

## WILDERNESS MEDICAL SOCIETY PRACTICE GUIDELINES

# Wilderness Medical Society Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update

Andrew M. Luks, MD<sup>1</sup>; Paul S. Auerbach, MD, MS<sup>2</sup>; Luanne Freer, MD<sup>3,4,5</sup>; Colin K. Grissom, MD<sup>6,7</sup>; Linda E. Keyes, MD<sup>8,9</sup>; Scott E. McIntosh, MD, MPH<sup>10</sup>; George W. Rodway, PhD, APRN<sup>11</sup>; Robert B. Schoene, MD<sup>12</sup>; Ken Zafren, MD<sup>2,13</sup>; Peter H. Hackett, MD<sup>14</sup>

<sup>1</sup>Division of Pulmonary, Critical Care and Sleep Medicine, University of Washington, Seattle, WA; <sup>2</sup>Department of Emergency Medicine, Stanford University School of Medicine, Stanford, CA; <sup>3</sup>Yellowstone National Park, WY; <sup>4</sup>Midway Atoll National Wildlife Refuge, Honolulu, HI; <sup>5</sup>Everest ER, Himalayan Rescue Association, Kathmandu, Nepal; <sup>6</sup>Division of Pulmonary and Critical Care Medicine, Intermountain Medical Center, Salt Lake City, UT; <sup>7</sup>Division of Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, UT; <sup>8</sup>Department of Emergency Medicine, University of Colorado, Denver, CO; <sup>9</sup>Boulder Community Health, Boulder, CO; <sup>10</sup>Division of Emergency Medicine, University of Utah, Salt Lake City, UT; <sup>11</sup>University of California, Davis School of Nursing, Sacramento, CA; <sup>12</sup>Division of Pulmonary and Critical Care Medicine, Sourd Physicians, St. Mary's Medical Center, San Francisco, CA; <sup>13</sup>Himalayan Rescue Association, Kathmandu, Nepal; <sup>14</sup>Altitude Research Center, Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO

To provide guidance to clinicians about best preventive and therapeutic practices, the Wilderness Medical Society (WMS) 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. Recommendations are graded based on the quality of supporting evidence and the 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 form of acute altitude illness 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 2010 and subsequently updated as the WMS Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness in 2014.

*Keywords:* high altitude, acute mountain sickness, high altitude pulmonary edema, high altitude cerebral edema, acetazolamide, dexamethasone, nifedipine

## Introduction

Travel to elevations above 2500 m is associated with risk of developing 1 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, clinicians working at facilities in high altitude regions or as members of expeditions

traveling to such areas can expect to see persons who are experiencing these illnesses and must be familiar with prophylactic regimens and proper treatment protocols.

To provide guidance to clinicians and disseminate knowledge about best practices, the Wilderness Medical Society (WMS) convened an expert panel to develop evidence-based guidelines for prevention and treatment of acute altitude illness. Preventive and therapeutic modalities are presented and recommendations made for each form of acute altitude illness. Recommendations are graded based on the quality of supporting evidence and consideration of benefits and risks/burdens associated with each modality. These recommendations are intended to apply to all travelers to high altitude, whether they are traveling to high altitude for work, recreation, or various activities including hiking, skiing, trekking, and mountaineering.

Corresponding author: Andrew Luks, MD, Pulmonary, Critical Care and Sleep Medicine, Harborview Medical Center, 325 Ninth Avenue, Box 359762, Seattle, WA 98104; e-mail: [aluks@uw.edu](mailto:aluks@uw.edu).

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## Methods

The original expert panel was convened at the 2009 annual meeting of the WMS in Snowmass, Colorado. Members were selected by the WMS based on their clinical and/or research experience. Relevant articles were identified through the MEDLINE database by keyword 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. English-language, peer-reviewed studies including adults and/or children that were 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 preventive and treatment modalities was assessed. Animal studies and abstract-only studies were not included. Conclusions from review articles were not considered in the formulation of recommendations but are cited to provide background information on the acute altitude illnesses and their management. The panel used a consensus approach to develop recommendations 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 (online Supplementary Table 1).<sup>1</sup>

This set of guidelines is an updated version of the original Wilderness Medical Society Consensus Guidelines for the Prevention and Treatment of Acute Altitude Illness published in 2010<sup>2</sup> and the update as the Wilderness Medical Society Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness published in 2014.<sup>3</sup> As for the 2014 update, the panel used the approach described to identify relevant studies, adding additional search terms to reflect updates in the literature. The new search terms for the current version included budesonide, acetaminophen, continuous positive airway pressure (CPAP), and hypoxic tents.

### Defining the threshold for “high altitude” and when to apply these guidelines

Unacclimatized individuals are at risk of high altitude illness when ascending to altitudes above 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.<sup>4–6</sup> HACE is typically encountered at higher elevations but has also been reported at around 2500 m in patients with concurrent HAPE.<sup>7</sup> Part of the difficulty in 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 nonspecific, as

demonstrated in several studies in which participants met criteria for the diagnosis of AMS despite no gain in altitude.<sup>8–10</sup> 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 reported incidence of AMS 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. Preventive measures should be considered based on the altitude to which the individual is traveling and also account for factors such as history of performance at high altitude, rate of ascent, and availability of acclimatization days (described in greater detail later). Diagnoses of AMS, HAPE, or HACE should not be excluded based on the fact that an ill individual is below 2500 m. These diagnoses should be strongly considered in the presence of compatible clinical features, with careful attempts to exclude other entities such as severe dehydration, hyponatremia, pneumonia, carbon monoxide poisoning, and hypoglycemia.

### 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.<sup>11–14</sup> From a clinical standpoint, HACE represents an extremely severe form of AMS; therefore, preventive and treatment measures for the 2 disorders can be addressed simultaneously.

### PREVENTION

Measures considered for prevention of AMS and HACE include the following.

#### *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,<sup>15,16</sup> this strategy has largely been evaluated retrospectively.<sup>17</sup> In planning the rate of ascent, the altitude at which someone sleeps is considered more important than the altitude reached during waking hours.

**Recommendation.** Gradual ascent, defined as a slow increase in sleeping elevation, is recommended for AMS and HACE prevention. A specific approach is described further later in the text. Recommendation Grade: 1B

### Acetazolamide

Multiple trials have established a role for acetazolamide in prevention of AMS.<sup>18–21</sup>

Acetazolamide contains a sulfa moiety but carries an extremely low risk of inciting an allergic reaction in persons with sulfonamide allergy. As a result, persons with known allergy to sulfonamide medications can consider a supervised trial of acetazolamide before the trip, particularly if planning travel to a location remote from medical resources.<sup>22</sup> Prior anaphylaxis to a sulfonamide medication or a history of Stevens-Johnson syndrome should be considered a contraindication to acetazolamide.

Some studies suggest that acetazolamide may have an adverse effect on maximum exercise capacity,<sup>23</sup> perceived dyspnea during maximal exercise tests,<sup>24</sup> and respiratory muscle function at high levels of work.<sup>25</sup> The small observed changes, however, are unlikely to affect overall exercise performance for the majority of activities in which high altitude travelers engage (hiking, skiing) or the chance of summit success for climbers at moderate and even extreme elevations. These changes should not be viewed as a reason to avoid acetazolamide.

The recommended adult dose for prophylaxis is 125 mg every 12 h (Table 1). Although doses up to 750 mg daily

are effective at preventing AMS compared to placebo, they are associated with more frequent and/or pronounced side effects, do not convey greater efficacy, and are not recommended for prevention. A recent, small study suggested that 62.5 mg every 12 h was noninferior to 125 mg every 12 h,<sup>26</sup> but further research with greater numbers of participants in different high altitude settings should be completed before a change in dose can be recommended. The pediatric dose of acetazolamide is 2.5 mg·kg<sup>-1</sup>·dose<sup>-1</sup> (maximum 125 mg·dose<sup>-1</sup>) every 12 h.<sup>27</sup>

**Recommendation.** Acetazolamide should be strongly considered in travelers at moderate or high risk of AMS with ascent to high altitude. Recommendation Grade: 1A.

**Recommendation.** Acetazolamide can be used in children for prevention of AMS. Recommendation Grade: 1C.

### Dexamethasone

Although dexamethasone does not facilitate acclimatization like acetazolamide, prospective trials have established a benefit for dexamethasone in AMS prevention.<sup>28,29</sup> The recommended adult doses are 2 mg every 6 h or 4 mg every 12 h. Very high doses (4 mg every 6 h) may be considered in very high-risk situations, such as military or search and rescue personnel being airlifted to altitudes >3500 m with

**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 every 12 h <sup>a</sup> Pediatrics: 2.5 mg·kg <sup>-1</sup> every 12 h
	AMS treatment <sup>b</sup>	Oral	250 mg every 12 h Pediatrics: 2.5 mg·kg <sup>-1</sup> every 12 h (maximum: 125 mg per dose)
Dexamethasone	AMS, HACE prevention	Oral	2 mg every 6 h or 4 mg every 12 h <sup>a</sup> Pediatrics: Should not be used for prophylaxis
	AMS, HACE treatment	Oral, IV, IM	AMS: 4 mg every 6 h HACE: 8 mg once, then 4 mg every 6 h Pediatrics: 0.15 mg·kg <sup>-1</sup> ·dose <sup>-1</sup> every 6 h (Maximum: 4 mg per dose)
Ibuprofen	AMS prevention	Oral	600 mg every 8 h
Nifedipine	HAPE prevention	Oral	30 mg ER version, every 12 h or 20 mg ER version every 8 h <sup>c</sup>
	HAPE treatment	Oral	30 mg ER version, every 12 h or 20 mg ER version every 8 h
Tadalafil	HAPE prevention	Oral	10 mg every 12 h <sup>c</sup>
Sildenafil	HAPE prevention	Oral	50 mg every 8 h <sup>c</sup>

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

<sup>a</sup> For individuals ascending to and remaining at a given elevation, after arrival at the target elevation, the medication should be continued for 2 d in individuals adhering to the recommended ascent rate and 2 to 4 d in individuals ascending faster than recommended rates. Individuals who ascend to a target elevation and immediately descend can stop the medication once descent is initiated.

<sup>b</sup> Acetazolamide can also be used at this dose as an *adjunct* to dexamethasone in HACE treatment, but dexamethasone remains the primary treatment for HACE.

<sup>c</sup> For individuals ascending to and remaining at a given elevation, after arrival at the target elevation, the medication should be continued for 4 d in individuals adhering to the recommended ascent rate and 4 to 7 d in individuals ascending faster than recommended rates. Individuals who ascend to a target elevation and immediately descend can stop the medication once descent is initiated.

immediate performance of physical activity, but should not be used except in these limited circumstances. Prolonged use carries a risk of adrenal suppression. Although some resources state that use of less than 2-wk duration does not require a taper,<sup>30</sup> in remote mountain environments a more conservative approach is warranted. If used for longer than 10 d, the medication should be tapered over a 1-wk period rather than stopped abruptly. Given the absence of data on the use of dexamethasone for AMS prevention in children and the availability of other safe alternatives—specifically, graded ascent and acetazolamide—dexamethasone is not recommended for AMS prevention in children.

**Recommendation.** Dexamethasone can be used as an alternative to acetazolamide for adult travelers at moderate or high risk of AMS. Recommendation Grade: 1A.

#### *Inhaled budesonide*

Two studies indicated that inhaled budesonide 200 micrograms twice daily was effective at preventing AMS when compared to placebo.<sup>31,32</sup> These studies were limited by methodological issues such as timing of the assessment for AMS<sup>31</sup> and number of participants in each study arm.<sup>32</sup> A clear mechanism of action was not apparent in these studies, but small improvements in spirometry and oxygen saturation—both of little clinical significance—were suggested as evidence that the benefit might derive from a direct lung effect. More recent, well-designed randomized controlled trials failed to replicate these results.<sup>33,34</sup>

**Recommendation.** Inhaled budesonide should not be used for altitude illness prophylaxis. Recommendation Grade: 1C

#### *Ginkgo biloba*

Although 2 trials demonstrated a benefit of *Ginkgo* in AMS prevention,<sup>35,36</sup> 2 other negative trials have also been published.<sup>37,38</sup> This discrepancy may result from differences in the source and composition of the *Ginkgo* products.<sup>39</sup> *Ginkgo* should be avoided in pregnant women<sup>40</sup> and used with caution in people taking anticoagulants.<sup>41</sup> Acetazolamide is considered far superior for AMS prevention.

**Recommendation.** *Ginkgo biloba* should not be used for AMS prevention. Recommendation Grade: 1C

#### *Ibuprofen*

Two trials demonstrated that ibuprofen (600 mg 3 times daily) is more effective than placebo at preventing AMS,<sup>42,43</sup> while a third, smaller study showed no benefit.<sup>44</sup> Another study claimed to show benefit, but the trial did not include a placebo arm and instead compared the incidence of AMS with ibuprofen with historically reported rates

from the region in which the study was conducted.<sup>45</sup> Although no studies have compared ibuprofen with dexamethasone, 2 studies have compared ibuprofen with acetazolamide. The first found an equal incidence of high altitude headache and AMS in the acetazolamide and ibuprofen groups, with both showing significant protection compared to placebo.<sup>46</sup> A more recent trial failed to show that ibuprofen was noninferior to acetazolamide (ie, ibuprofen is inferior to acetazolamide for AMS prophylaxis).<sup>47</sup> The aforementioned trials all used the medication for a short duration (~24–48 h). As a result, efficacy and safety (eg, the risk of gastrointestinal bleeding or renal dysfunction) over longer periods of use at high altitude remain unclear. For these reasons, as well as more extensive clinical experience with acetazolamide and dexamethasone, ibuprofen cannot be recommended over these medications for AMS prevention for rapid ascent.

**Recommendation.** Ibuprofen can be used for AMS prevention in persons who do not wish to take acetazolamide or dexamethasone or have allergies or intolerance to these medications. Recommendation Grade: 2B.

#### *Acetaminophen*

A single study demonstrated that acetaminophen 1000 mg 3 times daily was as effective as ibuprofen at preventing AMS in trekkers travelling between 4370 and 4940 m in elevation.<sup>45</sup> Rather than including a placebo arm, the study attempted to establish the benefit of acetaminophen by comparing the incidence rates in the study with those of untreated trekkers from prior studies that used the same ascent profile. Based on these data, acetaminophen is not recommended for use as a preventive agent over acetazolamide or dexamethasone.

**Recommendation.** Acetaminophen should not be used for AMS prevention. Recommendation Grade: 1C

#### *Staged ascent and preacclimatization*

Two studies showed that spending 6 to 7 d at moderate altitude (~2200–3000 m) before proceeding to higher altitude (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 4300 m.<sup>16,48</sup> Many travelers to high altitude visit mountain resorts at more moderate elevations between 2500 and 3000 m. The value of short stays at intermediate elevations of ~1500 m for decreasing the risk of AMS during such ascents makes sense from a physiologic standpoint. However, this approach has not been studied in a randomized fashion, aside from 1 cross-sectional study finding a decreased risk of AMS in travelers who spent 1 night at 1600 m before ascent to resort communities between 1920 and 2950 m.<sup>5</sup>

A larger number of studies examining the effects of repeated exposures to hypobaric or normobaric hypoxia in the days and week preceding high altitude travel (referred to as “preacclimatization”) showed mixed results, with some studies finding benefit in terms of decreased AMS incidence or severity<sup>49–51</sup> and others showing no effect.<sup>52–55</sup> A significant challenge in interpreting the literature on preacclimatization is the variability among the hypoxic exposure protocols used, as well as the fact that not all studies include evidence that their protocols induced physiologic responses consistent with acclimatization.

Implementation of either staged ascent or preacclimatization may be logistically difficult for many high altitude travelers. In general, short-term exposures (eg, 15–60 min of exposure to hypoxia, or a few hours of hypoxia a few times before ascent) are unlikely to aid acclimatization, whereas longer exposures (eg, >8 h daily for >7 d) are more likely to yield benefit. Hypobaric hypoxia is more effective than normobaric hypoxia in facilitating preacclimatization and preventing AMS.<sup>56</sup> Because the optimal methods for preacclimatization and staged ascent have not been fully determined, the panel recommends consideration of these approaches but does not endorse a particular protocol.

**Recommendation.** When feasible, staged ascent and preacclimatization can be considered as a means for AMS prevention. Recommendation Grade: 1C

### *Hypoxic tents*

Commercial products are available that allow individuals to sleep or exercise in hypoxic conditions for the purpose of facilitating acclimatization before a trip to high altitude. Only 1 placebo-controlled study has examined their utility.<sup>57</sup> Although this study demonstrated a lower incidence of AMS in persons who slept in simulated high altitude conditions compared to normoxia, technical difficulties with the system resulted in a substantial number of study participants not receiving the intended hypoxic dose. Although the systems are marketed to be of benefit and anecdotal reports suggest they are widely used by climbers and other athletes competing at high altitude, there are no data indicating increased likelihood of summit success or improved physical performance. As with the preacclimatization approaches previously described, any benefit that may accrue from these systems is more likely with long hypoxic exposures (>8 h per day) for at least several weeks before planned high altitude travel. Short and/or infrequent exposures, including exercise training, are likely of no benefit. In addition to the cost of the systems and power needed to run them, individuals face the risk of poor sleep, which over a long period of time could have deleterious effects on performance during an expedition.

**Recommendation.** Hypoxic tents can be used for facilitating acclimatization and preventing AMS, provided sufficiently long exposures can be undertaken regularly over an appropriate number of weeks and other factors, such as sleep quality, are not compromised. Recommendation Grade: 2B

### *Other options*

Chewed coca leaves, coca tea, and other coca-derived products are commonly recommended for travelers in the Andes mountains for AMS prevention. Their utility in prevention of altitude illness has not been properly studied, so 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,<sup>58</sup> iron,<sup>59</sup> dietary nitrates,<sup>60</sup> leukotriene receptor blockers,<sup>61,62</sup> phosphodiesterase inhibitors,<sup>63</sup> salicylic acid,<sup>64</sup> spironolactone,<sup>65</sup> and sumatriptan<sup>66</sup> can prevent AMS, but the current state of evidence does not support their use. “Forced” or “over” hydration has never been found to prevent altitude illness and might increase the risk of hyponatremia; however, maintenance of adequate hydration is important because symptoms of dehydration can mimic those of AMS. Nocturnal expiratory positive airway pressure (EPAP) administered via a single-use nasal strip during sleep is not effective for AMS prophylaxis,<sup>67</sup> nor is a regimen of remote ischemic preconditioning.<sup>68</sup>

No studies have examined short-term oxygen use in the form of either visits to oxygen bars or over-the-counter oxygen delivery systems by which individuals inhale oxygen-enriched gas from a small prefilled canister. Due to the small volume of gas (2–10 L/canister) and short duration of administration, these interventions are unlikely to be of benefit and, as a result, have no role in AMS/HACE prevention. Other over-the-counter products, such as powdered drink mixes, also lack any evidence of benefit.

### SUGGESTED APPROACH TO AMS/HACE PREVENTION

Because the rates of acclimatization and physiologic responses to high altitude vary considerably between individuals, clinicians must recognize that the recommendations that follow, although generally effective, do 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). The first priority should be ensuring gradual ascent to the target elevation. Travelers can lower their risk by sleeping 1 night at an intermediate altitude. For example, sea-level residents traveling to Colorado resort areas over 2800 m can spend

**Table 2.** Risk categories for acute mountain sickness

<i>Risk category</i>	<i>Description</i>
Low	<ul style="list-style-type: none"> <li>• Individuals with no history of altitude illness and ascending to <math>\leq 2800</math> m</li> <li>• Individuals taking <math>\geq 2</math> d to arrive at 2500–3000 m with subsequent increases in sleeping elevation <math>&lt; 500</math> m·d<sup>-1</sup> and an extra day for acclimatization every 1000 m</li> </ul>
Moderate	<ul style="list-style-type: none"> <li>• Individuals with history of AMS and ascending to 2500–2800 m in 1 d</li> <li>• No history of AMS and ascending to <math>&gt; 2800</math> m in 1 d</li> <li>• All individuals ascending <math>&gt; 500</math> m·d<sup>-1</sup> (increase in sleeping elevation) at altitudes above 3000 m but with an extra day for acclimatization every 1000 m</li> </ul>
High	<ul style="list-style-type: none"> <li>• Individuals with a history of AMS and ascending to <math>&gt; 2800</math> m in 1 d</li> <li>• All individuals with a history of HACE or HAPE</li> <li>• All individuals ascending to <math>&gt; 3500</math> m in 1 d</li> <li>• All individuals ascending <math>&gt; 500</math> m·d<sup>-1</sup> (increase in sleeping elevation) above <math>&gt; 3000</math> m without extra days for acclimatization</li> <li>• Very rapid ascents (eg, <math>&lt; 7</math> d ascents of Mt. Kilimanjaro)</li> </ul>

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

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 pertain to unacclimatized individuals.

1 night in Denver (1600 m). It should be recognized that a large number of people will travel directly by car or plane to commonly visited mountain high altitude locations, often located between 2500 and 3000 m, and may be unable to ascend gradually because of various logistical factors. In such situations, pharmacologic prophylaxis can be considered. Such individuals should also take care to slow the rate of further ascent beyond the altitude achieved at the start of their visit.

With travel above 3000 m, individuals should not increase their sleeping elevation by more than 500 m·d<sup>-1</sup> and should include a rest day (ie, no ascent to higher sleeping elevation) every 3 to 4 d. 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 prevent strict adherence to this approach and mandate larger gains in sleeping elevation over a single day. In such cases, acclimatization days should be strongly considered before and/or after these large gains

in elevation and elsewhere in the itinerary to ensure—at the very least and as an approximation of properly controlled ascent—that the overall ascent rate averaged over the entire trip (ie, total elevation gain divided by the number of days of ascent during the trip) is below the 500 m·d<sup>-1</sup> threshold.

Prophylactic medications are not necessary in low-risk situations but should be considered in addition to gradual ascent for use in moderate- to high-risk situations (Table 2). Acetazolamide is the preferred medication; dexamethasone may be used as an alternative in individuals with a history of intolerance of or allergic reaction to acetazolamide. In rare circumstances (eg, military or rescue teams that must ascend rapidly to and perform physical work at  $> 3500$  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 very rapid ascent.

Acetazolamide and dexamethasone should be started the day before ascent but 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 d at the highest altitude. Individuals ascending faster than the recommended ascent rates may consider continuing preventive medication for 2 to 4 d after arrival at the target altitude, but there are no data to support this approach. For individuals ascending to a high point and then descending toward the trailhead (eg, descending from the summit of Mt. Kilimanjaro), in the absence of AMS/HACE symptoms, preventive medications should be stopped when descent is initiated.

## TREATMENT

Potential therapeutic options for AMS and HACE include the following.

### *Descent*

Descent remains the single best treatment for AMS and HACE, but it is not necessary in all circumstances (discussed further later in the text). Individuals should descend until symptoms resolve unless terrain, weather, or injuries make descent impossible. Symptoms typically resolve after descent of 300 to 1000 m, but the required decrease in altitude varies among individuals. Individuals should not descend alone, particularly if they are experiencing HACE.

**Recommendation.** Descent is effective for any degree of AMS/HACE and is indicated for individuals with severe AMS, AMS that fails to resolve with other measures, or HACE. Recommendation Grade: 1A

*Supplemental oxygen*

Oxygen delivered by nasal cannula or mask at flow rates sufficient to relieve symptoms provides a suitable alternative to descent. A peripheral capillary oxygen saturation ( $S_pO_2$ )  $>90\%$  is usually adequate. Use of oxygen is not required in all circumstances and is generally reserved for mountain clinics and hospitals where supply is abundant. It should also be used when descent is recommended but not feasible or during descent in severely ill individuals. The inspired oxygen fraction will vary significantly between oxygen delivery systems, including nasal cannula, simple facemasks, Venturi masks, or non-rebreather masks. In addition, because of interindividual variability in inspiratory flow rates and minute ventilation, the inspired fractional concentration of oxygen ( $F_I O_2$ ) can vary significantly between patients for any given common oxygen delivery system, with the exception of high flow systems. For this reason, supplemental oxygen should be administered to target an  $S_pO_2$  of  $>90\%$  rather than a specific  $F_I O_2$ . Oxygen supply may be limited at remote high altitude clinics or on expeditions, necessitating judicious use. Short-term oxygen use in the form of visits to oxygen bars or use of over-the-counter oxygen canisters has not been studied for AMS treatment and should not be relied on for this purpose.

**Recommendation.** When available, ongoing supplemental oxygen sufficient to raise  $S_pO_2$  to  $>90\%$  or to relieve symptoms can be used while waiting to initiate descent or when descent is not practical. Recommendation Grade: 1A

*Portable hyperbaric chambers*

Portable hyperbaric chambers are effective for treating severe altitude illness<sup>69,70</sup> 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,<sup>71</sup> but this should not preclude use of the chamber when indicated. In many cases, ill individuals may improve sufficiently to enable them to assist in their evacuation and descend once symptoms improve. Use of a portable hyperbaric chamber should not delay descent in situations where descent is required.

**Recommendation.** When available, portable hyperbaric chambers should be used for patients with severe AMS or HACE when descent is infeasible or delayed and supplemental oxygen is not available. Recommendation Grade: 1B

*Acetazolamide*

Only 1 study has examined acetazolamide for AMS treatment. The dose studied was 250 mg every 12 h; whether a lower dose might suffice is unknown.<sup>72</sup> No studies have

assessed AMS treatment with acetazolamide in pediatric patients, but anecdotal reports suggest it has utility. The pediatric treatment dose is 2.5  $mg \cdot kg^{-1} \cdot dose^{-1}$  every 12 h up to a maximum of 250  $mg \cdot dose^{-1}$ .

**Recommendation.** Acetazolamide should be considered for treatment of AMS. Recommendation Grade: 1C

*Dexamethasone*

Dexamethasone is very effective for treating AMS.<sup>73–75</sup> The medication does not facilitate acclimatization, so further ascent should be delayed until the patient is asymptomatic while off the medication. Although systematic studies have not been conducted, extensive clinical experience supports using dexamethasone in patients with HACE. It is administered as an 8 mg dose (intramuscularly, IV, or orally) followed by 4 mg every 6 h until symptoms resolve. The pediatric dose is 0.15  $mg \cdot kg^{-1} \cdot dose^{-1}$  every 6 h.<sup>27</sup>

**Recommendation.** Dexamethasone should be considered for treatment of AMS. Recommendation Grade: 1B.

**Recommendation.** Dexamethasone should be administered to patients with HACE. Recommendation Grade: 1B

*Acetaminophen*

Acetaminophen has been found to relieve headache at high altitude<sup>76</sup> but has not been found to improve the full spectrum of AMS symptoms or effectively treat HACE.

**Recommendation.** Acetaminophen can be used to treat headache at high altitude. Recommendation Grade: 1C.

*Ibuprofen*

Ibuprofen has been found to relieve headache at high altitude<sup>76</sup> but has not been shown to improve the full spectrum of AMS symptoms or effectively treat HACE.

**Recommendation.** Ibuprofen can be used to treat headache at high altitude. Recommendation Grade: 1C.

*Continuous positive airway pressure*

Rather than affecting barometric pressure, CPAP works by increasing transmural pressure across alveolar walls, thereby increasing alveolar volume and improving ventilation-perfusion matching and gas exchange. Two reports have demonstrated the feasibility of administering CPAP to treat AMS,<sup>77,78</sup> but this has not been studied in a systematic manner. Logistical challenges to use in field settings include access to power and the weight and bulk of these systems.

**Recommendation.** Because of lack of data, no recommendation can be made regarding use of CPAP for AMS treatment.

## SUGGESTED APPROACH TO AMS/HACE TREATMENT

Care should be taken to exclude disorders whose symptoms and signs resemble those seen with AMS and HACE, such as carbon monoxide poisoning, dehydration, exhaustion, hypoglycemia, hypothermia, and hyponatremia. Persons with AMS of any severity or HACE should cease ascending and may need to consider descent, depending on the severity of illness and the circumstances (Table 3).<sup>11</sup> Patients with AMS can remain at their current altitude and use nonopioid analgesics for headache and antiemetics for nausea and vomiting. These individuals should be closely observed for signs of progression of altitude illness. Descent should be initiated for AMS if symptoms worsen or fail to improve after 1 to 2 d of appropriate interventions.

Although acetazolamide facilitates acclimatization and is somewhat effective for treating mild illness, it is likely better for prevention than for treatment. Dexamethasone is considered to be a more reliable treatment for moderate to severe AMS, which often also requires descent. Individuals with AMS may resume ascending once symptoms resolve. Further ascent or reascent to a previously attained altitude should never be undertaken if there are ongoing symptoms. After resolution of AMS, taking acetazolamide at preventive doses during reascent is prudent.

HACE is differentiated from severe AMS by neurological signs such as ataxia, confusion, or altered mental status in the setting of acute ascent to high altitude and may follow AMS or occur concurrently with HAPE. Individuals developing HACE in locations with access to hospitals or specialized clinics should be started on dexamethasone and supplemental oxygen sufficient to achieve an  $S_pO_2 > 90\%$ . In remote areas away from medical resources, descent

should be initiated in any suspected cases of HACE or if symptoms of AMS are worsening despite treatment with acetazolamide or dexamethasone. If descent is not feasible, supplemental oxygen or a portable hyperbaric chamber should be used. Persons with HACE should also be started on dexamethasone. There are no systematic data or case reports about reascent during the same trip or expedition after resolution of HACE. The prudent course is to avoid reascent in this situation, but if it is to be attempted, at a minimum the individual should be asymptomatic and no longer taking dexamethasone for at least 2 to 3 d before reascent.

### 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 extensive reviews.<sup>13,14,79,80</sup> Although some of the prophylactic and therapeutic modalities are the same for HAPE as for AMS and HACE, important differences in the underlying pathophysiology mandate certain alternative prevention 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 rate of ascent and disease incidence.<sup>17,81,82</sup>

**Recommendation.** Gradual ascent is recommended to prevent HAPE. Recommendation Grade: 1B

**Table 3.** Acute mountain sickness classification

Category	Mild AMS	Moderate–Severe AMS	High altitude cerebral edema (HACE)
Symptoms	Headache plus 1 or more other symptoms (nausea/vomiting, fatigue, lassitude, dizziness)	Headache plus 1 or more other symptoms (nausea/vomiting, fatigue, lassitude, dizziness)	Worsening of symptoms seen in moderate to severe AMS
Signs	All symptoms of mild intensity None	All symptoms of moderate–severe intensity None	Ataxia, severe lassitude, altered mental status, encephalopathy
Lake Louise AMS Score <sup>a</sup>	3–5	6–12	Not applicable

AMS, acute mountain sickness.

<sup>a</sup> Self-report AMS score. Roach et al.<sup>103</sup>

*Nifedipine*

A single, randomized, placebo-controlled study<sup>83</sup> 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 every 12 h. Hypotension was not noted in the study<sup>83</sup> and is generally not a concern with the extended-release version of the medication but may occur in a limited number of individuals.

**Recommendation.** Nifedipine is recommended for HAPE prevention in HAPE-susceptible people. Recommendation Grade: 1B

*Salmeterol*

In a single randomized, placebo-controlled study, the long-acting inhaled beta-agonist salmeterol decreased the incidence of HAPE by 50% in susceptible individuals.<sup>84</sup> Very high doses (125 micrograms twice daily) that are often associated with side effects, including tremor and tachycardia, were used in the study. Clinical experience with salmeterol at high altitude is limited.

**Recommendation.** Salmeterol is not recommended for HAPE prevention. Recommendation Grade: 2B.

*Tadalafil*

In a single, randomized placebo-controlled trial, 10 mg of tadalafil every 12 h was effective in preventing HAPE in susceptible individuals.<sup>85</sup> The number of individuals in the study was small, and 2 developed incapacitating AMS. Clinical experience with tadalafil is lacking compared to nifedipine. As a result, further data are necessary before tadalafil can be recommended over nifedipine.

**Recommendation.** Tadalafil can be used for HAPE prevention in known susceptible individuals who are not candidates for nifedipine. Recommendation Grade: 1C

*Dexamethasone*

In the same study that assessed the role of tadalafil in HAPE prevention, dexamethasone (8 mg every 12 h) was also found to prevent HAPE in susceptible individuals.<sup>85</sup> The mechanism for this effect is not clear, and there is very little clinical experience in using dexamethasone for this purpose. Further data are necessary before it can be recommended for HAPE prevention.

**Recommendation.** Dexamethasone can be used for HAPE prevention in known susceptible individuals who are not candidates for nifedipine and tadalafil. Recommendation Grade: 1C

*Acetazolamide*

Because acetazolamide hastens acclimatization, it should be effective at preventing all forms of acute altitude illness. It has also been shown to blunt hypoxic pulmonary vasoconstriction, a key factor in HAPE pathophysiology, in animal models<sup>86–88</sup> and in a single study in humans,<sup>89</sup> but there are no data specifically supporting a role in HAPE prevention. Clinical observations suggest acetazolamide may prevent reentry HAPE,<sup>90</sup> a disorder seen in individuals who reside at high altitude, travel to lower elevation, and then develop HAPE upon rapid return to their residence.

**Recommendation.** Because of lack of data, no recommendation can be made regarding use of acetazolamide for HAPE prevention.

**Recommendation.** Acetazolamide can be considered for prevention of reentry HAPE in people with a history of the disorder. Recommendation Grade: 1C

*Preacclimatization and staged ascent*

No study has examined whether preacclimatization strategies are useful for HAPE prevention. Staged ascent, with 7 d of residence at moderate altitude (~2200 m), has been found to blunt the hypoxia-induced increase in pulmonary artery pressure.<sup>48</sup> 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 HAPE-susceptible individuals. Although the risks of preacclimatization and staged ascent are likely low, feasibility is a concern for many high altitude travelers. 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 for implementation.

**Recommendation.** When feasible, staged ascent and preacclimatization can be considered as a means for HAPE prevention. Recommendation Grade: 1C

## SUGGESTED APPROACH TO HAPE PREVENTION

As noted earlier, because the rates of acclimatization and physiologic responses to high altitude vary considerably among individuals, the recommendations that follow, although generally effective, do not guarantee prevention in all high altitude travelers. A gradual ascent profile is the primary method for preventing HAPE; the recommendations provided for AMS and HACE prevention also apply to HAPE prevention. Pharmacologic prophylaxis should only be considered for individuals with a history of HAPE, especially multiple episodes. Nifedipine is the preferred drug in such situations; it should be started the day before

ascent and continued either until descent is initiated or the individual has spent 4 d at the highest elevation, perhaps up to 7 d if the individual's rate of ascent was faster than recommended. Note that these durations are longer than use of acetazolamide for AMS prevention. 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 when descent is initiated. Further research is needed before tadalafil or dexamethasone can be recommended over nifedipine for prevention. Acetazolamide facilitates acclimatization in general but should not be relied upon as the sole preventive agent in known HAPE-susceptible individuals.

## TREATMENT

Therapeutic options for HAPE include the following.

### *Descent*

As with AMS and HACE, descent remains the single best treatment for HAPE. Individuals should try to descend at least 1000 m or until symptoms resolve. They should exert themselves as little as possible while descending (eg, travel without a pack or via motor vehicle, helicopter, or animal transportation) because exertion can further increase pulmonary artery pressure and exacerbate edema formation.

**Recommendation.** Descent is indicated for individuals with HAPE. Recommendation Grade: 1A

### *Supplemental oxygen*

Oxygen delivered by nasal cannula or mask at flow rates sufficient to achieve an  $S_pO_2 > 90\%$  provides a suitable alternative to descent, particularly when patients can access healthcare facilities and be closely monitored.<sup>91–93</sup> As noted earlier in the section on AMS/HACE treatment, providers should target an  $S_pO_2$  of  $> 90\%$  rather than a particular  $F_I O_2$ . Short-term use in the form of visits to oxygen bars or use of over-the-counter oxygen canisters has no role in HAPE treatment.

**Recommendation.** When available, supplemental oxygen sufficient to achieve an  $S_pO_2$  of  $> 90\%$  or to relieve symptoms should be used while waiting to initiate descent when descent is infeasible and during descent in severely ill patients. Recommendation Grade: 1A

### *Portable hyperbaric chambers*

As for AMS and HACE, portable hyperbaric chambers can be used for HAPE treatment. They have not been systematically studied for this purpose, but their use for HAPE has been reported in the literature.<sup>94</sup> Use of a portable hyperbaric chamber should not delay descent in situations where descent is feasible.

**Recommendation.** When descent is infeasible or delayed or supplemental oxygen is unavailable, a portable hyperbaric chamber may be used to treat HAPE. Recommendation Grade: 1C

### *Nifedipine*

A single, nonrandomized, unblinded study demonstrated utility of nifedipine (10 mg of the short-acting version followed by 20 mg slow-release every 6 h) for HAPE treatment when oxygen or descent was not available.<sup>95</sup> Although participants in this study received a loading dose of the short-acting version of the medication, this initial dose is no longer employed because of concerns about provoking systemic hypotension. Although hypotension is less common with the extended-release preparation, it may develop when nifedipine is given to patients with intravascular volume depletion. A prospective, cross-sectional study of individuals with HAPE demonstrated that addition of nifedipine (30 mg sustained release every 12 h) to descent, oxygen, and rest offered no additional benefit in terms of time to resolution of hypoxemia and radiographic opacities or hospital length of stay.<sup>96</sup>

**Recommendation.** Nifedipine should be used for HAPE treatment when descent is impossible or delayed and reliable access to supplemental oxygen or portable hyperbaric therapy is unavailable. Recommendation Grade: 1C

### *Beta-agonists*

Although there are reports of beta-agonist use in HAPE treatment<sup>97</sup> and the risks of use are likely low, no data support a benefit from salmeterol or albuterol in patients experiencing HAPE.

**Recommendation.** No recommendation can be made regarding beta-agonists for HAPE treatment due to lack of data.

### *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,<sup>97,98</sup> no systematic study has examined the role of tadalafil or sildenafil in HAPE treatment as either mono- or adjunctive therapy. Combined use of nifedipine and sildenafil or tadalafil should be avoided because of risk of hypotension.

**Recommendation.** Tadalafil or sildenafil can be used for HAPE treatment when descent is impossible or delayed, access to supplemental oxygen or portable hyperbaric therapy is impossible, and nifedipine is unavailable. Recommendation Grade: 2C

*Continuous positive airway pressure*

As noted earlier, positive airway pressure works by increasing transmural pressure across alveolar walls, thereby increasing alveolar volume and improving ventilation-perfusion matching and, as a result, gas exchange. A small study demonstrated that EPAP, in which a mask system is used to increase airway pressure during exhalation only, improved gas exchange in patients with HAPE.<sup>99</sup> However, although several reports document use of CPAP for management of HAPE in hospital and field settings,<sup>6,78</sup> there is no systematic evidence that CPAP or EPAP improves patient outcomes compared to oxygen alone or in conjunction with medications. Given the low risks associated with the therapy, CPAP can be considered an adjunct to oxygen administration in a medical facility, provided the patient has normal mental status and can tolerate the mask. Although lithium battery-powered devices and decreased size and weight of CPAP machines have increased feasibility of field use, logistical challenges remain and currently limit overall utility in this setting.

**Recommendation.** CPAP or EPAP may be considered for treatment of HAPE when supplemental oxygen or pulmonary vasodilators are not available or as adjunctive therapy in patients not responding to supplemental oxygen alone. Recommendation Grade: 2C

*Diuretics*

Although their use is documented in older reports,<sup>100</sup> diuretics have no role in HAPE treatment, particularly because many patients with HAPE have intravascular volume depletion.

**Recommendation.** Diuretics should not be used for treatment of HAPE. Recommendation Grade: 1C.

*Acetazolamide*

Although clinical reports document use of acetazolamide for treatment of HAPE,<sup>97,98</sup> there are no systematic studies examining its role in HAPE treatment. The diuretic effect might provoke hypotension in the intravascularly depleted patient, and the added stimulus to ventilation might worsen dyspnea.

**Recommendation.** Acetazolamide should not be used for treatment of HAPE. Recommendation Grade: 1C

*Dexamethasone*

Considering its potential role in HAPE prevention noted earlier and studies demonstrating effects on maximum exercise capacity,<sup>101</sup> pulmonary inflammation, and ion transporter function in hypoxia,<sup>102</sup> dexamethasone may have a role in HAPE treatment. Although reports document clinical use in this regard,<sup>98</sup> no study has established whether it is effective for this purpose.

**Recommendation.** Because of insufficient evidence, no recommendation can be made regarding dexamethasone for HAPE treatment.

## SUGGESTED APPROACH TO HAPE TREATMENT

Before initiating treatment, consideration should be given to other causes of respiratory symptoms at high altitude, such as asthma, bronchospasm, mucous plugging, pneumonia, pneumothorax, pulmonary embolism, viral upper respiratory tract infection, or myocardial infarction. If HAPE is suspected or diagnosed, oxygen should be started if available, and descent to lower elevation should be initiated. If descent is infeasible or delayed, supplemental oxygen should be continued or the individual should be placed in a portable hyperbaric chamber. Patients who have access to supplemental oxygen and can be adequately monitored in a medical setting (eg, urgent care clinic or emergency department) may not need to descend to lower elevation and can be treated with oxygen alone at the current elevation. Descent should be initiated, however, if oxygenation fails to improve with supplemental oxygen and/or CPAP, if the patient's condition deteriorates despite achieving an oxygen saturation >90%, or if the patient fails to show signs of improvement with appropriate interventions for HAPE. In more remote settings, early descent should be considered.

Addition of nifedipine may not yield additional benefit in well-monitored settings.<sup>93,96</sup> In the field setting, where resources are limited, nifedipine can be used as an adjunct to descent, supplemental 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 the patient fails to respond to oxygen therapy alone. There is no established role for beta-agonists, diuretics, acetazolamide, or dexamethasone in the treatment of HAPE, although, as noted below, dexamethasone should be considered when concern is raised for concurrent HACE.

Selected patients (able to achieve an oxygen saturation >90%, with adequate support from family or friends, with adequate housing or lodging arrangements) may be discharged from direct medical care if they can continue using supplemental oxygen rather than being admitted to a healthcare facility. Individuals treated in this manner should be admitted to the hospital if they develop worsening symptoms and/or oxygen saturation while on supplemental oxygen. Descent to lower elevation should be pursued if oxygenation or other aspects of their condition worsen despite appropriate interventions for HAPE, as

this suggests they may have alternative pathology that requires further evaluation and management.

Individuals who develop HAPE may consider further ascent to higher altitude or reascent only when symptoms of HAPE have completely resolved and they maintain stable oxygenation at rest and with mild exercise while off supplemental oxygen and/or vasodilator therapy. Consideration may be given to using nifedipine or another pulmonary vasodilator upon 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 earlier for patients with HACE. Some patients with HAPE may have neurologic dysfunction caused by hypoxic encephalopathy rather than caused by HACE, but making the distinction between hypoxic encephalopathy and HACE in the field can be difficult. Therefore, dexamethasone should be added to the treatment regimen for patients with HAPE with neurologic dysfunction that does not resolve rapidly with administration of supplemental oxygen and improvement in oxygen saturation. If supplemental oxygen is not available, dexamethasone should be started in addition to the medications for HAPE in patients with altered mental status and/or suspected concurrent HACE. Nifedipine or other pulmonary vasodilators may be used in patients with concurrent HAPE and HACE, with care to avoid lowering mean arterial pressure, as this may decrease cerebral perfusion pressure and thus increase the risk for cerebral ischemia.

#### Conclusions

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 determining 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, preacclimatization, and hypoxic tents in altitude illness prevention.

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