High-Altitude Medicine

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KEYWORDS

• High altitude • Acute altitude illness • Acute mountain sickness
• High-altitude cerebral edema • High-altitude pulmonary edema • Prevention

KEY POINTS

- High altitude generally refers to elevations greater than 2000 m, although the risk of acute altitude illness does not increase significantly until individuals travel above 2500 m.
- Hypobaric hypoxia, the defining environmental feature of high altitude, leads to lower oxygen tensions at every point along the body's oxygen transport chain, which triggers multiple important physiologic responses.
- Travelers to high altitude should be prepared to prevent, recognize, and treat the 3 main forms of acute altitude illness: acute mountain sickness, high-altitude cerebral edema, and high-altitude pulmonary edema.
- The mainstay of prevention of acute altitude illness is gradual ascent; descent is the best treatment.
- Pretravel evaluation should include counseling about normal changes people experience at high altitude, the primary forms of acute altitude illness, and a systematic evaluation of the risks posed by any underlying medical conditions.

INTRODUCTION

Because of a growing interest in adventure travel, improved global travel infrastructure, and increased access to sites of historical and cultural significance, increasing numbers of people are traveling to high altitude. Although these individuals often enjoy amazing scenery and unperturbed landscapes, such travel is not without risk. All travelers ascending above 2500 m are susceptible to acute altitude illness, including acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE) while individuals with underlying medication conditions, even if

Funding: None.
Disclosures: The authors have no conflicts of interest, financial or otherwise, to report regarding the contents of this article.
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Med Clin N Am 100 (2016) 357–369
http://dx.doi.org/10.1016/j.mcna.2015.09.002 **medical.theclinics.com**
0025-7125/16/$ – see front matter

well compensated before travel, may be at increased risk for complications following ascent.

Given these risks, clinicians may encounter individuals planning high-altitude travel or who had problems on a recent trip. This article outlines a basic framework for counseling, evaluating, and managing these patients.

DEFINING "HIGH ALTITUDE"

Although no consensus definition exists, the term high altitude typically refers to elevations located above 2000 m (~6500 feet). Although observational studies have shown that individuals can develop acute altitude illness at elevations above 2000 m, the risk is not thought to increase substantially until individuals ascend above 2500 m (~8200 feet).[1,2] For most healthy individuals, it is only when traveling above this latter threshold that the altitude should be taken into account while planning a trip. For individuals with severe underlying medical conditions, such as severe chronic obstructive pulmonary disease (COPD) or pulmonary hypertension, the effect of the altitude may require consideration at lower elevations.

THE ENVIRONMENT AT HIGH ALTITUDE

With increasing altitude there is a nonlinear decrease in barometric pressure, which leads to decreased ambient partial pressure of oxygen (P_{O_2}).[3] This process causes a decrease in the P_{O_2} at every point along the oxygen transport cascade from inspired air to the alveolar space, arterial blood, the tissues, and venous blood, which in turn triggers several important physiologic responses.

Other important environmental changes include increased ultraviolet light exposure, decreased humidity, and decreased ambient temperature, which increase susceptibility to sunburn and ultraviolet keratitis, dehydration, and hypothermia, respectively.

PHYSIOLOGIC RESPONSES TO HIGH ALTITUDE

Hypobaric hypoxia causes many physiologic responses across multiple organ systems, such as hypoxic pulmonary vasoconstriction, increased minute ventilation, and increased cardiac output (**Table 1**).[3] The magnitude of these responses varies between individuals, and this variability affects individual tolerance of hypobaric hypoxia and susceptibility to acute altitude illness.

As a result of some of these physiologic responses, travelers feel different at rest and with exertion at high altitude in comparison with lower elevations (**Box 1**). Reviewing these differences is a key component of pretravel counseling, as it can prevent misinterpretation of normal responses as evidence of illness and facilitate identification of individuals who are truly becoming ill.

ACUTE ALTITUDE ILLNESS

For most individuals, the risk of altitude illness begins with ascent to higher than 2500 m. Because health care providers may not be available for consultation during travel, all travelers should be able to recognize AMS, HACE, and HAPE, and respond appropriately if these conditions develop.

Acute Mountain Sickness and High-Altitude Cerebral Edema

Definitions and clinical features

AMS is a clinical syndrome characterized by headache plus one of several other symptoms including anorexia, nausea, dizziness, malaise, or sleep disturbance. It

Table 1
Physiologic responses to high altitude

System	Responses
Pulmonary responses	Arterial hypoxemia triggers increased peripheral chemoreceptor output leading to an increase in minute ventilation and a respiratory alkalosis Respiratory alkalosis blunts the initial ventilatory responses With continued time at high altitude, minute ventilation rises further because of renal compensation for the respiratory alkalosis and increased sensitivity of the peripheral chemoreceptors Alveolar hypoxia triggers hypoxic pulmonary vasoconstriction, leading to an increase in pulmonary vascular resistance and pulmonary artery pressure
Cardiac responses	Cardiac output increases, largely because of an increase in heart rate Stroke volume declines because of a decrease in plasma volume Myocardial contractility is preserved Systemic blood pressure increases to a variable extent
Renal responses	Variable increase in diuresis and natriuresis following ascent leads to a decrease in circulating plasma volume Arterial hypoxemia triggers increased secretion of erythropoietin (EPO) within 24–48 h of ascent Increased bicarbonate excretion as compensation for the acute respiratory alkalosis
Hematologic responses	Initial increase in hemoglobin concentration and hematocrit caused by reduction in plasma volume Over days to weeks, further increases in red blood cell mass, hemoglobin concentration, and hematocrit owing to increased EPO concentrations

typically occurs 6 to 12 hours following ascent above 2500 m, although the altitude at which symptoms start varies between individuals.[4] HACE is a severe, potentially fatal, form of altitude illness marked by signs of global neurologic dysfunction including truncal ataxia, altered mental status, and depressed consciousness. Although the underlying pathophysiology of these 2 disorders remains unclear, they are generally seen as being on the opposite ends of the spectrum of severity of a common process. Few individuals who develop AMS ever go on to develop HACE, but the onset of neurologic symptoms and signs in any AMS patient should always prompt concern for the possibility of HACE. AMS symptoms are not necessarily seen before the onset of HACE.

Box 1
How travelers feel differently at high altitude

Heart rate at rest and with any level of exertion is higher than at altitude of residence

Increased respiratory rate and tidal volume

More frequent sighs

Increased frequency of urination

Dyspnea on exertion that resolves quickly with rest

Difficulty sleeping including frequent arousals, insomnia, vivid dreams

Transient lightheadedness on rising to a standing position

Epidemiology and risk factors

AMS incidence is largely a function of the altitude attained and the rate of ascent, occurring in approximately 10% to 25% of unacclimatized persons ascending to 2500 m and 50% to 75% of individuals climbing Kilimanjaro (elevation 5895 m).[4–6] HACE is rare, having been reported to affect only 0.5% to 1.0% of persons traveling to 4000 to 5000 m,[4] although methodological issues make defining the true prevalence difficult. Although studies have sought to identify factors that affect risk such as age, gender, and weight, the most important risk factors for AMS and other forms of altitude illness remain the rate of ascent and prior history of altitude illness (**Table 2**).[4,5]

Prevention

The single best means to prevent altitude illness is to undertake a slow ascent to high elevation.[2,5,7] Above 3000 m, individuals should not increase the sleeping elevation by more than 500 m per day and should include rest days during which they sleep at the same elevation for multiple nights every 3 to 4 days. The altitude at which someone sleeps is considered more important than the altitude reached during waking hours.

A variety of medications are also available for prevention (see **Table 2**). Acetazolamide is the preferred agent, as multiple trials have demonstrated its efficacy in preventing AMS.[2,8,9] Dexamethasone is an alternative for individuals with intolerance of or an allergic reaction to acetazolamide.[2,9–11] Recent evidence suggests that ibuprofen may prevent AMS, but is not part of standard protocols at present.[2,12] Gingko biloba has also received attention in the research literature but is not recommended for this purpose.[2] Phosphodiesterase inhibitors have no role in AMS prevention.

Treatment

Descent is the best treatment for acute altitude illness but is not necessary in all circumstances. Patients with AMS should remain at their current altitude, and use nonopiate analgesics for headache and antiemetics for gastrointestinal symptom relief. Acetazolamide can be added to treat mild illness, while dexamethasone is very effective in the treatment of any severity of AMS, especially moderate to severe disease (see **Table 2**).[2,13,14] Individuals with AMS may ascend further once symptoms resolve, and should strongly consider continuing acetazolamide for the remainder of the ascent. Descent is indicated if symptoms fail to resolve after 2 to 3 days of appropriate treatment. Further ascent should never be undertaken in the face of ongoing symptoms.

Any individual thought to have HACE should descend to lower elevation. If descent is infeasible owing to logistical issues, supplemental oxygen or a portable hyperbaric chamber should be considered, if available (**Fig. 1**). Dexamethasone should also be started and no further ascent attempted until the individual is asymptomatic while off medications.[2]

High-Altitude Pulmonary Edema

Definition and clinical features

HAPE is a noncardiogenic pulmonary edema caused by exaggerated hypoxic pulmonary vasoconstriction and overly large increases in pulmonary artery pressure, which lead to leakage of fluid into the interstitial and alveolar spaces of the lung.[15,16] In the early stages, individuals have dyspnea beyond that expected for the level of exertion and altitude, loss of stamina, and dry cough. In later stages they manifest dyspnea with simple activities or at rest, cyanosis, and cough productive of pink, frothy sputum. HAPE typically develops 2 to 5 days after exposure to altitudes above 2500 m, but has

Table 2
Doses and other considerations for medications used in the prevention and treatment of acute altitude illness

Medication	Indication	Dose For Prevention	Dose For Treatment	Other Considerations
Acetazolamide	Prevention and treatment of AMS	125 or 250 mg every 12 h	250 mg every 12 h	Caution in renal failure; adjust dose for GFR[a] Contraindicated in patients with cirrhosis Avoid in patients with severe ventilatory limitation (FEV_1 <25% predicted) Caution in patients with documented sulfa allergy
Dexamethasone	Prevention and treatment of AMS and HACE	2 mg every 6 h or 4 mg every 12 h	AMS: 4 mg every 6 h HACE: 8 mg once then 4 mg every 6 h	May increase blood glucose values in diabetic patients Avoid in patients at risk for peptic ulcer disease
Nifedipine	Prevention and treatment of HAPE	30 mg sustained-release version every 12 h	30 mg sustained-release version every 12 h	Caution when combining with other antihypertensive medications
Tadalafil[b]	Prevention and treatment of HAPE	10 mg every 12 h	10 mg every 12 h	Avoid concurrent use of nitrates and α-blockers
Salmeterol[c]	Prevention of HAPE	125 μg inhaled every 12 h	Not used for treatment	Potential for adverse effects in patients with coronary artery disease prone to arrhythmia

Abbreviations: AMS, acute mountain sickness; FEV_1, forced expiratory volume in 1 second; GFR, glomerular filtration rate; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema.

[a] Patients with a GFR of 10 to 50 mL/min should not take acetazolamide more frequently than every 12 hours; patients with GFR of less than 10 mL/min should not use the drug.

[b] Combination therapy involving calcium-channel blockers and phosphodiesterase inhibitors should be avoided.

[c] Salmeterol is not used as first-line monotherapy for HAPE prevention, and is generally reserved for use in addition to a pulmonary vasodilator medication.

Fig. 1. Portable hyperbaric chamber. (*A*) Once an ill individual is placed inside the bag, a tight-fitting zipper is closed and the bag is inflated using a foot pump. Barometric pressure rises inside the bag, simulating a descent in altitude, as shown in the photo of an individual holding an altimeter watch outside (*B*) and inside (*C*) the bag following inflation. The magnitude of simulated descent varies based on the altitude of use and inflation pressure. Continuous pumping is required after initial inflation to maintain pressure and ensure adequate ventilation.

been documented at lower elevations in individuals with underlying pulmonary hypertension.[17]

Epidemiology and risk factors

The risk of HAPE is a function of the altitude attained, rate of ascent, and individual susceptibility. Individuals ascending to 4500 m have an incidence of 0.2% when ascending to 4500 m over 4 days, and an incidence of 6% when the same ascent is done within 1 to 2 days.[4,18] Studies from the Alps suggest that climbers with a prior history of HAPE have a roughly 60% chance of recurrence on future ascents to the same elevation at a similar rate.[4,18]

Prevention

Given the relationship between rate of ascent and incidence, gradual ascent is the best method for preventing HAPE. Extensive clinical experience, along with a small randomized trial, has established a role for nifedipine as the first-line agent for pharmacologic prophylaxis in individuals with a prior history of HAPE (see **Table 2**).[2,19] Dexamethasone, tadalafil, and salmeterol have also been shown to be effective in HAPE prevention in known susceptible individuals, but have not supplanted nifedipine

for this purpose.[2,20] Acetazolamide can blunt hypoxic pulmonary vasoconstriction[21,22] but has not been shown to prevent HAPE, and should not be used for this purpose in known susceptible individuals.[7]

Treatment

If the affected individual can access a health facility, HAPE may be treated with rest and supplemental oxygen alone.[10,23] In the field, descent, supplemental oxygen, and nifedipine are the mainstays of therapy (see **Table 2**).[2,23,24] Care must be taken to avoid overexertion on descent, as this can raise pulmonary artery pressure and worsen HAPE. Phosphodiesterase inhibitors may be used as an alternative to nifedipine, although combination therapy should be avoided. If descent is infeasible because of logistical factors, supplemental oxygen or a portable hyperbaric chamber (see **Fig. 1**) should be used if available. There is no established role for acetazolamide, β-agonists, dexamethasone, or diuretics in HAPE treatment.

WHEN THE HIGH-ALTITUDE TRAVELER COMES TO CLINIC

Individuals may seek advice from their health care providers regarding high-altitude travel in 1 of 3 scenarios:

- *The altitude-naïve traveler* who has never ascended to high altitude before and seeks advice on how to ensure a safe trip.
- *The returning traveler* who had problems on a prior trip, and seeks information about what happened and how to prevent such problems in the future.
- *The potentially risky traveler* who has underlying medical problems that may worsen at high altitude or predispose to acute altitude illness.

The Altitude-Naïve Traveler

Many travelers have never been to high altitude, and seek advice about what to expect in this environment and how to prevent problems. Similarly, individuals who have traveled to high altitude before may be planning travel to a much higher elevation on a future trip, and seek advice about how their risk of problems may increase. These visits should include counseling about the normal changes to expect at altitude and the recognition, prevention, and management of altitude illness. A key decision is whether to prescribe pharmacologic prophylaxis against altitude illness. This decision should be based on assessment of the risk associated with the planned ascent (**Table 3**). Pharmacologic prophylaxis (see **Table 2**) is not indicated with low-risk ascent profiles but should be strongly considered for moderate-risk to high-risk ascent profiles.

The Returning Traveler

Travelers returning from high altitude often present for evaluation of problems that developed during their trip and how to prevent such issues in the future. A major challenge in these assessments is that the symptoms and signs have typically resolved by the time of evaluation, with little objective data available because travelers often do not access medical care at the time of their problem.

A key question is whether the problem was directly related to hypobaric hypoxia at high altitude. In general, symptoms and signs developing after ascent and resolving with descent are attributable to high altitude. The timing of onset relative to the ascent can also be useful, as AMS, HACE, and HAPE typically develop within 1 to 5 days of ascent and are extremely unlikely after 5 days at a given elevation.

Table 3
Risk categories for acute altitude illness in unacclimatized individuals

Risk Category	Description
Low	Individuals with no prior history of altitude illness and ascending to ≤2800 m Individuals taking ≥2 d 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 d No history of AMS and ascending to >2800 m in 1 d All individuals ascending >500 m/d (increase in sleeping elevation) at altitudes >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 d All individuals with a prior history of HACE or HAPE All individuals ascending to >3500 m in 1 d All individuals ascending >500 m/d (increase in sleeping elevation) >3000 m without extra days for acclimatization Very rapid ascents (eg, Mount Kilimanjaro)

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

Adapted from Luks AM, McIntosh SE, Grissom CK, et al. Wilderness Medical Society practice guidelines for the prevention and treatment of acute altitude illness: 2014 update. Wilderness Environ Med 2014;25:S7; with permission.

For individuals who developed acute altitude illness, prior performance at high altitude is a decent, but not perfect, predictor of outcomes on subsequent trips. Individuals with AMS and HACE do not warrant further testing to determine risk of recurrence, and can return to high altitude in the future. Because HAPE-susceptible individuals have a characteristic phenotype marked by excessive rises in pulmonary artery pressure in response to hypoxia and exercise, consideration can be given to evaluating for such responses in individuals with a concerning history, although this is not required in all circumstances. Whereas those with AMS may not require pharmacologic prophylaxis with future low-risk ascents (see **Table 3**), individuals with HACE or HAPE should use pharmacologic prophylaxis on future trips (see **Table 2**), as the consequences of these illnesses are potentially great. All individuals with prior altitude illness should receive counseling about the importance of slow ascent.

For problems other than acute altitude illness, the need for further evaluation depends on the particular problem. For example, individuals who developed chest pain on exertion at high altitude or those with symptomatic retinal hemorrhages may warrant further evaluation by the appropriate specialist.

The Potentially Risky Traveler

Although many travelers have no significant medical history, it is highly likely that some individuals who present for pretravel counseling will have underlying conditions that may pose a risk during the planned sojourn. These individuals warrant assessment to determine whether such issues will worsen at high altitude or affect the risk of acute altitude illness, particularly when the underlying disease is severe or affects the respiratory or cardiovascular systems.

A framework for assessing risk

Because information regarding the risks of travel with many of these problems is limited, providers can use a framework, based on 4 general questions, for determining

the safety of the planned sojourn, the need for further pretravel evaluation, and the appropriate risk-mitigation strategies. Several issues related to specific medical conditions are addressed in **Table 4**.

Question 1: Is the individual at risk for severe hypoxemia or impaired tissue oxygen delivery? Although all individuals develop varying degrees of hypoxemia at high altitude based on the altitude attained and the strength of their ventilatory responses, certain categories of patients, including those with moderate to severe COPD, interstitial lung diseases, severe cystic fibrosis, and cyanotic congenital heart disease are at risk for severe hypoxemia and, as a result, increased dyspnea and poor exertional tolerance.[25,26] With anemia, the arterial P_{O_2} and oxygen saturation are the same at rest as in normal individuals but oxygen-carrying capacity and delivery are decreased, which may also lead to severe dyspnea and exercise limitation.

Question 2: Is the individual at risk for impaired ventilatory responses to hypoxia? Arterial hypoxemia normally triggers increased minute ventilation, whose role is to maintain alveolar and arterial oxygen tensions at adequate levels. Individuals with impaired respiratory mechanics, as in severe COPD, obesity hypoventilation syndrome, and many neuromuscular disorders, or those with impaired respiratory drives, such as following carotid artery surgery, may be unable to mount the expected ventilatory responses and, as a result, may be at risk for severe hypoxemia following ascent.[25]

Question 3: Is the individual at risk from the expected pulmonary vascular responses to hypobaric hypoxia? Decreases in the alveolar P_{O_2} following ascent cause hypoxic pulmonary vasoconstriction and an increase in pulmonary artery pressure. This change is well tolerated in most individuals but could pose problems for patients with pulmonary hypertension or right heart disease.[17,25,26]

Question 4: Will environmental features of high altitude or the expected physiologic responses to hypobaric hypoxia worsen the underlying medical condition? Certain features of the environment at high altitude or the expected physiologic responses to hypoxia can affect some medical conditions. For example, cold dry air may adversely affect airway function in asthmatic individuals,[27] while increased sympathetic nervous system activity can worsen blood pressure in hypertensive individuals. Hypoxemia at high altitude can trigger vaso-occlusive crises in patients with sickle cell disease or provoke myocardial ischemia in patients with poorly controlled coronary artery disease (see **Table 4**).[26,28]

Further evaluation

If the answer to all of these questions is “no,” the individual is likely safe to travel to high altitude without further evaluation or risk-mitigation strategies beyond the general prevention measures described earlier.

For individuals deemed to be at risk based on nonreassuring answers to the first 3 questions, further risk assessment and risk-mitigation strategies may be necessary. One useful way to assess possible outcomes at high altitude is to expose patients to hypoxia and monitor their responses. The most feasible approach is the hypoxia altitude simulation test, whereby an individual breathes a hypoxic gas mixture while symptoms and physiologic responses are monitored.[29] The test can be supplemented with echocardiography to assess the pulmonary vascular responses to hypoxia. One challenge with the test is that its duration is short relative to the duration of the planned trip to high altitude, and may not reflect the full range of physiologic responses experienced by the patient during the trip. For individuals planning trips to distant places

Table 4
Common medical conditions and high-altitude travel

Disease	Key Issues For High Altitude Travel
Asthma	Well-controlled patients can travel as high as 6000 m. Data regarding travel to higher elevations are lacking, but such ascents are likely safe in well-controlled patients Avoid travel with worsening asthma control or following an acute exacerbation Continue inhaler regimen at high altitude and travel with an adequate supply of rescue medications. Keep inhalers warm in cold environments
Chronic obstructive pulmonary disease	Avoid high-altitude travel in patients with FEV_1 <1 L, CO_2 retention, pulmonary hypertension, or recent exacerbation Assess need for supplemental oxygen in patients with FEV_1 1.0–1.5 L Monitor pulse oximetry following ascent Continue inhaler regimen at high altitude and travel with an adequate supply of rescue medications. Keep inhalers warm in cold environments
Congestive heart failure	Avoid high-altitude travel with poorly compensated disease or following a recent exacerbation May ascend with well-compensated disease to altitudes <3000 m Monitor weight and blood pressure following ascent and adjust medications according to prearranged plan
Coronary artery disease	Avoid high-altitude travel with unstable angina, ischemia at low levels of exertion, or recent acute coronary syndrome (<3 mo, no revascularization) Consider risk stratification with stress test before travel Reduce level of exertion to slightly lower than that done at sea level Continue existing medications at high altitude
Diabetes mellitus	Increase frequency of blood glucose monitoring Avoid overly strict glucose control early in the trip because of concerns about glucometer accuracy a high altitude Evaluate for comorbid conditions (eg, coronary artery disease) that could worsen at high altitude Avoid vigorous exercise at high altitude if not experienced with high-level exercise at sea level
Hypertension	Mild or well-controlled disease: No indication for medication adjustments or routine blood pressure monitoring Poorly controlled or labile hypertension: monitor blood pressure following ascent and adjust medications for severely elevated blood pressures (>180/120 with symptoms or >220/140 without symptoms)
Obstructive sleep apnea	Patients with moderate to severe disease should travel with CPAP machine if access to power can be assured Consider adding acetazolamide to decrease the incidence of central sleep apnea
Pregnancy	Pretravel evaluation to ensure pregnancy remains low risk Avoid high-altitude travel with complicated or high-risk pregnancies (eg, impaired placental function, chronic hypertension, intrauterine growth retardation, anemia) Exercise at levels lower than at home; avoid dehydration Avoid travel to remote areas in the third trimester

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Table 4
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Disease	Key Issues For High Altitude Travel
Pulmonary hypertension	Avoid high-altitude travel without supplemental oxygen with moderate to severe disease (mean PA pressure >35 mm Hg or systolic PA pressure >60 mm Hg) In less severe disease, consider adding pulmonary vasodilator therapy or supplemental oxygen
Sickle cell diseases	Sickle cell anemia: avoid high-altitude travel because of increased risk of sickling and vaso-occlusive and splenic crises Sickle cell trait: high-altitude travel likely permissible, but patients should avoid heavy exertion and seek medical attention for left upper quadrant pain (possible splenic crisis)

Abbreviations: CPAP, continuous positive airway pressure; FEV_1, forced expiratory volume in 1 second; PA, pulmonary artery.

such as the Himalaya or Andes Mountains, another option, time permitting, would be taking test trips to mountain resorts or ski areas, where the individual can easily descend or access health facilities in the event of problems.

For nonreassuring answers to the fourth question, the approach varies according to the clinical circumstances. Further information about how to approach specific diseases is available in **Table 4** and in several reviews on these topics.[25,30–34]

SUMMARY

Travel to high altitude carries many rewards, but is not without risks. Travelers must be able to recognize, prevent, and treat the acute altitude illnesses and should receive pretravel evaluation for underlying medical conditions that may be affected by the altitude. Clinicians caring for such patients should be prepared to provide counseling about the normal changes at high altitude, stratify an individual's risk for altitude illness based on their planned ascent profile, and provide recommendations regarding prevention, recognition, and treatment of the main altitude illnesses and the management of underlying medical problems.

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