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HYPOXIC CHALLENGES AT ALTITUDE: MECHANISTIC INSIGHTS AND TRANSLATIONAL APPROACHES TO HIGH-ALTITUDE ILLNESS

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Keywords:

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ABSTRACT: High-Altitude Illness (HAI) refers to a spectrum of hypoxia-related syndromes occurring above 2,500 meters, ranging from mild acute mountain sickness (AMS) to life-threatening conditions like high-altitude cerebral edema (HACE) and pulmonary edema (HAPE). With the rise in trekking, tourism, and military operations in high-altitude regions, HAI has emerged as a significant public health concern. AMS typically develops within 6–12 hours of ascent, presenting with headache, dizziness, nausea, fatigue, and disturbed sleep. If untreated, AMS can progress to HACE, characterized by ataxia, altered mental status, and coma, or to HAPE, marked by dyspnea, cough, cyanosis, and pulmonary crackles. The underlying mechanisms include cerebral vasodilation, oxidative stress, and blood–brain barrier disruption in AMS/HACE, while HAPE results from abnormal hypoxic pulmonary vasoconstriction and alveolar-capillary leakage. Diagnosis is primarily clinical, with the Lake Louise Score being the most widely used tool despite field limitations. Prevention relies on gradual acclimatization, staged ascent, and avoidance of alcohol or sedatives, which improve ventilatory and hematologic adaptation. Pharmacologic options like acetazolamide, dexamethasone, and nifedipine may be useful in high-risk or rapid ascents, while newer therapies such as phosphodiesterase-5 inhibitors and iron supplementation are under study. The mainstay of treatment remains halting ascent and initiating descent, supplemented by oxygen and drug therapy when required. Prognosis is generally favorable with timely intervention, but delays, especially in HACE or HAPE, can be fatal.

INTRODUCTION: High-altitude illness (HAI) refers to a series of hypoxia-induced clinical syndromes that emerge when travelers ascend above 2,500 meters, where the altitude reduces both atmospheric pressure and availability of oxygen [1, 2].

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The two main forms are acute mountain sickness (AMS), which is typically self-limiting, and the more serious high-altitude cerebral edema (HACE) and high-altitude pulmonary edema (HAPE), both of which can be life-threatening if untreated [3-5].

Due to the participation of increasing numbers of people who are entering mountainous areas as trekkers, adventure tourists, or military deployments, HAI is a significant global health issue [6-12]. The rate of AMS varies widely, affecting 25-40% of travelers at 2500m to 3000m, and between 50-75% for elevations higher than 4,500 m, depending upon ascent rate, individual

susceptibility, and pre-acclimatization [13-21]. While HACE is a much less common syndrome with an incidence rate of approximately 0.5-1% of travelers above 4000m, it has a high mortality rate if untreated [22-26].

HAPE, also uncommon (0.2-6%), is the most common cause of altitude-related deaths throughout the world [27, 28]. In terms of pathophysiology, AMS and HACE relate to a combination of oxidative stress, cerebral vasodilation, and disruption of the blood-brain barrier, while HAPE is defined by capillary leakage and uneven hypoxic pulmonary vasoconstriction [29-31]. Genetic predisposition, endothelial function, and inflammatory pathways may also have an individual basis for altitude sickness [32-35]. With more unacclimatized travelers and military personnel being sent to high altitude, the burden of high-altitude illness on the public health system is increasing [36-40]. Prevention methods such as gradual ascent, staged acclimatization and pharmacological prophylaxis have been studied in depth [41-45]. There is also active research on predictive models, portable diagnostics, and new pharmacotherapy's [46-49]. This paper provides a structured overview of the epidemiology, pathophysiology, diagnosis, prevention, and management of high-altitude illness, highlighting both classical concepts and emerging evidence. By synthesizing data across clinical and experimental studies, it aims to inform both medical practitioners and policy-makers engaged in high-altitude health.

Epidemiology and Clinical Spectrum: High-altitude illness (HAI) occurs on a large clinical spectrum from mild acute mountain sickness (AMS) to potentially life-threatening high-altitude cerebral edema (HACE) and high-altitude pulmonary edema (HAPE) [50-53]. AMS is the most common form of HAI, typically occurring in the 6–12 hours following ascent, affecting around 25–40% of people above 2,500–3,000 m; this increased to >75% at altitudes above 4,500 m, especially with rapid ascents [54-57]. HACE is a serious but infrequent progression of AMS, occurring in 0.5–1.0% of individuals: >4,000 m. HACE is associated with ataxia, alteration of consciousness, and coma, and without treatment, the case fatality rate is high [29, 58]. HAPE is also relatively rare (0.2–6.0% incidence based on altitude and rate of ascent) but is the leading cause of altitude-related deaths globally, although it usually occurs in 2–5 days after ascent [59, 60] and is characterized by progressively worsening dyspnea, cough, orthopnea, cyanosis, and pulmonary edema [60-62]. Notably, HAPE can occur independently of AMS or HACE, suggesting distinct pathophysiological pathways [63]. Different groups have a variety of susceptibility: lowlanders who ascend quickly, those with previous episodes of high-altitude illness, and people with genetic or cardiopulmonary characteristics carry a higher risk [64, 35]. Meanwhile, high-altitude residents, which include native Andeans and Tibetans, exhibit adaptive phenotypes, such as greater oxygen delivery, and ventilator responses [65, 66]. It is difficult to estimate the global burden of HAI because of unreported cases, but it is acknowledged that large treks, military deployments, and tourism imply considerable morbidity [67]. For this reason, HAI remains an important clinical and public health issue, particularly in a time of an expanding adventure tourism sector and increasing high-altitude deployments (see **Fig. 1** & **Table 1**).

TABLE 1: CLINICAL SPECTRUM OF HIGH-ALTITUDE ILLNESS

Condition	Incidence	Typical Onset	Key Symptoms	Severity/Outcome
Acute Mountain Sickness (AMS)	25–40% above 2,500–3,000 m; >75% above 4,500 m	6–12 hours after ascent	Headache, nausea, dizziness, fatigue, sleep disturbance	Usually mild, but may progress
High-Altitude Cerebral Edema (HACE)	0.5–1% above 4,000 m	1–3 days after ascent, often following AMS	Ataxia, altered sensorium, coma	Life-threatening if untreated
High-Altitude Pulmonary Edema (HAPE)	0.2–6% depending on altitude/ascent	2–5 days after ascent	Dyspnea, cough, cyanosis, pulmonary crackles	Leading cause of altitude-related deaths

Pathophysiology of High-Altitude Illness: High-altitude illness arises from the maladaptive physiology of humans in response to hypobaric hypoxia (i.e., a drop in the partial pressure of

oxygen in the atmosphere with an increase in elevation [67]. The physiology involved in AMS/HACE and HAPE presents uniquely, suggesting different vulnerabilities regarding organ systems.

Acute Mountain Sickness (AMS) and High-Altitude Cerebral Edema (HACE):

- Cerebral hypoxia elicits vasodilation, producing increases in cerebral blood flow and intracranial pressure [29].
- One of the central mechanisms of AMS/HACE is the disruption of the blood-brain barrier and oxidative stress that contributes to interstitial cerebral edema [68].
- HACE may represent a severe extension of AMS, involving ataxia and disturbance in consciousness, and eventually coma [69].
- Neurohumoral contributors, including but not limited to cerebral nitric oxide and vascular endothelial growth factor, may regulate vascular permeability and edema associated with AMS/HACE [35].

High-Altitude Pulmonary Edema (HAPE):

- HAPE is largely due to the distribution of hypoxic pulmonary vasoconstriction, resulting in increased pulmonary artery pressures and spatially dependent capillary stress [27].
- As a consequence of increased alveolar-capillary permeability and decreased clearance of extravasated fluid, HAPE is a form of non-cardiogenic pulmonary edema [70].
- Improvement of HAPE may also be due to inflammatory mediators, genetic predisposition (e.g. gene isoforms of nitric oxide synthase and endothelial function) [73].

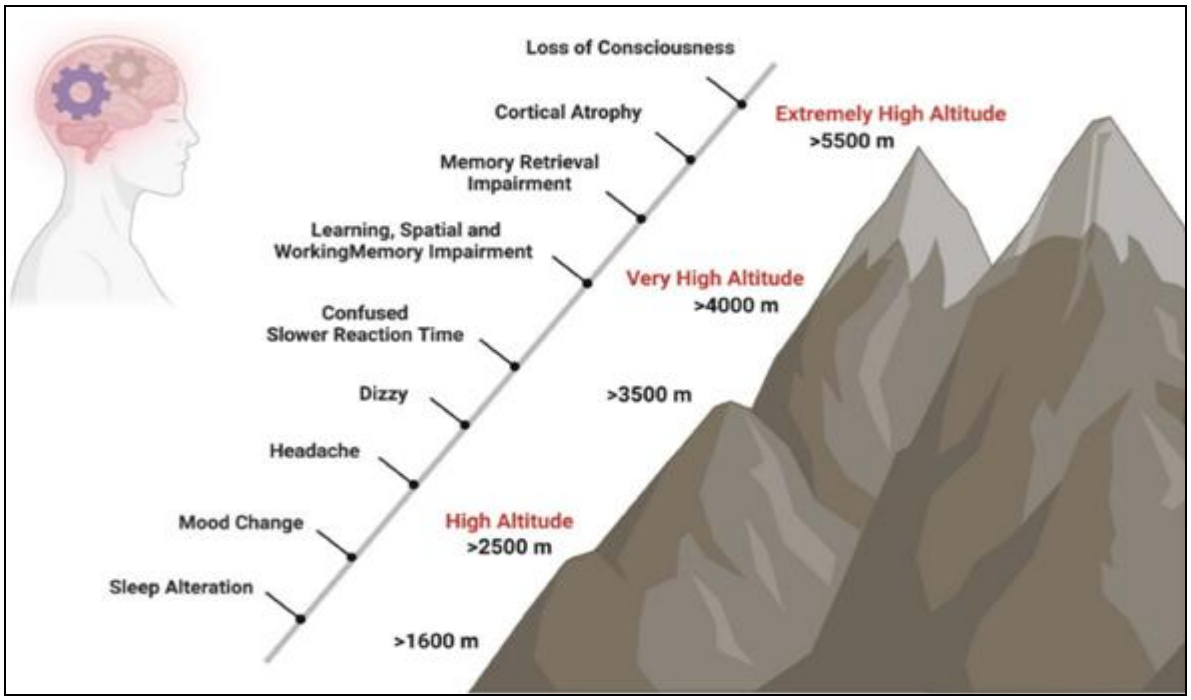

FIG. 1: COGNITIVE EFFECTS OF HIGH ALTITUDE PROGRESSIVE HYPOXIA LEADS TO SLEEP, MOOD, ATTENTION, AND MEMORY IMPAIRMENTS WITH INCREASING ELEVATION [74]

Acclimatization and Physiological Adaptation:

- When individuals gradually ascend, ventilatory adaptations occur, and there are haematological adaptations that lead to increased hyperventilation and increased red blood cell production (erythropoiesis), as well as better oxygen[46].
- Lack of acclimatization is the rationale for HAI formation and emphasizes the gradual ascent and/or surveillance [72].

Understanding these potential pathophysiologies is important with respect to preventive measures or pharmacological prophylaxis or providing care for those exposed to a high-altitude environment (see **Fig. 2** and **Table 2**).

TABLE 2: PATHOPHYSIOLOGY OF HIGH-ALTITUDE ILLNESS

Condition	Primary Mechanism	Key Pathophysiological Features	Contributing Factors
Acute Mountain Sickness (AMS)	Cerebral hypoxia	Cerebral vasodilation, mild interstitial edema, increased intracranial pressure	Rapid ascent, poor acclimatization, individual susceptibility
High-Altitude Cerebral Edema (HACE)	Extreme continuum of AMS	Severe vasogenic edema, blood–brain barrier disruption, oxidative stress	Cerebral nitric oxide dysregulation, vascular endothelial growth factor, prior AMS
High-Altitude Pulmonary Edema (HAPE)	Hypoxic pulmonary vasoconstriction	Uneven vasoconstriction, elevated pulmonary artery pressure, alveolar-capillary leak	Genetic predisposition, impaired fluid clearance, inflammatory mediators

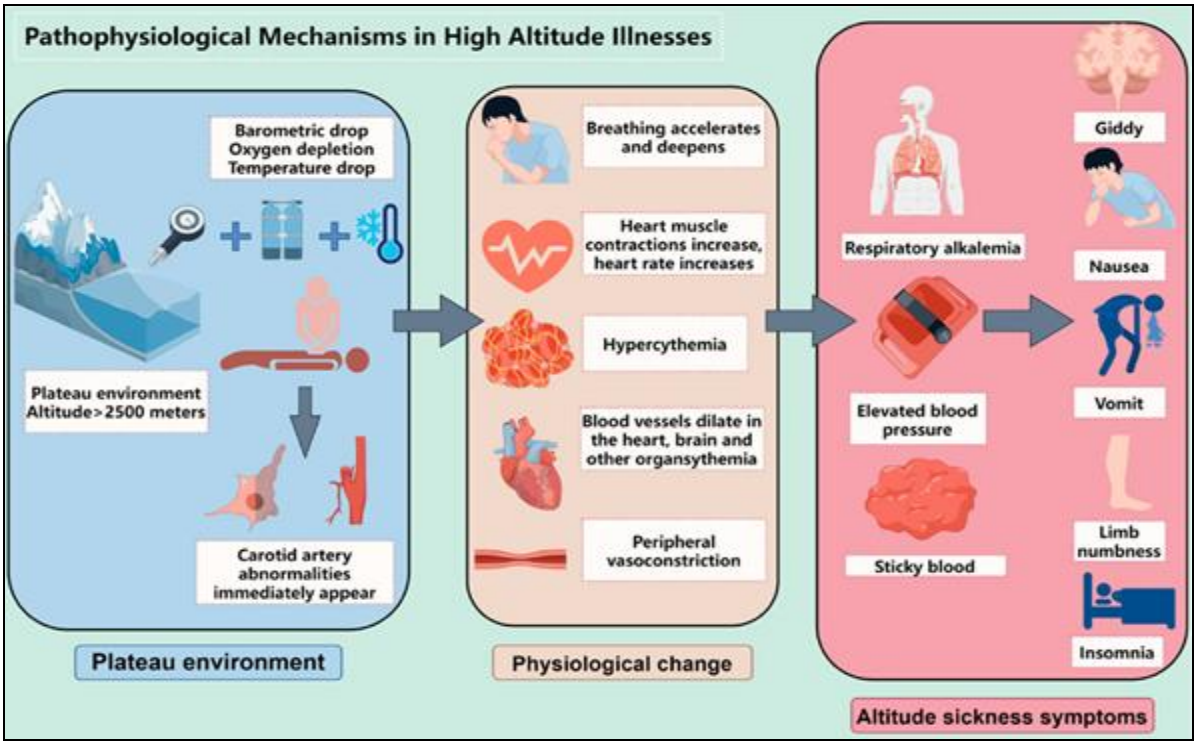

FIG. 2: PATHOPHYSIOLOGICAL MECHANISMS OF HIGH-ALTITUDE ILLNESS. ENVIRONMENTAL HYPOXIA AT ELEVATIONS ABOVE 2500 M TRIGGERS PHYSIOLOGICAL ADAPTATIONS—HYPERVENTILATION, CARDIOVASCULAR ACTIVATION, AND VASOMOTOR CHANGES [75]

Diagnosis of High-Altitude Illness: High-altitude illness (HAI) is mostly diagnosed clinically, based on the identification of classic signs and symptoms in someone who has just ascended to a high altitude[1]. Early recognition is crucial to avoid progression to high altitude cerebral edema (HACE) or high-altitude pulmonary edema (HAPE) that has a high morbidity and mortality rate.

Acute Mountain Sickness (AMS):

- Defined as headache plus at least one of nausea, vomiting, fatigue, lightheadedness, and/or sleep disturbance [37].
- The Lake Louise Score (LLS) is still the standard measure of AMS, rating it mild, moderate, or severe [43].
- Inevitably, these measures are limited by the subjective nature of reported symptoms, language problems to address, environmental stressors, and inter-observer renal reliability.

High-Altitude Cerebral Edema (HACE):

- HACE is suggested when ataxia, altered sensorium, confusion, or coma occurs with AMS [63].

- Neuroimaging (CT/MRI) can diagnose cerebral edema, but it is rarely practical in the field [29].
- Neurological assessment, such as gait and coordination testing, is also helpful in clinical diagnosis [35].

High-Altitude Pulmonary Edema (HAPE):

- HAPE includes progressive dyspnea, cough, orthopnea, cyanosis, or pulmonary rales [27].
- Chest x-ray may demonstrate pulmonary edema; however, in austere conditions, pulse oximetry and auscultation are key for initial detection [46].
- Cardiogenic pulmonary edema, pneumonia, asthma exacerbation, or pulmonary embolism must be ruled out [66].

Laboratory and Monitoring Tools:

- Pulse oximetry allows for early detection of hypoxemia prior to more significant symptoms emerging [6].
- Emerging technologies include portable hypoxia sensors, biomarkers of oxidative stress, and markers of inflammation currently being tested for predicting susceptibility to acute mountain sickness (AMS), high altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE) [47].
- Blood tests measuring hematocrit, hemoglobin and nitric oxide metabolites may aid in assessing physiological adaptation and risk [71].

Clinical Decision-Making:

- Diagnosis has a combination of symptom scoring, vital signs and oxygen saturation along with consideration of patient history and known risk factors [41].
- Prompt identification of altitude illness permits to stop climbing, descend, administer oxygen supplementation and institution of pharmacological therapy and has been seen to notably reduce morbidity and mortality [69].

Prevention of High-Altitude Illness: Prevention of high-altitude illness (HAI) is crucial, as early intervention is more effective than treatment after symptom onset. Strategies focus ongradual acclimatization, non-pharmacological measures, and pharmacological prophylaxis [1].

Gradual Ascent and Acclimatization: An important part of prevention involves progressive ascent, which allows for physiological adaptations, such as increases in ventilation, erythropoiesis, and improved oxygen delivery to the tissues [2].

The consensus guidelines recommend to not ascend more than 300–500 m/day above 3000 m, and to consider rest days every 1–2 days of ascent [1]. Pre-acclimatization methods, such as intermittent hypoxia training, simulated high altitude or staged high altitude exposure also may decrease the risk of high-altitude illness such as AMS, HACE, and HAPE in susceptible individuals.

Non-Pharmaceutical Interventions: Eliminating consumption of alcohol and sedatives and excessive physical activity during ascent help avoid altitude hypoxia and AMS symptom exacerbation [25]. Maintaining sufficient hydration and caloric consumption promotes metabolism adaptation and diminishes HAI susceptibility [73].

Monitoring individual symptoms, and utilizing buddy systems to identify warning signs of HAI, ultimately permits avoid sleeping disorders.

Pharmacological Prophylaxis:

- Acetazolamide is the leading option for AMS prevention; it promotes ventilation and acid-base balance [44].
- Dexamethasone is reserved for high-risk individuals or where acetazolamide is contraindicated, and it has particular application for AMS or HACE prevention [1].
- Nifedipine has been shown to reduce pulmonary arterial pressure and to prevent HAPE in risk factors [27].
- Pharmacological approaches for the prevention of AMS, HACE and HAPE, including phosphodiesterase-5 inhibitors, iron supplementation, antioxidants and new molecular therapy, are ongoing [49].

Special Considerations:

- High risk populations include rapid climbers, unacclimatized travellers, children, older adults, and previous HAI[46].
- Military personnel and athletes may require hypoxia conditioning prior to deployment and may require a specialized pharmacological regimen [6].
- Prevention, as most effective, should include acclimatization, behavioural approaches and pharmacological prophylaxis where applicable, thereby decreasing the incidence of AMS, HACE and HAPE and improving the safety of travel at high altitude.

TABLE 3: PREVENTION OF HIGH-ALTITUDE ILLNESS

Condition	Primary Prevention Strategy	Non-Pharmacological Measures	Pharmacological Prophylaxis	Notes / Special Considerations
Acute Mountain Sickness (AMS)	Gradual ascent; staged acclimatization	Limit ascent to 300–500 m/day above 3,000 m; rest days; avoid alcohol and sedatives; adequate hydration	Acetazolamide (125–250 mg twice daily); Dexamethasone in high-risk individuals	Pre-acclimatization training may reduce risk; monitor symptoms with Lake Louise Score
High-Altitude Cerebral Edema (HACE)	Prevention of AMS progression; early recognition	Same as AMS; monitor neurological signs; buddy system	Dexamethasone (4 mg every 6 h); Acetazolamide may be adjunctive	Rapid descent is critical if symptoms develop; avoid strenuous activity
High-Altitude Pulmonary Edema (HAPE)	Gradual ascent; limit rapid altitude gain	Limit exertion; maintain hydration; avoid alcohol	Nifedipine (20 mg every 8 h); Sildenafil or Tadalafil in specific cases; emerging therapies under investigation	High-risk individuals may require pre-acclimatization; portable oxygen may be used prophylactically

Management of High-Altitude Illness: The approach to high-altitude illness (HAI) consists of early recognition of symptoms, stopping any further ascent, descent, supplemental oxygen, and medication.

Management strategies can vary based on the type and severity of HAI, but the overall goal is to prevent further evolution to severe HAI, with life threatening outcomes (e.g., high-altitude cerebral edema (HACE) and high-altitude pulmonary edema (HAPE).

Acute Mountain Sickness (AMS):

- Often mild or moderate AMS is managed in situ via stopping an ascent to rest, or symptomatic therapy (e.g., anti-headache analgesics, or anti-nausea medications) [43].
- Acetazolamide (125-250 mg twice daily) improves illness recovery *via* enhanced ventilatory acclimatization [44].
- Severe AMS requires a descent of 300-1000 meters with supplemental oxygen, if available [1].

High-Altitude Cerebral Edema (HACE):

- HACE is a medical emergency, and rapid descent to lower altitude is required [1].
- Dexamethasone (4-8 mg, initially, then 4 mg every 6 hours) is effective in reducing cerebral edema and improving neurological status [63].
- Supplemental oxygen and a portable hyperbaric chamber can also be used when descent is delayed [62].

High-Altitude Pulmonary Edema (HAPE):

- Management of HAPE consists primarily of quick descent, supplemental oxygen, both of which can be lifesaving [28].
- Nifedipine (20mg every 8 hours) decreases pulmonary arterial pressure, decreases edema[62].
- Other pharmacological options include phosphodiesterase-5 inhibitors (Sildenafil, Tadalafil), dexamethasone, and portable hyperbaric therapy, in the event that descent is stalled [47].

Supportive Measures and Monitoring:

- Patients should continuously monitor oxygen saturations, and assess for neurological and respiratory signs.
- Patients should be rested and hydrated, and if symptoms worsen, they should be assessed and transferred to a lower altitude or nearby facility [6].

Prognosis:

- Patients who are recognized and treated quickly have a good chance of full recovery [3].
- Patients that do not receive treatment may experience fatal outcomes, especially HACE and HAPE patients, which indicate the importance of preventative measures and emergency action [69].

TABLE 4: MANAGEMENT OF HIGH-ALTITUDE ILLNESS

Condition	Severity	Immediate Actions	Pharmacological Therapy	Supportive Measures	Notes
Acute Mountain Sickness (AMS)	Mild–Moderate	Halt ascent, rest, monitor symptoms	Analgesics for headache, antiemetics for nausea; Acetazolamide (125–250 mg BID)	Hydration, light activity, symptom monitoring	Descent if symptoms worsen or severe AMS develops
AMS	Severe	Immediate descent 300–1000 m	Acetazolamide; consider Dexamethasone	Supplemental oxygen if available	Hospitalization if no improvement
High-Altitude Cerebral Edema (HACE)	Any	Immediate descent	Dexamethasone (4–8 mg initially, then 4 mg every 6 h)	Supplemental oxygen; portable hyperbaric chamber if descent delayed	Medical emergency; rapid intervention crucial
High-Altitude Pulmonary Edema (HAPE)	Mild–Moderate	Halt ascent; limit exertion	Nifedipine (20 mg every 8 h); PDE-5inhibitors (Sildenafil/Tadalafil) if needed	Supplemental oxygen; rest; monitor SpO_2	Rapid descent preferred; pre-acclimatized individuals may tolerate mild HAPE under close monitoring
HAPE	Severe	Immediate descent to lower altitude	Nifedipine; PDE-5 inhibitors; Dexamethasone (adjunct)	Supplemental oxygen; portable hyperbaric therapy if descent delayed	High-risk condition; life-threatening without timely intervention

Future Directions and Emerging Therapies: Even though there have been advances made in understanding and managing high-altitude illness (HAI), many important aspects remain challenging, including predicting individual susceptibility, finding the optimal pharmacologic prophylaxis, and treating cases at altitude or in environments with limited resources. Recently, research has been investigating molecular, novel pharmacotherapies, new wearable technology and new predictive tools to improve safety at altitude [47].

Molecular and Pharmacologic Interventions:

- Phosphodiesterase-5 (PDE-5) inhibitors, such as Sildenafil and Tadalafil, may have potential in preventing HAPE by lowering pulmonary artery pressure and improving oxygenation [57].
- Iron supplementation could be a helpful adjunctive therapy for hypoxic adaptation through erythropoiesis, especially in individuals with borderline iron stores [65].
- Oxidative stress pathways are being explored with the use of antioxidants and anti-inflammatory agents for treating cerebral and pulmonary edema in AMS, HACE, and HAPE [1].
- Potentially novel molecular therapies, targeting vascular endothelial growth factor (VEGF), nitric oxide pathways and hypoxia-inducible factors (HIF), could enable us to think about personalized prevention and treatment for HAIs [35].

Predictive and Monitoring Tools:

- Wearable pulse oximeters and portable hypoxia sensors enable real-time monitoring of oxygen saturation and early detection of signs of HAI [48].
- Plasma nitric oxide metabolites, inflammatory cytokines, and biomarkers for oxidative stress are being examined for the purposes of predicting susceptibility to AMS, HACE, and HAPE in the field [47].
- Artificial intelligence and machine learning models are in development to predict risk as a function of ascent profile, physiological measures, and genetic predisposition, thus personalizing prevention strategies [46].

Telemedicine and Remote Management:

- Remote consultation and telemonitoring using satellite communication devices and mobile apps are helpful to support early intervention and triage for high-altitude expeditions [41].
- Portable hyperbaric chambers and oxygen concentrators in conjunction with remote monitoring are helpful in providing life-saving measures if descent is impossible [28].

Research Gaps and Future Perspectives:

- Additional studies are warranted to authenticate emerging pharmacotherapies and molecular interventions in larger populations.
- The formulation of individually-tailored acclimatization guidelines based on genetic, biochemical, and physiological characteristics may play a role in lowering the incidence of HAI [35, 64].
- The application of products that employ wearable technologies, predictive AI models, and telemedicine may revolutionize high-altitude safety for trekkers, members of the armed forces, and residents [47, 48].
- In conclusion, approaches to manage HAI in the future will involve combination molecular interventions, predictive monitoring, and remotely delivered medical support in order to minimize morbidity and mortality while facilitating safer high-altitude exposure.

CONCLUSION: High-altitude illness (HAI) continues to be a major health issue for tourists, trekkers, military personnel, and residents experiencing hypobaric hypoxia above 2,500 meters. The clinical course of HAI ± which includes acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE) ± ranges from mild reversible signs and symptoms to sudden death. Early identification, accurate diagnosis, and timely management are paramount to mitigating morbidity and mortality (see **Fig. 3**).

Current prevention strategies, including a gradual ascent, staged acclimatization, behavioral approaches, and pharmacological prophylaxis, remain the foundations of HAI incidence reduction.

Management includes prevention of ascent, descent, supplemental oxygen, and specific pharmacotherapy, along with interventions specific to the severity level of an individual experiencing symptom of AMS, HACE, or HAPE. Innovative approaches, such as molecular therapies, wearable devices, biomarkers, and artificial intelligence-based predictive tools, may serve to personalize prophylaxis and early detection strategies.

Future efforts can still encounter obstacles related to predicting who is more susceptible, what type of preventative regime would be best, and how to provide management in remote locations. New areas of research that include physiological and genetic advancements along with the inclusion of technological advancements could lead to better high-altitude safety outcomes while not only mitigating disease burden, but also hospital and emergency medicine for the temporary visitors to and chronic high-altitude populations.

As a whole, a multifactorial approach using acclimatization, close observation, medications, and new technologies is the best way to mitigate high-altitude illness and its consequences. The most important factor in outcomes remains timely treatment, emphasizing the significance of education, planning, and evidence-based practice in high-altitude conditions.

TABLE 5: INTEGRATED OVERVIEW OF HIGH-ALTITUDE ILLNESS

Aspect	AMS	HACE	HAPE
Clinical Features	Headache, nausea, fatigue, dizziness, sleep disturbance	Ataxia, altered consciousness, confusion, coma	Dyspnea, cough, orthopnea, cyanosis, pulmonary crackles
Diagnosis	Clinical evaluation; Lake Louise Score; pulse oximetry	Clinical diagnosis; neurological exam; neuroimaging if available	Clinical evaluation; SpO_2 monitoring; chest radiography if feasible
Prevention	Gradual ascent (300–500 m/day above 3,000 m); rest days; avoid alcohol/sedatives; hydration	Prevent AMS progression; staged ascent; monitor neurological signs	Gradual ascent; avoid rapid altitude gain; hydration; limit exertion
Pharmacological Prophylaxis	Acetazolamide 125–250 mg BID; Dexamethasone in high-risk	Dexamethasone 4–8 mg initially, then 4 mg q6h	Nifedipine 20 mg q8h; PDE-5 inhibitors (Sildenafil/Tadalafil) if needed
Management	Halt ascent; rest; analgesics/antiemetics; acetazolamide; descent if severe	Immediate descent; Dexamethasone; supplemental oxygen; portable hyperbaric chamber if available	Immediate descent; supplemental oxygen; Nifedipine; PDE-5 inhibitors; portable hyperbaric therapy if needed
Supportive Measures	Hydration, symptom monitoring, light activity	Oxygen therapy, neurological monitoring	Oxygen therapy, monitoring SpO_2, rest
Emerging/Experimental Approaches	Pre-acclimatization *via* intermittent hypoxia; antioxidants	Molecular therapies targeting VEGF, nitric oxide, HIF pathways; predictive biomarkers	PDE-5 inhibitors, iron supplementation, wearable monitoring devices, AI-based risk prediction
Prognosis	Generally favorable if managed early; progression possible	Life-threatening if untreated; favorable with timely intervention	Life-threatening if untreated; rapid descent improves outcome

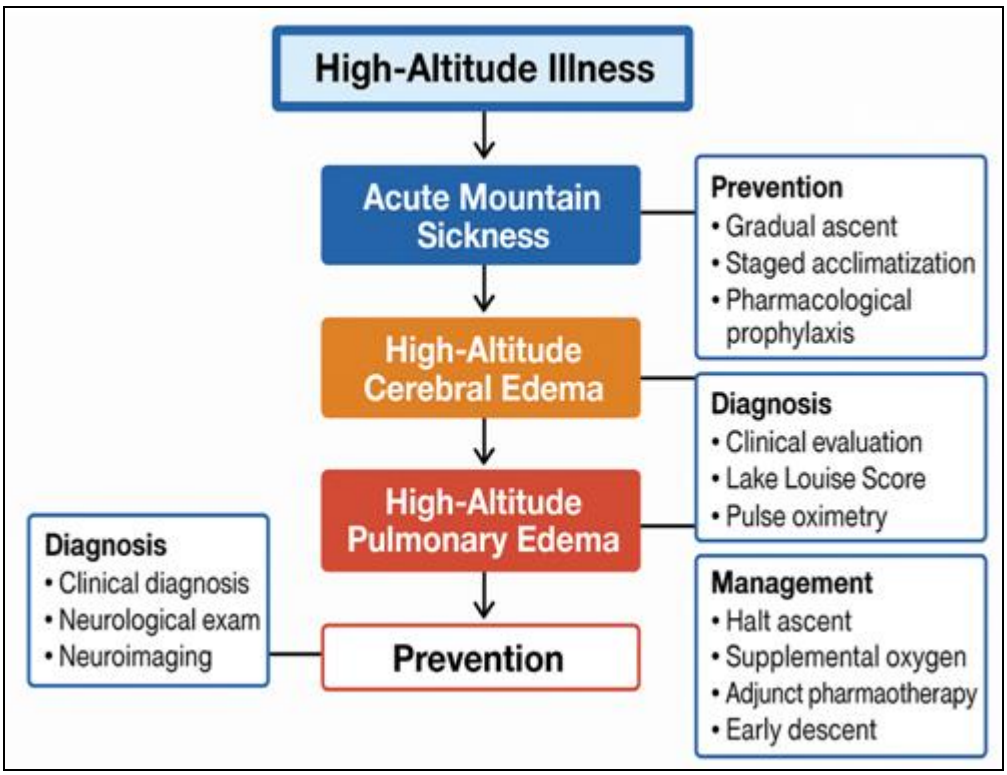

FIG. 3: AMS → HACE CONTINUUM AND SEPARATE HAPE PATHWAY, INTEGRATING PREVENTION, DIAGNOSIS, AND MANAGEMENT

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