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Advances in the Prevention and Treatment of High-Altitude Illnesses

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Abstract

Introduction and purpose

High-altitude environments (>1500 m) expose climbers to reduced atmospheric pressure and hypoxia. These conditions increase the risk of acute mountain sickness, high-altitude cerebral edema, and high-altitude pulmonary edema. This review aims to summarize current knowledge of high-altitude illnesses (HAI), their prevention and treatment, with particular emphasis on recent advances in this field.

A brief description of the state of knowledge

Prophylaxis of HAI is based on proper acclimatization and a suitable ascent rate. Acetazolamide is among the most commonly used agents for pharmacologic prophylaxis. Treatment in severe cases requires prompt descent, oxygen therapy, dexamethasone, or portable hyperbaric chambers. There are numerous novel strategies used for reducing the risk of HAI. Emerging evidence suggests that probiotics may facilitate acclimatization. Pre-acclimatization and hypoxic training at sea level enable preparation for high-altitude exposure. Wearable sensors and closed-loop systems may provide more precise risk assessment; however, their effectiveness in mountainous conditions

remains to be improved. Advanced prediction models, in turn, additionally improve the identification of people from risk groups and facilitate personalized prophylaxis.

Summary (conclusions)

HAI remain an important challenge in hypoxic, mountainous conditions. Apart from the currently well-established methods, novel strategies, such as probiotics, hypoxic training, and advanced monitoring technologies, may facilitate prophylaxis and individual risk assessment, thus improving the security of high-altitude expeditions.

Key words: Altitude Sickness; Acclimatization; Oxygen Saturation; Hypoxia; Prediction Algorithms.

1. Introduction

In recent decades, high-altitude travel has become increasingly popular, with millions of individuals visiting mountainous regions each year. This trend is reflected, for example, in the rapidly rising number of permits issued for trekking in restricted areas, such as in Nepal, where a more than sevenfold increase was observed between 2001 and 2024 (1)(2).

High-altitude exposure is commonly classified into three categories: high (1500–3500 m), very high (3500–5500 m), and extreme altitude (above 5500 m) (3). An appropriate rate of ascent, along with prior acclimatization, plays a pivotal role in preventing high-altitude illnesses (HAI). Lack of proper preparation can result in acute mountain sickness (AMS), the most common form of high-altitude illness, or more severe complications such as high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) (4).

High-altitude conditions necessitate specialized preventive and treatment measures, which constitute a distinct branch of medicine. For health care professionals interested in providing medical support in the mountains, it is possible to obtain a Diploma in Mountain Medicine, a qualification recognized by the International Climbing and Mountaineering Federation *(Fr. Union Internationale des Associations d'Alpinisme*, UIAA) (5).

Of note, the risk of developing HAI concerns not only mountaineers but also rescuers who need to ascend rapidly, often by helicopter, and perform rescue procedures at very high altitudes. It is important to distinguish between these groups and provide appropriate recommendations for each (6).

There are many available, well-established options designed to facilitate acclimatization to mountainous conditions. In recent years, numerous novel strategies have also been implemented. The aim of this review is to summarize currently available methods and provide information on emerging trends, including the use of probiotics, the implementation of wearable technologies, and the assessment of genetic susceptibility to HAI.

2. High-altitude Illnesses

2.1. AMS

Acute mountain sickness, characterized by symptoms such as headache, loss of appetite, sleep disturbances, fatigue, nausea, vomiting, and dizziness, is the most common form of HAI. It can occur at altitudes of 1500 m or higher, with the incidence increasing with altitude and ascent rate. Using air travel to reach high-altitude destinations significantly increases the incidence of AMS compared to climbing to those destinations. One study found that AMS was present in 39% of people who flew to 3350 m and in 84% of those who flew to 3740 m (7). Results from a different study assessing the incidence of AMS among mountaineers planning to climb Mount Fuji (3776 m) indicate that 29,5% experienced AMS symptoms (8).

The prevalence of AMS depends heavily on risk factors, including a prior history of AMS, starting the ascent from sea level rather than higher elevations, and a rapid rate of ascent of more than 500 meters per day (4, 9). It appears there is no marked gender difference, but some studies indicate that women are slightly more affected (4). Interestingly, there is no specific relationship between age and AMS susceptibility. In some studies, older people are less likely to experience AMS, perhaps because of reduced exertion or adaptive physiological changes (9).

AMS can be assessed based on various diagnostic instruments (10). One of the simplest tools is the AMS Clinical Functional Score, presented below. For research purposes and precise assessment, the Lake Louise Acute Mountain Sickness Score should be applied (11).

Table 1. Acute Mountain Sickness Clinical Functional Score

Points	**Overall, if you had AMS symptoms, how did they affect your activities?**
0	Not at all
1	Symptoms present, but did not force any change in activity or itinerary
2	My symptoms forced me to stop the ascent or to go down on my own power
3	Had to be evacuated to a lower altitude

Source: Roach RC, et al. The 2018 Lake Louise Acute Mountain Sickness Score. High Alt Med Biol. 2018;19(1):4-6
Notes: A result of ≥ 2 points signals clinically significant AMS and warrants more aggressive intervention (10).

2.2. HAPE

Among high-altitude illnesses, high-altitude pulmonary edema accounts for the majority of deaths (12). The symptoms begin with dyspnea on exertion, cough, and reduced physical performance, deteriorating to shortness of breath at rest and hemoptysis, accompanied by tachycardia, tachypnea, and fever (13). It has been established that hypoxic pulmonary vasoconstriction is causative for HAPE, leading to an increased capillary leak in susceptible individuals (14). HAPE is uncommon below 2500-3000 m. The higher the altitude and the rate of ascent, the greater the risk of developing this complication. The reported incidence of HAPE was 0,2% in people ascending 4500 m in 4 days and 2% in those ascending 5500 m in 7 days; however, reducing the ascent time of these altitudes to 1 or 2 days increased the incidence of HAPE to 6% and 15%, respectively (15).

Once HAPE is suspected, prompt intervention should be undertaken. Descent and supplemental oxygen therapy are the first steps. Administration of nifedipine and treatment with a portable hyperbaric chamber may be indicated in more severe cases (13).

2.3. HACE

Another HAI is high-altitude cerebral edema. It should be diagnosed whenever AMS is accompanied by ataxia or disturbed consciousness. Papilledema, retinal hemorrhage, and cranial nerve palsy may also occur due to increased intracranial pressure (12). Mild fever may also be present. It is crucial to early diagnose this condition, because if left untreated, it may lead to death due to brain herniation (15).

It has been proposed that HACE results from increased cerebral blood volume and blood–brain barrier dysfunction, leading to vasogenic edema primarily due to hypoxia (16). It usually occurs after spending at least 2 days at elevations above 4000 m, with a prevalence of approximately 0,5-1% among people at altitudes of 4000-5000 m (15).

Methods shown to be effective in treating AMS are also useful for treating HACE. Adequate steps comprise descent, oxygen therapy, acetazolamide, dexamethasone, and use of a hyperbaric chamber (17).

3. Well-established Prevention and Treatment Options

3.1. Acclimatization

There are several validated methods to prevent high-altitude illnesses. The “gradual acclimatization” approach assumes that, after reaching 2500 m, the altitude of overnight stays should be increased by only 300-500 m per day. One should also spend a full day on regaining strength every 3 to 4 days of ascending.

Another strategy, called “climb high, sleep low”, is based on intensive physical exercise during the day and returning to the base at night in order to recuperate.

One more method, known as “yo-yo”, consists of longer excursions to higher altitudes, where several days are spent, and returning to the base for regeneration (18). The core of these acclimatization strategies is giving the body time to adapt to the conditions of

the mountains.

3.2. Physical Fitness

It is worth noting that being physically fit does not prevent from developing HAI. Studies have shown that there is little or no association between physical fitness and susceptibility to acute mountain sickness (15). In fact, some evidence suggests that endurance-trained athletes may be at increased risk of developing AMS on the first day at high altitude. In one study of 38 men who ascended actively or passively to 3450 m, AMS symptoms were present in 42% of athletes compared with 11% of untrained controls. The suggested explanation was an increased parasympathetic activity and a higher resting metabolic rate in the athlete group. However, there was no difference in AMS incidence in the compared groups in the following days (19).

Due to reduced oxygen partial pressure, there is an estimated 1% loss of exercise capacity for every 100 m above 1500 m. A high level of physical endurance may attenuate this decline in performance, thereby enabling well-trained mountaineers to reach their targets (15). It should be emphasized that proper acclimatization and physical fitness are distinct domains, both of which are necessary to cope with high altitudes successfully.

3.3. Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor, was introduced for the prevention and treatment of AMS in the 1960s and has been tested in many randomized placebo-controlled studies since then. It was proven to be effective in AMS, but not in HAPE. In HACE, use of this medication plays a limited role, where it may be added to dexamethasone (20, 21). Acetazolamide exerts its beneficial effects by inducing metabolic acidosis, thereby increasing minute ventilation. Other mechanisms of action include increased chemoreceptor activity, improved sleep quality, and increased diuresis, all of which may attenuate AMS symptoms (22). The recommended dose of acetazolamide for the prevention of AMS is 125 mg every 12 h, starting one day before the ascent. In high-risk settings, 250 mg twice daily may be considered. Similarly, dosing for the treatment of AMS is 250 mg every 12 h (21).

3.4. Dexamethasone

The role of dexamethasone in the prevention and treatment of HAI is well-established. This substance mitigates AMS symptoms mainly due to its anti-inflammatory and antiemetic effects (23). Detailed dosing regimens depend on the clinical situation. For example, the starting dose in the prevention of AMS and HACE is 2 mg every 6 h or 4 mg every 12 h. While dexamethasone is effective in AMS and HACE, its use in HAPE requires further research (21).

3.5. Prophylaxis and Treatment of HAPE

As exaggerated pulmonary vasoconstriction constitutes a key mechanism in HAPE, vasodilatory agents are of significant value in both its prophylaxis and treatment. Prophylaxis with 30 mg of nifedipine, every 12 h (as an extended-release preparation) is recommended for people with a susceptibility to HAPE. In case this drug is contraindicated, tadalafil or sildenafil may be used (21). Recommendations for treatment of HAPE include descent, supplemental oxygen, nifedipine, and use of a portable hyperbaric chamber. Tadalafil or sildenafil may be used if other treatment options are unavailable. Of note, acetazolamide is contraindicated in HAPE. Administering this diuretic agent may cause hypotension due to possible intravascular volume depletion, and respiratory stimulation may worsen dyspnea (21).

3.6. Oxygen

With increasing altitude, atmospheric pressure decreases, reducing the partial pressure of oxygen and its availability, which underlies the development of high-altitude illness. Therefore, supplemental oxygen plays an important role in the treatment of AMS, HACE, and HAPE. An adequate treatment target, represented by oxygen saturation in these situations, is usually SpO_2 > 90% (21).

Specific recommendations concern unacclimatized rescuers, who are flown to very high altitudes to perform rescue actions. Use of oxygen in this group is indicated when operation time

exceeds 30 minutes in altitudes over 3500 m, and for any duration at altitudes greater than 4000 m. No pharmacologic prophylaxis is needed, as long as oxygen supply is guaranteed (6).

Supplemental oxygen may enable even unacclimatized mountaineers to reach their targets. At the summit of Mount Everest (8848 m), atmospheric pressure is equal to 253 mmHg, roughly 1/3 of the pressure at sea level (760 mmHg). With increasing altitude, the concentration of oxygen in the air remains the same, but the inhaled air becomes "thinner" due to lower atmospheric pressure. Results from a recent study by Wakeham et al., presented in the table below, provide insight into the altitude-lowering effect of an additional oxygen supply.

Table 2. Effect of Oxygen Intervention

Oxygen flow, L/min	**SpO_2 (% ± SD)**	**"Mask altitude"**
0	66 ± 9	8848 m
1	71 ± 0	7185 m
2	87 ± 3	4489 m
4	93 ± 3	2767 m
6	96 ± 2	2116 m

Source: Wakeham DJ et al. The Physiological and Altitude Lowering Effects of Different Supplemental Oxygen Flow Rates at Extreme Simulated Altitude: A Pilot Study. High Alt Med Biol. 2025

Notes: The results represent the altitude-lowering effect of supplemental oxygen delivered via the SUMMIT oxygen mask, used at extreme altitudes. "Mask altitude" refers to the estimated effective altitude within the mask. Data were collected at rest in a hypobaric chamber under simulated conditions at the Mount Everest peak, i.e., a pressure of 253 mmHg (24).

3.7. Hyperbaric Chamber

Another validated option for alleviating HAI symptoms is a portable hyperbaric chamber. This device simulates descent and may provide clinical improvement as a temporary measure while waiting for the actual descent (25). A hyperbaric chamber is indicated for patients with severe AMS or HACE, when it's not possible to descend to a lower altitude and supplemental oxygen is not available. It may also be used for HAPE, although data from the literature is limited in this indication. It is worth noting that treatment with a hyperbaric chamber may be difficult in patients who are vomiting or have claustrophobia. The use of a portable hyperbaric chamber requires

constant supervision and should not delay descent whenever feasible, as descent remains the definitive treatment for HAI (21).

4. Novel Therapeutic Approaches and Strategies

4.1. Bacteriotherapy

Emerging evidence suggests that the intestinal microbiota could be a new target for interventions to improve acclimatization and coping with high altitude. Firstly, there are significant changes in lowlanders who are acutely exposed to high altitudes. For example, in this scenario, the presence of short-chain fatty acid producers, such as *Bacteroides* or *Faecalibacterium*, is reduced (26). Furthermore, bacterial profiles differ significantly between people acutely exposed to high altitude and those who remain there for longer, as well as between the indigenous populations inhabiting high-altitude regions. While antibiotic treatment has been shown to cause dysbiosis and deteriorate high-altitude tolerance in animal studies, other interventions, namely fecal microbiome transplantation or use of probiotics, prebiotics, or synbiotics, have been theorized to alleviate oxidative stress, decrease inflammatory mediators, and improve the integrity of mucosal barriers (26).

One of the probiotic formulations, Oxxyslab, containing eight different bacterial strains, has recently been tested and is attracting growing attention. In an *in vitro* study by Lombardi et al. using human intestinal epithelial cells, this probiotic was shown to increase hypoxia-inducible factor 1α (HIF-1α) levels by upregulating the PI3K/AKT pathway. This, in turn, led to inhibition of NF-κB signaling, thereby counteracting the inflammatory response (27). Physiologically, HIF-1α serves as a transcription factor and mediates the response to low-oxygen environments. Stabilization of HIF-1α, achieved under hypoxic conditions, promotes cellular survival under low oxygen levels by shifting metabolism toward glycolysis (28). It appears that certain bacterial strains may enhance this adaptive reaction (27).

Very early human data concerning a randomized, placebo-controlled, double-blind study with the Oxxyslab probiotic support these observations. A group of 17 unacclimatized participants was transported to an altitude of 3800 m and ingested the mentioned probiotic or placebo daily for

4 days. Both daytime and nighttime blood oxygen saturation (SpO_2) were significantly higher in the treatment group (with mean increases of 3,6% and 5,1%, respectively). Moreover, AMS symptoms, as measured by the AMS survey score, were significantly lower in the treatment group during the first 2 days (29).

In a separate study, 32 unacclimatized participants were exposed to a reduced fraction of inspired oxygen (13.5%) in a hypoxic tent at an altitude of 50 m, simulating a high altitude of approximately 3500 m. They ingested a probiotic or placebo 2-6 hours before the start of the experiment, which lasted 40-60 minutes (different times were used across experiment arms), to examine the effects of probiotics on acute hypoxia. There were no significant differences regarding SpO_2 or heart rate between the study groups. However, in the probiotic group, the prevalence of headache, an AMS symptom, was significantly smaller. These results indicate that probiotics do not directly improve systemic oxygenation in healthy individuals in acute hypoxic conditions. However, they may alleviate AMS symptoms (30).

In turn, researchers examining the Oxxyslab probiotic as an addition to the routine therapy in COVID-19 patients observed improved blood oxygenation in the probiotic group and a reduction in the need for supplemental oxygen. They pointed to a possible “oxygen sparing effect” of this substance (31).

Although the precise mechanism for these effects has not yet been fully elucidated, probiotics may, in the future, constitute a plausible option for better coping with high altitude, for example, as a solution for those who cannot benefit from pharmacologic prophylaxis or as an addition to other approaches. Further research is needed in this field, as probiotics currently do not appear in any official recommendations for high altitude acclimatization.

4.2. Pulse Oximetry, Smart Devices, and Wearables

Peripheral oxygen saturation (SpO2), measured by pulse oximetry, provides useful information about coping with high altitude. For the precise measurement, a medical device compliant with an international standard should be used. Certified pulse oximeters provide accurate

results in the 70-100% range, whereas “low-cost” devices may be precise only within the 90-100% range (32).

With ascent to high altitudes, normal SpO2 values decrease in healthy mountaineers. The response of every organism to hypoxia is different; hence, normal SpO2 is represented as a range rather than a single value, as shown in the table below (33).

Table 3. Estimated Resting Oxygen Saturation in Healthy Persons

Altitude, meters	**SpO_2**
Sea level	> 96%
1500 m	93-97%
2500 m	90-95%
3500 m	82-88%
4500 m	75-85%
5500 m	70-80%

Source: Luks AM, Hackett PH. Medical Conditions and High-Altitude Travel. New England Journal of Medicine. 2022;386(4):364-73.
Notes: Values presented in the table are estimates of expected ranges of peripheral oxygen saturation measured at rest 24 to 48 hours after ascending to a given altitude. Data is derived from a large number of studies analyzed by Luks and Hackett (33).

Over the course of acclimatization, observed SpO_2 values increase. For example, in a group of 39 healthy mountaineers, initial SpO_2 at 4844 m was 82,1 ± 6,0% (mean ± SD), which rose to 86,3 ± 3,3% at the same altitude after 12 days of acclimatization (34).

In several studies, lower resting SpO_2 values measured at altitudes of 3500-4000 m were positively associated with an increased risk of AMS at higher elevations. However, there was substantial overlap in SpO_2 results between the AMS and the no-AMS groups. Hence, peripheral blood saturation should be interpreted in a broader clinical context and not as a standalone value (35).

A couple of measures should be taken to obtain reliable results. Standardized conditions should be met: the examined person should be resting in a seated position, the finger should be kept warm (to prevent vasoconstriction), while sensor movement and ambient light should be

reduced. It is important to consider the device manufacturer's specified maximum operating altitude and minimum temperature. The readings should then be averaged over 2-3 minutes (32).

Despite interindividual variability, finger pulse oximetry gives valuable insights into acclimatization assessment and AMS susceptibility.

Another measurement that could provide insight into AMS predisposition is exercise-induced oxygen desaturation. In one study, a reduction in SpO2 of >14% during maximal cardiopulmonary exercise predicted moderate to severe AMS, with a 74% correct classification rate. This analysis was performed in a group of 39 healthy mountaineers, who performed the exercise after arriving at 4844 m (34).

In addition to fingertip-based medical pulse oximeters, a large number of consumer products, such as smartwatches and wristbands, have been developed. They do not restrict movement and are, in fact, often marketed for use in sports such as mountaineering. Nevertheless, SpO_2 measurements with some of these products in high-altitude conditions have shown poor correlation with medical pulse oximeters or arterial blood gas analysis (36, 37). In fact, in the case of measurements performed at 4559 m, the values provided by one smartwatch were significantly overestimated in comparison to the blood gas analysis. Such a scenario would be particularly unwelcome during an expedition, as it may incorrectly suggest that a mountaineer who may already feel unwell is not at risk (36). In addition, some devices using photoplethysmography rely on green LED light for saturation measurements, which has been found to be less accurate in individuals with darker skin tones, likely due to greater melanin absorption of green light (38).

Peripheral blood saturation is a valuable parameter for coping with high altitude; however, further development of wearable technologies and careful medical attestation are required for the safe application of SpO2-measuring wearable consumer products.

4.3. Erythropoietin and Iron

The rationale for investigating agents targeting iron metabolism stems from the physiological response to high-altitude hypoxia, which induces erythropoietin (EPO) secretion. This, in turn, stimulates erythropoiesis and substantially increases systemic iron requirements.

Under physiological conditions, this demand is met by suppressing hepcidin, thereby facilitating enhanced intestinal iron absorption and mobilization of stored iron to sustain effective red blood cell production (39-41). However, during high-altitude exposure, adequate dietary iron intake may be compromised, particularly due to altitude-associated anorexia (39). Beyond its role in erythropoiesis, iron is a critical modulator of hypoxia-inducible factor activity. Dysregulation of this pathway promotes maladaptive responses, including pulmonary hypertension, pulmonary edema, and lung injury. Experimental data from animal models suggest that these effects may be attenuated through iron supplementation (42).

Iron supplementation in humans has been shown to significantly modulate hypoxic pulmonary vasoconstriction during high-altitude exposure. For instance, intravenous administration of 200 mg iron(III)-hydroxide sucrose was associated with a reduction in pulmonary artery systolic pressure (PASP) of approximately 7 mmHg under conditions of pronounced hypoxia, both in lowlanders and in healthy high-altitude residents at 4300 m (43). Comparable observations were reported by Willie et al. at an altitude of 5000 m (44). Despite these favorable hemodynamic effects, current evidence does not conclusively support a protective role of iron supplementation against AMS when administered prior to ascent. A Cochrane systematic review, incorporating two randomized, double-blinded, placebo-controlled trials, reported a reduction in AMS scores in iron-supplemented groups (administered either orally or intravenously). However, these findings did not reach statistical significance, and the overall certainty of evidence was rated as low (45-47). Furthermore, data from a 2025 study involving 39 participants – 14 of whom received intravenous iron (iron(III)-hydroxide sucrose, 200 mg administered twice over four weeks) – demonstrated no significant differences in AMS incidence or symptom severity compared to placebo, further underscoring the inconsistency of current evidence (48).

Evidence regarding EPO supplementation in the prevention of AMS remains limited and methodologically heterogeneous. An open-label randomized trial involving 39 participants demonstrated that weekly subcutaneous administration of epoetin alfa (10,000 IU for four weeks prior to ascent) was associated with a reduction in AMS incidence at 4130 m from 73.6% to 30% (RR 0.41, 95% CI 0.20–0.84) (48). However, the certainty of this evidence has been assessed as very low (45). In contrast, findings from a more recent randomized controlled trial indicate that

EPO supplementation has no beneficial effect. In this study, epoetin alfa administered at a dose of 50 IU/kg three times weekly for three weeks prior to ascent did not reduce AMS incidence or severity during a 14-day exposure to 3094 m. Notably, recombinant human erythropoietin also attenuated the endogenous erythropoietic response to hypoxia, with no significant difference in haemoglobin mass between the intervention and placebo groups (49).

Taken together, the available data are inconsistent and insufficient to support clinical implementation. Consequently, well-designed studies with larger sample sizes and rigorous methodology are required before definitive recommendations regarding iron and EPO use in AMS prophylaxis can be established (45).

4.4. Xenon

Xenon is a noble gas that has been used in medicine for years as an anesthetic agent and can also be used, among other applications, in radiological imaging. However, this latter use is not widely implemented in routine clinical practice (50-52). Xenon has also been shown to exert neuroprotective effects, offering promise for the development of novel therapies, particularly in the treatment of acquired brain injuries (53).

Recently, xenon inhalation has been promoted as a novel approach for use in pre-acclimatization to high-altitude conditions. The UIAA, in its 2025 position statement, advises against its use due to the lack of robust scientific evidence and the potential risks associated with xenon administration (54).

In a randomized controlled trial conducted in 2016, a 45-minute inhalation of a gas mixture containing 30% xenon increased EPO levels by 34% at 8 hours post-inhalation. Peak EPO levels were observed at 24 hours, reaching approximately 45% above baseline values (55). This effect is likely mediated by xenon-induced activation of hypoxia-inducible factor 1-alpha, which, via downstream effectors, increases EPO levels (56). However, another study did not observe a significant effect of prolonged, regular xenon inhalation on hemoglobin mass, EPO levels, maximal oxygen uptake, or exercise tolerance (57). Furthermore, it has been reported that the use of xenon is associated with an increased risk of adverse effects, including somnolence, euphoria,

elevated blood pressure, nausea, and vomiting (58). It is worth noting that the World Anti-Doping Agency has classified xenon as a prohibited substance in sport (55).

4.5. Pre-acclimatization

Instead of traveling to high-altitude environments, artificial exposure methods enable individuals to undergo intermittent sessions in simulated hypoxic conditions within controlled settings. These approaches can be integrated into everyday routines, providing practical and accessible means of pre-acclimatization. One of the applied methods is intermittent hypoxic exposure, which involves repeated periods of hypoxia interspersed with recovery phases in normoxic or hyperoxic conditions (59). The duration and frequency of exposure, as well as the oxygen concentration and barometric pressure, are variable factors on which numerous different protocols are based.

In one study with 40 healthy volunteers, 20 were exposed to normobaric hypoxia with an oxygen concentration of 12% for 4 hours per day over 4 consecutive days, while the other half served as a control group. Participants were then transferred to 3520 m, where they were observed for the next 7 days. In the experimental group, SpO_2 was significantly higher during the first 6 days (by around 2% during the first 3 days). The prevalence of AMS symptoms was significantly lower in this group during the first 3 days, indicating better acclimatization to altitude (60).

Overall, brief hypoxic exposures (e.g., 15–60 minutes or several short sessions prior to ascent) are unlikely to significantly enhance acclimatization, whereas more prolonged exposure (e.g., over 8 hours per day for more than 7 days) appears to be more beneficial. Hypobaric hypoxia has been shown to be more effective than normobaric hypoxia in promoting pre-acclimatization and reducing the risk of AMS. However, as the most effective strategies for pre-acclimatization and staged ascent have not yet been clearly established, expert panels suggest considering these methods without recommending any specific protocol (21).

One possible option for implementing hypoxia to facilitate acclimatization is the use of the so-called hypoxic tents. It includes sleeping or exercising in special chambers ventilated with a reduced oxygen concentration, obtained by different methods (59). Using hypoxic tents has been

reported to reduce AMS symptoms; however, well-validated, placebo-controlled studies to confirm these results are lacking. Current expert recommendations do not include using hypoxic tents for the prevention of AMS or improving chances of summit success (21).

Nevertheless, results of a recent analysis suggested that accumulating 200 hours of hypoxic exposure, in the form of simulated high-altitude conditions, may reduce the risk of AMS to nearly zero when ascending to altitudes over 3500 m, potentially up to 6000 m (61). In light of these findings, further research and identification of the best protocols using hypoxia are needed. Of note, 24,6% of mountaineers who have attempted to climb summits greater than 6000 m admitted to using hypoxic training systems for sleeping or exercising, as indicated by an anonymous survey (62).

Another approach for facilitating adaptation to high altitude is remote ischemic preconditioning (RIPC). Most commonly, it involves three to four cycles of 5-minute limb ischemia (either arm or leg), achieved by inflating a blood pressure cuff, followed by 5 minutes of reperfusion. In some cases, such cycles are repeated multiple times per day, whereas in others they are performed once daily over longer periods. The extent of the preconditioning effect appears to depend on both the number of cycles and the duration of ischemia and reperfusion. Evidence suggests that ischemic intervals shorter than 5 minutes or exceeding 15 minutes are ineffective, and that repeated stimuli are generally more beneficial than a single exposure. Nevertheless, the optimal sequencing of preconditioning stimuli remains unclear, and there is concern that excessive numbers of cycles could be harmful (63). The protective effects of RIPC are thought to involve activation of nitric oxide synthase, upregulation of antioxidant enzymes, and suppression of proinflammatory cytokines (63).

In a recent study with 250 participants, RIPC was performed once or twice daily for 1 or 4 weeks, and the results were compared with those of the control group. The participants were subsequently flown to an altitude of 3650 m, and their vital signs were analyzed during the next 7 days. The incidence and severity of AMS symptoms were significantly lower in groups subjected to RIPC for 4 weeks, but not in those subjected to RIPC for 1 week. Measured values of SpO_2 were significantly less decreased in one-week twice daily RIPC and in four-week once daily and twice daily RIPC groups in comparison to the control group. The authors concluded that RIPC contributed positively to acclimatization to the high altitude; however, a placebo effect might have

contributed to the perception of AMS symptoms (64). Evidence concerning RIPC remains experimental but shows promise for future research and potential implications for practice.

4.6. Closed-loop Systems

Medical technology that automatically monitors a subject's physiological state, compares it to a target value, and adjusts therapy accordingly is known as a physiological closed-loop system. It requires wearable sensors and smart software, capable of performing real-time assessment and determining the adequate intervention.

Application of this method could improve pre-acclimatization by analyzing the subject's SpO2, heart rate, and other parameters, and determining the optimal concentration of inhaled oxygen and the duration of physical activity. There is a marked interindividual difference in response to hypoxia, and this procedure could give better results than standardized pre-acclimatization protocols (59).

Another potential application of this technology would be in high-altitude conditions, where a multitude of physiological parameters of a mountaineer could be measured and analyzed in real time. Based on that, a health risk could be determined, and, for example, a suitable amount of oxygen could be supplied via a connected, dynamically responsive system (59). For that to take place, the development of high-quality, validated wearable sensors that enable continuous measurement during physical activity is necessary.

4.7. High-altitude Illnesses Prediction Models

Diverse HAI prediction models are being intensively developed and receive particular attention. With emerging machine learning technology, analyzing large amounts of data to yield precise predictive algorithms has become possible. Existing approaches are based on genetic factors, clinical information, and physiological monitoring during exercise in normoxic or hypoxic conditions (65).

One study by Yang et al. used blood samples from 21 healthy subjects exposed to hypoxic conditions present at 5260 m. Ten of these subjects developed severe AMS symptoms. Microarray data from blood samples were analyzed to provide insight into hypoxia-induced gene expression. Using machine learning, 2286 potential risk genes were evaluated, and a severe AMS prediction model was developed. This model is based on 10 genes and has established good predictive accuracy. 5 of the included genes function as upstream elements of microRNA-mediated hypoxia and inflammation pathways, and are therefore potentially useful as biomarkers for severe AMS (66).

Another study analyzed microRNA already circulating in the bloodstream before exposure to hypoxia. After a blood draw, 109 participants were taken to an altitude of 3648 m and observed for 5 days. Based on reported symptoms, they were divided into the AMS and non-AMS groups. A signature of three specific microRNA molecules was then retrospectively found to predict AMS susceptibility with 92.68% sensitivity in the analyzed population (67).

Wang et al., in turn, suggested a novel approach to the evaluation of AMS. Instead of relying solely on the subjective, questionnaire-based Lake Louise Score (LLS), a new tool - the Adaptive Domain of Hypoxia Tolerance - has been developed. This utility combined precise data collected during sleep in hypoxic conditions (such as sleep duration, deep sleep duration and ratio, mean SpO_2 during sleep, mean heart rate, duration and number of body movements, and others) as well as LLS score. In the next step, researchers developed a neural network to extract key data from a large array of analyzed physiological parameters and identify patterns characteristic of strong susceptibility to AMS. This method allowed classification of participants with 85,71% accuracy as having either strong or weak hypoxia tolerance and thus strong AMS susceptibility (68).

HAI prediction models become increasingly accurate. In the near future, we can expect to be able to routinely identify individuals with a particular risk concerning entering high altitude, so as to provide them with adequate preventive measures.

5. Conclusions

As research on human responses to high altitude continues to expand, novel strategies for the prevention and management of high-altitude illnesses are emerging. Established approaches

include appropriate acclimatization, evidence-based pharmacological interventions, supplemental oxygen to counteract reduced partial pressure at altitude, and portable hyperbaric chambers for temporary symptom relief.

Emerging evidence suggests that probiotics may support acclimatization, while pre-exposure hypoxic training under controlled conditions may reduce the risk of developing HAI. In addition, advances in wearable sensor technology and closed-loop systems offer promising opportunities for continuous physiological monitoring, potentially enhancing pre-acclimatization strategies and improving safety during high-altitude exposure. The precision of these systems, however, needs to be further improved in mountainous conditions.

Interventions aimed at increasing hemoglobin levels, such as administration of iron, EPO, or inhaling xenon, do not turn out to be plausible procedures for the prevention of AMS. Further studies are required to clarify the potential role of these substances. Currently, they do not appear in official recommendations.

Finally, the development of predictive models for HAI susceptibility may enable more accurate identification of individuals at increased risk. Such approaches could facilitate personalized counseling and targeted preventive measures prior to high-altitude exposure, thereby reducing the incidence of adverse health outcomes.

Disclosure

Author Contributions

F.K.: writing – rough preparation, conceptualization, project administration, and supervision. M.D.: writing – original draft, investigation, resources. O.S.: writing – original draft, investigation, consistency check. A.W.: review and editing, data curation, formal analysis.

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Use of Generative AI:

During the preparation of this work, the authors used **ChatGPT-5.4, OpenAI,** for the purpose of linguistic corrections and structural editing. The **OpenEvidence** AI search engine was used for browsing articles from the selected databases. After using these services, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.

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