An Approach to Children with Pulmonary Edema at High Altitude

Deborah R. Liptzin,¹ Steven H. Abman,¹ Ann Giesenhausen,² and D. Dunbar Ivy²

Abstract

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Introduction: Diagnosis of high-altitude illness can be more challenging in children, especially those who are preverbal. Families often travel to high elevations for family vacations, either for skiing, hiking, and/or camping. They may present to their primary care providers looking for anticipatory guidance before travel or may follow-up after developing high-altitude illness. High-altitude pulmonary edema (HAPE) can be fatal.

Observations: There is no indication for HAPE prophylaxis in altitude naive children. Children may develop HAPE either when traveling from low altitude to high altitude for vacation (classic HAPE), when returning to high-altitude homes after travel to low altitude (reentry HAPE), or even with a respiratory illness at high altitude without any change in elevation (high-altitude resident pulmonary edema or HARPE). Children may be more susceptible to HAPE because of increased vascular reactivity, immature control of breathing, and increased frequency of respiratory illnesses. Children with HAPE warrant evaluation for underlying cardiopulmonary abnormalities, including structural heart disease and pulmonary hypertension. Treatment of HAPE includes supplemental oxygen and descent, but underlying cardiopulmonary disease may also help guide treatment and prevention.

Conclusions and Relevance: Evaluation for structural heart disease and pulmonary hypertension should be considered in children with HAPE. Future studies should be done to elucidate the optimal strategies for prevention and treatment of HAPE and to better understand the development of HAPE in children.

Keywords: altitude; cardiac disease; pediatrics; pulmonary hypertension

Introduction

TRAVEL TO HIGH-ALTITUDE REGIONS is common and, in rare cases, can be deadly (Hackett and Roach, 2001). Approximately 33.6 million visitors make overnight trips in Colorado, and about 1/3 of the visitors are children (Longwoods International, 2015). Colorado has an average elevation of 2070 m (6800 feet) (Colorado Travel Facts, www.colorado.com/colorado-travel-facts), and most ski area bases and common tourist destinations are over 2500 m (8200 feet) (Colorado, www.onthesnow.com/colorado/statistics.html). Pediatricians may be asked about safety of travel to high elevation, prevention of altitude-related illness, and appropriate follow-up after an altitude-related illness, especially in patients with underlying

cardiac and/or pulmonary disease. High-altitude illnesses include acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE). There is a paucity of literature on children and high-altitude illness, and high-altitude illness can present differently in children versus adults (Pollard et al., 2001). 377,137 people live in counties in the United States with average elevations of >2500 m (Mills, n.d.), and this population is at risk for reentry HAPE. We briefly describe high-altitude illnesses and propose recommendations for evaluation and treatment of HAPE in children as well as investigate the underlying contributors to HAPE. We discuss high-altitude resident pulmonary edema (HARPE), a new entity (Ebert-Santos, 2017). We will also highlight areas for further research.

¹Breathing Institute and Pediatric Heart-Lung Center, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado.

²Heart Institute and Pediatric Heart-Lung Center, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado.

There are three major types of high-altitude illness (Table 1): AMS, HACE, and HAPE. AMS and HACE are thought to be on the same spectrum of increased intracranial pressure; once symptoms progress to HACE, patients are at risk of death (Hackett and Roach, 2001). Therefore, descent, oxygen, and/or medical therapy should be initiated immediately at the earliest sign of altered mental status, confusion, or ataxia. In children, symptoms of altitude-related illness may be more subtle, such as decreased activity, fussiness, irritability, and/or lethargy (Pollard et al., 2001).

HAPE was first described in the English literature in 1960 by Dr. Charles Houston as “acute pulmonary edema without heart disease brought on by the sum of three stresses: high altitude, cold, and heavy exertion” (Houston, 1960). A more contemporary definition is a noncardiogenic, noninfectious, noninflammatory, and potentially fatal pulmonary edema that occurs after 1–2 days at high altitude (>2500 m or >8200 feet) (Maggiorini et al., 2001; Swenson et al., 2002; Schoene, 2008; Swenson and Bartsch, 2012; West, 2012; Luks et al., 2014). However, HAPE has been reported to occur at altitudes as low as 1400 m, especially with preexisting cardiopulmonary disease (Gabry et al., 2003; Breitnauer et al., 2016). Pulmonary edema is thought to occur because of patchy, uneven hypoxic pulmonary vasoconstriction, which leads to an elevated pulmonary capillary pressure and edema (Maggiorini et al., 2001). HAPE can occur in three different settings (Table 1). Classic HAPE occurs in persons who live at lower elevations who travel to high altitude. Respiratory illnesses may predispose children to vascular permeability and development of HAPE (Durmowicz et al., 1997). Reentry HAPE occurs in persons who live at high altitude, travel to lower altitude for even 1–2 days, and then develop HAPE after returning home (Scoggin et al., 1977). Reentry HAPE is not well studied, but seems to be more common in children (Scoggin et al., 1977). HARPE occurs in children who develop pulmonary edema at high altitude without any change in altitude, typically triggered by upper respiratory tract illnesses (Ebert-Santos, 2017). In patients with HARPE, inflammation from the upper respiratory tract illness is likely a major contributor to HAPE development. HARPE is very poorly understood and challenges the Lake Louise definition of HAPE because there is no gain in altitude (Hackett and Oelz, The Lake Louise Consensus on the Definition and Quantification of Altitude Illness, 1992; Ebert-Santos, 2017).

Diagnosis of HAPE

The Lake Louise diagnostic criteria for HAPE requires a recent gain in altitude associated with at least two of the four typical symptoms (dyspnea at rest, cough, weakness/decreased exercise performance, and chest tightness/congestion) and at least two of the four typical signs (crackles/wheezes, central cyanosis, tachypnea, and tachycardia). The Lake Louise score has been adapted to pediatric patients as well (Yaron et al., 1998). Diagnosing HAPE in children can be challenging (Pollard et al., 2001). Initial evaluation of children with HAPE is demonstrated in Figure 1 and should include a chest radiograph (Fig. 2) to confirm the diagnosis of pulmonary edema with fluffy infiltrates (Houston, 1960). In some austere locations such as base camps, lung ultrasound may be a diagnostic tool that is available where chest radiography is impossible (Moore and Copel, 2011). The classic finding of “lung comets” (a sign of intraparenchymal edema)

TABLE 1. HIGH-ALTITUDE ILLNESS: SIGNS AND SYMPTOMS IN ADULTS AND OLDER CHILDREN AS WELL AS SPECIAL CONSIDERATIONS FOR INFANTS

		HAPE		
		AMS	HACE	Classic Reentry Resident
Signs and symptoms		Headache and at least one of nausea, vomiting, dizziness, fatigue, insomnia	AMS or HAPE with ataxia, altered mental status	Dyspnea with exertion, low oxygen saturation, reduced exercise ability, mild fever, dry cough, pink frothy sputum (late)
Pediatric specific additional signs and symptoms		Fussiness, less playful, difficulty sleeping, poor feeding, pallor	Sleepiness, lethargy	Pallor, cyanosis, retractions, increased work of breathing
Treatment		NSAID, rest, oxygen, carbonic anhydrase inhibitor	Oxygen, descent, corticosteroids, hospitalization	Live at low altitude, travel to high altitude Oxygen, descent, calcium channel blocker
Prevention*		Carbonic anhydrase inhibitor, corticosteroids	Carbonic anhydrase inhibitor, corticosteroids	Live at high altitude, travel to low altitude and return home Oxygen, calcium channel blocker, carbonic anhydrase inhibitor
				Oxygen, calcium channel blocker, carbonic anhydrase inhibitor

Treatment and prophylaxis in children, including different approaches for different forms of HAPE, adapted from Bartsch and Swenson (2013), Pollard et al. (2001).

*Acclimatization and slow ascent are nonpharmacologic preventative strategies for all forms of altitude illness.

**Phosphodiesterase inhibitors are cited in the adult literature Luks and Swenson (2008), Bartsch and Swenson (2013).

AMS, acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema; NSAID, non-steroidal anti-inflammatory drugs.

FIG. 1. Schematic for acute evaluation and treatment of pulmonary edema at high altitude. HAPE, high-altitude pulmonary edema; HARPE, high-altitude resident pulmonary edema.

FIG. 2. Chest radiograph with patchy and bilateral pulmonary edema.

on lung ultrasound is diagnostic for HAPE in the appropriate setting (Wimalasena et al., 2013). Using ultrasound to diagnose HAPE in children has not been well described, and therefore, cutoff values for comet tails in children have not been defined. If a patient has had at least one episode with radiographic evidence of HAPE, a repeat chest radiograph may not be necessary with subsequent episodes with similar presentations.

Treatment of HAPE

Primary treatment of HAPE (Fig. 1) includes increasing the partial pressure of inspired oxygen to relieve the pulmonary vasoconstriction and hypoxemia underlying this illness. This is achieved with oxygen and/or descent (Abman et al., 2015). Gamow bags (inflatable pressure chambers) have also been used in adults to simulate descent when oxygen or descent is not possible (Freeman et al., 2004). There is no literature to support when to descend versus stay at high altitude with oxygen therapy. HAPE can be deadly (Droma et al., 2001; Hackett and Roach, 2001; Schoene, 2001), and therefore, any decision to remain at high altitude with oxygen therapy must be made with caution. Children may successfully be treated with oxygen and rest while staying at high altitude with reliable equipment and savvy families

TABLE 2. SUGGESTED ORAL MEDICATIONS FOR HIGH-ALTITUDE ILLNESS ALONG WITH RECOMMENDED DOSAGES

	AMS/HACE	HAPE	Common side effects
Acetazolamide	<i>Preferred for AMS*</i>	(<i>Prophylaxis only</i>) 1.25 mg/kg/dose (max 125 mg) q12 hours	Paresthesias, dizziness, electrolyte disturbance
Prophylaxis/ treatment	1.25 mg/kg/dose (max 125 mg) q12 hours 2.5 mg/kg/dose (max 250 mg) q12 hours		
Dexamethasone Treatment	<i>Preferred for HACE, severe AMS</i> 0.15 mg/kg/dose (max 2 mg) q6 hours		Gastroesophageal reflux, behavior changes, increased appetite
Nifedipine** Prophylaxis		Extended release 1.5 mg/kg qday (max 40 mg)	Flushing, gastrointestinal distress, hypotension
Treatment		Extended release 1.5 mg/kg qday (max 40 mg)	
Amlodipine Prophylaxis treatment		2.5–5 mg daily	Flushing, abdominal pain, dizziness

Prophylaxis should be started 1–2 days before ascent and continued until 1–2 days at final altitude for AMS/HACE and 2–4 days for HAPE, adapted from Pollard et al. (2001), Luks et al. (2014).

*No guidelines for use of acetazolamide in treatment of AMS in children.

**Can use nifedipine immediate release 0.5 mg/kg (max 40 mg) q8 hours.

(Ebert-Santos, 2017). Oxygen can be provided via nasal cannula/mask, noninvasive ventilation (Pollard et al., 2001; Walmsley, 2013), or, if necessary, mechanical ventilation. Mechanical ventilation for HAPE is rarely necessary, and HAPE often occurs in resource limited areas where such options are limited. Optimizing pulmonary vasodilation and improving hypoxemia by targeting an oxygen saturation of at least 93% should be considered (Abman et al., 2015).

When descent is not possible and/or patients are in distress, pharmacologic treatment may be initiated in addition to oxygen therapy. Pharmacologic treatment of HAPE has traditionally involved vasodilation targeting the pulmonary vasculature (Oelz et al., 1992; Scherrer et al., 1996; Pollard et al., 2001), but there may be a role for increased alveolar fluid clearance with long-acting beta agonists (Luks and Swenson, 2008). In children, nifedipine has been recommended (Table 2) (Pollard et al., 2001), but amlodipine may also be used as it may be easier to dose in children (once daily dosing, suspension option). Furosemide or other diuretics are not recommended in the treatment of HAPE as most patients present with low intravascular volume.

Evaluation of Children with HAPE

Evaluation of the cardiopulmonary system is useful in the diagnostic workup of HAPE, and may guide future strategies for treatment and prevention (Fig. 3). An echocardiogram should be considered for every child with HAPE to evaluate for underlying cardiac disease and pulmonary hypertension (Das et al., 2004; Abman et al., 2015). This can be done in the acute setting if the patient is hospitalized, and the echocardiogram should be performed both on the current level of respiratory support, and, if safe to do so, without respiratory support to evaluate for vasoreactivity. A HAPE episode could be the first sign of an underlying congenital heart disease

(Sebbane et al., 1997). It is particularly important to rule out structural abnormalities that are known risk factors, such as an atrial septal defect, isolated pulmonary artery of ductal origin, coarctation of the aorta, ventriculoseptal defect, pulmonary vein stenosis, and patent foramen ovale (Das et al., 2004). The isolated pulmonary artery may be rehabilitated to establish normal antegrade flow with occasional resolution of pulmonary hypertension (Batlivala et al., 2014; Mery et al., 2014). If an adequate study cannot rule out these diagnoses, then a cardiac magnetic resonance imaging can be considered. Assessment of pulmonary hypertension includes evaluation for septal flattening and/or tricuspid regurgitation jet >2.9 m/s, and, if possible, to evaluate response to hypoxic challenge. The amount of reactivity for hypoxic challenge is not well defined in children, but an increase of >20% in mean pulmonary artery pressures with hypoxia would be concerning for abnormal pulmonary vasoreactivity. If the echocardiogram demonstrates pulmonary hypertension, it should be repeated once the child has recovered from the acute episode, as pulmonary hypertension is part of the pathophysiology of HAPE.

Children may have normal echocardiograms at their home elevation, but signs of pulmonary hypertension with hypoxic challenge. If a child with recurrent HAPE lives at or frequents high altitude, a hypoxic challenge (e.g., 16% oxygen via nonrebreather mask or at a low partial pressure of oxygen (i.e., 3000 m)) may be helpful in determining if the patient has pulmonary hypertension at high altitude. If pulmonary hypertension is present after resolution of HAPE, then the child should be referred to a pediatric cardiologist with expertise in pulmonary hypertension for consideration of cardiac catheterization to confirm the diagnosis, rule out anatomic abnormalities, and to determine response to vasoactive agents. Most children with a history of HAPE and baseline elevation of mean pulmonary artery pressures are

FIG. 3. Schematic for evaluation following acute pulmonary edema at high altitude. MRI, magnetic resonance imaging.

vasoreactive to acute vasodilator challenge and do well with chronic calcium channel blocker therapy (e.g., nifedipine or in our experience, amlodipine) (Das et al., 2004). The minimal hemodynamic change that defines a positive response to vasodilator testing for children should be considered as a $\geq 20\%$ decrease in PAP and pulmonary vascular resistance/systemic vascular resistance without a decrease in cardiac output (Abman et al., 2015).

If the child lives at high altitude or has recurrent HAPE, an overnight pulse oximetry at that altitude should be performed when well to ensure that there is no chronic hypoxemia contributing to the child's pulmonary vasoreactivity. If the child has any symptoms of sleep apnea, a sleep study should be performed, as obstructive sleep apnea can contribute to pulmonary hypertension (Abman et al., 2015). However, both obstructive sleep and central sleep apnea are worse at high altitude (Anholm et al., 1992; Weil, 2004; Lombardi et al., 2013), therefore, a normal sleep study at lower elevation may provide false reassurance regarding high-altitude sleep status. A home polysomnogram for high-altitude dwellers/frequenters is the most appropriate test, although this is not commercially available for children.

HAPE Susceptibility

HAPE susceptibility is certainly first and foremost related to altitude and rate of ascent, but there are some individuals who develop recurrent HAPE; HAPE susceptible people

have increased pulmonary capillary pressures at high altitude and exaggerated responses to hypoxia and exercise (Maggiolini et al., 2001). Genetic mutations have been described for some HAPE susceptible populations (Hanaoka et al., 1998; Droma et al., 2002; Kobayashi et al., 2013), although these polymorphisms have not been reproduced by other groups nor seen in Caucasian populations (Dehnert et al., 2002; Weiss et al., 2003). Congenital cardiovascular diseases, including pulmonary vein stenosis, atrial septal defect, ventricular septal defect, patent foramen ovale, and unilateral absence of a pulmonary artery, are also risk factors for HAPE (Hackett et al., 1980; Rios et al., 1985; Sebbane et al., 1997; Schoene, 2001; Das et al., 2004; Allemann et al., 2006), and echocardiogram should be considered for children with HAPE. If the child has recurrent HAPE or an unusual presentation of HAPE, the child should be evaluated for structural heart disease.

Children may have increased susceptibility to HAPE (Hultgren and Marticorena, 1978). Young children have increased vasoreactivity and altered control of breathing especially at high altitude or simulated high altitude (Parkins et al., 1998). Perinatal hypoxemia with pulmonary hypertension increases vascular reactivity at high altitude in adults (Sartori et al., 1999) and may predispose children and adults to HAPE. Previous work demonstrated that children who suffered from HAPE have increased pulmonary artery pressure and increased vasoreactivity to hypoxic challenges, even after recovery from the acute HAPE episode

(Fasules et al. 1985). Some high-dwelling children have pulmonary vascular remodeling (Naeye, 1965), but these changes appear to be reversible with descent (Grover et al., 1966). Respiratory infections in children increase capillary permeability, contributing to development of HAPE (Durmowicz et al., 1997).

Obstructive sleep apnea contributes to pulmonary hypertension (Abman et al., 2015) and therefore predisposes children to develop HAPE. Children with Trisomy 21 may have an increased risk of developing HAPE (Durmowicz, 2001), which is likely secondary to their increased risk of pulmonary hypertension, pulmonary vascular reactivity, congenital heart disease, alveolar and vascular simplification, and obstructive sleep apnea.

Prevention of HAPE

There is no indication for prophylaxis of HAPE in altitude-naïve patients. In adults with a history of HAPE, vasodilators, including calcium channel blockers (i.e., amlodipine/nifedipine) and phosphodiesterase inhibitors (i.e., sildenafil or tadalafil) as well as long-acting beta-agonists (salmeterol), have been used to prevent HAPE (Bartsch et al., 1991; Sartori et al., 2002; Maggiorini et al., 2006; Luks and Swenson, 2008). Dexamethasone has been suggested for adults who may be at altitude for shorter periods of time, such as fewer than 5 days (Maggiorini et al., 2006).

Pharmacologic prevention strategies are not recommended in children with no history of HAPE (Pollard et al., 2001). Patients with a history of underlying cardiac and/or pulmonary disease (structural heart disease, pulmonary hypertension, bronchopulmonary dysplasia, and severe obstructive and restrictive lung disease) should consult their physician. Patients who are on oxygen at baseline will need an increase in oxygen flow, depending on the altitude. A portable pulse oximeter can help guide how much oxygen the child needs.

In all children with a history of HAPE, especially with multiple episodes of HAPE, we suggest treating any underlying contributors to HAPE, including nocturnal hypoxemia at high altitude, sleep apnea, and pulmonary hypertension. We suggest three additional preventative approaches to prevent classic and reentry HAPE in previously affected children without underlying pulmonary hypertension; the specific approach depends on the child's history as well as patient/family preference. The first is a gradual ascent to high altitude with 1–2 nights at a medium elevation (e.g., 1500–2100 m or 5000–7000 feet) which may prevent development of HAPE. Observations in adults suggest ascent rates of 400 m per day for altitudes >2000 m (6500 feet) (Bartsch et al., 2003). The family could also consider vacationing at a lower elevation while still enjoying the same activities (e.g., Steamboat Springs at an elevation of 2052 m (6732 feet) rather than Breckenridge at an elevation of 2926 m (9600 feet), or at least staying at a lower elevation than where symptoms previously occurred. Second, prophylactic initiation of supplemental oxygen upon arrival to high altitude may prevent development of HAPE by optimizing pulmonary vasodilation. Depending on the child's insurance, this can be challenging to arrange. Third, pharmacologic therapy (Tables 1 and 2) can be started 1–2 days before ascent and continued for 3–4 days at the final altitude, and includes nifedipine extended release, acetazolamide, and amlodipine (Abman et al., 2015). Acetazolamide has not been previously described for HAPE pre-

vention in the literature, but has been frequently prescribed for patients with a history of reentry HAPE by physicians practicing at high altitude in Colorado. Acetazolamide is not indicated in the acute management of HAPE. Finally, if the child has an upper respiratory infection at the time of return, more conservative precautions should be taken, including delaying ascent during the acute illness.

For children with HARPE, starting on oxygen via nasal cannula with any illness onset may be sufficient. For children with recurrent episodes, we suggest starting nifedipine, amlodipine, or acetazolamide (Table 2) with illness onset. Some of these children may not be able to live at high elevation (Abman et al., 2015). Some children with underlying disease processes may never do well at high elevations (Grover et al., 1966). If children have underlying pulmonary hypertension and live at high altitude, they may benefit from relocation to lower altitude. Chronic calcium channel blocker therapy can be considered for children who are unable to relocate to lower elevation.

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Author Disclosure Statement

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Address correspondence to:

Deborah R. Liptzin, MD
Children's Hospital Colorado
13123 East 16th Avenue, Box 395
Aurora, CO 80045

E-mail: deborah.liptzin@childrenscolorado.org

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