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WILDERNESS MEDICAL SOCIETY PRACTICE GUIDELINES

Wilderness Medical Society Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2014 Update

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To provide guidance to clinicians about best practices, the Wilderness Medical Society convened an expert panel to develop evidence-based guidelines for prevention and treatment of acute mountain sickness, high altitude cerebral edema, and high altitude pulmonary edema. These guidelines present the main prophylactic and therapeutic modalities for each disorder and provide recommendations about their role in disease management. Recommendations are graded based on the quality of supporting evidence and balance between the benefits and risks/burdens according to criteria put forth by the American College of Chest Physicians. The guidelines also provide suggested approaches to prevention and management of each disorder that incorporate these recommendations. This is an updated version of the original WMS Consensus Guidelines for the Prevention and Treatment of Acute Altitude Illness published in *Wilderness & Environmental Medicine* 2010;21(2):146–155.

Key Words: high altitude, acute mountain sickness, high altitude pulmonary edema, high altitude cerebral edema, acetazolamide, dexamethasone

Introduction

Travel to elevations above 2500 m is associated with risk of developing one or more forms of acute altitude illness: acute mountain sickness (AMS), high altitude cerebral edema (HACE), and high altitude pulmonary edema (HAPE). Because large numbers of people travel to such elevations, many clinicians are faced with questions from patients about the best means to prevent these disorders. In addition, healthcare providers working at facilities in high altitude regions or as part of expeditions traveling to such areas can expect to see persons who are suffering from these illnesses and must be familiar with prophylactic regimens and proper treatment protocols.

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To provide guidance to clinicians and disseminate knowledge about best practices in this area, the Wilderness Medical Society (WMS) convened an expert panel to develop evidence-based guidelines for prevention and treatment of acute altitude illness. Prophylactic and therapeutic modalities are presented for each disorder and recommendations made about their role in disease management. Recommendations are graded based on the quality of supporting evidence and consideration of benefits and risks/burdens for each modality.

Methods

The expert panel was originally convened at the 2009 Annual Meeting of the WMS in Snowmass, Colorado. Members were selected by the WMS based on their clinical or research experience. Relevant articles were identified through the MEDLINE database using a key

word search using the terms acute mountain sickness, high altitude pulmonary edema, high altitude cerebral edema, treatment, prevention, acetazolamide, dexamethasone, ibuprofen, nifedipine, tadalafil, sildenafil, and salmeterol. Peer-reviewed studies related to prevention and treatment of acute altitude illnesses, including randomized controlled trials, observational studies, and case series, were reviewed, and the level of evidence supporting various prophylaxis and treatment modalities was assessed. Abstract-only studies were not included. Conclusions from review articles were not considered in the formulation of recommendations but are cited as part of efforts to provide background information on the various diseases and their management. The panel used a consensus approach to develop recommendations regarding each modality and graded each recommendation according to criteria stipulated in the American College of Chest Physicians statement on grading recommendations and strength of evidence in clinical guidelines (see online Supplementary Table 1).[1]

Defining the Threshold for High Altitude and Where to Apply These Guidelines

There is a risk of high altitude illness when unacclimatized individuals ascend to more than 2500 m. Prior studies and extensive clinical experience, however, suggest that susceptible individuals can develop AMS, and potentially HAPE, at elevations as low as 2000 m.[2–4] Part of the difficulty of defining a specific threshold at which altitude illness can develop is the fact that the symptoms and signs of AMS, the most common form of altitude illness, are highly nonspecific, as demonstrated in several studies in which subjects met criteria for the diagnosis of AMS despite no gain in altitude.[5–7] As a result, studies assessing AMS incidence at modest elevations may label individuals as having altitude illness when, in fact, symptoms are related to some other process, thereby falsely elevating the incidence of the disease at that elevation.

Recognizing the difficulty in defining a clear threshold, the expert panel recommends an approach to preventing and treating acute altitude illness that does not depend strictly on the altitude to which an individual is traveling. Altitude illness is more common above 2500 m but can be seen at lower elevations. As a result, preventive measures should be considered not only based on the altitude to which the individual is traveling but should also take into account factors such as the prior history of performance at high altitude, rate of ascent, and availability of rest days for acclimatization (described in greater detail below). Similarly, the diagnoses of AMS, HAPE, or HACE should not be excluded simply based on the fact that an individual is ill below 2500 m. They should be strongly considered in the presence of compatible clinical features with careful attempts to exclude other entities such as severe dehydration, hyponatremia, pneumonia, or hypoglycemia, which may present in a similar manner.

Acute Mountain Sickness and High Altitude Cerebral Edema

Information on the epidemiology, clinical presentation, and pathophysiology of AMS and HACE is provided in several extensive reviews.[8–11] From a clinical standpoint, HACE represents an extreme form of AMS and, as a result, preventive and treatment measures for the 2 disorders can be addressed simultaneously.

PREVENTION

Prophylactic measures for AMS and HACE, the evidence supporting them, and their recommendation grades are described below. Further information about how to apply these measures is then provided as part of a suggested approach to prevention.

Gradual ascent

Controlling the rate of ascent, in terms of the number of meters gained per day, is a highly effective means of preventing acute altitude illness; however, aside from 2 recent prospective studies,[12,13] this strategy has largely been evaluated retrospectively.[14] In planning the rate of ascent, the altitude at which someone sleeps is considered more important than the altitude reached during waking hours. Recommendation Grade: 1B.

Acetazolamide

Multiple trials have established a role for acetazolamide in prevention of AMS.[15–18] The recommended adult dose for prophylaxis is 125 mg twice daily (Table 1). Although doses up to 750 mg daily are effective at preventing AMS compared with placebo, they are associated with more frequent or increased side effects, do not convey greater efficacy, and, therefore, are not recommended for prevention. Recommendation Grade: 1A. The pediatric dose of acetazolamide is 2.5 mg/kg/dose (maximum 125 mg/dose) every 12 hours.[19] Recommendation Grade: 1C.

Dexamethasone

Prospective trials have established a benefit for dexamethasone in AMS prevention.[20,21] The recommended adult doses are 2 mg every 6 hours or 4 mg every 12 hours. Very high doses (4 mg every 6 hours) may be considered in very high-risk situations such as military or search and rescue

Table 1. Recommended dosages for medications used in the prevention and treatment of altitude illness

Medication	*Indication*	*Route*	*Dosage*
Acetazolamide	AMS, HACE Prevention	Oral	125 mg twice a day Pediatrics: 2.5 mg/kg every 12 hours
	AMS Treatment[a]	Oral	250 mg twice a day Pediatrics: 2.5 mg/kg every 12 hours
Dexamethasone	AMS, HACE Prevention	Oral	2 mg every 6 hours or 4 mg every 12 hours Pediatrics: Should not be used for prophylaxis
	AMS, HACE Treatment	Oral, IV, IM	AMS: 4 mg every 6 hours HACE: 8 mg once then 4 mg every 6 hours Pediatrics: 0.15 mg/kg/dose every 6 hours
Nifedipine	HAPE Prevention	Oral	30 mg ER version every 12 hours
	HAPE Treatment	Oral	30 mg ER version every 12 hours
Tadalafil	HAPE Prevention	Oral	10 mg twice a day
Sildenafil	HAPE Prevention	Oral	50 mg every 8 hours
Salmeterol	HAPE Prevention	Inhaled	125 μg twice a day[b]

AMS, acute mountain sickness; ER, extended release; HACE, high altitude cerebral edema; HAPE, high altitude pulmonary edema.

[a] Acetazolamide can also be used at this dose as an *adjunct* to dexamethasone in HACE treatment, but dexamethasone remains the primary treatment for that disorder.

[b] Should not be used as monotherapy and should only be used in conjunction with oral medications.

personnel being airlifted to altitudes greater than 3500 m with immediate performance of physical activity but should not be used outside these limited circumstances. The duration of use should not exceed 10 days to prevent glucocorticoid toxicity or adrenal suppression. Recommendation Grade: 1A. Dexamethasone should not be used for prophylaxis in the pediatric population because of the potential for side effects unique to this population and the availability of other safe alternatives—specifically graded ascent and acetazolamide.

Ginkgo biloba

Although several trials have demonstrated a benefit of ginkgo in AMS prevention,[22,23] several negative trials have also been published.[24,25] This discrepancy may result from differences in the source and composition of the ginkgo products.[26] Acetazolamide is considered far superior prophylaxis for AMS prevention. Recommendation Grade: 2C.

Ibuprofen

Two trials have demonstrated that ibuprofen (600 mg 3 times a day) is more effective than placebo at preventing AMS[27,28]; however, these trials did not include a comparison with acetazolamide. That comparison has been made in only a single other trial, which found equal incidence of high altitude headache and AMS between the 2 groups.[29] No studies have compared ibuprofen with dexamethasone. Clinical experience with ibuprofen to prevent AMS is not extensively documented, so at this time ibuprofen cannot be recommended over acetazolamide and dexamethasone for AMS prevention. Recommendation Grade: 2B.

Preacclimatization and staged ascent

Several studies have shown that repeated exposure to hypobaric or normobaric hypoxia in the time preceding a high altitude excursion (referred to as preacclimatization) or spending up to 6 to 7 days at a moderate altitude (approximately 2200–3000 m) before proceeding to higher altitudes (referred to as staged ascent) decreases the risk of AMS, improves ventilation and oxygenation, and blunts the pulmonary artery pressure response after subsequent ascent to higher altitudes.[30–32] Implementation of such strategies may be logistically difficult. Because the optimal methods for preacclimatization and staged ascent have not been fully determined, the panel recommends consideration of these approaches, but cannot endorse a particular protocol regarding their implementation. In general, short-term exposures (eg, 15–60 minutes of exposure to hypoxia, or a few hours of hypoxia a few times before ascent) are unlikely to be of use, whereas longer exposures (eg, >8 h/d for >7 days) are more likely to yield benefit. Recommendation Grade: 1C.

Other options

Chewed coca leaves, coca tea, and other coca-derived products are commonly recommended for travelers in the Andes for prophylaxis, and anecdotal reports suggest they are now being used by trekkers in Asia and Africa for similar purposes. Their utility in prevention of

altitude illness has never been studied, however, and they should not be substituted for other established preventive measures described in these guidelines. Multiple studies have sought to determine whether other agents, including antioxidants, leukotriene receptor blockers, phosphodiesterase inhibitors, salicylic acid, spironolactone, and sumatriptan, can prevent AMS, but the current state of evidence does not support a role in AMS prevention for any of these agents. "Forced" or overhydration has also never been shown to prevent altitude illness and may even increase the risk of hyponatremia; however, maintenance of adequate hydration is important because symptoms of dehydration can mimic those of AMS.

Suggested approach to AMS/HACE prevention

Because the physiologic responses to high altitude and rates of acclimatization vary considerably between individuals, clinicians must recognize that the recommendations that follow, although generally effective, will not guarantee successful prevention in all high altitude travelers. The approach to prevention of AMS and HACE should be a function of the risk profile of the individual traveling to high altitude (Table 2). In low-risk situations, prophylactic medications are not necessary and individuals should rely on a gradual ascent profile. Above an altitude of 3000 m, individuals should not increase the sleeping elevation by more than 500 m per day and should include a rest day (ie, no ascent to higher sleeping elevation) every 3 to 4 days. The increase in sleeping elevation should be less than 500 m for any given day of a trip. In many areas, terrain and other logistical factors often prevent strict adherence to this approach and mandate larger gains in sleeping elevation in a single day. In such cases, rest days should be strongly considered before or after such large gains in elevation and elsewhere in the itinerary to ensure that the overall ascent rate averaged over the entire trip (eg, total elevation gain divided by the number of days of ascent during the trip) falls below the 500 m/d threshold.

Prophylactic medications should be considered in addition to gradual ascent for use in moderate-to-high risk situations. Acetazolamide is the preferred agent, but dexamethasone may be used as an alternative in individuals with prior history of intolerance of or allergic reaction to acetazolamide. In rare circumstances (eg, military or rescue teams who must ascend rapidly to and perform physical work >3500 m), consideration can be given to concurrent use of acetazolamide and dexamethasone. This strategy should be avoided except in these particular or other emergency circumstances that mandate a very rapid ascent.

Table 2. Risk categories for acute mountain sickness

Risk category	*Description*
Low	• Individuals with no prior history of altitude illness and ascending to ≤ 2800 m • Individuals taking ≥ 2 days to arrive at 2500–3000 m with subsequent increases in sleeping elevation <500 m/d and an extra day for acclimatization every 1000 m
Moderate	• Individuals with prior history of AMS and ascending to 2500–2800 m in 1 day • No history of AMS and ascending to >2800 m in 1 day • All individuals ascending >500 m/d (increase in sleeping elevation) at altitudes above 3000 m but with an extra day for acclimatization every 1000 m
High	• Individuals with a history of AMS and ascending to >2800 m in 1 day • All individuals with a prior history of HACE • All individuals ascending to >3500 m in 1 day • All individuals ascending >500 m/d (increase in sleeping elevation) above >3000 m without extra days for acclimatization • Very rapid ascents (eg, <7-day ascents of Mt Kilimanjaro)

AMS, acute mountain sickness; HACE, high altitude cerebral edema.
Notes:

- Altitudes listed in the table refer to the altitude at which the person sleeps.
- Ascent is assumed to start from elevations <1200 m.
- The risk categories described above pertain to unacclimatized individuals.

Acetazolamide carries a low risk of cross-reactivity in persons with sulfonamide allergy, but persons with known allergy to sulfonamide medications should consider a supervised trial of acetazolamide before the trip, particularly if planning travel into an area remote from medical resources.[33] A history of anaphylaxis to sulfonamide medications should be considered a contraindication to acetazolamide. Acetazolamide and dexamethasone should be started the day before ascent (but will still have beneficial effects if started on the day of ascent). For individuals ascending to and staying at the same elevation for more than several days, prophylaxis may be stopped after 2 days at the target altitude. Individuals ascending faster than the recommended ascent rates should continue prophylaxis for a total of 4 days after arrival at the target altitude. Recommendation Grade: 2C. For individuals ascending to a high point and then descending toward the trailhead (eg, descending from the summit of Kilimanjaro), prophylactic medications should be stopped once descent is initiated.

TREATMENT

Potential therapeutic options for AMS and HACE include the following.

Descent

When feasible, descent remains the single best treatment for AMS and HACE. However, it is not necessary in all circumstances (discussed further below). Individuals should descend until symptoms resolve, unless impossible because of terrain. Symptoms typically resolve after descent of 300 to 1000 m, but the required descent will vary between persons. Individuals should not descend alone, particularly in cases of HACE. Recommendation Grade: 1A.

Supplemental oxygen

Oxygen delivered by nasal cannula at flow rates sufficient to raise S_pO_2 to $>90\%$ provides a suitable alternative to descent. Use is not required in all circumstances and is generally reserved for severe cases when descent is not feasible. Unlike at hospitals or large clinics, the supply of oxygen may be limited at remote high altitude clinics or on expeditions, necessitating careful use of this therapy. Recommendation Grade: 1C.

Portable hyperbaric chambers

These devices are effective for treating severe altitude illness[34,35] but require constant tending by care providers and are difficult to use with claustrophobic or vomiting patients. Symptoms may recur when individuals are removed from the chamber.[36] Use of a portable hyperbaric chamber should not delay descent in situations in which descent is feasible. Recommendation Grade: 1B.

Acetazolamide

Only 1 study has examined acetazolamide for treatment of AMS. The dose studied was 250 mg twice daily and whether a lower dose might suffice is unknown.[37] Recommendation Grade: 1B. No studies have assessed treatment of AMS in pediatric patients, but anecdotal reports suggest it has utility in this regard. The pediatric treatment dose is 2.5 mg/kg/dose twice daily up to a maximum of 250 mg/dose. Recommendation Grade: 1C.

Dexamethasone

Dexamethasone is very effective in the treatment of AMS.[38–40] The medication does not facilitate acclimatization, and further ascent should be delayed until the patient is asymptomatic while off the medication. Recommendation Grade 1B. Extensive clinical experience supports the use of dexamethasone in patients with HACE. It is administered as an 8-mg dose (IM, IV, or PO) followed by 4 mg every 6 hours until symptoms resolve. The pediatric dose is 0.15 mg/kg/dose every 6 hours.[19] Recommendation Grade: 1C.

Suggested approach to AMS/HACE treatment

Care should be taken to exclude disorders whose symptoms and signs may resemble those seen in AMS and HACE, such as dehydration, exhaustion, hypoglycemia, hypothermia, or hyponatremia.[8] Persons with altitude illness of any severity should stop ascending and may need to consider descent depending on the clinical circumstances and severity of illness (Table 3).[8] Patients with AMS can remain at their current altitude and use nonopiate analgesics for headache and antiemetics for gastrointestinal symptom relief; that may be all that is required. Acetazolamide will help treat AMS by facilitating acclimatization through increased ventilation and diuresis, but these physiologic effects may work better for prevention than for treatment. Although acetazolamide is good for treating mild illness, experienced clinicians have found dexamethasone a more reliably effective treatment for moderate-to-severe disease, which often requires descent as well. Individuals with AMS may resume their ascent once symptoms resolve, but further ascent or reascent to a previously attained altitude should never be undertaken in the face of ongoing symptoms. After resolution of AMS, reascent with acetazolamide is prudent.

HACE is differentiated from severe AMS by neurological signs such as ataxia, confusion, or altered mental

Table 3. Acute mountain sickness classification

Category	*Mild AMS*	*Moderate-severe AMS*	*High altitude cerebral edema (HACE)*
Symptoms	Headache plus one or more other symptoms (nausea/vomiting; fatigue, lassitude, dizziness; difficulty sleeping) All symptoms of mild intensity	Headache plus one or more other symptoms (nausea/vomiting; fatigue, lassitude, dizziness; difficulty sleeping) All symptoms of moderate-severe intensity	Worsening of symptoms seen in moderate-severe AMS
Signs	None	None	Ataxia, severe lassitude, altered mental status, encephalopathy
Lake Louise AMS Score[a]	2–4	5–15	Not applicable

[a] Self-report AMS score.[43]

status in the setting of acute ascent to high altitude and may follow AMS or occur concurrently with HAPE. Individuals developing HACE in populated areas with access to hospitals or specialized clinics should be started on supplemental oxygen and dexamethasone. In remote areas away from medical resources, descent should be initiated in any suspected HACE victim or if symptoms of AMS are not responding to conservative measures or treatment with acetazolamide or dexamethasone. If descent is not feasible owing to logistical issues, supplemental oxygen or a portable hyperbaric chamber should be considered. Persons with HACE should also be started on dexamethasone. No further ascent should be attempted until the victim is asymptomatic and no longer taking dexamethasone.

High Altitude Pulmonary Edema

Information on the epidemiology, clinical presentation, and pathophysiology of HAPE, the majority of which comes from studies in adults, is provided in several extensive reviews.[10,11,41,42] Although some of the prophylactic and therapeutic modalities are the same for HAPE as for AMS and HACE, important differences in the underlying pathophysiology of the disorder dictate different management and treatment approaches.

PREVENTION

Potential preventive measures for HAPE include the following.

Gradual ascent

No studies have prospectively assessed whether limiting the rate of increase in sleeping elevation prevents HAPE; however, there is a clear relationship between the rate of ascent and disease incidence.[14,43,44] Recommendation Grade: 1C.

Nifedipine

A single randomized, placebo-controlled study[45] and extensive clinical experience have established a role for nifedipine in HAPE prevention in susceptible individuals. The recommended dose is 30 mg of the extended-release preparation administered twice daily. Recommendation Grade: 1A.

Salmeterol

In a single randomized, placebo-controlled study, the long-acting inhaled β-agonist salmeterol decreased the incidence of HAPE by 50% in susceptible individuals.[46] Very high doses (125 μg twice daily) that are often associated with side effects were used in the study. Clinical experience with the medication at high altitude is limited. As a result, salmeterol is not recommended as monotherapy but may be considered as a supplement to nifedipine. Recommendation Grade: 2B.

Tadalafil

In a single randomized, placebo-controlled trial, 10 mg twice daily of tadalafil was effective in preventing HAPE in susceptible individuals.[47] The number of individuals in the study was small, and 2 subjects experienced incapacitating AMS. Clinical experience with tadalafil is lacking compared with nifedipine. As a result, further data are necessary to validate these results. Recommendation Grade: 1C.

Dexamethasone

In the same study that assessed the role of tadalafil in HAPE prevention, dexamethasone (16 mg/d in divided

doses) was also shown to prevent HAPE in susceptible individuals. The mechanism for this effect is not clear, and there is very little, if any, clinical experience using dexamethasone for this purpose. Further data are necessary to validate this result. Recommendation Grade: 1C.

Acetazolamide

Because acetazolamide hastens acclimatization, it should be effective at preventing all forms of acute altitude illness. It has been shown to blunt hypoxic pulmonary vasoconstriction in animal models[48,49] and in a single study in humans,[50] but there are no data specifically supporting a role in HAPE prevention. Clinical observations suggest acetazolamide may prevent reentry HAPE, a disorder seen in children who reside at high altitude, travel to lower elevation, and then develop HAPE upon rapid return to their residence. Recommendation Grade: 2C.

Preacclimatization and staged ascent

No study has examined whether preacclimatization strategies are useful for HAPE prevention. Staged ascent, with 7 days of residence at moderate altitude (approximately 2200 m), has been shown to blunt the hypoxia-induced increase in pulmonary artery pressure, a key feature of the pathophysiology of HAPE.[31] However, uncertainty remains as to the magnitude and duration of moderate altitude exposure necessary to yield benefit, and no study has specifically investigated whether the strategy is of benefit in known HAPE-susceptible individuals. Although the risks of preacclimatization and staged ascent are likely low, feasibility is a concern for many high altitude travelers. No specific recommendations regarding the appropriate preacclimatization or staging regimen can be made at this time. Recommendation Grade: 2C.

Suggested approach to HAPE prevention

As noted earlier, because the physiologic responses to high altitude and rates of acclimatization vary considerably between individuals, the recommendations that follow, while generally effective, will not guarantee successful prevention in all high altitude travelers. A gradual ascent profile is the primary recommended method for preventing HAPE; the recommended ascent rate noted above for AMS and HACE prevention also applies with HAPE prevention. Drug prophylaxis should only be considered for individuals with a prior history of HAPE, especially multiple episodes, and nifedipine is the preferred option in such situations. It should be started the day before ascent and continued either until descent is initiated or the individual has spent 4 days at the target elevation. The duration of use at the target elevation should be extended to 7 days if the individual ascended faster than recommended ascent rates. Recommendation Grade: 2C. For individuals ascending to a high point and then descending toward the trailhead (eg, descending from the summit of Kilimanjaro), prophylactic medications should be stopped once descent is initiated. Further research is needed before tadalafil or dexamethasone can be recommended for this purpose. Acetazolamide is a rational choice for HAPE prevention and clinical experience supports this, but data are lacking. Salmeterol should only be considered as a supplement to nifedipine in high-risk individuals with a clear history of recurrent HAPE.

TREATMENT

Potential therapeutic options for HAPE include the following.

Descent

As with AMS and HACE, descent remains the single best treatment for HAPE, but is not necessary in all circumstances. Individuals should try to descend at least 1000 m or until symptoms resolve. They should exert themselves as little as possible on descent (eg, travel without a pack or via animal transportation) because exertion can further increase pulmonary artery pressure and exacerbate edema formation. Recommendation Grade: 1A.

Supplemental oxygen

Oxygen delivered by nasal cannula or face mask at flow rates sufficient to achieve goal S_pO_2 greater than 90% provides a suitable alternative to descent, particularly when patients can access healthcare facilities and be monitored closely.[51,52] Recommendation Grade: 1B.

Portable hyperbaric chambers

As with AMS and HACE, portable hyperbaric chambers can be used for HAPE treatment. They have not been systematically studied in this role, but their use in HAPE has been reported in the literature.[53] Use of a portable hyperbaric chamber should not delay descent in situations in which descent is feasible. Recommendation Grade: 1B.

Nifedipine

A single, nonrandomized, unblinded study demonstrated the utility of nifedipine in HAPE treatment when oxygen or descent is not available.[54] No other treatment studies have

been conducted, but there is extensive clinical experience with its use as an adjunct to oxygen or descent. Thirty milligrams of the extended-release version is administered twice daily without a loading dose. It should not be relied on as the sole therapy unless descent is impossible and access to supplemental oxygen or portable hyperbaric therapy cannot be arranged. Recommendation Grade: 1C (for use as adjunctive therapy).

β-Agonists

Although there are reports of β-agonist use in HAPE treatment,[55] no data support a benefit from salmeterol or albuterol in patients suffering from HAPE. Recommendation Grade: 2C.

Phosphodiesterase inhibitors

By virtue of their ability to cause pulmonary vasodilation and decrease pulmonary artery pressure, there is a strong physiologic rationale for using phosphodiesterase inhibitors in HAPE treatment. Although reports document their use for this purpose,[55] no systematic studies have examined the role of either tadalafil or sildenafil in HAPE treatment. Recommendation Grade: 2C.

Continuous positive airway pressure

A small study demonstrated that expiratory positive airway pressure (EPAP), in which a mask system is used to increase airway pressure during exhalation only, improved gas exchange in HAPE patients.[56] However, no studies have established that this modality or the more commonly used continuous positive airway pressure (CPAP), in which a continuous level of pressure is applied to the airways through the entire respiratory cycle, improves patient outcomes. Given the low risks associated with the therapy, it can be considered an adjunct to oxygen administration in the hospital setting, provided the patient has intact mental status and can tolerate the mask. It is generally not feasible in the field setting at present but may become more feasible in the future as technology improves and smaller, battery-powered devices become more widely available. Recommendation Grade: 2B.

Diuretics

Although their use has been documented in the literature,[29] diuretics have no role in HAPE treatment, particularly because many HAPE patients have concurrent intravascular volume depletion. Recommendation Grade: 2C.

Dexamethasone

Considering its potential role in HAPE prevention, noted above, and studies demonstrating effects on maximum exercise capacity,[57] pulmonary inflammation, and ion-transporter function in hypoxia,[58] dexamethasone may have a role in HAPE treatment. Although reports document its clinical use in this regard,[59] no study has established whether it is effective for this purpose. Recommendation Grade: 2C.

Suggested approach to HAPE treatment

Before initiating treatment, care should be taken to rule out other causes of respiratory symptoms at high altitude, such as pneumonia, viral upper respiratory tract infection, mucus plugging, bronchospasm, or myocardial infarction.[8] Descent is the first treatment priority in persons with HAPE. If descent cannot be initiated as a result of logistical factors, supplemental oxygen or a portable hyperbaric chamber should be used. Patients who have access to oxygen (eg, a hospital or high altitude medical clinic) may not need to descend to lower elevation and can be treated with oxygen at the current elevation. In the field setting, where resources are limited and there is a lower margin for error, nifedipine can be used as an adjunct to descent, oxygen, or portable hyperbaric therapy. It should only be used as primary therapy if none of these other measures is available. A phosphodiesterase inhibitor may be used if nifedipine is not available, but concurrent use of multiple pulmonary vasodilators is not recommended. In the hospital setting, CPAP can be considered as an adjunct to supplemental oxygen, and nifedipine can be added if patients fail to respond to oxygen therapy alone. In well-selected patients (adequate support from family or friends, adequate housing or lodging arrangements), it is feasible to discharge them from care with supplemental oxygen, rather than admitting them to a healthcare facility. There is no established role for acetazolamide, β-agonists, or diuretics in the treatment of HAPE.

Individuals who develop HAPE may consider further ascent to higher altitudes or reascent to join their party only when symptoms of their disease have resolved and they maintain stable oxygenation at rest and with mild exercise while off supplemental oxygen or vasodilator therapy. Consideration may be given to using nifedipine or another pulmonary vasodilator on resuming ascent.

Suggested approach for patients with concurrent HAPE and HACE

Dexamethasone should be added to the treatment regimen of patients with concurrent HAPE and HACE at the doses described above for those with HACE. Some patients with

HAPE may have neurologic dysfunction caused by hypoxic encephalopathy rather than true HACE, but making the distinction between hypoxic encephalopathy and HACE in the field can be difficult, and as a result, dexamethasone should be added to the treatment regimen for HAPE patients with neurologic dysfunction that does not resolve rapidly with administration of supplemental oxygen and improvement in the patient's oxygen saturation. Nifedipine or other pulmonary vasodilators may be used in patients with concurrent HAPE and HACE, but care should be exercised to avoid lowering mean arterial pressure, as this may decrease cerebral perfusion pressure and as a result increase the risk for cerebral ischemia.

Conclusions

To assist practitioners caring for people planning travel to or already at high altitude, we have provided evidence-based guidelines for prevention and treatment of acute altitude illnesses, including the main prophylactic and therapeutic modalities for AMS, HACE, and HAPE, and recommendations regarding their role in disease management. Although these guidelines cover many of the important issues related to prevention and treatment of altitude illness, several important questions remain to be addressed and should serve as a focus for future research. Such research includes the optimal rate of ascent to prevent altitude illness, the role of acetazolamide in HAPE prevention and treatment, proper dosing regimens for prevention and treatment of altitude illness in the pediatric population, and the role of staged ascent and preacclimatization in altitude illness prevention.

Supplementary tables

Supplementary ACCP Table 1 and Evidence Tables 2–4 are available online at http://dx.doi.org/10.1016/j.wem.2014.06.017.

References

1. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest*. 2006;129:174–181.
2. Montgomery AB, Mills J, Luce JM. Incidence of acute mountain sickness at intermediate altitude. *JAMA*. 1989; 261:732–734.
3. Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med*. 1993;118:587–592.
4. Gabry AL, Ledoux X, Mozziconacci M, Martin C. High-altitude pulmonary edema at moderate altitude (<2,400 m; 7,870 feet): a series of 52 patients. *Chest*. 2003;123:49–53.
5. Southard A, Niermeyer S, Yaron M. Language used in Lake Louise Scoring System underestimates symptoms of acute mountain sickness in 4- to 11-year-old children. *High Alt Med Biol*. 2007;8:124–130.
6. Muhm JM, Rock PB, McMullin DL, et al. Effect of aircraft-cabin altitude on passenger discomfort. *N Engl J Med*. 2007;357:18–27.
7. Theis MK, Honigman B, Yip R, McBride D, Houston CS, Moore LG. Acute mountain sickness in children at 2835 meters. *Am J Dis Child*. 1993;147:143–145.
8. Hackett PH, Roach RC. High-altitude illness. *N Engl J Med*. 2001;345:107–114.
9. Hackett PH, Roach RC. High altitude cerebral edema. *High Alt Med Biol*. 2004;5:136–146.
10. Schoene RB. Illnesses at high altitude. *Chest*. 2008;134: 402–416.
11. Bärtsch P, Swenson ER. Clinical practice: Acute high-altitude illnesses. *N Engl J Med*. 2013;368:2294–2302.
12. Bloch KE, Turk AJ, Maggiorini M, et al. Effect of ascent protocol on acute mountain sickness and success at Muztagh Ata, 7546 m. *High Alt Med Biol*. 2009;10:25–32.
13. Beidleman BA, Fulco CS, Muza SR, et al. Effect of six days of staging on physiologic adjustments and acute mountain sickness during ascent to 4300 meters. *High Alt Med Biol*. 2009;10:253–260.
14. Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet*. 1976;2:1149–1155.
15. Forwand SA, Landowne M, Follansbee JN, Hansen JE. Effect of acetazolamide on acute mountain sickness. *N Engl J Med*. 1968;279:839–845.
16. Basnyat B, Gertsch JH, Holck PS, et al. Acetazolamide 125 mg BD is not significantly different from 375 mg BD in the prevention of acute mountain sickness: the prophylactic acetazolamide dosage comparison for efficacy (PACE) trial. *High Alt Med Biol*. 2006;7:17–27.
17. van Patot MC, Leadbetter G III, Keyes LE, Maakestad KM, Olson S, Hackett PH. Prophylactic low-dose acetazolamide reduces the incidence and severity of acute mountain sickness. *High Alt Med Biol*. 2008;9: 289–293.
18. Low EV, Avery AJ, Gupta V, Schedlbauer A, Grocott MP. Identifying the lowest effective dose of acetazolamide for the prophylaxis of acute mountain sickness: systematic review and meta-analysis. *BMJ*. 2012;345:e6779.
19. Pollard AJ, Niermeyer S, Barry P, et al. Children at high altitude: an international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, March 12, 2001. *High Alt Med Biol*. 2001;2: 389–403.
20. Ellsworth AJ, Larson EB, Strickland D. A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. *Am J Med*. 1987;83:1024–1030.
21. Ellsworth AJ, Meyer EF, Larson EB. Acetazolamide or dexamethasone use versus placebo to prevent acute mountain sickness on Mount Rainier. *West J Med*. 1991; 154:289–293.

22. Roncin JP, Schwartz F, D'Arbigny P. EGb 761 in control of acute mountain sickness and vascular reactivity to cold exposure. *Aviat Space Environ Med*. 1996;67:445–452.
23. Moraga FA, Flores A, Serra J, Esnaola C, Barriento C. Ginkgo biloba decreases acute mountain sickness in people ascending to high altitude at Ollagüe (3696 m) in northern Chile. *Wilderness Environ Med*. 2007;18:251–257.
24. Chow T, Browne V, Heileson HL, Wallace D, Anholm J, Green SM. Ginkgo biloba and acetazolamide prophylaxis for acute mountain sickness: a randomized, placebo-controlled trial. *Arch Intern Med*. 2005;165:296–301.
25. Gertsch JH, Basnyat B, Johnson EW, Onopa J, Holck PS. Randomised, double blind, placebo controlled comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the Prevention of High Altitude Illness Trial (PHAIT). *BMJ*. 2004;328:797.
26. Leadbetter G III, Keyes LE, Maakestad KM, Olson S, Tissot van Patot MC, Hackett PH. Ginkgo biloba does—and does not—prevent acute mountain sickness. *Wilderness Environ Med*. 2009;20:66–71.
27. Gertsch JH, Corbett B, Holck PS, et al. Altitude Sickness in Climbers and Efficacy of NSAIDs Trial (ASCENT): randomized, controlled trial of ibuprofen versus placebo for prevention of altitude illness. *Wilderness Environ Med*. 2012;23:307–315.
28. Lipman GS, Kanaan NC, Holck PS, Constance BB, Gertsch JH, PAINS Group. Ibuprofen prevents altitude illness: a randomized controlled trial for prevention of altitude illness with nonsteroidal anti-inflammatories. *Ann Emerg Med*. 2012;59:484–490.
29. Gertsch JH, Lipman GS, Holck PS, et al. Prospective, double-blind, randomized, placebo-controlled comparison of acetazolamide versus ibuprofen for prophylaxis against high altitude headache: the Headache Evaluation at Altitude Trial (HEAT). *Wilderness Environ Med*. 2010;21:236–243.
30. Beidleman BA, Muza SR, Fulco CS, et al. Intermittent altitude exposures reduce acute mountain sickness at 4300 m. *Clin Sci (Lond)*. 2004;106:321–328.
31. Baggish AL, Fulco CS, Muza S, et al. The impact of moderate-altitude staging on pulmonary arterial hemodynamics after ascent to high altitude. *High Alt Med Biol*. 2010;11:139–145.
32. Fulco CS, Muza SR, Beidleman BA, et al. Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude. *Am J Physiol Regul Integr Comp Physiol*. 2011;300:R428–R436.
33. Luks AM, Swenson ER. Medication and dosage considerations in the prophylaxis and treatment of high-altitude illness. *Chest*. 2008;133:744–755.
34. Bärtsch P, Merki B, Hofstetter D, Maggiorini M, Kayser B, Oelz O. Treatment of acute mountain sickness by simulated descent: a randomised controlled trial. *BMJ*. 1993;306:1098–1101.
35. Keller HR, Maggiorini M, Bärtsch P, Oelz O. Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. *BMJ*. 1995;310:1232–1235.
36. Taber RL. Protocols for the use of portable hyperbaric chambers for the treatment of high altitude disorders. *J Wilderness Med*. 1990;1:181–192.
37. Grissom CK, Roach RC, Sarnquist FH, Hackett PH. Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange. *Ann Intern Med*. 1992;116:461–465.
38. Ferrazzini G, Maggiorini M, Kriemler S, Bärtsch P, Oelz O. Successful treatment of acute mountain sickness with dexamethasone. *Br Med J (Clin Res Ed)*. 1987;294:1380–1382.
39. Hackett PH, Roach RC, Wood RA, et al. Dexamethasone for prevention and treatment of acute mountain sickness. *Aviat Space Environ Med*. 1988;59:950–954.
40. Levine BD, Yoshimura K, Kobayashi T, Fukushima M, Shibamoto T, Ueda G. Dexamethasone in the treatment of acute mountain sickness. *N Engl J Med*. 1989;321:1707–1713.
41. Stream JO, Grissom CK. Update on high-altitude pulmonary edema: pathogenesis, prevention, and treatment. *Wilderness Environ Med*. 2008;19:293–303.
42. Bärtsch P, Mairbäurl H, Maggiorini M, Swenson ER. Physiological aspects of high-altitude pulmonary edema. *J Appl Physiol*. 2005;98:1101–1110.
43. Bärtsch P, Maggiorini M, Mairbäurl H, Vock P, Swenson ER. Pulmonary extravascular fluid accumulation in climbers. *Lancet*. 2002;360:571; author reply 571–572.
44. Singh I, Kapila CC, Khanna PK, Nanda RB, Rao BD. High-altitude pulmonary oedema. *Lancet*. 1965;191:229–234.
45. Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O. Prevention of high-altitude pulmonary edema by nifedipine. *N Engl J Med*. 1991;325:1284–1289.
46. Sartori C, Allemann Y, Duplain H, et al. Salmeterol for the prevention of high-altitude pulmonary edema. *N Engl J Med*. 2002;346:1631–1636.
47. Maggiorini M, Brunner-La Rocca HP, Peth S, et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. *Ann Intern Med*. 2006;145:497–506.
48. Höhne C, Krebs MO, Seiferheld M, Boemke W, Kaczmarczyk G, Swenson ER. Acetazolamide prevents hypoxic pulmonary vasoconstriction in conscious dogs. *J Appl Physiol*. 2004;97:515–521.
49. Shimoda LA, Luke T, Sylvester JT, Shih HW, Jain A, Swenson ER. Inhibition of hypoxia-induced calcium responses in pulmonary arterial smooth muscle by acetazolamide is independent of carbonic anhydrase inhibition. *Am J Physiol Lung Cell Mol Physiol*. 2007;292:L1002–L1012.
50. Teppema LJ, Balanos GM, Steinback CD, et al. Effects of acetazolamide on ventilatory, cerebrovascular, and pulmonary vascular responses to hypoxia. *Am J Respir Crit Care Med*. 2007;175:277–281.
51. Marticorena E, Hultgren HN. Evaluation of therapeutic methods in high altitude pulmonary edema. *Am J Cardiol*. 1979;43:307–312.

52. Zafren K, Reeves JT, Schoene R. Treatment of high-altitude pulmonary edema by bed rest and supplemental oxygen. *Wilderness Environ Med*. 1996;7:127–132.
53. Freeman K, Shalit M, Stroh G. Use of the Gamow Bag by EMT-basic park rangers for treatment of high-altitude pulmonary edema and high-altitude cerebral edema. *Wilderness Environ Med*. 2004;15:198–201.
54. Oelz O, Maggiorini M, Ritter M, et al. Nifedipine for high altitude pulmonary oedema. *Lancet*. 1989;2:1241–1244.
55. Fagenholz PJ, Gutman JA, Murray AF, Harris NS. Treatment of high altitude pulmonary edema at 4240 m in Nepal. *High Alt Med Biol*. 2007;8:139–146.
56. Schoene RB, Roach RC, Hackett PH, Harrison G, Mills WJ Jr. High altitude pulmonary edema and exercise at 4,400 meters on Mount McKinley. Effect of expiratory positive airway pressure. *Chest*. 1985;87:330–333.
57. Siebenmann C, Bloch KE, Lundby C, Nussbamer-Ochsner Y, Schoeb M, Maggiorini M. Dexamethasone improves maximal exercise capacity of individuals susceptible to high altitude pulmonary edema at 4559 m. *High Alt Med Biol*. 2011;12:169–177.
58. Urner M, Herrmann IK, Booy C, Roth-Z' Graggen B, Maggiorini M, Beck-Schimmer B. Effect of hypoxia and dexamethasone on inflammation and ion transporter function in pulmonary cells. *Clin Exp Immunol*. 2012;169:119–128.
59. Jones BE, Stokes S, McKenzie S, Nilles E, Stoddard GJ. Management of high altitude pulmonary edema in the Himalaya: a review of 56 cases presenting at Pheriche medical aid post (4240 m). *Wilderness Environ Med*. 2013;24:32–36.