High Altitude Pulmonary Edema in Children: A Single Referral Center Evaluation

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Objective To describe the clinical features of children who presented to Children's Hospital Colorado (CHCO) with high-altitude pulmonary edema (HAPE).

Study design We performed a retrospective chart review in children discharged from CHCO (an elevation of 1668 m) with a clinical diagnosis of HAPE and a chest radiograph consistent with noncardiogenic pulmonary edema. Descriptive statistics were used to describe the demographics, presentations, and treatment strategies.

Results From 2004 to 2014, 50 children presented to CHCO who were found to have a clinical diagnosis of HAPE and a chest radiograph consistent with noncardiogenic pulmonary edema. Most (72%) patients were male, and most (60%) of the children in the study were diagnosed with classic HAPE, 38% with re-entry HAPE, and 2% with high altitude resident pulmonary edema. Elevation at symptom presentation ranged from 1840 to 3536 m. Patients were treated with a variety of medications, including diuretics, steroids, and antibiotics. Four patients were newly diagnosed with structural heart findings: 2 patients with patent foramen ovale and 2 with atrial septal defects. Eleven patients had findings consistent with pulmonary hypertension at the time of echocardiography.

Conclusions HAPE symptoms may develop below 2500 m, so providers should not rule out HAPE based on elevation alone. Structural heart findings and pulmonary hypertension are associated with HAPE susceptibility and their presence may inform treatment. Inappropriate use of antibiotics and diuretics in children with HAPE suggest that further education of providers is warranted. *(J Pediatr 2019;210:106-11)*.

At an average elevation of 2072 m,[1] Colorado has the greatest mean elevation of any state in the US and welcomed 82.4 million visitors in 2016.[2] Visitors to Colorado are at risk of acute mountain sickness, high altitude cerebral edema, and high altitude pulmonary edema (HAPE).[3,4] HAPE is an acute noncardiogenic pulmonary edema caused by patchy hypoxic pulmonary vasoconstriction.[5,6] Classic HAPE presents in people who travel from lower elevation to high elevation (>2500 m) and is related to altitude and rate of ascent.[3,7,8] People who live at high altitude can also develop HAPE, either when they return from lower elevations (re-entry HAPE)[4,9-11] or with a concurrent respiratory infection and no elevation change (high altitude resident pulmonary edema or HARPE).[12,13] Re-entry HAPE appears to be more common in children.[9-11] At Children's Hospital Colorado (CHCO), we are in a unique position to comment on pediatric HAPE because we are the academic children's hospital at the highest elevation in the country and we receive referrals from mountain communities at higher elevations.

The literature describing HAPE in children is sparse and has primarily been found in case reports and expert opinion.[4,5,9-11,14,15] Our objective was to better understand pediatric HAPE and to guide future studies for management and prophylaxis of HAPE.

Methods

We performed a retrospective chart review under an institutional review board approved protocol. Informatics for Integrating Biology and the Bedside was used to query the electronic medical record for the diagnosis (billing, encounter, and problem list) of "unspecified effects of high altitude" (*International Classification of Diseases, Ninth Revision* code 993.2) from 2004 to 2014; this code includes diseases such as acute mountain sickness, barotrauma of ascent/descent,

HAPE	High altitude pulmonary edema
PFO	Patent foramen ovale
ASD	Atrial septal defect
HARPE	High altitude resident pulmonary edema

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chronic mountain sickness, diving barotrauma, high altitude pulmonary edema, high altitude cerebral edema, high altitude pulmonary hypertension, high altitude retinopathy, and suit squeeze. We included 50 patients in this review (Figure 1). To be included, patients needed to have a clinical history consistent with HAPE documented by the treating provider and a chest radiograph suggestive of noncardiogenic pulmonary edema (Figure 2). A pediatric radiologist with expertise in chest radiology reviewed the chest radiographs of all patients with a clinical diagnosis of HAPE to determine if chest radiographs had a high probability (eg, Figure 2), equivocal, or low probability of noncardiogenic pulmonary edema. The chest radiographs were also evaluated for lobar pneumonia. Data collection from chart review included demographic data, clinical presentation, past medical history, examination findings, evaluation, treatment, and follow-up. Patients presented either directly from homes/hotels or from mountain community facilities. Data were entered into a Research Electronic Data Capture (REDCap) database.[16] Echocardiograms and cardiac catheterizations were clinically performed at the discretion of the treating physician. All statistical tests were considered significant at the alpha = 0.05 level. Demographic characteristics and clinical interventions were summarized as frequencies (%) and medians with range. Individuals were subgrouped based on type of HAPE (classic, re-entry, or HARPE). Group comparisons were performed between classic and re-entry HAPE patients using Fisher exact test and Wilcoxon rank sum test. All analyses were conducted using R v 3.4.1 software (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/).

Results

At CHCO, 411 children were evaluated and were coded as 993.2 "other effects of high altitude." However, 316 patients were excluded because they did not have a clinical presentation consistent with HAPE or a chest radiograph to suggest noncardiogenic pulmonary edema (Figure 1). Many of the excluded patients were infants receiving oxygen. Fifty patients with clinical histories and chest radiographs suggestive of noncardiogenic pulmonary edema (Figure 2) were included in the analysis. Twenty (40%) patients of the 50 patients had chest radiographs with findings suggestive of lobar pneumonia. Demographics (Table) are notable for a male predominance (n = 36, 72%). This sex difference was most notable when comparing children <11 years and >11 years of age (P = .004) This sex difference was also driven by patients with classic HAPE (P = .007) rather than re-entry HAPE (P = .25). The most common symptoms in the entire cohort were shortness of breath (n = 38, 76%), cough (n = 36, 72%), and emesis (n = 27, 54%) and are reported in the Table. Ten children (20%) presented with headache.

Median age at presentation was 10.2 years (range 0.6-19 years). One-half of the children in the cohort (n = 26, 52%) were older than 10 years, 36% (n = 18) were between 5 and 10 years of age, and 12% (n = 6) were under 5 years of age. The youngest patient was a 7-month-old male child originally from Texas who presented from a facility at 2500 m elevation with hypoxemia, respiratory infection, and chest radiograph with concerns for pulmonary edema.

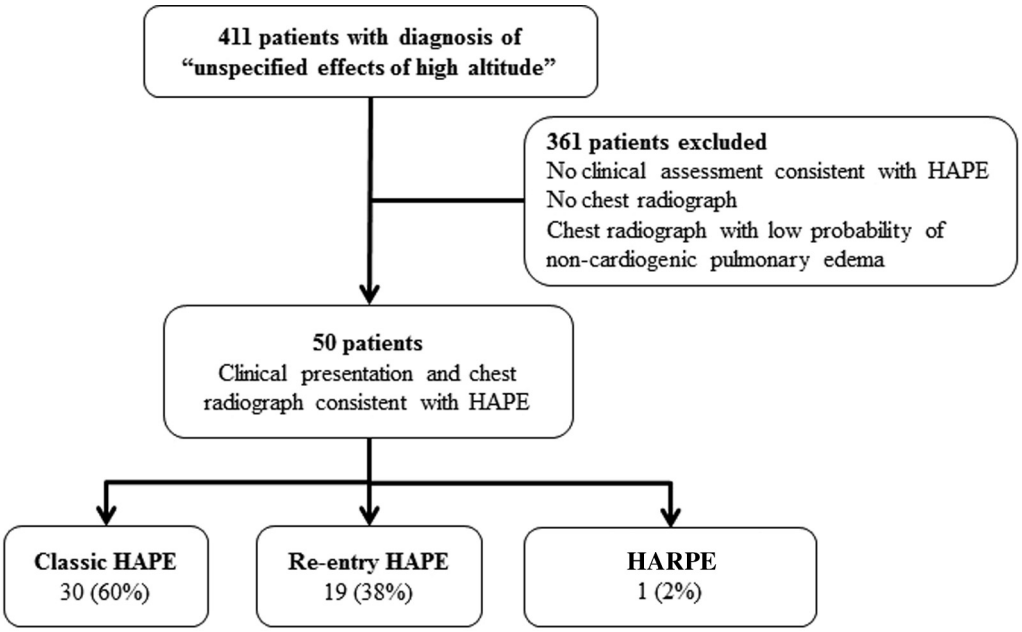

Figure 1. Consort diagram demonstrating the patients evaluated for the current study and the final study cohort.

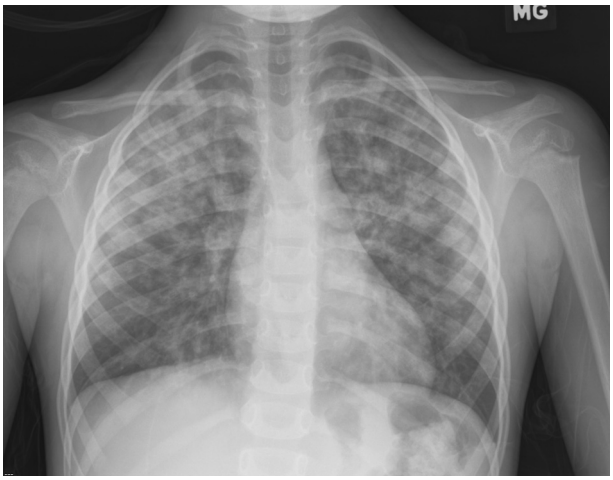

Figure 2. Chest radiograph demonstrating bilateral ill-defined nodular opacities consistent with HAPE, in this case predominantly in the upper lobes.

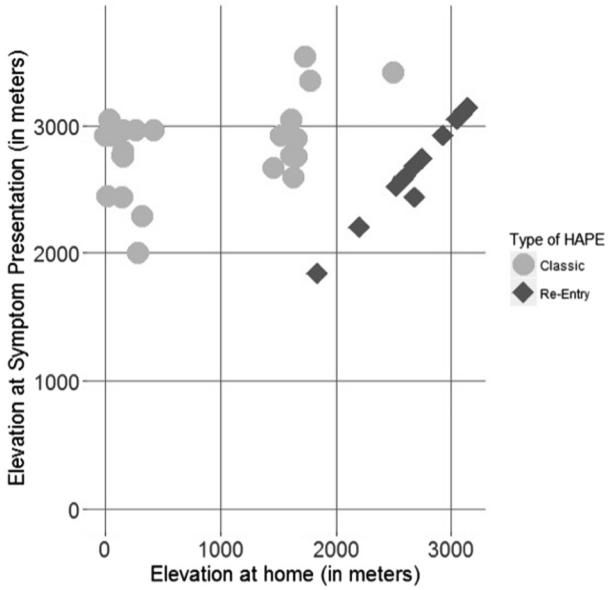

Figure 3. Elevation of symptom presentation in meters by type of HAPE and home elevation in meters. Patients with classic HAPE typically lived at low elevations or moderate elevations (between 0 and 2000 m). Patients with re-entry HAPE lived at moderate to high (>2000 m) elevations. One patient had HARPE and lived at approximately 2926 m.

The median pulse oximetry in room air at first recorded presentation (either at CHCO at an outside hospital, or by emergency medical services) was 74% (range 20%-94%). Symptoms of a concurrent respiratory infection were documented in 14 patients (28%). No patients were noted to have otitis media. Most patients had classic HAPE (n = 30, 60%), followed by re-entry HAPE (n = 19, 38%), and 1 patient had HARPE (n = 1, 2%) (**Figure 3**). Children with re-entry HAPE spent a median length of 7 days (range 1-30 days) at lower altitudes. Most HAPE presentations occurred in the spring (46%), followed by winter (34%), summer (12%), and fall (8%). Thirteen of the children (26%) were skiing, 4 (8%) were camping, and 1 (2%) of the children was hiking. Other patients were visiting, snowshoeing, returning home, or mountain biking. Median elevation at symptom presentation was 2789 m (range 1840-3536 m) (**Figure 3**). The median home elevation was 1655 m (range 2.7-3139 m) (**Figure 3**). Eight children of the 50-patient cohort (16%) included in the analysis had a maximum elevation of <2500 m; 2 of these 8 reached a maximum elevation lower than 2000 m. Median duration of stay at CHCO for admitted patients was 2.2 days.

Table. Demographics and presentation of 50 children who presented to CHCO with high altitude pulmonary edema

Median age in y [range]	10.2 [0.6-19.2]
Sex, n (%)	
Male:female	36 (72):14 (28)
Type of HAPE, n (%)	
Classic	30 (60)
Re-entry	19 (38)
Resident	1 (2)
Home elevation in meters [range]	1655 [2.7-3139]
Elevation of symptom onset [range]	2798 m [1840-3536]
Symptoms, n (%) (49 patients reporting)	
Shortness of breath	38 (78)
Coughing	36 (73)
Emesis	27 (55)
Fever	13 (27)
Cyanotic	13 (27)
Fast breathing	12 (24)
Headache	10 (20)

Seven children (14%) of the cohort had a history of structural heart findings prior to their HAPE presentation; 3 of these notably presented at altitudes lower than 2500 m. Of the 7 with a history of structural heart findings, 2 had atrial septal defects (ASD), 1 had a patent foramen ovale (PFO) and an ASD, 1 had an absent pulmonary artery, 1 had a ventricular septal defect/coarctation of the aorta/bicuspid aortic valve, and 2 had pulmonary stenosis. There was no significant difference in presentation with classic vs re-entry HAPE between patients that had pre-existing heart conditions to those who did not prior to their HAPE diagnosis.

Children with classic and re-entry HAPE were additionally compared in terms of structural heart findings, season of presentation, and initial pulse oximetry, and there was no significant difference between groups.

Treatment

All patients presented to CHCO (elevation 1668 m) after descending from higher elevations. Level of respiratory support during HAPE episode and recovery varied for each patient. Six patients (12%) were not treated with oxygen upon evaluation at CHCO, as descent had been sufficient to treat their HAPE episode. Most patients (n = 34 of 49 patients, 69%)

were treated with oxygen, 6 children (12%) were initiated on noninvasive ventilation, and 4 (8%) were intubated and invasively ventilated. Children who were treated with noninvasive or invasive ventilation (ie, markers of severe disease,) vs no ventilation were compared, and there was no significant difference in type of HAPE, age, underlying heart disease, initial pulse oximetry, concurrent infection, and change in elevation from home.

Medication data during the acute HAPE episode were available from 41 patients and included furosemide (n = 8, 20%), calcium channel blockers such as nifedipine or amlodipine (n = 4, 10%), acetazolamide (n = 3, 7%), systemic corticosteroids such as dexamethasone, prednisolone, or prednisone (n = 9, 22%), and antibiotics (variety) (n = 35, 85%).

Echocardiograms were conducted at CHCO in 24 patients (48%); 20 patients had echocardiograms during the acute illness/recovery period (ie, within 5 days of presentation). The remainder either had previous echocardiograms (2 patients) or echocardiograms after recovery (2 patients). Eleven of the 24 who underwent echocardiograms displayed evidence of pulmonary hypertension defined as septal flattening and/or tricuspid regurgitation jet of 3 m/s or greater. One additional patient had evidence of pulmonary hypertension by cardiac catheterization (see below), but not by echocardiography. Several additional patients did not meet the above criteria for pulmonary hypertension, but had echo findings suggestive of pulmonary hypertension, including decreased right ventricular function, right ventricular dilation, and/or dilated pulmonary artery. Four patients (17%) of the 24 who underwent echocardiogram were diagnosed with new structural heart findings (new PFO in 2 and new ASD in 2).

Follow-Up

Fifteen patients (30%) had a follow-up with cardiology clinic and 17 (34%) followed up in pulmonology clinic. Recommendations varied from patient to patient and included slow ascent, prophylaxis with medications, oxygen with sleep and/or at high altitudes, overnight pulse oximetry monitoring, and further evaluation including hypoxic echocardiography, cardiac catheterization, polysomnography, and cardiopulmonary exercise testing. Five patients were noted to have asthma. One patient was evaluated with polysomnogram and was determined to have borderline obstructive sleep apnea at 1668 m.

In cardiology or pulmonary follow-up, 3 patients had hypoxic echocardiograms (echocardiograms performed in hypoxic conditions, typically 16% oxygen or at 2766 m at rest) and all 3 had signs of pulmonary hypertension with the hypoxic challenge. Seven patients of the 50 (14%) underwent cardiac catheterizations (at 1668 m) either before the HAPE episode or following the HAPE episode. The mean pulmonary artery pressures median was 18.5 mm Hg (range 15-22 mm Hg, normal mean pulmonary pressures 11-12 mm Hg).[17] Not all patients were evaluated with hypoxia or oxygen, but those that were evaluated on oxygen had mean pulmonary artery pressures ranging from 13 to 15 mm Hg, and those that were evaluated on 16% oxygen had mean pulmonary artery pressures ranging from 18 to 80 mm Hg. Pulmonary vascular resistance index median was 3.06 Woods units (range 2.05-3.89 Woods units); 5 patients had Woods units of 3 or greater, indicative of pulmonary hypertension. One of these patients underwent cardiac catheterization prior to the HAPE episode and was noted to have pulmonary hypertension at that time (3.47 Woods Units).

At CHCO, children were prescribed a variety of prophylactic medications to prevent future HAPE episodes, including calcium channel blockers (nifedipine [n = 10, 20%] or amlodipine [n = 3, 6%]) and acetazolamide (n = 9, 18%). The prescribing patterns were provider dependent and typically included starting 1-2 days prior to ascending in elevation and ending 1-2 days after reaching final elevation vs continuing the medication for the entire duration at high altitude. Eight patients suffered from known HAPE recurrence.

Discussion

At CHCO, approximately 5 children a year were evaluated with a clinical diagnosis of HAPE and chest radiograph suggestive of noncardiogenic pulmonary edema. We found that HAPE may present at elevations lower than 2500 m, as reported in the literature.[18-20] Although HAPE is traditionally not an inflammatory process,[21] viral-induced inflammation leads to increased vascular permeability and may predispose children to HAPE.[22,23] In this retrospective cohort, male patients were more likely to present with HAPE, and this was especially true in older patients with classic HAPE.

Our review is not a comprehensive review of the incidence of pediatric HAPE in Colorado as our study is limited by its retrospective design. The incidence is likely significantly higher than we report as many children had clinical histories consistent with HAPE and either had a chest radiograph at an outside facility that was not available for review or did not have a chest radiograph. Many more children may never have presented to CHCO if they were treated at local emergency departments and discharged on oxygen and/or advised to go to lower elevation (<2500 m). Other children may have never presented to care.

Ten (20%) of children in the cohort presented with headache, and 27 (54%) presented with emesis suggestive of acute mountain sickness. There is crossover between these different manifestations of high altitude; in adults, 50% of patients with HAPE also have acute mountain sickness,[24] but this has not been well established in children.

Antibiotics are not indicated for the treatment of HAPE,[4,8] however, 35 patients (85%) were treated with antibiotics. HAPE may be misdiagnosed as pneumonia or pneumonia may be a comorbid disease process; in our cohort, 40% of patients had chest radiographs suggestive of lobar pneumonia. It is unclear whether these patients in fact had concurrent pneumonia or whether the findings of HAPE on radiography mimicked pneumonia. Eight patients were treated with furosemide, which is not recommended for HAPE because of the

risk of further volume depletion in patients with already low intravascular volume.[25] More education about HAPE recognition and treatment may be helpful for our emergency medicine, intensivist, hospitalist, cardiology, and pulmonary colleagues.

Children with pulmonary hypertension and structural heart findings may be predisposed to HAPE, and proper precautions should be given to these families. Evaluation for structural heart findings and pulmonary hypertension has been suggested following a HAPE episode, both for classic and re-entry HAPE.[13] Structural heart findings are a known contributor to HAPE, including unilateral absence of the pulmonary artery, ASD, coarctation of the aorta, and ventricular septal defect.[5,20,26-29] PFO is a known association with HAPE susceptibility[30] and is present in 10%-35% of the population.[31] Eleven patients (22% of all patients; 46% of those who had an echocardiogram) in our study had structural heart findings (7 previously known, 4 newly diagnosed). Pulmonary hypertension is expected to be present during the acute episode of HAPE, but if it persists after recovery or with subsequent hypoxic challenge, then the child should be further evaluated for etiology of pulmonary hypertension and appropriately treated.[13,32] The prevalence of pulmonary hypertension in an otherwise healthy pediatric population is not well studied, but in extremely low birth weight infants (eg, <1 kg), pulmonary hypertension affects 18% of children.[33] Nearly one-half of the patients did not undergo an echocardiogram, therefore, pulmonary hypertension and structural heart findings may have been missed in these patients, or there may have been a bias to whom was evaluated with echocardiogram. Only 15 patients (30%) had follow-up with cardiology and 17 (34%) had follow-up with pulmonology, and contributors to pulmonary hypertension such as obstructive sleep apnea was assessed in only 1 patient.

We found that a significant majority of the patients were male. The sex difference was most notable in patients greater >11 years of age, suggesting that sex hormones play a role in HAPE susceptibility, either that male sex hormones predispose patients to HAPE or that female sex hormones are protective. Prior pediatric case series have demonstrated a male predominance.[5] Young male patients have a higher respiratory morbidity than young female patienrts.[34] Although the literature supports a higher prevalence of HAPE in adult male patients,[7,11] this is typically thought to be because they are more likely to be at higher altitudes participating in recreational activities. In children, we think activity choice for this sex difference is unlikely as they are typically traveling with their families. We hope to further investigate this sex difference in future prospective studies.

We suggest that seasonal variation is reflective of vacation timing (ski vacations during winter break for lowlanders and sea-level travel during spring break for Coloradans) and respiratory illness season rather than differences in the seasons themselves, although atmospheric pressures—and therefore partial pressure of oxygen—are lowest in the winter, so there may be a geophysical explanation for some of the seasonal findings.

Our study was limited by its retrospective design, including lack of demographic information, missing data surrounding the presentation of HAPE, and limited long-term follow-up. A major limitation is that many children with HAPE would never have presented to CHCO and would, therefore, not be captured by the current study.

There is practice variation in terms of treatment and prophylaxis of HAPE, and future studies should evaluate best practice patterns for type of both acute and prophylactic medication and timing as well as comparison with slower rate of ascent (ie, spending a night in Denver) and use of nocturnal oxygen.

Use of antibiotics, steroids, and diuretics raise questions regarding limited knowledge about HAPE treatment guidelines, poor recognition of HAPE, and/or concern for coexisting medical conditions. This review suggests emergency medicine, intensivists, pulmonologists, cardiologists, and hospitalists may benefit from additional education regarding HAPE diagnosis and treatment. This variability in terms of evaluation and both acute and prophylactic medications also creates opportunities for research into evidence based best practice. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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