Turkish Journal of Emergency Medicine 19 (2019) 121–126

Contents lists available at ScienceDirect

Turkish Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/tjem

Review Article

High-altitude illness: Management approach

Gökhan Aksel[a,*], Şeref Kerem Çorbacıoğlu[b], Can Özen (뭐)[c]

[a] University of Health Sciences, Ümraniye Training and Research Hospital, Emergency Medicine Clinic, İstanbul, Turkey
[b] University of Health Sciences, Keçiören Training and Research Hospital, Emergency Medicine Clinic, Ankara, Turkey
[c] Emergency Department, King's College Hospital, London, UK

ARTICLE INFO

Keywords:
Altitude sickness
Mountain sickness
Altitude hypoxia
Brain edema
Emergency medicine

ABSTRACT

In high altitudes, usually above 2500 m, travelers are faced with decreased partial pressure of oxygen along with decreased barometric pressure. High-altitude illness, a syndrome of acute mountain sickness, high-altitude cerebral edema and high-altitude pulmonary edema, occurs due to the hypobaric hypoxia when there is inadequate acclimatization.

This review provides detailed information about pathophysiology, clinical features, prevention and treatment strategies for high-altitude illness according to the current literature.

1. Introduction

People are increasingly interested in travelling to high altitudes for several purposes; for fun, for work or sportive activities. In high altitudes, usually accepted as above 2500 m, travelers are faced with decreased partial pressure of oxygen along with decreased barometric pressure.[1] The adaptability of the human body to hypobaric hypoxia is quite successful but requires time to do so. If the time of high elevation is faster than the process of acute acclimatization, then high-altitude illness (HAI) occurs.

High-altitude illness is a group of syndromes that results from hypoxia which is the major parameter causing a series of physiological alterations.[2] HAI has three forms; acute mountain sickness (AMS), high-altitude cerebral edema (HACE) and high-altitude pulmonary edema (HAPE). The pathophysiology of HAI is partially well understood while prevention and treatment strategies are mostly based on low quality evidences.

In this review it is intended to provide detailed information about pathophysiology, clinical features, prevention and treatment strategies for HAI according to current literature.

2. The pathophysiology of high-altitude illness

Although some prior studies report that AMS and potentially HAPE can be seen at lower elevations (2000–2500 m), HAI is more common above 2500 m.[3–7] At high altitudes, environmental features differ from the ones at sea level. As altitude increases, temperature and humidity decreases, ultraviolet radiation increases, more importantly, barometric pressure and partial pressure of oxygen decreases. The barometric pressure at sea level is 760 mmHg and 370 mmHg at 5791 m.[8] Hypobaric hypoxemia in high altitude is caused by low air pressure which decreases partial oxygen pressure. This make it difficult for oxygen to diffuse in to the pulmonary capillaries although the proportion of oxygen in the air remains the same.[9] Estimated partial oxygen pressure is 90–100 mmHg in sea level while it is 65–80 mmHg at 1610 m, 45–70 mmHg at 2440 m, 42–53 mmHg at 3660 m and < 50 mmHg at 5300 m.[10] These environmental changes may trigger a series of physiological responses including respiratory alkalosis which develops due to higher alveolar paO_2 and lower alveolar $paCO_2$ caused by increased minute ventilation, higher red blood cell aggregation and hematocrit levels, increased cerebral blood flow to compensate for the reduced arterial oxygen content.[2,11,12] This stressful situation is accompanied by specific adaptations, which depend on the level of altitude and duration of exposure.[13–15] In case of inadequate acclimatization, cerebral and pulmonary edema may develop consequently due to overperfusion of the microvascular beds, elevated hydrostatic capillary pressure and leakage in both the blood-brain barrier and blood-gas barrier in the lungs.[10,16] The individual's adaptation capacity to hypobaric hypoxia which is termed as acclimatization lasting from hours to weeks, depends on both the magnitude and the rate of onset of hypoxia.[2]

In high altitude, cardiac output and systemic blood pressure were increased due to increased sympathetic nervous tone. After a few days,

Peer review under responsibility of The Emergency Medicine Association of Turkey.
* Corresponding author. Ümraniye Training and Research Hospital, Emergency Medicine Clinic, Elmalikent Mahallesi Adem Yavuz Cad. No:1, Umraniye, Istanbul, Turkey. Tel.: +905053508690.
E-mail address: aksel@gokhanaksel.com (G. Aksel).

https://doi.org/10.1016/j.tjem.2019.09.002
Received 14 September 2019; Received in revised form 15 September 2019; Accepted 15 September 2019
Available online 19 September 2019

cardiac output decreases due to diuresis which is also defined as high altitude diuresis so that maximum oxygen delivery to the tissues reduces.[9]

3. Definitions and clinic aspects

The severity of high-altitude illness can range from nonspecific symptoms to life-threatening illness and it may develop at any time following ascent to elevation. Although it is partly easy to diagnose HACE and HAPE, diagnosis of AMS is a bit compelling. AMS which is the most common form of HAI, is a non-fatal condition while HACE and HAPE are serious diseases which will progress to death in hours to days if not diagnosed and treated properly.[8]

3.1. Acute mountain sickness

The clinical features of AMS may be so occult that it may either be underestimated, or the symptoms of the patient may be attributed to AMS, although they may inadvertently belong to another disease. Most common symptoms are headache, nausea/vomiting, light-headedness, insomnia, and fatigue.[9,17] According to The Lake Louise AMS score which was developed in 1993 and revised in 2018, if the individual had at least 1 point for headache and at least 3 points in total of four symptoms (headache, gastrointestinal symptoms, fatigue and/or weakness, dizziness/light headedness) and had no neurological findings then AMS can be diagnosed. It is suggested to apply this score for the individuals who gained altitude and exposed to hypoxia at least 6 h duration. Although some authors suggest different thresholds, the authors of The Lake Louise AMS score classified AMS severity according to the total score as 3–5 mild, 6–9 moderate and 10–12 severe AMS,[18] (Table 1).

3.2. High-altitude cerebral edema

Many authors accept HACE as an extreme form of AMS. Ataxia and altered mental status are the classic findings of HACE in which the patients usually suffer from preceding other forms of HAI.[10] *Medical Society Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2014 Update* defined HACE as worsening symptoms seen in moderate-severe AMS with any of following neurological findings; ataxia, severe lassitude, alter mental status and encephalopathy.[1]

3.3. High-altitude pulmonary edema

This is the most mortal form of HAI and defined as noncardiogenic (left ventricular function is preserved) pulmonary edema caused by pulmonary blood-gas barrier leak in the lung. Decreased exercise performance and dry cough are the earliest symptoms of HAPE. As HAPE progresses, tachycardia, tachypnea, lassitude, productive cough and cyanosis worsen and eventually coma develop. Electrocardiography may reveal findings of right heart strain. Chest radiographs typically show patchy lung infiltrates with normal heart size and absence of these infiltrates suggest alternative diagnosis.[10] Typically, partial pressure of arterial oxygen is measured about 30–40 mmHg.[19]

Table 1
2018 Lake Louise acute mountain sickness score.[18]

Headache
0—None at all
1—A mild headache
2—Moderate headache
3—Severe headache, incapacitating
Gastrointestinal symptoms
0—Good appetite
1—Poor appetite or nausea
2—Moderate nausea or vomiting
3—Severe nausea and vomiting, incapacitating
Fatigue and/or weakness
0—Not tired or weak
1—Mild fatigue/weakness
2—Moderate fatigue/weakness
3—Severe fatigue/weakness, incapacitating
Dizziness/light-headedness
0—No dizziness/light-headedness
1—Mild dizziness/light-headedness
2—Moderate dizziness/light-headedness
3—Severe dizziness/light-headedness, incapacitating

4. Prevention

Although prevention strategies have favorable results, they don't guarantee prevention in all individuals because everyone's response to high altitude varies. As pathophysiology of AMS and HACE is similar, most authors recommend joint management of the AMS and HACE, but separately managing the HAPE. Therefore, in the prevention section of this review, AMS and HACE was discussed under same headings while HAPE was not.

4.1. Prevention of acute mountain sickness and high-altitude cerebral edema

4.1.1. Gradual ascent and preacclimatisation

Preventing the occurrence of HAI should be a priority over treatment. Gradual ascent is the best prevention strategy to prevent all forms of HAI. As the major risk factors for HAI is the absolute change in altitude and rate of ascent, gradual ascent gives sufficient time to develop an adequate degree of altitude acclimatization.[1,9,18,20] Beidleman et all reported that staging at 2200 m for 6 days before ascending to 4300 m reduced the incidence and severity of AMS.[21] Although a 2019 Cochrane review reported that the effect of preacclimatisation strategies on improving the risk of AMS as uncertain, it is still sensible recommending gradual ascent according to the results of the studies and extensive clinical experiences.[22] Travelers are recommended to spend 6–7 days at moderate altitude like 2200–3000 m before proceeding higher altitude. This is necessary only if the individual plans ascending to > 2500 m.[21,23] It is also recommended for the travelers ascending above 3000 m not to increase sleeping elevation by more than 500 m daily.[1] It should never be forgotten that proceeding to higher sleeping altitude is never recommended when an individual had symptoms of HAI.

4.1.2. Modifying the risk factors specific to individual

Risk factors specific to individual was not well defined, so the prevention strategies are not mostly based on them but on gradual ascent and medical prophylaxis. Only a few studies defined those risk factors for not acute but chronic mountain sickness (CMS) which is seen especially in Andean population: modifying smoking, obesity and lung diseases.[9] Although there is not enough evidence on this subject, we believe that these risk factors may also raise the risk of HAI due to similar psychopathological processes and so the recommendations for CMS can be applied to any forms of HAI.

4.1.3. Pharmacologic strategies

Prophylactic medications are not recommended for the individuals with low risk (ascending < 2500 m and with no known history of HAI) but for the ones with moderate to high risk like known previous history of HACE or HAPE and ascending to sleeping altitude (> 500 m/day) above 2500 m or any individual ascending > 3000 m.[1,10] As a general acceptance, recommendations for AMS are also applicable to HACE.

4.1.4. Acetazolamide

Acetazolamide is the main medical agent for prevention of both AMS and HACE. Many reviews and studies comparing acetazolamide with placebo reported that acetazolamide is an effective in prevention

of acute HAI.[1,24,25] Meta-analysis conducted by Low showed that acetazolamide at all doses (250, 500 or 750 m daily) is effective to prevent AMS when compared to placebo[26] and 250 mg daily is reported as the lowest effective dose. In the Cochrane systematic review of 16 trials with 2301 participants and moderate quality, it was reported that risk of AMS was reduced by almost half with acetazolamide.[3] Although a recent study reported that 125 mg daily dose is noninferior to 250 mg, it is needed further studies for dosage lowering. It is strongly recommended acetazolamide starting the day before ascent at a dosage of 125 mg every 12 h (250 mg daily and 2.5 mg/kg for children) until descent is initiated.[27,28]

4.1.5. Dexamethasone

In comparison, dexamethasone is not inferior to acetazolamide, and has even been shown to be superior to some randomized controlled studies.[24,29] However, acetazolamide is the commonly suggested as first line medical agent for AMS prevention because of having better side effect profile and being more investigated by a large number of studies. Dexamethasone can be a very good alternative agent and be considered for persons who cannot tolerate acetazolamide. Preferred dose for dexamethasone is 2 mg every 6 h or 4 mg every 12 h.[10] Dexamethasone should be stopped when descent once initiated and never be use more than 7 days given the risk of adrenal suppression.[2] Some authors recommend acetazolamide and dexamethasone combined therapy for the individuals like military or rescue personals who had to ascend rapidly > 3500 m.[1]

4.1.6. Ibuprofen

Recent studies showed that ibuprofen may be a good alternative for AMS prevention. Although the study results revealed that ibuprofen was effective when compared to placebo, the result of the ones comparing to acetazolamide are contradictory.[30–33] Considering the serious side effects such as gastrointestinal bleeding, it makes sense to use ibuprofen (1800 mg daily) when the individual cannot tolerate both acetazolamide and dexamethasone.

4.1.7. Other options

There some other alternatives for prevention of AMS like budesonide, ginkgo biloba, chewed coca leaves and acetaminophen. As the current literature has either insufficient or low quality evidence for these options or the results are conflicting, there is a need for more detailed and quality studies on these drugs, but then we can decide if they are good alternatives.[34–36] Their routine use for prevention of AMS and HACE is not recommended.

4.2. Prevention of high-altitude pulmonary edema

4.2.1. Gradual ascent and preacclimatisation

Results of the study conducted by Baggish support suggesting gradual ascent for the prevention of HAPE with the same recommendations for prevention of AMS and HACE. It was investigated whether gradual ascent, some authors define as staged ascent, effects pulmonary arterial pressure (PAP). They showed that if direct ascent was performed, PAP was significantly increased and this was also found to be negatively correlated with both SaO_2 and PaO_2 levels. When staged ascent was performed (7 days at moderate altitude), PAP was slightly increased and this result was not correlated with either SaO_2 or PaO_2.[23] Despite the low quality evidences, gradual ascent still seems to be the most effective prevention recommendation not only for HAPE but also for all forms of HAI.

4.2.2. Pharmacologic strategies

Prophylactic medications are not routinely recommended for prevention of HAPE. The only indication is known previous HAPE history, especially multiple episodes.[1]

4.2.3. Nifedipine

Nifedipine, a calcium channel blocker, is the most effective medication in prevention of HAPE. It reduces pulmonary vascular resistance, leading to a reduction of the pulmonary hypertension.[37] A randomized placebo-controlled study reported that nifedipine is effective in lowering pulmonary-artery pressure and preventing HAPE without significant hypotension.[38] Prophylaxis should be started 24 h before ascent and recommended dose is 20 mg of a slow-release preparation every 8 h.

4.2.4. Tadalafil

Tadalafil seems to be effective in preventing HAPE while it's known that it is not effective for AMS.[39] Furthermore, tadalafil and sildenafil may exacerbate AMS by an unknown mechanism.[40] 10 mg of tadalafil every 12 h may be alternative when the traveler is intolerant to nifedipine.

4.2.5. Dexamethasone

Although it was reported by a randomized placebo-controlled trial that 8 mg of dexamethasone every 12 h was effective in prevention of HAPE, we have limited clinical experience and insufficient data to suggest this medication as a first line choice.[39] Dexamethasone is indicated for HAPE prevention only when nifedipine and tadalafil cannot be used.

4.2.6. Other options

As clinical experience and data about effectiveness of salmeterol is limited, it is not recommended for HAPE prevention.[1] Acetazolamide may play a role in HAPE prophylaxis, but the evidences supporting its efficiency are insufficient. Since acetazolamide is the most effective medication in prevention of AMS and HACE, despite its not being indicated for HAPE prevention, it should be considered as the first drug of choice in individuals having risk for HAI.

5. Treatment

As defined above, the most important stage of treatment in all forms of HAI is prevention. The evidence behind the current treatment options and their effectiveness are limited. The medical supplies and equipment are not sufficient for the management. Therefore, in most cases, immediate descent is the best and the only treatment option, especially for HACE and HAPE. Other medical and pharmacological interventions should be considered as the first line only when immediate descent is not possible. Unlike prevention section, the treatment of all forms of HAI will be discussed separately.

5.1. Treatment of acute mountain sickness

When AMS is suspected or diagnosed, ascent should be stopped immediately. Then, severity of AMS based on the symptoms, whether they are progressive or not, should be assessed by physical examination. The treatment options, after the diagnosis is confirmed, are as follows;

5.1.1. Descent

As stated above, immediate descent (300–1000 m) is the best and the first option of treatment for the majority of HAI. However, for AMS patients, descent decision can be delayed until the response to the initial symptomatic treatments and other management options are assessed. Patients who do not respond to initial treatment should be descended 300–1000 m or until the symptoms resolve.[1,2,10]

5.1.2. Symptomatic treatment

Majority of the patients with mild AMS can be treated by resting and symptomatic treatment options such as; non-opiate analgesic agents for headache, anti-emetics for gastrointestinal symptoms.[2] Ibuprofen (600 mg) and acetaminophen (650–1000 mg) are two unique non-

opioid agents that were shown effective in AMS with randomized controlled studies.[41,42] Although there are no controlled studies for antiemetics, experienced authors suggest oral ondansetron tablets (4 mg every 4–6 h) for treatment of nausea and vomiting in patients with AMS.[10]

5.1.3. Acetazolamide

Although multiple trials have proved the effectivity of acetazolamide in prevention of AMS, there is only one small study that evaluated role of acetazolamide as a treatment option.[43] According to this study, 250 mg acetazolamide given at baseline and at 8 h was superior to placebo in treatment of AMS. Therefore, some authors suggest that 250 mg acetazolamide twice daily can be considered for patients who do not respond to symptomatic treatment.[1,2]

5.1.4. Dexamethasone

Dexamethasone is the most studied pharmacological agent and it is shown to be the most effective medication for treatment of AMS. Nevertheless, it should be noted that the evidence is based on studies which are conducted with very small sample sizes. According to the results of three controlled studies, 8 mg loading dose, followed by 4 mg every 6 h (oral, intramuscular, or intravenous) is more effective than placebo in treatment of AMS.[44–46] Even though there are no studies which combined acetazolamide and dexamethasone for the treatment, some authors suggest that combined therapy can be considered, especially in moderate-severe AMS patients.

5.1.5. Supplemental oxygen

No studies assessed the role of supplement oxygen therapy in AMS patients, but it is broadly accepted that oxygen delivered at low flow rates is helpful to reduce symptoms in AMS, on the basis of extensive clinical experience. Therefore, some authors recommend that supplemental oxygen can be given to raise oxygen saturation > 90% or to resolve symptoms.[10]

5.2. Treatment of high-altitude cerebral edema

5.2.1. Descent

Descent is the main treatment option in patients with HACE, and the descent decision should be made as soon as possible. Descent altitude should be 300–1000 m or to a level where the patient is asymptomatic. Other treatment options should never delay descent and only be considered when descent is not possible or is delayed.

5.2.2. Supplemental oxygen

Although there are no studies that evaluated the role of supplement oxygen therapy in HACE patients, many authors recommend that supplemental oxygen can be given to raise oxygen saturation > 90% or to resolve symptoms based on clinical experience.[1,10]

5.2.3. Portable hyperbaric chambers

Limited number of clinical trials and case reports have shown that portable hyperbaric chambers are effective alternatives of treatment when descent is not possible or is delayed.[47–49] To improve symptoms, patients have to stay in the chamber for long hours, and this long period of time can cause several problems in some cases such as; vomiting, voiding, communication difficulties, and claustrophobia.[10] In addition, rescuers should be aware that the symptoms can recur after the hyperbaric treatment is terminated.[50]

5.2.4. Dexamethasone

Although there are several trials focused on the role of dexamethasone in AMS patients, no study is focused on its effects in HACE patients. However, some authors suggest that 8 mg loading dose, followed by 4 mg every 6 h (intravenous or intramuscular) should be added to treatment based on clinical experience.[1,2]

5.2.5. Acetazolamide

The role of acetazolamide in the treatment of AMS is based on one small study and there are no studies about its effectivity in HACE patients.[43] Therefore, routine administration of acetazolamide is not recommended.

5.2.6. Other treatment options

Routine administration of diuretics, mannitol, hypertonic saline are not recommended in management of patients with HACE, since the there are no studies on this subject. Non-steroidal analgesic agents such as acetaminophen (650–1000 mg) or ibuprofen (600 mg) have no effect on the pathophysiology of HACE, but they can be administered to relieve headache related to high altitude.

5.3. Treatment of high-altitude pulmonary edema

5.3.1. Descent

As in other forms of high-altitude illness, a descent of at least 1000 m is the best and the most certain treatment option in HAPE. However, in fully conscious patients with mild-moderate HAPE, or when descent is not possible, supplemental oxygen, portable hyperbaric chambers and pulmonary vasodilator agents (nifedipine and phosphodiesterase-5 inhibitors) may be helpful to resolve the symptoms. It should be noted that most of the treatment options in HAPE patients are mainly based on case series, a small number of observational studies and randomized controlled studies. Generally, the main reason of using these treatment options is based on the convincing physiologic effect mechanisms of these agents and clinical experience.

5.3.2. Supplemental oxygen

One randomized clinical trial and one case-control study showed that supplemental oxygen treatment at low flow rates with bed rest is an effective alternative of descent.[51,52] Therefore, along with bed rest, use of supplemental oxygen to maintain an oxygen saturation level above 90% is recommended to resolve the symptoms.[1,10]

5.3.3. Portable hyperbaric chambers

Evidence of using portable hyperbaric chambers in treatment is based on only case reports.[53] However, chambers may be considered when descent is impossible and supplement oxygen is not available. Similar to the indications of AMS and HACE, to improve symptoms, patients have to stay long hours in the chamber, and they may experience several problems related to the treatment.[1,10]

5.3.4. Continuous positive airway pressure

As the evidence behind portable hyperbaric chambers, recommendations about continuous positive airway pressure (CPAP) is based on case series.[54,55] Because of several technical or patient-related problems, it is suggested that CPAP should only be used when supplemental oxygen and other treatment agents (nifedipine and phosphodiesterase-5 inhibitors) are not available, or as a secondary line of treatment option in patients whose symptoms fail to resolve with supplemental oxygen alone.[1]

5.3.5. Nifedipine

Although one non-randomized, experimental study showed that nifedipine may be helpful for treatment of HAPE,[56] a case-control study and another randomized controlled study in more recent years, showed that nifedipine with supplemental oxygen was not superior to treatment with supplemental oxygen only.[52,57] However, based on clinical experience, 30 mg nifedipine twice daily is suggested when oxygen is not available and descent is not possible.[10]

5.3.6. Phosphodiesterase-5 inhibitors

Similarly, there is convincing physiologic rationale for the use of phosphodiesterase-5 inhibitors in treatment of HAPE. The evidence on

this topic is limited with only case series.[58,59] However, these agents are used commonly by physicians, and some authors suggest that 10 mg tadalafil or 50 mg sildenafil may be used when descent is not possible, oxygen/portable hyperbaric chambers and nifedipine are not available.[1,10]

5.3.7. Acetazolamide

Although there are case reports that recommend the use of acetazolamide for treatment, there is no systematic study that evaluated the role of acetazolamide in treatment of HAPE.[58,59] Therefore, routine administration of acetazolamide is not recommended due to the potential problems caused by diuretic effects such as hypotension.[1,2,10]

5.3.8. Dexamethasone

The effectivity of dexamethasone in prevention of HAPE is well established with several trials, but the evidence on its use in treatment of HAPE is very limited.[59,60] In addition, one randomized controlled study showed that use of dexamethasone with supplemental oxygen was not superior to treatment with supplemental oxygen only.[52] Therefore, routine administration of dexamethasone is not recommended by guidelines.[1,2,10]

5.3.9. Beta-agonists and diuretics

Some case reports suggest the use of salmeterol and diuretics but there are no systematic studies that evaluated their role in treatment of HAPE.[58,61] Therefore, routine administration of beta-agonist and diuretics is not recommended by guidelines.[1,2,10]

Funding

No funding was needed for this original article.

Author contribution statement

Gökhan AKSEL and Şeref Kerem ÇORBACIOĞLU conceived and designed the study; Gökhan AKSEL and Şeref Kerem ÇORBACIOĞLU and Can ÖZEN performed the literature review, management and collection of the data and wrote the paper.

Conflict of interest statement

The authors declare no conflict of interest.

References

1. Luks AM, Auerbach PS, Freer L, et al. Wilderness medical society Practice guidelines for the prevention and treatment of acute altitude illness: 2019 update. *Wilderness Environ Med.* 2019 Jun 24. https://doi.org/10.1016/j.wem.2019.04.006 pii: S1080-6032(19)30090-0.
2. Luks AM, Swenson ER, Bärtsch P. Acute high-altitude sickness. *Eur Respir Rev.* 2017 Jan 31;26(143):160096. https://doi.org/10.1183/16000617.0096-2016. Print 2017 Jan.
3. Nieto Estrada VH, Molano Franco D, Medina RD, et al. Interventions for preventing high altitude illness: Part 1. Commonly-used classes of drugs. *Cochrane Database Syst Rev.* 2017 Jun 27;6:CD009761. https://doi.org/10.1002/14651858.CD009761.pub2 (submitted for publication).
4. Montgomery AB, Mills J, Luce JM. Incidence of acute mountain sickness at intermediate altitude. *J Am Med Assoc.* 1989;261:732–734.
5. Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med.* 1993;118:587–592.
6. Gabry AL, Ledoux X, Mozziconacci M, et al. Highaltitude pulmonary edema at moderate altitude (o2,400 m; 7,870 feet): a series of 52 patients. *Chest.* 2003;123:49–53.
7. Hackett PH, Yarnell PR, Weiland DA, et al. Acute and evolving MRI of high-altitude cerebral edema: microbleeds, edema, and pathophysiology. *AJNR Am J Neuroradiol.* 2019;40(3):464–469.
8. Kurtzman RA, Caruso JL. High-altitude illness death investigation. *Acad Forensic Pathol.* 2018 Mar;8(1):83–97. https://doi.org/10.23907/2018.006 Epub 2018 Mar 7.
9. Leissner KB, Mahmood FU. Physiology and pathophysiology at high altitude: considerations for the anesthesiologist. *Int J Obstet Anesth.* 2009;23(4):543–553.
10. Davis C, Hackett P. Advances in the prevention and treatment of high altitude illness. *Emerg Med Clin North Am.* 2017 May;35(2):241–260. https://doi.org/10.1016/j.emc.2017.01.002.
11. Raberin A, Nader E, Ayerbe JL, et al. Evolution of blood rheology and its relationship to pulmonary hemodynamic during the first days of exposure to moderate altitude. *Clin Hemorheol Microcirc.* 2019 Aug 23. https://doi.org/10.3233/CH-190671.
12. Willie CK, Smith KJ, Day TA, et al. Regional cerebral blood flow in humans at high altitude: gradual ascent[Title] AND 2 wk at 5,050m. *J Appl Physiol.* 2014 Apr 1;116(7):905–910. https://doi.org/10.1152/japplphysiol.00594.2013.
13. Dempsey JA, Morgan BJ. Humans in hypoxia: a conspiracy of maladaptation?!. *Physiology.* 2015;30(4):304–316. https://doi.org/10.1152/physiol.00007.2015 192 191.
14. West JB. High-altitude medicine. *Am J Respir Crit Care Med.* 2012;186(12):1229–1237. https://doi.org/10.1164/rccm.201207-1323CI 193.
15. Bartsch P, Saltin B. General introduction to altitude adaptation and mountain sickness. *Scand J Med Sci Sport.* 2008;18(Suppl 1):1–10. https://doi.org/10.1111/j.1600-0838.2008.00827.x. 195 194.
16. Hackett PH, Roach RC. High-altitude illness. *N Engl J Med.* 2001 Jul 12;345(2):107–114.
17. Palmer BF. Physiology and pathophysiology with ascent to altitude. *Am J Med Sci.* 2010;340(1):69–77.
18. Roach RC, Hackett PH, Oelz O, et al. The 2018 Lake Louise acute mountain sickness score. *High Alt Med Biol.* 2018 Mar;19(1):4–6. https://doi.org/10.1089/ham.2017.0164.
19. Scherrer U, Vollenweider L, Delabays A, et al. Inhaled nitric oxide for high-altitude pulmonary edema. *N Engl J Med.* 1996;334:624–629.
20. Hackett PH, Roach RC. High altitude cerebral edema. *High Alt Med Biol.* 2004;5(2):136–146 Summer (submitted for publication).
21. Beidleman BA, Fulco CS, Muza SR, et al. Effect of six days of staging on physiologic adjustments and acute mountain sickness during ascent to 4300 meters. *High Alt Med Biol.* 2009;10(3):253–260. https://doi.org/10.1089/ham.2009.1004 Fall.
22. Molano Franco D, Nieto Estrada VH, Gonzalez Garay AG, et al. Interventions for preventing high altitude illness: Part 3. Miscellaneous and non-pharmacological interventions. *Cochrane Database Syst Rev.* 2019 Apr 23;4:CD013315. https://doi.org/10.1002/14651858.CD013315.
23. Baggish AL, Fulco CS, Muza S, et al. The impact of moderate-altitude staging on pulmonary arterial hemodynamics after ascent to high altitude. *High Alt Med Biol.* 2010;11(2):139–145. https://doi.org/10.1089/ham.2009.1073 Summer.
24. Ellsworth AJ, Meyer EF, Larson EB. Acetazolamide or dexamethasone use versus placebo to prevent acute mountain sickness on Mount Rainier. *West J Med.* 1991;154(3):289–293.
25. van Patot MC, Leadbetter 3rd G, Keyes LE, et al. Prophylactic low-dose acetazolamide reduces the incidence and severity of acute mountain sickness. *High Alt Med Biol.* 2008;9(4):289–293.
26. Low EV, Avery AJ, Gupta V, et al. Identifying the lowest effective dose of acetazolamide for the prophylaxis of acute mountain sickness: systematic review and meta-analysis. *BMJ.* 2012 Oct 18;345:e6779. https://doi.org/10.1136/bmj.e6779.
27. McIntosh SE, Hemphill M, McDevitt MC, et al. Reduced acetazolamide dosing in countering altitude illness: a comparison of 62.5 vs 125 mg (the RADICAL Trial). *Wilderness Environ Med.* 2019;30(1):12–21.
28. Pollard AJ, Niermeyer S, Barry P, et al. Children at high altitude: an international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, March 12, 2001. *High Alt Med Biol.* 2001;2(3):389–403.
29. Ellsworth AJ, Larson EB, Strickland D. A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. *Am J Med.* 1987;83(6):1024–1030.
30. Gertsch JH, Corbett B, Holck PS, et al. Altitude Sickness in Climbers and Efficacy of NSAIDs Trial (ASCENT): randomized, controlled trial of ibuprofen versus placebo for prevention of altitude illness. *Wilderness Environ Med.* 2012;23(4):307–315.
31. Lipman GS, Kanaan NC, Holck PS, et al. Ibuprofen prevents altitude illness: a randomized controlled trial for prevention of altitude illness with nonsteroidal anti-inflammatories. *Ann Emerg Med.* 2012;59(6):484–490.
32. Gertsch JH, Lipman GS, Holck PS, et al. Prospective, double-blind, randomized, placebo-controlled comparison of acetazolamide versus ibuprofen for prophylaxis against high altitude headache: the Headache Evaluation at Altitude Trial (HEAT). *Wilderness Environ Med.* 2010;21(3):236–243.
33. Burns P, Lipman GS, Warner K, et al. Altitude sickness prevention with ibuprofen relative to acetazolamide. *Am J Med.* 2019;132(2):247–251.
34. Zheng CR, Chen GZ, Yu J, et al. Inhaled budesonide and oral dexamethasone prevent acute mountain sickness. *Am J Med.* 2014;127(10):1001–1009.e2.
35. Moraga FA, Flores A, Serra J, et al. Ginkgo biloba decreases acute mountain sickness in people ascending to high altitude at Ollague (3696 m) in northern Chile. *Wilderness Environ Med.* 2007;18(4):251–257.
36. Gertsch JH, Basnyat B, Johnson EW, et al. Randomised, double blind, placebo controlled comparison of Ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT). *BMJ.* 2004;328(7443):797.
37. Hackett PH, Roach RC, Hartig GS, et al. The effect of vasodilators on pulmonary hemodynamics in high altitude pulmonary edema: a comparison. *Int J Sports Med.* 1992;13(Suppl 1):68–71.
38. Bartsch P, Maggiorini M, Ritter M, et al. Prevention of high-altitude pulmonary edema by nifedipine. *N Engl J Med.* 1991;325(18):1284–1289.
39. Maggiorini M, Brunner-La Rocca HP, Peth S, et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. *Ann Intern Med.* 2006;145(7):497–506.
40. Maggiorini M. Prevention and treatment of high-altitude pulmonary edema. *Prog Cardiovasc Dis.* 2010 May-Jun;52(6):500–506. https://doi.org/10.1016/j.pcad.2010.03.001.

41. Broome JR, Stoneham MD, Beeley JM, et al. High-altitude headache: treatment with ibuprofen. *Aviat Space Environ Med.* 1994;65:19–20.
42. Harris NS, Wenzel RP, Thomas SH. High altitude headache: efficacy of acetaminophen vs. ibuprofen in a randomized, controlled trial. *J Emerg Med.* 2003;24:383–387.
43. Grissom CK, Roach RC, Sarnquist FH, et al. Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange. *Ann Intern Med.* 1992;116:461–465.
44. Ferrazzini G, Maggiorini M, Kriemler S, et al. Successful treatment of acute mountain sickness with dexamethasone. *Br Med J.* 1987;294(6584):1380–1382.
45. Hackett PH, Roach RC, Wood RA, et al. Dexamethasone for prevention and treatment of acute mountain sickness. *Aviat Space Environ Med.* 1988;59(10):950–954.
46. Levine BD, Yoshimura K, Kobayashi T, et al. Dexamethasone in the treatment of acute mountain sickness. *N Engl J Med.* 1989;321(25):1707–1713.
47. Bartsch P, Merki B, Hofstetter D, et al. Treatment of acute mountain sickness by simulated descent: a randomised controlled trial. *BMJ.* 1993;306(6885):1098–1101.
48. Keller HR, Maggiorini M, Bartsch P, et al. Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. *BMJ.* 1995;310(6989):1232–1235.
49. Zafren K. Gamow bag for high-altitude cerebral oedema. *Lancet.* 1998;352:325–326.
50. Taber RL. Protocols for the use of portable hyperbaric chambers for the treatment of high-altitude disorders. *J Wilderness Med.* 1990;1:181–192.
51. Zafren K, Reeves JT, Schoene R. Treatment of high-alti- tude pulmonary edema by bed rest and supplemental oxy- gen. *Wilderness Environ Med.* 1996;7(2):127–132.
52. Yanamandra U, Nair V, Singh S, et al. Managing high-altitude pulmonary edema with oxygen alone: results of a randomized con- trolled trial. *High Alt Med Biol.* 2016;17(4):294–299.
53. Freeman K, Shalit M, Stroh G. Use of the Gamow Bag by EMT-basic park rangers for treatment of high-altitude pulmonary edema and high-altitude cerebral edema. *Wilderness Environ Med.* 2004;15(3):198–201.
54. Gabry AL, Ledoux X, Mozziconacci M, et al. High-alti- tude pulmonary edema at moderate altitude (< 2,400 m; 7,870 feet): a series of 52 patients. *Chest.* 2003;123(1):49–53.
55. Walmsley M. Continuous positive airway pressure as adjunct treatment of acute altitude illness. *High Alt Med Biol.* 2013;14(4):405–407.
56. Oelz O, Maggiorini M, Ritter M, et al. Nifedipine for high altitude pulmonary oedema. *Lancet.* 1989;2:1241–1244.
57. Deshwal R, Iqbal M, Basnet S. Nifedipine for the treatment of high altitude pulmonary edema. *Wilderness Environ Med.* 2012;23(1):7–10.
58. Fagenholz PJ, Gutman JA, Murray AF, et al. Treatment of high altitude pulmonary edema at 4240 m in Nepal. *High Alt Med Biol.* 2007;8(2):139–146.
59. Jones BE, Stokes S, McKenzie S, et al. Management of high altitude pulmonary edema in the Himalaya: a review of 56 cases presenting at Pheriche medical aid post (4240 m). *Wilderness Environ Med.* 2013;24(1):32–36.
60. Siebenmann C, Bloch KE, Lundby C, et al. Dexamethasone improves maximal exercise capacity of individuals susceptible to high altitude pulmonary edema at 4559 m. *High Alt Med Biol.* 2011;12(2):169–177.
61. Singh I, Lal M, Khanna PK, et al. Augmentation of frusemide diuresis by morphine in high altitude pulmonary oedema. *Br Heart J.* 1967 Sep;29(5):709–713. https://doi.org/10.1136/hrt.29.5.709.