CLINICAL PRACTICE

Acute High-Altitude Illnesses

Peter Bärtsch, M.D., and Erik R. Swenson, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 45-year-old healthy man wishes to climb Mount Kilimanjaro (5895 m) in a 5-day period, starting at 1800 m. The results of a recent exercise stress test were normal; he runs 10 km 4 or 5 times per week and finished a marathon in less than 4 hours last year. He wants to know how he can prevent becoming ill at high altitude and whether training or sleeping under normobaric hypoxic conditions in the weeks before the ascent would be helpful. What would you advise?

THE CLINICAL PROBLEM

From the University Clinic, Department of Internal Medicine, Division VII: Sports Medicine, Heidelberg, Germany (P.B.); and Pulmonary and Critical Care Medicine, Department of Medicine, Veterans Affairs Puget Sound Health Care System, University of Washington, Seattle (E.R.S.). Address reprint requests to Dr. Bärtsch at the University Clinic, Department of Internal Medicine, Division VII: Sports Medicine, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany, or at peter.bartsch@med.uni-heidelberg.de.

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Persons who are not acclimatized and ascend rapidly to high altitudes are at risk for any of several debilitating and potentially lethal illnesses (Table 1) that occur within the first days after arrival at high altitudes.[1] Traditionally, 2500 m has been used as the threshold for high-altitude illnesses; in rare cases, mild illness occurs in persons who have ascended above 2000 m but below 2500 m.

ACUTE MOUNTAIN SICKNESS

Headache that occurs with an increase in altitude is the cardinal symptom of acute mountain sickness and is usually accompanied by anorexia, nausea, dizziness, malaise, sleep disturbance, or a combination of these symptoms.[2] Acute mountain sickness generally occurs within 6 to 12 hours after a person ascends to 2500 m or higher. Its prevalence and severity increase with increasing altitude. Acute mountain sickness occurs in approximately 10 to 25% of unacclimatized persons who ascend to 2500 m. Symptoms are usually mild at this altitude and have little effect on activity. However, acute mountain sickness occurs in 50 to 85% of unacclimatized persons at 4500 to 5500 m and may be incapacitating.[3-5]

In a retrospective study, major independent risk factors for acute mountain sickness included a history of acute mountain sickness, fast ascent (≥625 m per day above 2000 m), and lack of previous acclimatization (<5 days above 3000 m in the preceding 2 months).[6] A prospective study involving trekkers and climbers who went to altitudes between 4000 and 8848 m showed the same major risk factors for incapacitating acute mountain sickness and other severe altitude illnesses[7] (described below). Other possible risk factors include female sex, an age younger than 46 years, and a history of migraine. Exercise may exacerbate acute mountain sickness, but good physical fitness is not protective.[6-8] Symptoms usually resolve within 1 to 2 days when appropriate measures are taken (see below).

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HIGH-ALTITUDE CEREBRAL EDEMA

High-altitude cerebral edema is characterized by truncal ataxia, decreased consciousness, and usually mild fever.[2,9] Without appropriate treatment, coma may evolve rapidly, followed by death from brain herniation within 24 hours. Headache

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KEY CLINICAL POINTS

ACUTE HIGH-ALTITUDE ILLNESSES

- Acute high-altitude illnesses occur in persons who are not acclimatized during the first days at an altitude of 2500 m or higher, with wide variation in the incidence according to patient characteristics and history.
- Headache is the major symptom of acute mountain sickness. If acute mountain sickness is not treated adequately, it can progress to life-threatening high-altitude cerebral or pulmonary edema.
- High-altitude illnesses can be prevented by ascending 300 to 500 m per day at altitudes above 3000 m and including a rest day every 3 to 4 days.
- Risks of acute mountain sickness and high-altitude cerebral edema are reduced with the use of acetazolamide or dexamethasone; the risk of high-altitude pulmonary edema is reduced with the use of nifedipine, phosphodiesterase-5 inhibitors, or dexamethasone.
- Acute mountain sickness may be treated by a day of rest and nonsteroidal antiinflammatory drugs for headache, but when it is severe, descent or supplemental oxygen is indicated. Dexamethasone is indicated for severe acute mountain sickness or high-altitude cerebral edema, and nifedipine or phosphodiesterase-5 inhibitors are indicated for high-altitude pulmonary edema; treatment with these agents should be followed by descent as soon as possible.

that is poorly responsive to nonsteroidal antiinflammatory drugs (NSAIDs) and vomiting indicate probable progression of acute mountain sickness to high-altitude cerebral edema, but the absence of headache and other symptoms of acute mountain sickness does not rule it out. High-altitude cerebral edema usually develops after at least 2 days at altitudes above 4000 m. The prevalence is estimated to be 0.5 to 1.0% among persons at 4000 to 5000 m.[10] Magnetic resonance imaging in patients with high-altitude cerebral edema shows vasogenic edema[11] and microhemorrhages that are located predominantly in the corpus callosum.[12]

HIGH-ALTITUDE PULMONARY EDEMA

High-altitude pulmonary edema is characterized by loss of stamina, dyspnea, and dry cough with exertion, followed by dyspnea at rest, rales, cyanosis, cough, and pink, frothy sputum.[13] Deterioration in gas exchange also increases the risk of high-altitude cerebral edema. This condition develops 2 or more days after exposure to altitudes above 3000 m and is rare in persons at altitudes below 2500 to 3000 m. The risk increases with increased altitude and faster ascent. For example, the incidence among persons with an unknown history of high-altitude pulmonary edema is 0.2% if they ascend to 4500 m in 4 days and 2% if they ascend to 5500 m in 7 days; the incidence increases to 6% and 15%, respectively, when these altitudes are reached within 1 to 2 days. The risk is further increased among persons with a history of high-altitude pulmonary edema (e.g., the risk of recurrence is 60% among persons who ascend to 4500 m in 2 days).[14] The estimated mortality among persons with untreated high-altitude pulmonary edema is 50%. This disorder is a noncardiogenic pulmonary edema caused by exaggerated hypoxic pulmonary vasoconstriction and abnormally high pulmonary-artery pressure and capillary pressure.[15] These high pressures lead to a noninflammatory and hemorrhagic alveolar capillary leak that secondarily may evoke an inflammatory response.[16]

STRATEGIES AND EVIDENCE

RISK ASSESSMENT

Risk assessment (Table 2) should start with a clinical evaluation directed toward any cardiopulmonary diseases that might worsen during a sojourn involving high altitude. Although a discussion of the effect of altitude in persons with preexisting disease is not within the scope of this article, reviews of this topic are available.[17,18] Given that previous altitude illness is a strong predictor of recurrence, detailed information about the person's history with respect to visits to high-altitude areas, acclimatization before pre-

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Table 1. Symptoms, Signs, and Differential Diagnosis of High-Altitude Illnesses.

Variable	Acute Mountain Sickness	High-Altitude Cerebral Edema	High-Altitude Pulmonary Edema
Symptoms	Headache plus one or more of the following symptoms: nausea, vomiting, dizziness, fatigue, and insomnia. Mild-to-moderate illness: a few symptoms of mild-to-moderate intensity within 6 to 12 hr after exposure to altitudes of ≥2500 m; severe illness: many or all symptoms of severe intensity, usually evolving from mild-to-moderate illness	Moderate-to-severe symptoms of acute mountain sickness	Initial illness: inappropriate dyspnea during exercise, reduced exercise performance, mild fever; advanced illness: orthopnea, pink frothy sputum, drowsiness
Signs	None	Lassitude, truncal ataxia, altered mental status such as drowsiness or loss of consciousness, often mild fever	Tachypnea, arterial oxygen saturation considerably below average value for other persons in climbing group, mild fever, signs of high-altitude cerebral edema with advanced stages
Differential diagnosis	Exhaustion, dehydration, hangover, migraine	Transient ischemic attack or stroke, acute psychosis, intoxication (from carbon monoxide, alcohol, or drugs)	Hyperventilation syndrome, pulmonary embolism, mucus plugging

vious ascents, maximum altitudes for climbing and sleeping, rates of ascent, and any altitude illness should be obtained. The estimation of risk is most reliable for persons with previous rates of ascent and final altitudes that were similar to those planned.

OTHER ASSESSMENTS

The assessment of ventilation in response to exposure to hypoxic conditions at rest or during exercise has been proposed as a means of refining risk prediction for altitude sickness. The increase in ventilation at rest or during exercise while breathing 11.5% oxygen,[19] as well as arterial oxygen saturation after the first 30 minutes of exposure to an altitude of 3000 m or to corresponding normobaric hypoxic conditions,[20] is on average significantly lower in persons who are susceptible to acute altitude sickness than in those who are not. However, considerable overlap between groups classified as susceptible and those classified as not susceptible in a retrospective study[20] and between a group classified as having acute mountain sickness and a group classified as unaffected in a prospective study[19] makes it impossible to define cutoff values that are sufficiently sensitive and specific to be useful in practice. A multivariate analysis of risk factors for severe high-altitude illness[7] showed that the hypoxic ventilatory response and other physiological measurements under hypoxic conditions add little to the discrimination provided by patient characteristics and history (i.e., sex, level of physical activity, rate of previous ascent, and status with respect to previous severe high-altitude illness and migraines).

Persons who are considered to be susceptible to high-altitude pulmonary edema because of two previous episodes of high-altitude pulmonary edema have abnormally high systolic pulmonary-artery pressure (>40 mm Hg) under hypoxic conditions (12% oxygen in ambient air at sea level).[21] In a study of a western European population, exaggerated hypoxic pulmonary-artery pressure was detected in about 10% of study participants,[22] but high-altitude pulmonary edema develops in only 15% of persons with exaggerated hypoxic pulmonary-artery pressure responses who make a rapid ascent (unpublished data). For this reason and because of a very low pretest probability of high-altitude pulmonary edema (e.g., an incidence of 1 to 2% among trekkers to the Mount Everest base camp), measurement of pulmonary-artery pressure under hypoxic conditions cannot be recommended as a means of identifying persons who are susceptible to high-altitude pulmonary edema.

Although athletic persons are more likely to reach the summit than persons who are not athletic,[19] physical fitness appears to have no association[8,19] or at most a modest association[7] with susceptibility to acute mountain sickness and high-altitude pulmonary edema. Thus, an exercise test is not indicated to assess the risk of acute high-altitude illness. Information about the amount and intensity of the person's regular

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Table 2. Risk Assessment for Acute High-Altitude Illnesses.*

Risk	Planned Ascent and Clinical History
Low	Slow ascent (≤500 m/day above 2500 m); no history of acute mountain sickness, high-altitude cerebral edema, or high-altitude pulmonary edema with previous exposure to similar altitude; rapid ascent (>500 m/day above 2500 m) for persons who are partially acclimatized (exposure to high altitudes of <3000 m in preceding weeks)
Moderate	Unknown history of acute mountain sickness, high-altitude cerebral edema, or high-altitude pulmonary edema and fast ascent (>500 m/day above 3000 m); unknown history of acute mountain sickness and rapid ascent (ascent to >3000 m in 1 day)
High	Unknown history of acute mountain sickness, high-altitude cerebral edema, or high-altitude pulmonary edema, very rapid ascent (considerably >500 m/day), and high final altitude (>4000 m); history of acute mountain sickness, high-altitude cerebral edema, or high-altitude pulmonary edema with previous exposure to high altitude that is similar to the planned ascent

* All ascent altitudes refer to ascent from the altitude at which the person has slept.

exercise as well as his or her level of athletic performance is helpful in estimating whether there is sufficient reserve to cope with the expected loss of exercise capacity at high altitudes of about 1% for every 100 m above 1500 m.[23] Persons without athletic training should be encouraged to begin regular physical exercise several weeks to months before the planned ascent, particularly when rigorous outdoor activities are planned at high altitudes.

PREVENTION

Nonpharmacologic Approaches

Although data are lacking from prospective studies that systematically assess the influence of the rate of ascent (defined as the gain in altitude between the altitudes at which one sleeps on 2 consecutive nights) on prevention of acute high-altitude illnesses, guidelines for ascents to altitudes above 3000 m[24,25] recommend ascent rates of 300 to 500 m per day and a day of rest every 3 to 4 days (Table 3). However, there are large differences among persons with respect to ascent rates that are not associated with poor outcomes. A person without previous experience in high altitudes should follow the ascent rates recommended by these guidelines. If the planned ascent rate is faster, additional measures, such as acclimatization strategies before the ascent or prophylactic medications, should be considered.

Mountaineering or residence with regular physical activity at altitudes above 3000 m in the weeks preceding a climb to 4500 m is associated with a reduced incidence of acute mountain sickness that is independent of the person's susceptibility to this condition and the rate of ascent.[6] An ascent made after 1 week at an altitude of 2000 m or higher, as compared with an ascent from near sea level, reduces both the incidence and severity of acute mountain sickness at 4300 m by 50%.[26] It has been hypothesized that exposure to normobaric hypoxic conditions before an ascent might provide protection against acute mountain sickness. In double-blind, placebo-controlled trials, however, repeated intermittent exposure to normobaric hypoxia equivalent to an altitude of 2500 to 4500 m for 60 to 90 minutes[27,28] or continuous exposure to normobaric hypoxia equivalent to an altitude of 2500 to 3000 m during 8 hours of sleep on 7 consecutive nights[29] did not significantly reduce the incidence or severity of acute mountain sickness at altitudes of 4300 to 4559 m. On the basis of these data, a recommended strategy to reduce the risk of high-altitude illness is to remain at an altitude between 2000 and 3000 m for about a week[6,26] and to include day hiking or climbing at higher altitudes. This should be done as close in time as possible to the trek or expedition, since it is not known how quickly acclimatization diminishes with time.[30]

Prophylactic Medication

Randomized, placebo-controlled trials have shown a significant reduction in the risk of headache with the use of acetylsalicylic acid at a dose of 320 mg taken three times at 4-hour intervals, starting 1 hour before ascent,[31] or ibuprofen at a dose of 600 mg three times per day,[32,33] starting a few hours before ascent to altitudes between 3480 and 4920 m. Headache is a defining symptom of acute mountain sickness, and the incidence of this condition was reduced in all these trials, which lasted 1 or 2 days only. A risk asso-

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Table 3. Prevention of High-Altitude Illnesses.

Method	Description
Acclimatization before exposure	Sojourning several days at intermediate altitudes at or above 2000 m (staging), hiking or climbing on day tours above 3000 m, or both
Slow ascent	Ascent rate of 300–500 m/day above 2500–3000 m, with a day of rest every 3–4 days; appropriate treatment of early symptoms of acute mountain sickness for prevention of severe high-altitude disease
Drugs for prevention of acute mountain sickness, high-altitude cerebral edema, or both	
Moderate risk	Acetazolamide, 125 mg twice/day; if there are side effects with or contraindications to acetazolamide, dexamethasone, 4 mg twice/day, can be used
High risk	Acetazolamide, 250 mg two or three times/day (three times/day recommended for rapid ascent, though efficacy uncertain); dexamethasone, 4 mg three times/day, if acetazolamide has unacceptable side effects or is contraindicated
Drugs for prevention of high-altitude pulmonary edema in persons with history of this condition	
First line	Nifedipine, 30 mg of slow-release formulation twice/day
Second line	Phosphodiesterase-5 inhibitors (e.g., tadalafil, 10 mg twice/day) or dexamethasone, 8 mg twice/day
Third line	Inhaled salmeterol (125 μg twice/day) appears to be less effective than other options and may cause tremor and tachycardia in some persons with this dose

ciated with these medications is gastrointestinal bleeding, which may be increased at high altitudes,[34] but studies were not powered to assess this risk.[31-33]

When risk assessment indicates a high probability of the development of acute mountain sickness (Table 2), acetazolamide is recommended. In a large, prospective, observational study, the use of acetazolamide was associated with a 44% reduction in the risk of severe high-altitude illnesses.[7] A meta-analysis of randomized trials of various doses of acetazolamide initiated before ascent likewise showed a significantly reduced risk of acute mountain sickness; the authors of this meta-analysis concluded that the lowest effective dose for prevention is 125 mg twice per day.[35] This dose has been shown to be effective in reducing the incidence of acute mountain sickness associated with rapid ascent from a baseline altitude of 1600 to 4300 m[36] or during further ascent to 4900 m among trekkers who have ascended to 4200 m without illness.[37] However, a study that showed acute mountain sickness in more than 50% of persons who received acetazolamide at a dose of 250 mg twice per day during a rapid ascent of Mount Kilimanjaro (5895 m in 5 days)[38] suggested that low-to-moderate doses may be inadequate with more rapid ascents and higher final altitudes; it is not known whether higher doses are more effective in persons at these altitudes. Acetazolamide should be started 1 day before the ascent and discontinued after 2 days at the final altitude or during the descent. A meta-analysis showed that acral paresthesias occurred in 35 to 90% of persons receiving acetazolamide, and polyuria occurred with the first several doses in 8 to 55%, with distaste for carbonated beverages in 4 to 14%.[35] Nausea and tiredness developed in about 20% of persons who received 250 mg of acetazolamide three times per day at low altitudes.[39] Thus, testing for side effects of the drug before the ascent might be useful to avoid confusion of a side effect with a symptom of acute mountain sickness. If side effects occur, the person should be advised not to use this prophylactic agent.

If there is a contraindication to acetazolamide or if it has intolerable side effects, an alternative is dexamethasone at a dose of 4 mg two or three times per day. In a randomized, placebo-controlled trial, dexamethasone was associated with a significant reduction in the incidence and severity of acute mountain sickness among persons who ascended to 2700 m.[40] Several smaller randomized trials, including one head-to-head trial,[39] have also shown these results at 4300 to 4570 m, with a magnitude of effect similar to that of acetazolamide.[10] Given the potential adverse effects of dexamethasone (e.g., hyperglycemia, adrenal suppression, and psychosis), its use for pre-

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Table 4. Treatment of Acute High-Altitude Illnesses.

Treatment	Acute Mountain Sickness	High-Altitude Cerebral Edema	High-Altitude Pulmonary Edema
General measures	Mild to moderate: day of rest, descend 500–1000 m if no improvement with day of rest Severe: descend as soon as possible to lowest possible altitude; administer oxygen at a rate of 2–4 liters/min or with the use of hyperbaric bag until descent or evacuation possible	Descend as soon as possible to lowest possible altitude; administer oxygen at a rate of 2–4 liters/min or with the use of hyperbaric bag until descent or evacuation possible	Descend as soon as possible to lowest possible altitude; administer oxygen at a rate of 2–4 liters/min or with the use of hyperbaric bag until descent or evacuation possible
Drugs	Mild to moderate: nonsteroidal anti-inflammatory drugs, antiemetic agents, acetazolamide (125–250 mg twice/day) to enhance acclimatization Severe: intravenous, intramuscular, or oral dexamethasone, 8 mg, followed by 4 mg every 6 hr	Intravenous, intramuscular, or oral dexamethasone, 8 mg, followed by 4 mg every 6 hr	Nifedipine, 60–80 mg of slow-release formulation/24 hr in several doses
Measures after recovery	Reascent possible when recovery is complete without use of drugs, except for acetazolamide; consider acetazolamide, 250 mg twice/day, during reascent	Reascent possible with complete recovery after discontinuation of dexamethasone; consider acetazolamide, 250 mg twice/day, during reascent	Reascent possible when symptoms have resolved and oxygenation at rest and during exercise is normal for altitude without supplemental oxygen; continue nifedipine, 60 mg of slow-release formulation/day

vention of acute mountain sickness should be limited to persons with unequivocal indications, and it should be administered for less than 1 week.

Since there appears to be a continuum from acute mountain sickness to high-altitude cerebral edema, drugs that prevent the first condition will probably also reduce the risk of the second one. However, systematic data are lacking to confirm this theory.

Small randomized trials involving persons with a history of high-altitude pulmonary edema have shown that the risk of recurrence can be reduced with the use of medications that lower the high pulmonary-artery pressure that is typical in susceptible persons. Nifedipine in a slow-release formulation at a dose of 30 mg twice per day,[41] tadalafil (a phosphodiesterase-5 inhibitor) at a dose of 10 mg twice per day, and dexamethasone at a dose of 8 mg twice per day[42] appear to be similarly effective in lowering pulmonary-artery pressure and reducing the incidence of high-altitude pulmonary edema from approximately 70% to approximately 10% or less. Although it has not been compared directly with these agents, inhaled salmeterol, a long-acting β_2-agonist, at a high dose of 5 puffs (125 μg) twice per day, appears to be less effective; in a placebo-controlled trial, it was associated with a reduction in the incidence of high-altitude pulmonary edema from 74% to 33%.[43]

TREATMENT

The treatment of mild-to-moderate acute mountain sickness (Table 4) generally consists of a day of rest, NSAIDs for headache, and possibly antiemetic drugs. One small, placebo-controlled, crossover trial showed that ibuprofen reduced headache significantly in affected persons.[44] Treatment with oxygen and acetazolamide may also facilitate more rapid recovery, although there are only limited data from randomized trials to support the benefit of acetazolamide in persons in whom acute mountain sickness has already developed.[45] In remote areas, a descent of 500 to 1000 m is indicated if symptoms of acute mountain sickness persist despite a day of rest and symptomatic treatment. If descent is not possible because of logistical constraints or the person's condition, improvement sufficient to allow descent can be achieved with one or a combination of the following interventions: administration of dexamethasone at a dose of 4 to 8 mg every 6 hours,[46] provision of supplemental oxygen (2 to 4 liters per minute), or treatment in a manually pressurized, body-length, portable hyperbaric bag.[47]

Immediate descent is lifesaving when severe symptoms suggest the onset of high-altitude cerebral edema or high-altitude pulmonary edema. In persons with high-altitude pulmonary edema, pulmonary-artery pressure should be lowered by means of supplemental oxygen (2 to

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4 liters per minute), descent to a lower altitude, or pulmonary vasodilators (of which only nifedipine has been tested in a prospective study, which was uncontrolled).[48] Anecdotal reports describe a benefit of phosphodiesterase-5 inhibitors for the treatment of high-altitude pulmonary edema, but they do not provide support for the use of dexamethasone.[49] Although descent to a lower altitude is the primary goal for the management of high-altitude pulmonary edema in remote areas, allowing a fully conscious person with mild-to-moderate high-altitude pulmonary edema to remain in a mountainous resort area is reasonable when supplemental oxygen and oral pulmonary vasodilators can be provided under the supervision of a local physician or in an emergency facility.[50] There is no role for diuretics in the treatment of high-altitude pulmonary edema.

AREAS OF UNCERTAINTY

Since high-altitude cerebral edema and high-altitude pulmonary edema occur infrequently in remote areas, rigorous data are lacking to guide their management. Although numerous trials provide support for the use of acetazolamide for prophylaxis against acute mountain sickness, the appropriate dosage for persons planning an ascent to higher altitudes (above 4500 to 5000 m) or a rapid ascent is uncertain; data are lacking from randomized trials comparing dexamethasone with high doses of acetazolamide in these circumstances. The magnitude and duration of a reduced risk of acute mountain sickness associated with various forms of exposure to high altitudes before an ascent remain unclear.

GUIDELINES

Our recommendations are generally concordant with the guidelines of the Wilderness Medical Society for the prevention and treatment of high-altitude illnesses.[45]

CONCLUSIONS AND RECOMMENDATIONS

The person described in the vignette has planned a rapid ascent of Mount Kilimanjaro (5895 m over a period of 5 days). In addition to the need for region-specific prophylaxis against infectious disease such as malaria, he should be advised that his plan involves a 40% risk of the development of acute mountain sickness that would be severe enough to prevent him from reaching the peak, as well as a small risk of high-altitude pulmonary edema or high-altitude cerebral edema. To improve his chances of staying relatively symptom-free and reaching the summit, we would recommend that he spend several days hiking and living at intermediate altitudes of 2000 to 3000 m near his home before departure; consider climbing Mount Meru, a 4500-m neighboring peak, in 3 or 4 days before ascending Mount Kilimanjaro; or plan a flexible timetable to allow additional stops at intermediate altitudes according to his clinical condition. Since randomized trials have shown no significant reduction in the incidence of high-altitude illness with athletic training in hypoxic conditions, such training should not be recommended, but we would encourage regular endurance training, since good aerobic performance will help to make mountaineering less strenuous. There are currently no reliable tests to predict susceptibility to high-altitude illnesses during an ascent. If acclimatization before the ascent or a slower ascent rate is not possible, we would recommend that prophylaxis with acetazolamide, at a dose of 250 mg two or three times per day, be initiated at the mountain base after testing for side effects of the drug at home. However, the efficacy of acetazolamide for particularly high and fast climbs such as this one is uncertain. It would be reasonable to provide the patient with dexamethasone for use as rescue medication during descent, if severe acute mountain sickness or high-altitude cerebral edema develops suddenly, and he should be advised not to delay the descent, if it is indicated.

Anyone climbing to a high altitude should be educated about high-altitude illnesses and the steps that should be taken if symptoms develop. Good sources of information include www.ismmed.org and www.medex.org.uk. Steps include resting for a day if acute mountain sickness develops and descending if there is no improvement in symptoms with the use of NSAIDs and antiemetic agents within 1 day, and descending immediately at the first appearance of symptoms or signs of high-altitude pulmonary edema or high-altitude cerebral edema.

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