[Primary Care]

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Return to Activity at Altitude After High-Altitude Illness

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Context: Sports and other activities at high altitude are popular, yet they pose the unique risk for high-altitude illness (HAI). Once those who have suffered from a HAI recover, they commonly desire or need to perform the same activity at altitude in the immediate or distant future.

Evidence Acquisition: As based on key text references and peer-reviewed journal articles from a Medline search, this article reviews the pathophysiology and general treatment principles of HAI.

Results: In addition to the type of HAI experienced and the current level of recovery, factors needing consideration in the return-to-play plan include physical activity requirements, flexibility of the activity schedule, and available medical equipment and facilities. Most important, adherence to prudent acclimatization protocols and gradual ascent recommendations (when above 3000 m, no more than 600-m net elevation gain per day, and 1 rest day every 1 to 2 ascent days) is powerful in its preventive value and thus strongly recommended. When these are not practical, prophylactic medications (acetazolamide, dexamethasone, salmeterol, nifedipine, or phosphodiesterase inhibitors, depending on the type of prior HAI) may be prescribed and can reduce the risk of illness. Athletes with HAI should be counseled that physical and mental performance may be adversely affected if activity at altitude continues before recovery is complete and that there is a risk of progression to a more serious HAI.

Conclusion: With a thoughtful plan, most recurrent HAI in athletes can be prevented.

Keywords: altitude illness; athlete; activity

Mountaineering, trekking, downhill skiing, and other sports at high altitude are popular throughout the world. Participants often travel to remote parts of the globe to reach new heights, to enjoy nature, and to challenge the limits of endurance. Although these activities can be extremely gratifying, there are risks that must be considered. In addition to the typical athletic injuries, these sports are unique in their risk of causing high-altitude illness (HAI).

Although a great deal is known about the diagnosis and treatment of HAI, there is a dearth of literature on how to prudently send an athlete back to altitude sports once he or she has been treated. This article examines the medical literature regarding the pathophysiology, treatment, and prevention of HAI, and it presents reasonable guidelines for returning high-altitude athletes back to activity and competition.

PHYSIOLOGY OF ACCLIMATIZATION TO ALTITUDE

HAI results from the effects of hypobaric hypoxia on the body. As one ascends, atmospheric pressure gradually decreases; therefore, the partial pressure of oxygen declines, which results in decreased arterial pressure of oxygen and arterial oxygen saturation. Although the human body has mechanisms to adapt to hypoxia, illness results if ascent occurs too rapidly. Such illness manifests itself in 3 syndromes: acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE).

Acclimatization is the process of adapting to hypobaric hypoxia, to minimize its effects on the body. This process is most effective if done incrementally as a person gains elevation; however, the rate of acclimatization varies among individuals. Most persons can acclimatize up to approximately 5500 m if

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given sufficient time (weeks to a few months for full effect), and they deacclimatize in the same time frame upon returning to low altitude. Above this altitude, the body is unable to fully compensate, and some illness occurs.

Increased ventilation is the body's first adjustment, as driven by the hypoxic ventilatory response. The resulting tachypnea somewhat increases arterial pressure of oxygen but also results in respiratory alkalosis because of the concomitant drop in arterial carbon dioxide. Individuals vary in the strength of their hypoxic ventilatory response; those with a lower response are at higher risk of HAI. Hypoxia also causes generalized pulmonary arteriolar vasoconstriction, presumably to evenly distribute blood throughout the lungs and maximize oxygen absorption. This vasoconstriction leads to pulmonary artery hypertension, which plays a larger role in the pathophysiology of HAPE than it does in acclimatization.[13] Pulmonary arterioles that are exposed to high pressures begin to remodel by increasing intimal smooth muscle. This process, which occurs over several days, protects the downstream pulmonary capillaries from overperfusion, thereby preventing capillary wall damage and alveolar flooding. This structural change likely explains why HAPE rarely occurs after 3 to 5 days at a particular altitude.[25]

The respiratory alkalosis induced by increased ventilation necessitates bicarbonate excretion by the kidneys to maintain a reasonable blood pH. This excretion causes a fluid diuresis, leading to a small increase in hemoglobin concentration within 2 days after ascent. Hypoxia also stimulates the kidneys to produce erythropoietin, leading to new red blood cell production within 5 days. Over weeks to months, red blood cell mass stabilizes in proportion to the level of hypoxemia, and plasma volume increases, resulting in a 5% to 6% lasting increase in hematocrit and significantly increased total blood volume; it reverses in about the same time frame after descent.

Because of the sigmoidal shape of the oxyhemoglobin dissociation curve (Figure 1), oxygen saturation of arterial blood is maintained up to 3000 m despite the significant decrease in atmospheric partial pressure of oxygen. The respiratory alkalosis described above shifts the curve to the left. Although this may facilitate increased oxygen binding in the lungs, it inhibits release of oxygen to the tissues. This change is offset by increased production of 2,3-diphosphoglycerate in the red blood cells, which shifts the curve back to the right.[17] Only at extreme altitude (>5500 m) has an alkalosis-driven left shift of the curve been shown to predominate.[28]

The cardiovascular response to high altitude begins within hours, with a moderate increase in heart rate, blood pressure, and cardiac output owing to increased sympathetic tone. After about 24 hours, cardiac output decreases because of bicarbonate diuresis (see below), and heart rate gradually decreases to sea-level baseline with acclimatization (except at very high altitude). Cerebral blood flow significantly increases on abrupt ascent to altitude and returns to normal over 3 to 5 days. Overall, cerebral oxygen delivery and energy metabolism are fairly well maintained.[13]

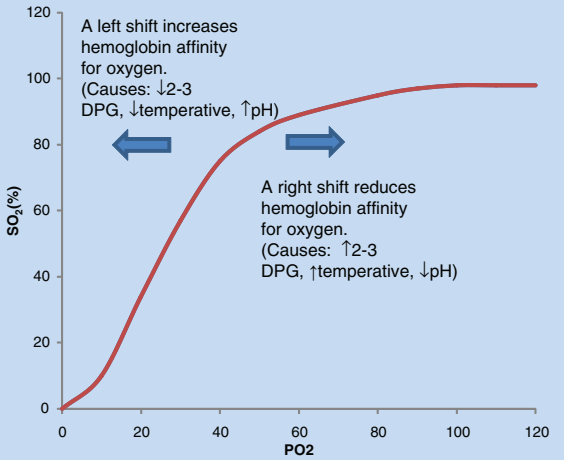

Figure 1. Oxyhemoglobin dissociation curve showing the change in oxygen saturation of hemoglobin (SAO_2) with changes in partial pressure of oxygen (PO_2). 2,3-DPG, 2,3-diphosphoglycerate.

Altitude can have a significant effect on the athletic performance of endurance athletes. When exposed to moderate altitudes, the numerous physiologic responses that occur can compromise performance, lowering maximum aerobic power by as much as 15% to 20%.[31] The optimal training regimen for events at altitude varies, depending on the athlete's altitude of residence and the altitude of the planned event. For aerobic competitions at greater than 2000 m, 10 to 20 days of acclimatization may be necessary. Highly anaerobic activities at intermediate altitudes (1500 to 3500 m) do not require acclimatization; however, symptoms of AMS may become a problem.[17]

For decades, using altitude in training regimens for elite athletes has been of great interest. Although a detailed discussion of this topic is beyond the scope of this article, a few points are worth noting. Approaches to altitude training include 3 basic models: training and living at altitude (live high, train high), living at altitude and training at sea level (live high, train low), and living at sea level and training at altitude (live low, train high). In locations where these models are not geographically feasible, techniques of simulated altitude have been employed, such as hypobaric living environments. "Live high, train high" methods are widely used because of a general consensus among athletes that it improves endurance performance. However, although training for 3 to 8 weeks at altitude does allow acclimatization, empiric performance data are equivocal. The positive results seen in some uncontrolled studies can be explained by a placebo effect.[31] "Live high, train low" methods (usually training in oxygen-enhanced environments to simulate sea-level normoxia) have clear benefit not only in acclimatization but also in enhancing exercise performance at altitude and sea level.[37] "Live low,

train high" methods (involving intermittent hypoxic exposures with or without exercise training) have been shown to be effective in preacclimatization in athletes before ascending to high altitude, but the effect on performance has shown mixed results.[37]

TYPES OF HAI

HAI presents as 3 syndromes: AMS, HACE, and HAPE. AMS and HACE are generally considered different manifestations along a spectrum of progressive cerebral pathology. HAPE, however, has a unique pathophysiology that can occur in isolation or in conjunction with AMS or HACE.

Acute Mountain Sickness

The Lake Louise Consensus on the Definition and Quantification of Altitude Illness defined AMS as a high-altitude-related headache plus one or more of the following symptoms: anorexia, nausea, or vomiting; fatigue or weakness; dizziness or lightheadedness; or difficulty sleeping.[15] AMS is by far the most common form of HAI. It can occur at any altitude above 1500 m, but it most typically occurs with rapid ascent above 2500 m.[17] Symptoms can manifest as early as 1 hour after ascent, but they more commonly begin after 6 to 10 hours.[13] AMS severity is classified as *mild* or *moderate to severe* (based on severity of the above symptoms), although severe AMS is generally regarded as HACE.

The effect of AMS on the body ranges from an annoyance to a temporarily incapacitating condition, and recovery can range from a few days to many weeks, depending on severity and treatment. A report of 840 Indian soldiers with incapacitating but untreated AMS at 5486 m described that 37% recovered within 3 days, 21% in 4 to 7 days, and 13% by 14 days. The remaining 37% took 15 to 150 days to recover.[34] Although most persons with mild AMS are able to participate in their high-altitude activity, they may not function at their highest levels. Talbot et al documented a lower rate of race completion among those treated for HAI in a 238-mile race at high altitude.[35]

AMS is considered a cerebral form of HAI, given that neurological dysfunction is often a part of this syndrome. Neuropsychological tests in patients with AMS have detected subtle to overt deficits in memory storage and recall, speech, concentration, and finger-tapping speed.[19] Deficits in memory, reaction time, and concentration can last up to 75 days after single exposures to 5000 m.[5] Many victims of AMS, despite having normal neurological exams, develop reversible brain lesions on magnetic resonance imaging (MRI), including edema of the globus pallidus,[20] cortical atrophy, and periventricular hyperintensity.[14]

High-Altitude Cerebral Edema

The main risk of untreated AMS is its potential to progress to HACE. The suspected pathophysiology of HACE is cerebral edema due to hypoxia-induced cerebral overperfusion and increased expression of vascular leakage mediators. Whether AMS is also due to cerebral edema or vasodilatation alone is not known.[13] All brains swell to some degree at altitude, but there is no definitive correlation of this swelling to AMS or HACE.[26] MRI is usually abnormal in patients with HACE, demonstrating increased signal in the white matter, particularly in the splenium of the corpus callosum.[18]

When HACE occurs, it progresses in severity over 24 to 36 hours. HACE can occur at altitudes above 2000 m, but it most commonly occurs with abrupt ascent beyond 3000 m. In addition to AMS symptoms, altered level of consciousness and ataxia are the distinguishing features of this syndrome. Papilledema and urinary retention or incontinence occur in half of HACE victims, whereas a third have abnormal plantar reflexes. Less commonly noted findings include abducens nerve palsy, pupil differences, visual field loss, speech difficulty, hearing loss, and flapping tremor. If untreated, HACE can progress to coma and death from brain herniation secondary to cerebral edema.[16]

High-Altitude Pulmonary Edema

HAPE is an uncommon form of HAI, but it accounts for most deaths attributable to these illnesses. In surveillance of Himalayan expeditions, the fatality rate is reported to be about 50% in untreated cases.[22] The pathophysiology of HAPE begins with hypobaric hypoxia, which causes elevated pulmonary artery pressure, leading to regional overperfusion and hydrostatic damage to small pulmonary arterioles. These changes eventually cause alveolar edema and hemorrhage.[21]

HAPE can occur as low as 1400 m but is most common above 2500 m.[12] It is defined by at least 2 symptoms (dyspnea at rest, cough, weakness or decreased exertional performance, chest tightness or congestion) and at least 2 signs (crackles or wheezing, central cyanosis, tachypnea, or tachycardia).[15] Chest radiographs usually reveal findings consistent with noncardiogenic pulmonary edema: unilateral or bilateral fluffy infiltrates with normal heart size.[17] Signs and symptoms of AMS usually precede the onset of HAPE. The incidence of HACE increases in patients with HAPE; therefore, rather than just attribute such changes to severe hypoxia, HACE must be considered in all HAPE patients with mental status changes.[16] Owing to acclimatization changes within the lungs, HACE rarely occurs after 3 to 5 days at a particular altitude.[16]

RISK FACTORS FOR HAI

The main risk factors for all types of HAI include increased altitude and rapid ascent rate. As the altitude and ascent rate increase, hypoxic stress may overpower the body's ability to adapt. AMS occurs in about 20% to 25% of tourists who visit 2500 m and in about 40% to 50% of trekkers near 4000 m. More than 90% of trekkers experience AMS if they ascend to 4000 m over several hours, as opposed to days. The incidence of HACE in tourists is about 0.01% at 2500 m and 1% to 2% in

mountaineers at 4000 m. The incidence of HAPE in climbers is between 2% and 6% at 4000 m but more than 15% at 5500 m.[13]

Prior history of HAI is a strong predictor of future HAI. If a person is exposed to the same acclimatization regimen (or lack thereof), the same altitude, and the same ascent rate at which HAI previously occurred, HAI will likely recur.[34] The approximate rate of recurrence for HAPE has been documented at 60% in the absence of preventive measures.[1]

AMS and HACE seem to affect men and women equally, although men appear to be more susceptible to HAPE.[17] HAI is less common in persons older than 50 years, whereas HAPE is more common and more severe in children and young adults.[13] Physical fitness is not protective against HAI. Furthermore, physical exertion at altitude can increase the incidence and/or severity of HAI, presumably because it worsens tissue hypoxia.[13] Medications and drugs that reduce ventilatory drive or alter sleep patterns, such as alcohol, benzodiazepines, and other sedatives/hypnotics, may exacerbate progression to HAI and should thus be used with caution.[13]

Cold air creates additional physiologic stress and elevates pulmonary arterial pressures; therefore, it is a risk factor for HAPE.[13] Genetic factors are believed to provide a predisposition to HAPE.[17] Such factors include increased sympathetic activity, decreased endogenous nitric oxide production, and defects in the transepithelial fluid transport mechanism in alveolar cells.[17]

Factors that appear to be protective of HAI include residence at more than 900 m and slow ascent.[17] Slow ascent, generally regarded as 600 m per day, is thought to allow sufficient time for acclimatization to occur, but it is not absolutely protective. Extremes in altitude combined with individual susceptibility may still lead to HAI.[17]

TREATING HAI

Treatment for HAI depends on the particular syndrome that occurs, the severity, and the availability of treatment modalities (see Tables 1 and 2). In general, minimum treatment should include rest and halt of ascent. Rest prevents increases in hypoxia and permits more time for acclimatization. It may be the only treatment needed for mild AMS. Descent to a lower altitude increases tissue oxygenation and should be done for moderate to severe AMS, HAPE, or HACE. Keeping patients with HAPE warm is also important to minimize the pulmonary artery hypertension associated with hypothermia.

In mild to moderate AMS, oxygen can be used as a substitute for or in addition to descent. A few hours of oxygen therapy may be sufficient to alleviate symptoms. Oxygen should be used with descent in all patients with HAPE or HACE. Unfortunately, oxygen equipment is cumbersome and may be available only at base camps or medical facilities.

If available, commercially made, portable hyperbaric treatment bags provide an alternative to descent. AMS may respond quickly to hyperbaric therapy, but HAPE and HACE will require prolonged treatment.

Medications can be useful in the prevention and treatment of AMS. Care should be taken, however—these may be banned substances. For example, acetazolamide and oral glucorticosteroids are both on the banned substance list for the World Anti-Doping Agency and the US Anti-Doping Agency. As of January 1, 2010, salmeterol requires a declaration of use. Consultation with the World Anti-Doping Agency (www.wada-ama.org) and/or the US Anti-Doping Agency (www.usada.org) is recommended before prescribing medication to athletes. In addition, there are little data on the effects of these medications on performance in general or at altitude. Studies have shown varying effects—positive, negative, and neutral—depending on the medications and conditions under which the testing occurred.[6,7,11]

Acetazolamide, a carbonic anhydrase inhibitor, can greatly assist acclimatization. It centrally acts to stimulate the hypoxic ventilatory response, reducing pulmonary artery hypertension and maintaining oxygenation during sleep. It stimulates the kidneys to excrete bicarbonate, allowing further respiratory acclimatization. It also decreases cerebral spinal fluid production and thereby mitigates increases in cerebral spinal fluid pressure. Although the optimal dose is continually debated, numerous studies have shown acetazolamide to be effective in preventing AMS in persons who are rapidly taken to altitudes of 3000 to 4500 m.[13,17] In addition to its prophylactic value, acetazolamide is useful for treatment of AMS. It may be used to treat HACE but only in conjunction with corticosteroids. Recent studies have suggested that acetazolamide attenuates pulmonary vascular responses to hypoxemia and decreases pulmonary vascular resistance. These findings suggest that acetazolamide may be effective in the prevention and treatment of HAPE, but further studies are necessary before considering it a substitute for known therapies.[33]

Dexamethasone is the most commonly used and most widely studied steroid for treating HAI. Its mechanism of action is unknown, but it may act in the brain by decreasing blood volume or blocking capillary leakage. Although it has no effect on acclimatization, it is beneficial for the prevention and treatment of AMS and HACE.[23] Because dexamethasone does not enhance acclimatization, rebound symptoms of AMS or HACE are possible after discontinuation, so caution is advised when withdrawing treatment. There is limited evidence that dexamethasone may play a role in the prevention of HAPE, but further studies are necessary before recommending its use.[24]

Nifedipine, the most studied pharmacologic treatment for HAPE, is proven to be beneficial in the prevention and treatment of HAPE.[4,27] Nifedipine acts on the pulmonary smooth muscles, reducing pulmonary artery pressure. It is not necessary in most cases, however, because descent and oxygen are highly effective.

Salmeterol, a long-acting inhaled β-agonist, appears to be effective for the prevention of HAPE. It acts by increasing clearance of alveolar fluid via stimulation of the alveolar

Table 1. Medical therapies for high-altitude illness.[a]

Indication	Medications[b]	Route	Preventive Dose	Treatment Dose
AMS	Acetazolamide	Orally	125-250 mg twice a day	250 mg twice a day
	Dexamethasone	Orally, intramuscularly, intravenously	2 mg every 6 hr or 4 mg every 12 hr[c]	4 mg every 6 hr
HACE	Dexamethasone	Orally, intramuscularly, intravenously	2 mg every 6 hr or 4 mg every 12 hr[c]	8 mg immediately, then 4 mg every 6 hr
HAPE	Nifedipine	Orally	20-30 mg sustained release every 12 hr	10 mg quick release, then 20-30 mg sustained release every 12 hr
	Salmeterol	Inhalation	125 μg every 8 hr	Unknown
	Sildenafil	Orally	50 mg every 8 hr	Unknown
	Tadalafil	Orally	10 mg twice a day	Unknown
	Adjunctive Therapies[d]			
Any HAI	Oxygen	Cannula or mask	—	Initially 2-4 L/min, titrate arterial oxygen saturation >90%
	Portable hyperbaric chamber	Full-body immersion	—	Varies by model, 2-4 psi for at least 2 hr
	Descent	—	—	Minimum 500 m for moderate AMS, 500-1000 m for HAPE, 1000 m for HACE

[a]AMS, acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema; HAI, high-altitude illness. Dash (—) indicates *not applicable*.
[b]Preventive doses begin 1 day before ascent and continue until 2 days at maximum altitude. Treatment doses begin at onset of symptoms. Discontinue with caution. Check banned substance list for athletes who fall under World Anti-Doping Agency or US Anti-Doping Agency jurisdiction.
[c]Initial studies were performed on sedentary individuals. For those exercising at altitudes at or above 4000 m, treatment doses may be necessary to prevent HAI.[8]
[d]Begin adjunctive therapies at onset of symptoms. Discontinue with caution.

transepithelial sodium transport mechanism.[30] In a study of 37 patients with a prior history of HAPE, administration of salmeterol reduced its incidence from 74% to 33%.[29] These results have not been validated in follow-up studies. Salmeterol is typically used as an adjunct to nifedipine as prophylaxis; however, there are reports that it has been used as treatment. This has not yet been formally investigated in clinical trials.[23] Albuterol has anecdotal evidence of effectiveness in treating HAPE but has not yet been studied.[13]

Because of their pulmonary vasodilatory effects, the phosphodiesterase inhibitors tadalafil and sildenafil may be useful in the prevention of HAPE. Maggiorini et al[24] compared dexamethasone, tadalafil, and placebo in 29 adults with previous HAPE during ascension to 4559 m. HAPE developed in 7 of 9 participants receiving placebo, 1 of the 8 receiving tadalafil, and none of the 10 receiving dexamethasone. Sildenafil has been shown to improve exercise performance at altitude,[33] and tadalafil failed to improve exercise performance in one study,[10] but neither agent has been formally evaluated in the treatment of HAPE.

RETURN-TO-ALTITUDE PLANNING FOR ATHLETES AFTER HAI

There are 2 categories of return-to-altitude planning for a person with a history of HAI: The first involves the athlete with a remote history of HAI; the second involves the athlete who is currently experiencing or has just recovered from a HAI but wants to or must resume his or her high-altitude activity. In either case, the physician and the athlete must formulate

Table 2. Mechanisms of action, side effects, and contraindications to common medical therapies for high-altitude illness.[8,13,23]

Medication	Mechanism of Action	Common Side Effects	Contraindications
Acetazolamide	Carbonic anhydrase inhibitor. Causes bicarbonate diuresis, stimulates respiration (increased arterial pressure of oxygen), decreases cerebral spinal fluid formation, and may increase ion transport through the blood-brain barrier.	Weight loss, diarrhea, anorexia, nausea, vomiting, altered taste, confusion, paresthesias, somnolence, depression, polyuria	Severe hepatic or renal insufficiency, hyponatremia, hypokalemia, adrenal gland failure, noncongestive angle-closure glaucoma, metabolic acidosis. *Avoid use:* concomitant long-term high-dose aspirin therapy, sulfonamide allergies, pulmonary obstruction, emphysema, concurrent use of topiramate, potassium-wasting diuretics, ophthalmic carbonic anhydrase inhibitors
Dexamethasone	Unknown. May decrease brain blood volume or reduce blood-brain barrier leaks.	Mood changes, hyperglycemia, hypertension, dyspepsia, rebound symptoms upon withdrawal	Known systemic fungal infections. *Avoid use:* peptic ulcer disease or history of upper gastrointestinal bleeding. Reduce adverse events by minimizing duration of use.
Nifedipine	Calcium-channel blocker. Decreases pulmonary artery pressures by decreasing smooth muscle tone.	Hypotension, palpitations, peripheral edema, flushing, constipation, reflux, nausea, dizziness, headache	Use caution in conjunction with other antihypertensive medications and in individuals with recent myocardial infarction, aortic stenosis, congestive heart failure, hepatic or renal insufficiency, hypotension, or unstable angina.
Salmeterol	Beta-agonist. Increases clearance of alveolar fluid by upregulating transepithelial sodium transport.	Tachyarrhythmia, dizziness, headache, tremor, throat irritation	Caution in those with cardiovascular disorders (arrhythmias, hypertension, coronary insufficiency), laryngeal spasms, or milk allergies
Sildenafil	Phosphodiesterase inhibitor. Causes pulmonary vasodilatation by relaxation of pulmonary vascular smooth musculature	Flushing, rash, headache, dizziness, congestion	Contraindicated with use of nitrates. Caution with use of alpha-blockers, hepatic or renal insufficiency, cardiovascular disease, bleeding disorders, and retinal abnormalities.
Tadalafil	Phosphodiesterase inhibitor. Causes pulmonary vasodilatation by relaxation of pulmonary vascular smooth musculature	Reflux, nausea, flushing, myalgias, backache, headache, upper respiratory infection	Contraindicated with use of nitrates. Caution with use of alpha-blockers, recent stroke, sickle cell anemia, multiple myeloma, leukemia, or severe renal impairment. Dose adjustments with renal or hepatic insufficiency and concurrent use of CYP3A4-inhibiting medications.

a plan. Consideration should be given to the severity of the athlete's HAI, the future ascent and activity requirements, the flexibility of the itinerary, and the availability of medical treatment.[3]

Athletes With Remote History of HAI

In the athlete with a remote history of HAI and a full recovery, attention must be given to proper acclimatization protocols and

Table 3. Graded ascent and acclimatization recommendations.

Avoid abrupt ascents beyond 3000 m.
Spend 2 to 3 nights at 2500-3000 m before ascending further.
Above 3000 m, allow 1 additional night of acclimatization every 600-900 m at each new altitude.
Limit increases in sleeping altitudes to 600 m each day once above 2500 m.
Preexposure to 5 or more days above 3000 m in the 2 months before ascent may enhance acclimatization rate.

graded ascent, if possible. Such precautions are effective in the prevention of HAI[17,32] (see Table 3).

Schneider et al[32] performed a prospective study on the influence of prior HAI history, altitude preexposure, and ascent rate on the incidence of AMS during ascent to 4559 m. Participants were not allowed to use prophylactic medications. The researchers found that in persons with a prior history of AMS, preexposure to 5 or more days (not necessarily consecutive) above 3000 m during the prior 2 months reduced the incidence of AMS from 58% to 29%. Recurrence of AMS was only 33% in those who limited ascent to less than 640 m per day once above 2000 m. In those who had a history of preexposure to altitude and slow ascent, the incidence was only 7%. Bärtsch[2] reported 2 climbers with prior histories of 2 to 4 episodes of HAPE who successfully undertook a collective 3 ascents to 6000 to 7000 m by ascending only 330 to 350 m per day net sleeping altitude. None of them developed HAPE. These studies illustrate the preventive power of acclimatization and slow ascent even after a severe form of HAI.

If an athlete has no recent exposure to high altitude or is unable to comply with graded ascent recommendations, use of prophylactic medication may be prudent. Again, caution should be used in athletes who fall under World Anti-Doping Agency or US Anti-Doping Agency jurisdiction. For those with a history of AMS, acetazolamide should be adequate. For those who cannot tolerate acetazolamide, dexamethasone may be used in its place. Although there are no evidence-based recommendations regarding the combination of these medications, dexamethasone can be used as treatment for AMS symptoms that occur despite acetazolamide prophylaxis.[17]

Those with prior HACE or HAPE should strongly consider adherence to acclimatization and graded ascent recommendations, given the seriousness of the illness and the high risk of recurrence. If medical care will not be readily available, if descent will not be practical, or if ascent will be faster than recommended, strong consideration should be given to pharmacologic prophylaxis. For those with prior HACE, the prophylaxis regimen is identical to that of AMS.[13] Prophylaxis for HAPE could include nifedipine, salmeterol, or tadalafil. Nifedipine is the most studied of these agents; however, no studies have shown clear superiority of one agent over the other. Dexamethasone and acetazolamide may have benefit in the prevention of HAPE; however, further studies are necessary before their use is recommended over that of established agents. The usefulness and safety of combination treatments is unknown.

Immediate Return to Activity After a Recent HAI

When considering return to activity at altitude for those with a current or recent HAI, one must make several considerations in addition to those described above. The first is the safety of continued activity at altitude and what activity should be allowed. The second is how long the athlete's symptoms take to resolve and how soon physical and mental functions normalize. Theoretically, a person could experience a worse episode of HAI on altitude reexposure before complete recovery.

Mild AMS is usually a self-limiting illness. Anecdotal evidence supports the acceptability of treating the athlete in place without descent. However, physical and/or mental functioning may be impaired, thereby leading to performance decrements and possibly placing the athlete at a greater risk for injury. These risks need to be weighed against the disadvantages of treatment (mainly, time lost). Talbot et al[35] documented the incidence of AMS in a 10-day 238-mile race at high altitude in which no prophylaxis was allowed. Those who sought treatment were allowed oxygen, analgesics, or descent. Eleven cases of mild AMS were identified by questionnaire before the race began, but none of the participants sought treatment. Of those 11, only 64% completed the race, compared to the overall race completion rate of 74%. Thirty-three other cases of AMS were treated during the race. Although 88% returned to the competition, only 58% finished.

Ideally, the athlete with mild AMS should rest at altitude until asymptomatic and avoid excessive exertion. Pharmacologic treatment can be considered. Options include symptom-based treatments, such as acetaminophen or nonsteroidal anti-inflammatory drugs for headache and antiemetics for nausea. Initiation of HAI medications may also be considered. Acetazolamide may expedite acclimatization, whereas acetazolamide and dexamethasone can both help to control symptoms and prevent progression of illness. If available, oxygen therapy and portable hyperbaric chambers can effectively eliminate symptoms—and quickly, often in a matter of hours. Most athletes are able to continue with their activities.

If an athlete is unable to remain at a fixed altitude for acclimatization, prophylaxis should be instituted before further ascent. In situations where prophylaxis and rest are not possible, athletes should be counseled about the risk of prolonged or worsening AMS symptoms. They should be further counseled on the risk of progression to HACE and/or the development of HAPE.

Moderate AMS presents as protracted or worsening headache, nausea, vomiting, dizziness, anorexia, and/or fatigue, and it can be quite disabling. Treatment options are identical to those of mild AMS; however, the athlete will likely require a longer duration (1 to 2 days) of resting at altitude. If such interventions are not effective or available, descent greater than 500 m should be considered. Strong consideration should be given to the use of dexamethasone and/or acetazolamide.[13] Affected athletes should not be allowed to proceed untreated. Once the symptoms of moderate AMS are gone, there still may be subtle neuropsychological deficits that will persist until weeks after return to low altitude. The athlete should understand the possible effects of these deficits not only on the current activity but on functioning when back at home.

The data from Schneider et al[32] can be extrapolated for those who have been treated for recent AMS. Provided that the athlete is at an altitude of least 3000 m and has been at that altitude for at least 5 days before resuming ascent, the risk of recurrent AMS may be low if he or she follows ascent rate recommendations. If this is not possible, prophylactic medication may be prudent.

Higher altitude, greater severity of illness, continued ascent, and a history of severe HAI imply a greater risk of experiencing HACE and/or HAPE. These factors should further prompt strong consideration of the use of prophylaxis medications. Further ascent should be limited to a 600-m net gain per day, and a rest day should be allowed every 600 to 1200 m to allow continued acclimatization. Mountaineers should be cautioned that even these measures cannot prevent all cases of HAI. Further illness should be recognized quickly and treated aggressively.

HACE is generally regarded as severe AMS, often presenting with classic findings of ataxia and/or mental status changes. When HACE occurs, activity should cease, and immediate aggressive therapy should be commenced. Treatment involves immediate descent, oxygen supplementation, and dexamethasone. Hyperbaric treatment can be used if descent is not possible.

Once the patient is in a hospital, a chest radiograph should be performed to rule out HAPE, which often occurs concurrently. Brain MRI should be considered if alternate causes of mental status changes are possible. If coma ensues, treatment involves airway management and bladder drainage. Attempts to decrease intracranial pressure with diuretics and/or controlled hyperventilation should only be done cautiously, if at all, because maintenance of adequate intravascular volume and perfusion pressures are critical.[16] Hospital discharge criteria for athletes with HACE include normal level of consciousness and oxygen saturation on room air, grossly normal neurological examination (or at least stable if persistent deficits are present) and control of seizures if present. The time for recovery from HACE varies considerably. There is not a strong correlation between recovery time and the severity of illness at presentation. One case series documented a range of 1 day to 12 weeks for symptoms and neuropsychological function to normalize and 1 day to 5 weeks for MRI findings to resolve.[38] Nineteen cases in another series took up to 3 days for symptoms to resolve, but resolution of papilledema required 3 to 4 weeks.[34]

Given the variability of recovery times and the known risk for recurrence of severe HAI, return to altitude should be done cautiously. Full recovery before reascent is prudent. Attention to careful acclimatization, slow ascent, rest days, and pharmacologic prophylaxis should be considered. Preexposure to altitude in the months before activity may provide additional protection. Some climbers are even using dexamethasone on summit day for HACE prevention, although this has no proof of efficacy.

HAPE is a medical emergency. As with HACE, activity should be suspended, and aggressive treatment should begin immediately. Treatment should begin with immediate descent because this provides the quickest recovery. The athlete should be provided warmth, rest, and oxygen supplementation—maintaining an arterial oxygen saturation of at least 90%. Portable hyperbaric therapy may be lifesaving if descent and oxygen are not immediately available. Nifedipine and salmeterol may be useful adjuncts to treatment; however, nifedipine should be avoided in patients with concomitant HACE, given that it can excessively lower blood pressure. If arterial oxygen saturation remains at least 90% on 2 to 4 L per minute of oxygen, athletes can be observed for several hours and discharged with outpatient low-flow oxygen. Arterial oxygen saturation should be checked at least every day, and oxygen can be discontinued once saturation is maintained above 90% on room air. In athletes with concomitant HACE, with oxygen requirements greater than 4 L per minute, with comorbid cardiopulmonary conditions, or at extremes of age, admission to a hospital should be considered. Dexamethasone should be used only in patients with concomitant HACE because it does not have proven efficacy for HAPE.[13]

The physician should counsel the athlete to resume normal activities gradually and only after oxygen saturation is normal on room air. Athletes may require up to 2 weeks to regain complete strength and stamina.[17] Those who are treated at some degree of altitude probably benefit from the remodeling of pulmonary arterioles, which is part of acclimatization. They may be able to cautiously resume activity at altitude earlier than others.

There is some limited evidence that patients with recent HAPE may cautiously return to altitude immediately after treatment. One small case series described 3 mountaineers who developed HAPE and were treated at moderate altitude for 2 to 4 days before returning to their expeditions. With no medical prophylaxis but with a slow ascent (less than 600 m per day) and several rest days, they all reached their summits without any symptoms of HAI. One even reached the summit of Mount Everest at 8850 m.[21] In these instances, however, prophylaxis with nifedipine or salmeterol may have been advisable.[9]

Clinical Recommendations

SORT: Strength of Recommendation Taxonomy
A: consistent, good-quality patient-oriented evidence
B: inconsistent or limited-quality patient-oriented evidence
C: consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Clinical Recommendation	SORT Evidence Rating
Following graded ascent and rest recommendations, especially when combined with preexposure to altitudes before activity, can prevent most recurrent high-altitude illnesses.[32]	A
Descent is the most effective immediate treatment for an individual experiencing symptoms of high-altitude illness.[17]	C
When available, portable hyperbaric bags and oxygen can provide a substitute for descent when treating high-altitude illness.[17]	C
Mild AMS can be treated at altitude without discontinuing participation.[35]	C
Moderate AMS can be treated and returned to competition, but return to participation should not continue without some form of treatment for high-altitude illness.[17]	C
Severe high-altitude illness (high-altitude cerebral edema, high-altitude pulmonary edema) should result in immediate cessation of activity and descent.[16,17,21,38]	C
Return to activity after severe high-altitude illness should not occur until symptoms have completely resolved.[9,13,21,34,38]	C

For more information about the SORT evidence rating system, see www.aafp.org/afpsort.xml and Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician.* 2004;69:549-557.

CONCLUSION

HAI is a relatively common occurrence for those who participate in activities at altitude. HAI has an excellent prognosis if treated promptly; however, prevention with graded ascent and time for acclimatization is ideal. Athletes with remote histories of HAI can return to altitude cautiously, with strong consideration for prudent ascent protocols and/or prophylactic medications. Those with a recent HAI may also return to altitude, although full recovery from HACE and HAPE are strongly advised, and prophylaxis may be prudent.

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