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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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NEW PERSPECTIVES ON ACUTE MOUNTAIN SICKNESS: FROM PATHOPHYSIOLOGY TO PREVENTION AND TREATMENT – A REVIEW ARTICLE

Jakub Sapikowski *(Corresponding Author, Email: jmsapikowski@gmail.com)*
7th Naval Hospital in Gdańsk, Polanki 117 street, 80-305 Gdańsk, Poland
ORCID ID: 0009-0008-7253-514X

Agata Juchniewicz
7th Naval Hospital in Gdańsk, Polanki 117 street, 80-305 Gdańsk, Poland
ORCID ID: 0009-0009-4014-3413

Maria Janiszewska
Dr Rafał Masztak Grochowski Hospital, Grenadierów 51/59 street, 04-073 Warszawa, Poland
ORCID ID: 0009-0008-6704-8742

Iga Kuba
Pabianice Medical Centre, Jana Pawła II street, 95-200 Pabianice, Poland
ORCID ID: 0009-0001-5834-9075

Julita Jagodzińska
Maria Skłodowska-Curie Provincial Specialist Hospital in Zgierz, Parzęczewska 35 street, 95-100 Zgierz, Poland
ORCID ID: 0009-0004-9403-9850

Mikołaj Góralczyk
The Baptism of Poland Memorial Hospital in Gniezno, Św. Jana 9 street, 62-200 Gniezno, Poland
ORCID ID: 0009-0009-2733-1428

Martyna Grześkowiak
Florian Ceynowa Specialist Hospital in Wejherowo, Dr A. Jagalskiego 10 street, 84-200 Wejherowo, Poland
ORCID ID: 0009-0003-8434-4870

Jakub Idziński
Independent Public Multispecialist Healthcare Centre of the Ministry of Internal Affairs and Administration in Bydgoszcz, Ks. Ryszarda Markwarta 4-6 street, 85-015 Bydgoszcz, Poland
ORCID ID: 0009-0006-1058-9615

ABSTRACT

Purpose: The purpose of this paper is to present the physiological changes occurring in the human body with increasing altitude and decreasing barometric pressure, and to summarize current knowledge on high-altitude diseases, with particular emphasis on Acute Mountain Sickness (AMS). The article outlines the pathophysiological basis of its clinical manifestations, risk factors, diagnostic criteria, differentiation from other conditions, and methods of prevention and treatment. It also aims to raise awareness of high-altitude risks and promote safe practices during mountain travel. This work is intended as educational material for medical students, health professionals, travellers, and those beginning their high-altitude journeys.
Materials and methods: This review paper is based on data obtained from peer-reviewed scientific articles and reports published in reputable databases and journals, including PubMed, Taylor & Francis, CDC, SAGE Journals, ScienceDirect, and Practical Medicine, as well as Modern Management Review, The American Journal of Medicine, PLOS One, and High Altitude Medicine & Biology. The analysis also draws on the official position of the UIAA Medical Commission. Clinical studies, reviews, guidelines, and reports on high-altitude diseases published between 2010 and 2025 in English or Polish were included.
Conclusions: Acute mountain sickness arises from inadequate acclimatization to high-altitude hypoxia. Key risk factors include rapid ascent and prior AMS episodes. Gradual acclimatization is the most effective preventive measure, while pharmacological support may aid high-risk individuals. Early symptom recognition and prompt intervention are essential to prevent severe, potentially life-threatening complications, underscoring the importance of understanding human physiological limits and adaptation in extreme environments.

KEYWORDS

Acute Mountain Sickness (AMS), High Altitude, Physiology, Pathophysiology, Symptoms, Treatment and Prevention

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1. Introduction

High-altitude diseases are a group of conditions associated with being at high altitude. It is a very interesting and important issue, especially for those planning expeditions to mountains above 2500 meters above sea level, where there is lower atmospheric pressure and reduced oxygen content in the air. This is because the human body, unaccustomed to such conditions on a daily basis, reacts to hypoxia (oxygen deficiency) in a variety of ways - from mild symptoms to life-threatening conditions. Among the most important of the high altitude diseases are:

1. Acute mountain sickness (AMS) - the most common form
2. High altitude cerebral edema (HACE - High Altitude Cerebral Edema) - a life-threatening condition, develops in the absence of AMS treatment
3. High altitude pulmonary edema (HAPE - High Altitude Pulmonary Edema) - a dangerous pulmonary edema associated with seepage of fluid into the alveoli. [1]

In recent years, there has been a marked increase in the number of tourists in the high mountains - trekking and expeditions at altitudes above 2500-3000 m. Places such as: Himalayas (e.g. Everest Base Camp), Tibet (Lhasa), Colorado ski resorts (e.g. Breckenridge), Peru (Cusco), Tanzania (Mount Kilimanjaro) are attracting more and more people - including those without much mountain experience and often without adequate knowledge of the dangers, which can lead to a number of dangerous incidents. [2] [3] [4] [5]

Every year there are cases of deaths due to HAPE or HACE, which - with acclimatization and early intervention - are mostly preventable. Hence the importance of education and prevention efforts, which should be more widely available and promoted, as just having even basic knowledge of the symptoms of AMS, HACE and HAPE can save lives. [1] [6]

In addition, helicopter evacuations or rescue operations due to sudden illnesses are increasingly common in popular high altitude areas, which places a burden on emergency services, generating: high costs, risks for rescuers, strain on local medical and logistical systems. [7] Hence again - it is important to disseminate knowledge about prevention (including the use of acetazolamide and dexamethasone, which have been recognised by many studies as agents that can be used in the prevention of altitude sickness [8] [9]), symptoms and effective methods of improving the well-being of those affected by AMS (including non-pharmacological ones), so that by familiarizing themselves with such information, hikers can better plan and prepare for their hikes, acquire the ability to recognize the condition and not underestimate the symptoms, and effectively manage their symptoms even under difficult conditions of lack of access to medical services at high altitude. After all, often specialised medical care is not required, and improvement in well-being can already be achieved with simple and uncomplicated procedures, such as descent, rest, hydration and painkillers - it is enough to have the necessary knowledge, not to mention that prevention of the disease is generally much simpler and less costly than subsequent treatment. [10]

2. Physiology

2.1 Physiological Response of the Body to Altitude

A key factor in the pathophysiology of acute mountain sickness (AMS) is hypoxia resulting from the decrease in partial pressure of oxygen (PaO_2) with increasing altitude. At high altitudes above 2500 m, the drop in barometric pressure (from 760 mmHg at sea level to 370 mmHg at 5791 m) leads to reduced PaO_2, impairing oxygen diffusion into pulmonary capillaries despite the constant oxygen fraction in the air (21%). [11][12] Estimated PaO_2 values range from 90–100 mmHg at sea level but decrease to 65–80 mmHg at 1610 m, 45–70 mmHg at 2440 m, and below 50 mmHg at 5300 m. [12] This places the human body in a state of hypobaric hypoxia, triggering a series of physiological responses that enable adaptation in most individuals. However, in some cases, maladaptive reactions occur, leading to AMS, high-altitude cerebral edema (HACE), or high-altitude pulmonary edema (HAPE). [1]

2.2 Immediate Physiological Responses to Altitude (Minutes to Hours)

Upon exposure to hypoxia, compensatory mechanisms are activated to maintain adequate tissue oxygenation. One of the first reactions is hyperventilation (hypoxic ventilatory response – HVR), triggered by the stimulation of carotid body chemoreceptors responding to reduced PaO_2. Increased ventilation lowers carbon dioxide partial pressure ($PaCO_2$) and raises alveolar PaO_2, improving the oxygen diffusion gradient. The ventilatory response peaks around 8–10 days of acclimatisation before stabilising. [13][14][17][20] Simultaneously, hypoxic pulmonary vasoconstriction (HPV) occurs, increasing pulmonary vascular resistance and arterial pressure. This enhances perfusion of well-oxygenated lung regions, improving ventilation-perfusion (V/Q) matching, but at high altitudes, it may contribute to HAPE. [11][13][14][17][18] At the cellular level, hypoxia activates the hypoxia-inducible factor (HIF) pathway, upregulating genes involved in adaptation, such as erythropoietin (EPO) and vascular endothelial growth factor (VEGF). HIF also promotes glycolytic metabolism and reduces mitochondrial oxygen consumption. [20] Concurrently, the sympathetic nervous system is activated, leading to tachycardia, increased blood pressure, and metabolic reserve mobilisation, enhancing cerebral and cardiac perfusion. [12][13][14][17][19][20]

2.3 Adaptive Changes Over Hours to Days

Within days of hypoxia exposure, autonomic nervous system adaptation occurs. After approximately 10 days, β-adrenergic receptor desensitisation protects the myocardium from excessive energy expenditure—although heart rate decreases, the blood pressure remains elevated. Maximal heart rate during exercise also declines, which benefits myocardial oxygenation. [13][17] In response to hypoxemia, cerebral blood flow (CBF) increases, though hyperventilation-induced hypocapnia partially limits this rise. [11][13][21] Initially, CBF surges significantly—for example, during an 8-day ascent to 5050 m, a 60% increase from baseline was observed, while a rapid climb to 5260 m led to a 70% rise. After 1–3 weeks, CBF typically returns to sea-level values. [15] The body compensates for respiratory alkalosis caused by hyperventilation. The initial decrease in $PaCO_2$ is counteracted by renal bicarbonate (HCO_3^-) excretion, restoring the capacity for further hyperventilation. [13][14][17] HIF pathway activation stimulates erythropoietin secretion, enhancing red blood cell production in the bone marrow. This process improves oxygen transport capacity, though full erythropoietic effects take weeks to manifest. [13][14]

2.4 Long-Term Adaptations (Weeks to Months)

Prolonged hypoxia stabilises erythropoiesis, which is crucial for sustained acclimatization. However, some individuals, particularly high-altitude natives, may develop chronic mountain sickness (CMS), characterised by excessive erythropoiesis, increased blood viscosity, pulmonary hypertension, and heart failure. Populations such as Tibetans, Andeans, and Ethiopians exhibit genetic adaptations to hypoxia, including variations in HIF-related genes that reduce CMS risk. Tibetans display low hemoglobin concentrations but lack pulmonary hypertension, whereas Andeans often develop pulmonary hypertension and right ventricular hypertrophy. [13] Studies show that both Tibetans and Andeans have greater uterine blood flow than lowlanders, protecting fetal growth. [16] Additionally, Tibetans exhibit 20% higher CBF than Andeans at similar altitudes, possibly due to higher oxygen saturation in Andeans. [15][16] Both populations also optimize oxygen utilization by favoring carbohydrate metabolism over fats, yielding more ATP per mole of O_2. [6]

3. Pathophysiology of Ams

3.1 Central Nervous System (CNS) Dysfunction in AMS

AMS arises from complex CNS changes induced by hypobaric hypoxia. Hypoxia triggers adaptive and pathological reactions, with increased CBF playing a central role. Combined with limited intracranial fluid compensatory capacity, this elevates intracranial pressure (ICP), leading to cerebral edema. Impaired CBF autoregulation and venous outflow obstruction due to edema may also contribute. [11][13][20][22][24] Notably, AMS symptoms often develop after overnight rest. During sleep, oxygen desaturation (SpO_2 may drop to 70%) worsens, exacerbating vasomotor changes and blood-brain barrier (BBB) permeability. The supine position further impedes venous drainage. [19][24][26] Cerebral edema involves cytotoxic, interstitial, and vasogenic mechanisms. Cellular hypoxia impairs Na^+/K^+-ATPase function, causing intracellular sodium and water accumulation resulting in cytotoxic edema. Extracellular sodium and water depletion create an osmotic gradient, driving fluid influx from the vasculature, leading to interstitial edema. Finally, vasogenic edema develops due to BBB disruption from elevated hydrostatic pressure, inflammation, oxidative stress, matrix metalloproteinases, and HIF-regulated permeability factors such as VEGF or endothelial nitric oxide synthase - eNOS. [14] AMS-related headaches may stem from sensitization of trigeminovascular sensory fibers innervating cerebral vessels. Sensitization is driven by exercise-induced ICP fluctuations (due to reduced intracranial compliance), chemical factors like reactive oxygen species (ROS) and proinflammatory cytokines. [11][24][20] Autonomic center irritation in the brainstem generates nausea and vomiting. [22] Studies indicate that calcitonin gene-related peptide (CGRP) may play a significant role in the pathogenesis of headache. CGRP levels increase during prolonged hypoxic exposure, and this neuropeptide is a well-established mediator of migraine pain. Populations residing at high altitudes exhibit a higher prevalence of migraines. Furthermore, migraine is a strong risk factor for AMS, increasing the likelihood of its occurrence by up to sixfold. [23][24] Neurotransmitter dysregulation also contributes to AMS. Key neurotransmitters affected include serotonin, dopamine, and acetylcholine, which are hypoxia-sensitive. Studies demonstrate reduced serotonin synthesis at high altitudes, while dopamine production increases. Postsynaptic receptor and signaling pathway alterations may underlie these abnormalities. Furthermore, dysregulation of dopaminergic and glutamatergic signaling may result from accumulation of toxic metabolites, such as lactic acid. These neurotransmitter abnormalities may explain neurological deficits observed in AMS, including disorientation, mood fluctuations, and balance disorders. [14][21] In 1985, neurologist Ross proposed an anatomical explanation for AMS, later termed the 'tight fit' hypothesis. This model posits that individuals with reduced intracranial volume reserve are more susceptible to AMS symptoms even with minor brain swelling, which may account for the significant interindividual variability in symptom presentation. [14]

3.2 Gastrointestinal Dysfunction in AMS

High-altitude exposure also causes gastrointestinal symptoms - including nausea, vomiting, diarrhea, and anorexia - in up to 80% of AMS cases. Recent evidence highlights gut barrier disruption, increased intestinal permeability, bacterial translocation, and systemic inflammation as key mechanisms. Sympathetic activation induces splanchnic vasoconstriction, reducing intestinal blood flow and causing ischemia. Ischemia and hypoxia impair enterocyte ATP production, increase lactate accumulation, and elevate oxidative stress, damaging cell membranes and structural proteins. Animal models and in vitro cell cultures (e.g., Caco-2) have demonstrated that hypoxia downregulates tight junction proteins (ZO-1, claudin-3, occludin) critical for maintaining intestinal barrier integrity. These findings are corroborated by human studies showing significantly increased intestinal permeability after just a few days at altitudes of 4000-5000 m above sea level.

Impairment of intestinal barrier function facilitates the translocation of Gram-negative bacteria and their endotoxins (lipopolysaccharide - LPS) into systemic circulation. These pathogen-associated molecular patterns activate the immune system through TLR-4 receptors. Consequently, intestinal macrophages and hepatic Kupffer cells release proinflammatory cytokines (IL-6, TNF-α, IL-1β), leading to elevated concentrations of inflammatory markers (e.g., CRP) that correlate with AMS symptom severity. This process may be further exacerbated by physical exertion. Studies demonstrate that exercise under hypoxic conditions induces a more pronounced increase in plasma concentrations of I-FABP (a marker of enterocyte damage) and endotoxins compared to identical exercise performed in normoxia. These findings suggest a synergistic effect between hypoxia and exercise-induced reduction in intestinal blood flow. [29]30][31]

3.3 Role of inflammation, oxidative stress and the vascular endothelial growth factor (VEGF)

Hypobaric hypoxia initiates a cascade of inflammatory responses and oxidative stress that serve as critical pathogenic factors in AMS. The oxygen deprivation leads to increased production of reactive oxygen species (ROS) through NADPH oxidase activation and mitochondrial respiratory chain dysfunction [14]. These ROS compounds damage vascular endothelium, promote vasoconstriction, and activate the NF-κB inflammatory pathway, ultimately increasing vascular permeability. [17[]21] The oxidative damage manifests through elevated biomarkers of oxidative stress including malondialdehyde (MDA), 8-hydroxy-2'-deoxyguanosine (8-OH-dG), and isoprostanes. Clinical studies have demonstrated enhanced lipid peroxidation in AMS patients, as evidenced by increased concentrations of exhaled MDA - a finding that underscores the crucial role of oxidative stress in disease development. [27] Numerous studies have confirmed that individuals resistant to AMS exhibit a more robust anti-inflammatory response. These subjects are characterized by higher concentrations of IL-1 receptor antagonist (IL-1RA), IL-10, HSP-70 protein, and adrenomedullin compared to AMS-susceptible individuals. Notably, decreased IL-10 levels showed significant correlation with higher Lake Louise Scores in clinical studies. Under hypobaric hypoxia conditions, the NF-κB pathway and NLRP3 inflammasome become activated, inducing pyroptosis - a form of programmed cell death accompanied by inflammatory response. Research has also demonstrated elevated levels of inflammatory markers in AMS patients, including IL-6, IL-17F, CCL-8, TNF-α, and C-reactive protein, confirming the fundamental importance of inflammatory processes in AMS pathophysiology. [11][25][28] At the molecular level, the role of VEGF is particularly significant. Its expression is stimulated by HIF-1α factor. VEGF not only increases vascular permeability but also promotes angiogenesis, which may lead to blood-brain barrier destabilization. Certain isoforms of inducible nitric oxide synthase can also be activated by hypoxia. The resulting nitric oxide interacts with proinflammatory cytokines, potentially increasing blood-brain barrier permeability and contributing to cerebral edema formation. [14]

3.4 Individual Risk Factors

Individual susceptibility to AMS shows considerable variability, stemming from complex interactions between genetic, physiological, and environmental factors. Research on high-altitude populations (Tibetans, Andeans) has revealed significant genetic differences in hypoxia-responsive genes, including those encoding HIF-1α and antioxidant enzymes. [14] Specific variants in EPAS1 and EGLN1 genes in Tibetans are associated with lower hemoglobin concentrations and reduced pulmonary artery pressure, conferring protective adaptation to high-altitude exposure. [16] Studies have also demonstrated the importance of polymorphisms in HIF-1, EPO, and VEGF genes in determining individual acclimatization capacity. Certain variants of ACE and eNOS genes may serve as potential biomarkers for AMS susceptibility. Individuals with chronic cardiopulmonary diseases, anemia, or pregnancy are at higher risk of developing AMS. Conversely, prior high-altitude exposure and acclimatization training act as protective factors against altitude-related illnesses. Psychological stress and anxiety further increase hypoxia sensitivity [32], whereas age and sex show no significant impact on acclimatization ability [33]. Another key physiological determinant is the hypoxic ventilatory response (HVR). Individuals with a weaker HVR are more prone to AMS due to exacerbated hypoxemia. Research confirms that HVR is one of the strongest predictors of AMS severity. [11] Among environmental factors influencing AMS onset, the most significant are altitude, exposure duration, and ascent rate. Each 1000 m elevation gain nearly doubles AMS risk. Prolonged exposure to low PaO_2 conditions and rapid ascent rates significantly increase AMS likelihood. Also, adverse weather conditions in the form of extreme cold or high temperatures may further impair an individual's hypoxia tolerance. [21]

4. Symptoms

Symptoms of Acute Mountain Sickness (AMS) appear at altitudes ≥2500 meters, between 4 and 12 hours after ascent, in individuals who are not previously acclimatized. The symptoms are nonspecific and tend to peak after the first night spent at the new altitude. With appropriate management, they usually resolve spontaneously. The dominant and essential symptom for diagnosing AMS according to the most widely used scoring system is headache. However, this criterion is questioned by some researchers, as approximately 5% of individuals with AMS symptoms may not experience a headache. Other symptoms include nausea or vomiting, fatigue or weakness, and dizziness. Insomnia may suggest AMS but is common even among healthy individuals at high altitudes. The progression of symptoms, nausea that is resistant to antiemetic medication, headache unresponsive to painkillers, and increasing weakness may indicate the development of high-altitude cerebral edema (HACE). [11] This is a major, severe, and potentially fatal complication of AMS. It can develop over hours or days and, without proper treatment, may lead to brain herniation. It presents with altered mental status and truncal ataxia.[14] The Lake Louise AMS Scoring System, used for over 25 years in countless publications, has proven to be an effective tool for diagnosing and assessing the severity of AMS in scientific research. A diagnosis of AMS requires a minimum score of 3 points, including at least 1 point for headache, in a person who has recently ascended to a higher altitude. Besides headache, the scale assesses gastrointestinal symptoms, fatigue/weakness, and dizziness. Mild AMS is diagnosed with a score of 3 to 5 points, moderate with 6 to 9 points, and severe with 10 to 12 points. Assessment should be performed 6 hours after altitude change to rule out travel-related symptoms or responses to acute hypoxia. The scale can be completed by the individual, with researcher assistance, or using a two-step method.[34] Alternative diagnoses to AMS should be considered if headache is absent, if symptoms appear after 3 days at the same altitude, or if they persist despite descent and oxygen therapy. Differential diagnoses include migraine, dehydration, carbon monoxide poisoning, subarachnoid hemorrhage, and intracranial tumors.[35] To date, studies have not confirmed a significant link between gender or age and the risk of developing AMS. [33][36] In contrast to demographic factors, psychological factors show a correlation with AMS. In particular, trait anxiety, observed at low altitudes, has proven to be an independent predictor of severe AMS at high altitudes. State anxiety also correlates with AMS, influencing both the incidence and severity of symptoms. [32] These findings suggest that psychological factors may play a key role in the pathogenesis of AMS, which should be taken into account in prevention programs and risk assessment. AMS, in turn, negatively affects mood, and associated insomnia impairs cognitive function, potentially undermining team cooperation and increasing the risk of errors in judgment at high altitudes.[37]

5. Treatment and Prevention of Ams

5.1 Prevention: Acclimatization, gradual ascent, preparation

One of the most effective ways to prevent acute mountain sickness (AMS) is to ascend very slowly and gradually. [38] A randomized trial showed that spending two days at an altitude of 2500–4300 m can improve sleep quality at very high altitudes (4300 m). However, in terms of preventing AMS, the most beneficial acclimatization strategy was spending two nights at 3500–4300 m. [40] During subsequent days of trekking, the altitude gain above 2500 m should not exceed 300–500 m per day. Additionally, it is recommended to stay two nights at the same altitude every 2–4 days. On the day between the overnight stays, a "climb high, sleep low" strategy is advisable — ascend to a higher elevation during the day, then return to the lower sleeping altitude. [10]

Physical preparation, proper hydration, and adequate energy intake are fundamental pillars of primary AMS prevention. [10] Nutritional strategies should be tailored to individual needs, considering physical activity level, length of stay at altitude, and individual physiological responses. Increased carbohydrate intake is recommended to meet higher energy demands and improve exercise performance under hypoxic conditions. Maintaining muscle mass is crucial; increased protein intake is recommended, especially under conditions of increased catabolism. High altitude increases fluid loss through respiration and diuresis; therefore, regular fluid intake is essential, even in the absence of thirst. [39]

5.2 Conservative Treatment: Rest, descent to lower altitude

The treatment approach depends on the severity of AMS. In mild cases, rest at the current altitude, hydration, and analgesics (as needed) are generally sufficient. More severe cases may require rapid descent, oxygen therapy, acetazolamide, or dexamethasone. [10] Descent should continue until the patient's condition improves. Recovery is variable between individuals but usually occurs after descending 300–1000 meters. The decision on how far to descend should consider the patient’s condition, the terrain (e.g., long ascents on the return route), and weather conditions. If possible, physical exertion should be minimized. [38] [10]

5.3 Pharmacology

5.3.1 Acetazolamide

One of the best known and used drugs in the prevention of altitude sickness is Acetazolamide. Many scientific studies point to its significant role in the prevention of altitude sickness. [8] [9] Acetazolamide is a carbonic anhydrase inhibitor. This means that the drug works by blocking the breakdown of carbonic acid, leading to its accumulation. As a result, the blood pH decreases (becoming more acidic) due to the increased amount of carbonic acid, which reversibly dissociates into hydrogen ions and bicarbonate ions. [42] The main role of carbonic anhydrase is to catalyze the conversion of carbon dioxide to carbonic acid and back again. Carbonic anhydrase, located in the proximal tubule of the nephron and in red blood cells, plays a role in the reabsorption of sodium, bicarbonate, and chloride. When acetazolamide inhibits this enzyme, these ions are excreted instead of reabsorbed, leading to the loss of excess water as well. Clinically, this results in lowered blood pressure, reduced intracranial pressure, and decreased intraocular pressure. The increased excretion of bicarbonate also causes blood acidity to rise. In the eyes, aqueous humor production is reduced, and the body compensates for the increased blood acidity through mechanisms such as hyperventilation. [42] A commonly cited, though oversimplified, explanation for acetazolamide's effectiveness in reducing acute mountain sickness (AMS) is as follows: [43] 1) At high altitudes, the reduced barometric pressure (PB) and the lower partial pressure of inspired oxygen (PIO_2) lead to hypoxemia, which stimulates an increase in minute ventilation 2) Hyperventilation causes respiratory alkalosis, which in turn limits further ventilatory drive and contributes to the symptoms of AMS 3) By inducing a metabolic acidosis, acetazolamide counteracts the effects of respiratory alkalosis, thereby enhancing ventilation and improving symptoms of AMS To date, a number of studies have been produced on the selection of the appropriate dose of acetazolamide in the prevention of altitude sickness. The effect of the drug (acetazolamide) on the incidence of altitude sickness was studied half a century ago. Double blind study of forty-three volunteers given acetazolamide or placebo, 250mg every eight hours, for 32 hours before and 40 hours after abrupt transportation from sea level to 12,800 feet. A significant effect on the reduction of symptoms of altitude sickness has been noted [44] A more recent study compared different doses of acetazolamide. Participants were randomly assigned to receive 375mg bd of acetazolamide (82 participants), 125 mg bd of acetazolamide (74 participants), or a placebo (66 participants), beginning at 3440m for up to 6 days as they ascended to 4928m. The results were similar and both doses of acetazolamide improved oxygenation equally. [45] The recommendation of Wilderness Medical Society [38] was updated in 2024. The recommended adult dose for prophylaxis is 125mg every 12h, while the pediatric dose is 1.25mg/kg/dose (maximum 125mg/dose) every 12h, and should be started the night before ascent. The authors "recommend that acetazolamide be strongly considered in travelers at moderate or high risk of AMS" [38][41] Dose for AMS treatment are higher (250mg every 12h for adults; 2.5mg/kg every 12h (maximum 250mg per dose)) however, using acetazolamide for treatment of AMS has low-quality evidence. [38][46] Descending to a lower altitude remains the best method of treating any degree of AMS and HACE.

5.3.2 Glucocorticoids in the Acute Mountain Sickness (AMS) Prevention

Dexamethasone is among the most extensively studied pharmacological agents for both the prevention and treatment of AMS, with successful applications dating back to the 1980s. Gradual ascent remains the cornerstone of AMS prevention; however, certain scenarios—such as emergency situations involving rescue personnel—preclude adequate acclimatization. In such cases, pharmacological prophylaxis becomes essential. The Wilderness Medical Society currently recommends both acetazolamide and dexamethasone for AMS prevention. Dexamethasone is advised as an alternative to acetazolamide in adults at moderate to high risk of AMS, administered at 2 mg every 6 hours or 4 mg every 12 hours. In situations of very high risk—such as rapid aerial deployment of medical or military personnel to elevations exceeding 3,500 meters with immediate physical exertion—higher doses, like 4 mg every 6 hours, may be considered. Prophylactic use of dexamethasone in children is not recommended due to insufficient data.

Beyond existing guidelines, this paper aims to explore studies that directly examine the application of dexamethasone in both the prevention and treatment of AMS.

Numerous studies have demonstrated the efficacy of dexamethasone in preventing AMS, though its precise mechanism of action in this context remains unclear. In a study by Hilty et al., dexamethasone administered at 8 mg twice daily, starting 24 hours before summit ascent, effectively prevented AMS. [47] This study focused on the correlation between inflammatory responses and high-altitude illnesses, specifically evaluating the levels of soluble urokinase-type plasminogen activator receptor (suPAR) as a predictor for High-Altitude Pulmonary Edema (HAPE) and AMS. Forty-one healthy alpinists were assessed at sea level and again

24 hours after ascending to 4,559 meters. An acute inflammatory response, indicated by elevated suPAR levels, was observed in all participants except those who received dexamethasone.

Kumar et al. investigated the suppression of altitude-induced inflammatory responses in the India-Leh-Dexamethasone-Expedition-2020.[48] In this study, half of the 16 participants received oral dexamethasone prophylaxis at 4 mg twice daily, starting one day before ascent. Peripheral blood mononuclear cell (PBMC) transcriptomes were analyzed, revealing that high-altitude exposure led to gene expression changes, particularly in inflammatory pathways. Dexamethasone prophylaxis resulted in fewer such changes.

Combining acetazolamide and dexamethasone presents an intriguing prophylactic approach. In a study by Bernhard et al., the combination of extended-release acetazolamide (500 mg once daily in the afternoon) and low-dose dexamethasone (4 mg every 12 hours) proved more effective in alleviating symptoms than acetazolamide monotherapy. [49] Thirteen participants were randomly assigned to receive either the combination therapy or acetazolamide alone. Heart rate and oxygen saturation were monitored, with the monotherapy group exhibiting greater increases in heart rate and decreases in oxygen saturation.

Li et al. examined the impact of glucocorticoids on the renin-angiotensin-aldosterone system (RAAS) in AMS prevention. [50] Involving 138 men who ascended from 400 to 3,450 meters over two days, participants were randomized to receive budesonide, dexamethasone, or placebo, starting one day before high-altitude exposure and continuing through the third day. The study found that individuals with heightened RAAS activity were more susceptible to AMS. Inappropriate aldosterone elevation at altitude was associated with fluid retention, electrolyte imbalances, and hypoxemia, predisposing individuals to AMS. In the budesonide group, aldosterone levels remained low, whereas they increased in the dexamethasone and placebo groups. Additionally, the budesonide group exhibited lower angiotensin-converting enzyme (ACE) levels. Dexamethasone did not significantly affect aldosterone or ACE levels. While these findings suggest a role for RAAS in AMS pathophysiology, further research is needed. Nonetheless, both budesonide and dexamethasone reduced AMS incidence compared to placebo.

In a randomized, double-blind study by Cheng-Rong Zheng et al., the efficacy of inhaled budesonide (200 μg twice daily) and oral dexamethasone (4 mg twice daily) was compared to placebo for AMS prevention. [51] The study involved 138 men who traveled by car from 400 to 3,900 meters. Treatment commenced one day before high-altitude exposure and continued through the third day. Both budesonide and dexamethasone effectively prevented AMS, mitigated declines in SpO_2, and improved pulmonary function. Dexamethasone also alleviated altitude-induced sleep disturbances, though polysomnography was not utilized. Four participants reported dexamethasone-related adverse effects. Budesonide had fewer side effects and caused a smaller reduction in forced vital capacity (FVC). Despite these promising results, the Wilderness Medical Society currently does not recommend inhaled budesonide for AMS prophylaxis.

5.4 Treatment

The widespread use of corticosteroids in treating high-altitude illnesses is justified by their broad-spectrum effects. Erik R. Swenson's research on AMS pharmacology outlines potential mechanisms of corticosteroid action, including suppression of inflammatory pathways, reduction of vascular permeability, and maintenance of oxidative-antioxidative balance. [52] Dexamethasone appears to inhibit the nuclear translocation of hypoxia-inducible factor 1 (HIF-1) and its binding to target genes, such as vascular endothelial growth factor (VEGF), which increases cerebral vascular permeability leading to cerebral edema in AMS. Additionally, dexamethasone may block the production of monocyte chemoattractant protein-1 (MCP-1), which also enhances vascular permeability. Hypoxia is associated with oxidative stress and reactive oxygen species (ROS) formation. In vitro studies indicate that dexamethasone suppresses ROS production in microglial cells; however, the role of ROS in AMS remains uncertain.

According to Wilderness Medical Society guidelines, dexamethasone is administered to patients with High-Altitude Cerebral Edema (HACE) at an initial dose of 8 mg intramuscularly, intravenously, or orally, followed by 4 mg every 6 hours until symptom resolution. The pediatric dosage is 0.15 mg/kg body weight every 6 hours. For AMS, the guidelines suggest considering dexamethasone use.

A study comparing AMS treatments—hyperbaric chambers and dexamethasone—was conducted at the Capanna Regina Margherita research laboratory, situated at 4,559 meters on Monte Rosa in the Valais Alps. [53] The study involved 31 alpinists exhibiting AMS symptoms, most of whom had not undergone prior acclimatization. Participants received either one hour of hyperbaric chamber treatment at 193 mbar pressure or an initial oral dose of 8 mg dexamethasone, followed by 4 mg after 6 hours. Both treatments effectively

alleviated AMS symptoms and increased blood oxygen saturation. Compared to hyperbaric therapy, dexamethasone administration is simpler and yields more sustained, albeit slower, improvement.

In summary, glucocorticoids, particularly dexamethasone, are effective in both the prevention and treatment of AMS. Clinical studies and systematic reviews indicate that dexamethasone doses ranging from 8 to 16 mg per day significantly reduce AMS risk in individuals ascending above 3,000–4,000 meters and effectively mitigate established symptoms. This medication is especially valuable when rapid ascent precludes adequate acclimatization or when other drugs, such as acetazolamide, are contraindicated or insufficiently effective.

5.5 Portable Hyperbaric Chambers

In selected cases of severe acute mountain sickness (AMS), high-altitude cerebral edema (HACE), or high-altitude pulmonary edema (HAPE), the use of a portable hyperbaric chamber may be indicated. [54][55][56] This device, typically resembling a single-person, airtight bag, is equipped with a hand or foot pump and a pressure valve [57]. Several types of portable hyperbaric chambers exist, differing in dimensions, shape, weight, ease of use with non-cooperative patients, pumping mechanism, achievable pressure, frequency of inflation required to maintain optimal pressure and air-flow. [56] Due to their compact size and low weight, such chambers can be included in expedition equipment even at high altitudes and in remote locations.

A portable hyperbaric chamber creates an internal pressure of approximately 2 psi using manual inflation, which corresponds to a descent of about 1500–2500 meters. The recommended duration of treatment is 60–120 minutes, depending on symptom resolution. In most cases, this results in temporary alleviation of AMS symptoms for several hours [55][57]. Additionally, the use of a hyperbaric chamber may aid in the management or prevention of hypothermia and frostbite [58].

Indications for hyperbaric therapy include severe AMS. The use of the chamber should be part of a comprehensive treatment strategy including descent or evacuation, oxygen therapy, and pharmacologic management. It should be employed only when it does not delay descent or if descent is impossible. Symptomatic improvement may facilitate further descent or evacuation. In the event of symptom recurrence, treatment may be repeated. [54][56][59][60][61]

During therapy, thermal comfort, hydration, and, if possible, supplemental oxygen should be ensured. Pulse oximetry monitoring should be visible. The patient should void urine and stool before entering the chamber. Continuous inflation at a frequency recommended by the manufacturer is necessary to maintain pressure and prevent CO_2 accumulation. [56][61]

Use may be challenging in patients who are vomiting, claustrophobic, or have difficulty equalizing middle ear pressure. In cases of vomiting, antiemetic medication should be considered and a disposable bag placed inside the chamber. The operator should maintain verbal and visual contact with the patient to ensure comfort. Nasal xylometazoline may assist with pressure equalization in the middle ear. [56]

5.6 Non-opioid Analgesics

Ibuprofen and paracetamol can be safely used for symptomatic relief of high-altitude headache. [54][59][60][62] Acetylsalicylic acid is not recommended due to an increased risk of bleeding. [60]

5.7 Oxygen Therapy

Passive oxygen supplementation is an important element in the management of AMS when descent is not feasible or in patients with severe symptoms. Nasal cannulae and face masks are most commonly used. [5][54][57] Oxygen administered at a rate sufficient to maintain SpO_2 above 90% typically alleviates headache within 30 minutes, with resolution of other AMS symptoms within several hours. [5][59][65] Low-flow oxygen therapy (1–2 L/min for over 2 hours) is more effective than short-term high-flow treatments. Due to the limited capacity of portable oxygen cylinders, effective oxygen therapy is usually feasible only in mountain clinics or hospitals with a continuous oxygen supply. [5][54][65]

5.8 Antiemetic drugs

In cases of vomiting associated with AMS, antiemetic drugs such as dimenhydrinate or ondansetron may be administered. [59][60][5] This is particularly important to facilitate effective use of a portable hyperbaric chamber, reduce physical strain, and minimize the risk of dehydration.

5.9 Prophylaxis

Ibuprofen Ibuprofen is effective in preventing AMS in cases of rapid ascent [54]. However, its prophylactic efficacy is inferior to acetazolamide [63]. Therefore, ibuprofen is recommended only for individuals with hypersensitivity or intolerance to acetazolamide or dexamethasone. [54][59] The typical dosage is 600 mg orally every 8 hours.[5] [59] A meta-analysis confirmed that ibuprofen is more effective than placebo in preventing high-altitude headache (HAH) and may serve as an alternative to acetazolamide or dexamethasone for HAH prophylaxis. [62][64][65]

6. Conclusions

High-altitude illnesses, especially AMS, are common yet often preventable conditions affecting travelers at elevations above 2,500 meters. Increased tourism and underprepared ascent pose significant health risks.

This paper emphasizes that:

- Early recognition and basic knowledge of symptoms can prevent progression to life-threatening complications such as HACE or HAPE.
- Education of both travelers and healthcare providers is essential.
- Evidence-based strategies—like proper acclimatization, pharmacologic prophylaxis, and emergency interventions—should be widely promoted.

Ultimately, prevention is not only safer but more cost-effective than treatment. Informed preparation is the most powerful tool in ensuring safety and health during high-altitude expeditions.

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Authors' contribution:

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Methodology - Agata Juchniewicz, Jakub Sapikowski, Julita Jagodzińska

Software - not applicable

Verification - Martyna Grześkowiak, Iga Kuba, Maria Janiszewska

Formal analysis - Agata Juchniewicz, Jakub Sapikowski, Jakub Idziński, Mikołaj Góralczyk

Research - Agata Juchniewicz, Jakub Sapikowski, Jakub Idziński, Mikołaj Góralczyk, Julita Jagodzińska, Martyna Grześkowiak, Iga Kuba, Maria Janiszewska

Resources - Jakub Idziński, Mikołaj Góralczyk, Julita Jagodzińska

Data curation - Jakub Sapikowski, Jakub Idziński, Mikołaj Góralczyk

Writing - rough preparation - Agata Juchniewicz, Jakub Sapikowski, Jakub Idziński, Mikołaj Góralczyk, Julita Jagodzińska

Writing - review and editing - Martyna Grześkowiak, Iga Kuba, Maria Janiszewska

Visualization - Agata Juchniewicz, Iga Kuba, Jakub Idziński

Supervision - Jakub Sapikowski, Iga Kuba, Maria Janiszewska

Project administration - Agata Juchniewicz, Jakub Sapikowski, Jakub Idziński, Mikołaj Góralczyk, Julita Jagodzińska, Martyna Grześkowiak, Iga Kuba, Maria Janiszewska

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