-brain barrier (BBB), with extravasation of fluid and plasma proteins into the cerebral interstitium; a cytotoxic (cellular) component may also contribute (Lafuente et al., 2016; McGowan, Huecker, & Vincent, 2025). Magnetic resonance imaging in affected patients typically shows white matter edema and microhemorrhages, particularly in the corpus callosum, consistent with vascular leak (McGowan, Huecker, & Vincent, 2025). Proposed mechanisms of BBB breakdown include increased hydrostatic pressure from hypoxic cerebral vasodilation, HIF and vascular endothelial growth factor (VEGF) mediated increases in permeability, reduced nitric oxide bioavailability, and oxidative and inflammatory injury to endothelial tight junctions (Lafuente et al., 2016; Cai et al., 2026). Recent experimental work has emphasized neuroinflammation as an amplifier of injury: hypoxia-induced overactivation of microglia, regulated by transcription factors such as nuclear respiratory factor 1 (NRF1), potentiates BBB damage and aggravates edema, and endothelial mediators such as caveolin-1 accelerate hypoxic endothelial dysfunction (Wang et al., 2022; Xue et al., 2022). These findings position the neurovascular unit and microglial activation as candidate therapeutic targets.

4.2 HAPE

HAPE is a noncardiogenic, hydrostatic form of pulmonary edema that occurs in individuals

with normal cardiac function. Its pathophysiological cornerstone is exaggerated, spatially uneven hypoxic pulmonary vasoconstriction (HPV) (Sydykov et al., 2021; Yang, Liu, & Wu, 2025). In HAPE-susceptible people, HPV is markedly amplified driven by reduced endothelial nitric oxide production, elevated endothelin-1, sympathetic overactivity and endothelial dysfunction producing a steep rise in pulmonary artery pressure (Sydykov et al., 2021). Because vasoconstriction is regionally heterogeneous, blood is redistributed from strongly constricted areas into less constricted vascular beds, which become overperfused. The resulting high microvascular pressure exceeds the structural tolerance of the alveolar capillary barrier, leading to "capillary stress failure" with leakage of protein-rich fluid and erythrocytes into the alveolar space (Cai et al., 2026; Yang, Liu, & Wu, 2025). Impaired alveolar fluid clearance, related to reduced epithelial sodium and water reabsorption under hypoxic and hypocapnic conditions compounds the problem. Inflammation, once proposed as a primary driver, is now generally regarded as a secondary consequence that further worsens permeability rather than initiating the edema (Cai et al., 2026). A blunted hypoxic ventilatory response and conditions that elevate pulmonary blood flow or pressure (e.g., patent foramen ovale, pre-existing pulmonary hypertension) increase susceptibility (Sydykov et al., 2021).

5. Symptoms and Clinical Presentation

AMS is a clinical diagnosis based on a characteristic symptom complex in someone who has recently ascended. Headache is the cardinal feature, typically accompanied by one or more of the following: gastrointestinal symptoms: anorexia, nausea, or vomiting, fatigue or weakness, and dizziness or lightheadedness (Roach et al., 2018; Lopez, Holdridge, & Mendizabal, 2013). Sleep disturbance, formerly part of the diagnostic criteria, was removed in the 2018 revision of the Lake Louise scoring system because disrupted sleep at altitude correlates poorly with AMS and is more closely related to periodic breathing and hypoxia per se (Roach et al., 2018).

Under the 2018 Lake Louise criteria, AMS is defined as a total score of three or more points across the four rated symptoms, including at least one point for headache, in the setting of recent ascent; severity is sometimes stratified as mild (3-5), moderate (6-9) or severe (10-12) (Roach et al., 2018). The symptoms are nonspecific, and the differential diagnosis includes dehydration, exhaustion, hypothermia, migraine, viral illness and carbon monoxide exposure (Luks & Hackett, 2022).

HACE represents progression along the neurological continuum and is heralded by signs of central nervous system dysfunction superimposed on AMS or HAPE. The hallmark is gait ataxia, often demonstrable on tandem (heel-to-toe) walking before more dramatic findings appear; it is accompanied by progressive alteration in consciousness, confusion, irrational behavior, severe headache, and vomiting (McGowan, Huecker, & Vincent, 2025). Without treatment, deterioration to stupor, coma and death from brain herniation can occur within 12 to 24 hours (McGowan, Huecker, & Vincent, 2025). Atypical neurological presentations, including focal deficits, transient ischemic attack-like events, cranial nerve palsies and seizures, are increasingly recognized at altitude and may mimic other neurological emergencies, highlighting the diagnostic challenge in the field (Łagowski, Grodzka, & Domitrz, 2025).

HAPE typically presents two to four days after ascent. Early symptoms are decreased exercise tolerance and a dry cough; as edema progresses, dyspnea occurs at rest, the cough may become productive of frothy and eventually pink (blood-tinged) sputum Patients develop tachypnea, tachycardia, low-grade fever, crackles on auscultation and cyanosis (Sydykov et al., 2021; Yang, Liu, & Wu, 2025). Resting hypoxemia disproportionate to altitude is a key clue, and HAPE may coexist with HACE in severe cases (Luks et al., 2024).

6. Prevention

Prevention rests first on behavior chiefly graded ascent with pharmacological prophylaxis reserved for those at moderate to high risk (Zafren, 2014; Luks et al., 2024). Because the altitude at which a person sleeps is more important than the maximum altitude reached during the day, controlling the nightly gain in sleeping elevation is the most effective single measure. Contemporary guidance, reflected in the WMS guidelines, advises avoiding ascent to a sleeping altitude above roughly 2,800 m in a single day where feasible, limiting increases in sleeping altitude to no more than about 500 m per day once above 3,000 m, and incorporating a rest day (no net gain in sleeping altitude) every three to four days; staging an intermediate night and pre-acclimatization further reduce risk (Luks et al., 2024; McGowan, Thurman, & Huecker, 2025). The "climb high, sleep low" principle and adequate hydration without overhydration are widely recommended adjuncts (Zafren, 2014).

Acetazolamide is the best-established pharmacological prophylactic agent. As a carbonic anhydrase inhibitor, it induces a mild metabolic acidosis that stimulates ventilation, thereby accelerating the acclimatization process rather than merely masking symptoms (Luks et al., 2024). A Cochrane systematic review of commonly used drug classes concluded that acetazolamide reduces the incidence of AMS, supporting its role in prevention (Nieto Estrada et al., 2017). The commonly recommended adult prophylactic dose is 125 mg twice a day, begun the day before ascent and continued for two to four days after reaching the target altitude (Luks et al., 2024). Although it is a sulfonamide, clinically significant cross-reactivity is rare; it is contraindicated only in patients with a prior anaphylactic or Stevens-Johnson syndrome reaction to a sulfonamide (Luks et al., 2024).

Dexamethasone is an effective alternative for AMS and HACE prophylaxis, particularly when acetazolamide is not tolerated or when rapid ascent precludes acclimatization, but unlike acetazolamide it does not promote acclimatization and symptoms may rebound on

discontinuation (Burtscher et al., 2025; Luks et al., 2024). Typical prophylactic dosing is 2 mg every 6 hours or 4 mg every 12 hours, with higher doses reserved for exceptional rapid-ascent scenarios and prolonged use avoided because of adrenal suppression (Burtscher et al., 2025). For HAPE prevention in susceptible individuals, the pulmonary vasodilator nifedipine (sustained-release) is the agent of choice; phosphodiesterase-5 inhibitors (tadalafil, sildenafil) and, for HAPE specifically, salmeterol are alternatives supported by more limited evidence (Sydykov et al., 2021; Luks et al., 2024). Cochrane reviews of less commonly used drugs and of miscellaneous and non-pharmacological interventions found that the evidence base for many alternative agents remains limited, reinforcing acetazolamide, dexamethasone and nifedipine as the mainstays (Gonzalez Garay et al., 2018; Molano Franco et al., 2019). Ibuprofen has shown benefit for AMS prevention in some trials and is a reasonable over-the-counter option for those unable to take the primary agents (Luks et al., 2024).

7. Treatment

The governing principle of treatment is that descent reverses the disease, because removing the hypoxic stimulus addresses the root cause. For all forms of altitude illness, halting further ascent is the minimum response, and descent is mandatory for severe AMS, HACE or HAPE (Luks et al., 2024). Even a modest descent of roughly 300 to 1,000 m often produces marked clinical improvement.

Mild AMS can usually be managed with rest, avoidance of further ascent, analgesics such as ibuprofen or acetaminophen for headache, antiemetics as needed, and time for acclimatization. Acetazolamide can be added to speed recovery (Luks et al., 2024). Supplemental oxygen titrated to an oxygen saturation above 90% relieves symptoms and is especially valuable when descent is delayed. Moderate to severe AMS that does not respond to these measures warrants urgent descent and consideration of dexamethasone (Luks et al., 2024).

HACE is a medical emergency. The cornerstones are immediate descent and supplemental oxygen, together with dexamethasone, which is the primary pharmacological agent (a commonly cited regimen is an initial dose of about 8 mg followed by 4 mg every 6 hours); acetazolamide may be used as an adjunct (Luks et al., 2024; McGowan, Huecker, & Vincent, 2025). When descent is impossible because of terrain or weather, a portable hyperbaric chamber that simulates lower altitude can be life-saving as a temporizing measure (Luks et al., 2024).

HAPE treatment likewise prioritizes descent and oxygenation; restoring oxygenation reduces hypoxic pulmonary vasoconstriction and pulmonary artery pressure, often producing rapid improvement (Sydykov et al., 2021; Luks et al., 2024). Supplemental oxygen, minimizing exertion, and preventing heat loss are first-line measures. Portable hyperbaric chamber serves the same temporizing role as in HACE when descent is not feasible. Where oxygen and descent are unavailable or insufficient, nifedipine is the recommended pharmacological adjunct to lower pulmonary artery pressure; phosphodiesterase-5 inhibitors are alternatives, though no drug substitutes for descent and oxygen (Luks et al., 2024; Yang, Liu, & Wu, 2025). Because HACE and HAPE can coexist, clinicians should evaluate for both when either is present.

8. Discussion

Several themes emerge from the current literature. First, acute altitude illness is largely a disease of ascent behavior, which makes it one of the more preventable serious conditions encountered in travel medicine. The persistence of AMS even among knowledgeable mountaineers, however, suggests that knowledge alone is insufficient and that practical implementation of graded-ascent schedules and risk-appropriate prophylaxis is what changes outcomes (Gatterer et al., 2024; Luks et al., 2024). Second, the relationship between AMS and

HACE remains incompletely resolved. Although the two are clinically and therapeutically treated as a continuum, the absence of consistent imaging evidence of edema in mild AMS leaves open the question of whether AMS is truly early HACE or a related but mechanistically distinct entity (Turner et al., 2021). Resolving this has practical implications for how aggressively early symptoms should be managed.

Third, mechanistic research is rapidly expanding our understanding beyond the classical hemodynamic models. The recognition of microglial activation, oxidative stress, HIF and VEGF signaling, tight-junction proteins and endothelial mediators such as caveolin-1 in HACE points toward future targeted neuroprotective therapies, though these remain preclinical (Wang et al., 2022; Xue et al., 2022; Cai et al., 2026). For HAPE, the consolidation of the exaggerated, heterogeneous HPV model with secondary inflammation provides a coherent rationale for the established efficacy of descent, oxygen and pulmonary vasodilators (Sydykov et al., 2021; Yang, Liu, & Wu, 2025). Fourth, clinical vigilance must extend to atypical neurological presentations, which can be mistaken for primary cerebrovascular events and delay the only definitive treatment" descent (Łagowski, Grodzka, & Domitrz, 2025).

Important limitations temper these conclusions. Much of the evidence base derives from field studies in self-selected, healthy mountaineer populations, limiting generalizability to older travelers and those with comorbidities, who increasingly visit high-altitude destinations (Luks & Hackett, 2022). The rarity of HACE and HAPE precludes large randomized trials of treatment, so the strongest treatment recommendations (descent, oxygen) rest on physiological rationale and observational data, and several preventive agents have only low- to moderate-quality supporting evidence (Gonzalez Garay et al., 2018; Molano Franco et al., 2019; Luks et al., 2024). As a narrative review, the present synthesis is also subject to selection bias in the sources cited.

9. Conclusions

Acute altitude illness, comprising AMS, HACE and HAPE is a predictable consequence of ascending faster than the body can acclimatize to hypobaric hypoxia. AMS is common and usually benign, but it exists on a continuum with the rare and life-threatening cerebral and pulmonary syndromes that account for most altitude-related deaths. The pathophysiology centers on hypoxia-driven cerebral vasodilation and blood-brain barrier disruption in the cerebral forms, and on exaggerated heterogeneous hypoxic pulmonary vasoconstriction with capillary stress failure in HAPE. Prevention through graded ascent, supplemented where appropriate by acetazolamide, dexamethasone or nifedipine, is highly effective, and treatment is anchored by the intervention of descent complemented by supplemental oxygen and targeted pharmacotherapy. Early recognition of warning signs especially ataxia and resting dyspnea remain the most important determinants of survival. Continued mechanistic research may yet yield targeted adjunctive therapies, but for the foreseeable future, education, prudent ascent profiles and prompt descent will remain the foundation of safe high-altitude travel.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of the use of generative AI

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

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