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High Altitude Diseases: Epidemiology, Pathophysiology, Diagnosis, Prevention and Treatment

Szymon Kosek, MD
ORCID: https://orcid.org/0009-0001-7350-2306
kosek.med@gmail.com
5th Military Hospital with Polyclinic in Cracow
Wrocławska 1-3, 30-901 Cracow, Poland

Justyna Klonowska, MD
ORCID: https://orcid.org/0009-0002-8170-9187
justynajklonowska@gmail.com
Hospital of Ministry of the Interior and Administration in Cracow
Kronikarza Galla 25, 30-053 Cracow, Poland

Radosław Jan Walkowski, MD
ORCID: https://orcid.org/0009-0006-9933-6437
radwalk.med@gmail.com
Central Clinical Hospital of UCC WUM
Banacha 1A, 02-097 Warsaw, Poland

Weronika Wasiniewska, MD
ORCID: https://orcid.org/0009-0001-9263-5710
wasiwer@gmail.com
Voivodeship Clinical Centre of the Jeleniogórska Basin
Ogińskiego 6, 58-506 Jelenia Góra, Poland

Marcin Barański, MD
ORCID: https://orcid.org/0009-0003-7792-5837
baranskimarcin23@gmail.com
Voivodeship Clinical Centre of the Jeleniogórska Basin
Ogińskiego 6, 58-506 Jelenia Góra, Poland

Tomasz Kandefer, MD
ORCID: https://orcid.org/0009-0004-2714-8344
tomekkandefer92@gmail.com
Frederic Chopin University Clinical Hospital in Rzeszów
Fryderyka Chopina 2, 35-055 Rzeszów, Poland

Maria Izabela Sroka, MD
ORCID: https://orcid.org/0009-0002-8743-8963
marsrokaa@gmail.com
Frederic Chopin University Clinical Hospital in Rzeszów
Fryderyka Chopina 2, 35-055 Rzeszów, Poland

ABSTRACT

High altitude diseases—encompassing acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE)—represent a spectrum of potentially life-threatening conditions affecting individuals ascending above 2,500 meters. AMS affects 20–75% of unacclimatized travelers, while HAPE and HACE demonstrate lower incidence (0.1–15.5% and 0.5–1.5%, respectively) but substantially higher mortality without intervention. Rapid ascent exceeding 500 m/day and genetic susceptibility to hypoxic responses emerge as critical modifiable risk factors. Pathophysiological mechanisms involve hypobaric hypoxia-induced cytotoxic edema and cerebral vasodilation in AMS/HACE, mediated by

hypoxia-inducible factors and blood-brain barrier disruption, while exaggerated pulmonary artery pressure elevation and capillary stress failure characterize HAPE. Diagnosis relies on clinical criteria including the Lake Louise Score for AMS, radiographic evidence for HAPE, and neurological signs with advanced imaging for HACE. Prevention strategies prioritize graded ascent (≤300 m/day above 3,000 m) and pre-acclimatization; when rapid ascent is unavoidable, acetazolamide prophylaxis (125–250 mg twice daily) reduces AMS risk by approximately 50%. Treatment algorithms emphasize immediate descent asthe gold standard, supplemented by supplemental oxygen and pharmacotherapy tailored to illness severity: acetazolamide for AMS, dexamethasone for cerebral edema, and nifedipine for pulmonary hypertension A multidisciplinary approach integrating physiological understanding with pragmatic prevention strategies, early recognition through standardized diagnostic tools, and prompt evidence-based intervention optimizes outcomes and reduces morbidity and mortality in high-altitude environments.
Keywords: high altitude illness, hypoxia, pulmonary edema, cerebral edema, acclimatization, Acute mountain sickness

Introduction

High altitude diseases, encompassing acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE), pose significant health risks to individuals ascending above 2,500 m. AMS affects 20–75% of unacclimatized travelers, presenting with headache, nausea, and fatigue, while HAPE and HACE exhibit lower incidence (0.1–15.5% and 0.5–1.5%, respectively) but higher mortality without intervention[1]. Risk factors include rapid ascent (>500 m/day), prior altitude illness, and genetic susceptibility to hypoxic vasoconstriction [2]. Pathophysiological mechanisms involve hypobaric hypoxia-induced cerebral vasodilation and blood-brain barrier disruption in HACE, as well as exaggerated pulmonary artery pressure elevation leading to capillary leakage in HAPE [3]. Diagnosis relies on clinical criteria such as the Lake Louise Score for AMS, radiographic evidence of pulmonary infiltrates for HAPE, and neurological signs for HACE [4]. Immediate

descent (>500 m) remains critical for severe cases, supplemented by oxygen therapy and pharmacologic interventions: acetazolamide (125–250 mg BID) for AMS prophylaxis, dexamethasone (8 mg/day) for cerebral edema, and nifedipine (30 mg SR BID) for pulmonary hypertension [5]. Prevention strategies emphasize graded ascent (<300 m/day above 3,000 m) and pre-acclimatization, particularly for high-risk populations [5]. This synthesis underscores the importance of early recognition, evidence-based treatment, and tailored preventive measures to mitigate morbidity and mortality in high-altitude environments

Epidemiology

Incidence and Altitude Thresholds

The incidence of AMS escalates with elevation, particularly above 2,500 m. In the Western Alps, AMS prevalence on the day of ascent was 5.8% (Lake Louise Score ≥3) at 2,850 m and 21.9% at 4,559 m[6]. Overnight stays amplified prevalence at higher altitudes, increasing from 10.1% to 14.5% at 3,650 m and 15% to 25.2% at 4,559 m. However some studies indicate occurance of AMS up to 75% in non-acclimated travelers at 3000 m approaches [7]. Younger adults exhibited higher susceptibility, likely due to vigorous exertion, while pre-acclimatization (≥5 days above 3,000 m in the preceding two months) reduced risk [6]. Rapid ascent (>500 m/day sleeping elevation) tripled AMS odds, though slower ascents (<300 m/day above 3,000 m) mitigated severity [8] .

HAPE incidence varies widely based on altitude and ascent rate. At 2,500 m, skiers experience a 0.01% incidence, while Indian soldiers rapidly ascending to 4,500 m face 15.5% prevalence. Recurrence risk reaches 60% in susceptible individuals upon rapid re-ascent above 4,500 m. Untreated HAPE mortality exceeds 50%, but prompt oxygen therapy and descent reduce this to <1% [9]. Critical thresholds emerge above 2,500–3,000 m, with symptoms typically manifesting within 2–4 days of ascent [9]. Exaggerated hypoxic pulmonary vasoconstriction and genetic factors (e.g., impaired nitric oxide synthesis) drive capillary stress failure, leading to protein-rich alveolar edema [10]. HACE is the rarest and most severe neurological manifestation of high-altitude illness, occurring in 0.5–1.5% of individuals ascending above 4,000 m. While uncommon below 2,500 m, cases have been reported at elevations as low as 2,100 m in susceptible individuals. Mortality exceeds 50% without treatment, but early intervention reduces this to <5% [1].

Risk Factors for Acute Mountain Sickness

The 2023 cross-sectional study of 1,370 mountaineers in the Western Alps identified history of AMS, altitude, pre-acclimatization status, age, and ascent rate as critical risk factors for AMS

[8]. A history of AMS was the strongest predictor, with susceptible individuals facing 7–9× higher odds of recurrence compared to non-susceptible mountaineers. Rapid ascent is a primary modifiable risk factor for AMS. A case-control study of travelers in Nepal's Mustang district (2,500–3,000 m) found rapid ascenders faced 6.4-fold higher odds of AMS compared to slow ascenders (sleeping elevation gain ≤600 m/day above 3,000 m). This aligns with earlier findings that ascending >500 m/day triples AMS risk, particularly above 3,000 m, where hypobaric hypoxia overwhelms acclimatization mechanisms. At 4,559 m, AMS prevalence rises to 21.9% within 24 hours of arrival, emphasizing the critical role of graded ascent in mitigating hypoxic stress [11]. While age, smoking and sex differences were non-significant factors, younger adults (18–30 years) showed nonspecific trends toward higher susceptibility, likely due to exertion intensity. However some studies showed that on moderate altitudes, there was noted attenuated AMS risk in older cohorts, possibly from reduced physical activity or adaptive physiological changes [12].

Patophysiology

Environmental Hypoxia and Acclimatization

Ascent to high altitude exposes individuals to hypobaric hypoxia, characterized by a progressive decline in barometric pressure and partial pressure of oxygen (PO_2). At 5,500 m, atmospheric PO_2 drops to ~50% of sea-level values, challenging oxygen delivery to tissues. Acclimatization-the physiological adaptation to hypoxia-involves integrated responses to maintain tissue oxygenation, though efficacy varies widely among individuals. The immediate response to hypoxia is a 40–60% increase in alveolar ventilation within hours of ascent, driven by carotid body chemoreceptors. This reduces arterial PCO_2 (~20–30 mmHg at 4,000 m) and raises alveolar PO_2, improving oxygen diffusion [2]. However, respiratory alkalosis inhibits this response until renal compensation (bicarbonate excretion) restores pH balance over 2–4 days [13]. There are also other adaptive mechanisms, such as hemoglobin modulation [14], such as plasma volume reduction by ~20%, which produces heamoconcentration, which happens acutely and producing erythropoietin, however this happens over longer period of time (1–2 g/dL of hemoglobin increase per week at 4500m) . There are also several molecular and genetic mechanisms, which affect our individual responses to high altitudes. Central to these processes are hypoxia-inducible factors (HIFs), particularly HIF-1α and HIF-2α, which orchestrate gene expression to enhance oxygen delivery and metabolic efficiency. HIF activation upregulates erythropoietin for red blood cell production, vascular endothelial growth factor (VEGF) for angiogenesis, and glycolytic enzymes to shift energy production from

oxidative phosphorylation to anaerobic pathways [15]. Genetic polymorphisms influence acclimatization efficiency. Tibetan and Andean populations exhibit adaptive variants in *EPAS1* (HIF-2α) and *EGLN1* (PHD2), which attenuate erythrocytosis and enhance nitric oxide (NO) synthesis, respectively. Susceptibility to HAIs correlates with SNPs in *NOS3* (impaired NO production), exacerbating pulmonary hypertension and oxidative stress [16].

Patophysiology of AMS, HACE and HAPE

AMS, HACE and HAPE share the same origin and differ in severity. It is not fully known what is responsible for occurence of these illnessess.

Traditional theories attributed AMS to vasogenic cerebral edema from blood-brain barrier (BBB) disruption mediated by hypoxia-induced vascular endothelial growth factor (VEGF) [14]. However, recent neuroimaging reveals intracellular cytotoxic edema due to fluid shifts from extracellular spaces, without significant BBB compromise. Hypoxia triggers cerebral vasodilation, elevating intracranial pressure, while oxidative stress and mitochondrial dysfunction exacerbate neuronal swelling. Genetic factors, such as *HIF-1α* and *EPAS1* variants in high-altitude populations, modulate susceptibility by influencing hypoxic ventilatory responses and redox homeostasis. Although AMS and high-altitude cerebral edema (HACE) share hypoxic origins, AMS primarily involves cytotoxic edema, whereas HACE progresses to vasogenic edema with BBB leakage. Controversy persists regarding AMS as a precursor to HACE, but emerging evidence underscores the role of inflammatory mediators, ROS overproduction, and impaired nitric oxide signaling in driving early pathophysiology. This synthesis redefines AMS as a distinct entity rooted in cellular osmotic dysregulation rather than classical vasogenic mechanisms, highlighting avenues for targeted therapies [17]. High-altitude pulmonary edema (HAPE) arises from hypobaric hypoxia-driven exaggerated pulmonary artery pressure (PAP) elevation, mediated by biphasic hypoxic pulmonary vasoconstriction (HPV) [18]. Microvascular pressures exceeding ~20 mmHg initiate interstitial fluid filtration via dynamic relaxation of endothelial tight junctions and transcellular vesicular transport, overwhelming lymphatic clearance. Prolonged pressure elevation leads to capillary stress failure, characterized by endothelial/epithelial barrier rupture, protein-rich alveolar flooding, and hemorrhage.

Due to 3 different times on which the symptoms peaked [19], there are works suggesting 3 theories linked to patophysiological mechanisms. AMS with peak symptoms on day 1 arises from parasympathetic overactivity and elevated metabolic demand, failing to reduce oxygen consumption during initial hypoxic exposure. AMS with peak on day 2 correlates with pronounced nocturnal hypoxemia due to low hypoxic ventilatory response and cerebral venous

outflow restriction during supine positioning. AMS with peak on day 3 involves delayed subclinical pulmonary edema, evidenced by widened alveolar-arterial oxygen gradients. Hypoxemia drives these pathways via cerebral vasodilation, blood-brain barrier disruption, and autonomic imbalance, while individual variability in acclimatization explains inconsistent prior correlations between AMS and singular factors like cerebral blood flow or oxidative stress.
There is also some evidence that Venous outflow restriction due to anatomical variations of the sinus transversus, which leads to cerebral vein congestion plays a part at developing an AMS [9].

Diagnosis

Acute Mountain Sickness (AMS) is diagnosed clinically through self-reported symptoms, as objective signs are typically absent in early stages. The Lake Louise Scoring System is the most widely used diagnostic tool, requiring the presence of headache plus a score ≥3 on a 0–3 scale across four additional symptoms: gastrointestinal distress (nausea/vomiting), fatigue, dizziness, and sleep disturbance [2]. While the Lake Louise criteria standardize AMS assessment, inter-subject variability in symptom interpretation and the lack of definitive biomarkers pose diagnostic challenges. Differential diagnosis must exclude dehydration, migraines, and infections. Despite limitations, this scoring system remains the gold standard for field and research applications, emphasizing the need for clinical vigilance in high-altitude settings. HACE, a life-threatening progression of AMS, manifests with ataxia (assessed by heel-to-toe walking) and altered mental status, often alongside AMS symptoms. Without intervention, HACE can rapidly progress to coma and death. There has been shown a use for MRI imaging in diagnosing HACE. MRI findings in acute HACE include T2-weighted and FLAIR hyperintensities in the splenium of the corpus callosum and subcortical white matter, indicative of vasogenic edema. Diffusion-weighted imaging (DWI) may reveal cytotoxic edema in severe cases, with restricted diffusion in affected regions. Susceptibility-weighted imaging (SWI) at 3T detects microbleeds acutely, which persist as hemosiderin deposits long after clinical recovery, serving as a "footprint" of prior HACE [1].
HAPE presents with respiratory and systemic symptoms, including dyspnea at rest, cough, weakness, and chest tightness, alongside clinical signs such as rales, cyanosis, tachypnea, and tachycardia. Symptoms often develop overnight 1–4 days post-ascent, with portable pulse oximetry revealing hypoxemia and chest radiographs showing patchy infiltrates [5]. Key differential diagnoses include dehydration, migraine, hypoglycemia, central nervous system infections, transient ischemic attack, carbon monoxide poisoning, and substance abuse. Unlike

AMS, dehydration may improve with fluid resuscitation, while migraines lack the temporal association with altitude ascent and do not resolve with supplemental oxygen. CNS infections often present with fever or focal neurological deficits absent in AMS. Persistent symptoms beyond 72 hours, lack of response to descent, or absence of headache should prompt evaluation for alternative etiologies. Clinicians must prioritize altitude exposure history and symptom chronology to distinguish AMS from mimics, ensuring timely intervention and preventing progression to life-threatening high-altitude cerebral edema (HACE) [3].

Differential diagnosis of HACE should include hypoglycemia, hyponatremia, hypothermia, migraine, seizure disorder or transient ischemic attack.

Prevention

Non-pharmacological methods

Gradual ascent is the most effective strategy for preventing acute mountain sickness (AMS) in individuals traveling to high altitudes. Evidence from prospective and retrospective cohort studies demonstrates that limiting sleeping altitude increases to no more than 600 meters per day above 2,500 meters significantly reduces the incidence of AMS compared to rapid ascent. Additional acclimatization, such as adding a rest day for every 600 to 1,200 meters of elevation gain, further lowers risk. Studies show that those who walk to higher altitudes experience lower rates of AMS than those who ascend rapidly by air or vehicle. When gradual ascent is not practical, pharmacologic prophylaxis with acetazolamide is recommended, but the primary and most reliable preventive measure remains a slow, staged increase in sleeping altitude [20]. Avoiding overexertion during ascent is recommended to minimize hypoxemia and hemodynamic stress, though evidence for its efficacy remains mixed. Forced hydration, often misperceived as protective, lacks empirical support and may increase risks of hyponatremia or pulmonary edema [21]. By prioritizing controlled ascent rates and physiologic adaptation, nonpharmacologic strategies effectively reduce acute mountain sickness (AMS) incidence and prevent progression to severe altitude-related complications.

Pharmacological methods

In rapid-ascent context where gradual acclimatization (<300 m/day sleeping elevation gain) is impractical, 125 mg acetazolamide emerges as the cornerstone of AMS prevention. Acetazolamide's benefits were robust across field studies, particularly at doses of 125–250 mg twice daily, which reduced AMS risk by ~50% with manageable side effects (e.g., transient paresthesias) [22]. Acetazolamide (125 mg, 250 mg, and 375 mg twice daily), dexamethasone, and ibuprofen significantly reduces AMS incidence compared to placebo. Acetazolamide 125

mg and 250 mg twice daily demonstrated the strongest evidence, with trial sequential analysis confirming sufficient data for these doses. All acetazolamide regimens and dexamethasone also lowered severe AMS risk, while ibuprofen showed efficacy in reducing severe headache. However, acetazolamide was associated with paraesthesia, particularly at higher doses. Evidence quality was moderate for acetazolamide 125 mg and 250 mg, but low or very low for other interventions [23].Combined with hydration, nutrition, and controlled ascent protocols, this regimen optimizes safety and performance in high-altitude environments. Acetazolamide, a carbonic anhydrase inhibitor, facilitates acclimatization by inducing metabolic acidosis, enhancing ventilatory drive. Adverse effects included paresthesias. Contraindications include sulfa allergies, necessitating pre-ascent testing for allergic individuals. While use of dexamethasone and Ginkgo biloba is discussed, evidence supporting their use remained limited, reinforcing acetazolamide as the preferred prophylactic. There are studies which show that taladafil and Dexamethasone prevent HAPE in high-risk individuals by mitigating hypoxic pulmonary hypertension [24], however it is worth to mention that The study involved a small sample of adults. Dexamethasone's glucose-elevating effects necessitate monitoring, while tadalafil offers a favorable safety profile. These findings support targeted pharmacoprophylaxis for susceptible populations undertaking rapid high-altitude ascent.

Treatment

Current evidence supports immediate descent as the gold standard, supplemented by acetazolamide or dexamethasone for symptom management. Hyperbaric chambers and oxygen provide interim solutions in resource-limited settings. Despite low-quality evidence, these interventions reduce morbidity and prevent progression to life-threatening complications. Prioritizing gradual ascent and pre-acclimatization remains essential, with pharmacotherapy reserved for high-risk scenarios. Robust trials are urgently needed to optimize dosing and evaluate emerging therapies [25].

Pharmacotherapy includes acetazolamide (250 mg twice daily) to accelerate acclimatization by inducing metabolic acidosis and enhancing ventilatory drive, reducing symptom severity within 24 hours. Dexamethasone (4 mg every 6 hours) offers rapid relief (within 12 hours) by mitigating cerebral edema and is particularly effective in moderate to severe AMS. For refractory cases, combination therapy (acetazolamide + dexamethasone) is recommended. Early recognition is vital, as untreated AMS progresses to HACE, marked by ataxia and altered mental status, necessitating urgent evacuation. Adjunctive measures include rest, hydration, and avoiding further ascent until symptoms resolve [26].

Portable hyperbaric chambers simulate descent and are effective in remote settings, showing comparable efficacy to oxygen therapy in symptom resolution [1]. Non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen address headache but lack prophylactic benefits [4]. Emerging research highlights oxidative stress and mitochondrial dysfunction as contributors to altitude illnesses, suggesting future therapeutic targets, such as antioxidants and REDOX homeostasis modulators, though evidence remains preliminary.

Clinicians must balance efficacy and side effects, with acetazolamide as first-line prophylaxis and dexamethasone reserved for high-risk cases or treatment [27]. This multidisciplinary approach—combining descent, oxygen, pharmacotherapy, and innovative interventions—ensures effective AMS management, reducing progression to life-threatening complications like high-altitude cerebral edema (HACE)

Conclusions

High altitude diseases represent a spectrum of potentially life-threatening conditions that demand a comprehensive understanding of their epidemiological patterns, pathophysiological mechanisms, and evidence-based management strategies. The synthesis of current research underscores several critical insights that should guide clinical practice and expedition planning in high-altitude environments. The epidemiological data reveal a clear altitude-dependent gradient of risk, with acute mountain sickness affecting up to 75% of unacclimatized travelers at 3,000 m, while the more severe manifestations—HAPE and HACE—demonstrate lower incidence but substantially higher mortality rates when left untreated. The identification of modifiable risk factors, particularly rapid ascent rates exceeding 500 m per day in sleeping elevation, provides actionable targets for prevention. Equally important is the recognition that individual susceptibility varies dramatically based on prior altitude illness history, genetic polymorphisms affecting hypoxic responses, and acclimatization status, emphasizing the need for personalized risk assessment. Recent advances in understanding the pathophysiology have challenged traditional paradigms, particularly the shift from vasogenic to cytotoxic edema models in AMS pathogenesis, while elucidating the critical role of hypoxia-inducible factors and genetic variations in determining individual responses to hypobaric hypoxia. The mechanistic insights into exaggerated pulmonary vasoconstriction in HAPE and blood-brain barrier disruption in HACE have refined our approach to targeted pharmacological interventions. However, the complexity of these processes—involving autonomic dysregulation, oxidative stress, mitochondrial dysfunction, and vascular permeability changes—suggests that single-pathway interventions may have limitations. The cornerstone of

prevention remains graded ascent, with sleeping elevation gains limited to 300 m per day above 3,000 m and strategic rest days incorporated into climbing itineraries. When rapid ascent is unavoidable, acetazolamide prophylaxis at 125-250 mg twice daily demonstrates robust efficacy with acceptable tolerability. For treatment, immediate descent remains the definitive intervention for severe cases, supplemented by supplemental oxygen and pharmacotherapy tailored to the specific altitude illness: acetazolamide for AMS, dexamethasone for cerebral edema, and nifedipine for pulmonary hypertension. Despite substantial progress, several knowledge gaps persist, including the need for validated biomarkers for early diagnosis, optimization of combination pharmacotherapy regimens, and investigation of emerging therapeutic targets such as antioxidants and REDOX modulators. Future research should prioritize high-quality randomized controlled trials to refine dosing protocols and evaluate novel interventions while maintaining focus on practical applications for diverse populations including recreational trekkers, military personnel, and high-altitude workers. Ultimately, reducing morbidity and mortality from high altitude diseases requires integrating physiological understanding with pragmatic prevention strategies, early recognition through standardized diagnostic tools, and prompt evidence-based intervention when symptoms emerge.

Disclosure

Author's contribution:

Conceptualization: Marcin Barański; Methodology: Weronika Wasiniewska; Check: Marcin Barański; Formal analysis: Justyna Klonowska; Investigation: Maria Izabela Sroka; Resources: Tomasz Kandefer; Data curation: Szymon Kosek; Writing - rough preparation: Weronika Wasiniewska; Writing - review and editing: Justyna Klonowska; Visualization: Maria Izabela Sroka; Supervision: Marcin Barański; Project administration: Tomasz Kandefer; Receiving funding: no specific funding

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