8-2008

Acute Mountain Sickness, High Altitude Cerebral Edema and High Altitude Pulmonary Edema

Vaheed Sevvom

Pacific University

Follow this and additional works at: http://commons.pacificu.edu/pa

Part of the Medicine and Health Sciences Commons

Recommended Citation
Acute Mountain Sickness, High Altitude Cerebral Edema and High Altitude Pulmonary Edema

Abstract
Recreation and business draw countless visitors to high altitude locations across the country every year. Many people coming from low land elevations are unacclimatized to the lower oxygen levels at higher altitude and develop symptoms of altitude illness. The most common type of altitude illness is Acute Mountain Sickness (AMS), followed by the more rare conditions of High Altitude Cerebral Edema (HACE) and High Altitude Pulmonary Edema (HAPE), both of which can be life threatening. The purpose of this literature review was to use information from various internet search engines, online medical journals, research articles, and textbooks to compile the latest information on the pathophysiology, signs and symptoms, treatment and prevention of AMS, HACE, and HAPE.

AMS and the other altitude illnesses are clinical diagnoses in relation to recent arrival to altitude in a person who is otherwise unacclimated to high elevation. The clinical criteria for diagnosing AMS involves the following findings in the context of recent arrival to high altitude; a headache with one or more of the following: anorexia, nausea or vomiting, fatigue or weakness, dizziness or lightheadedness, or difficulty sleeping. HACE is considered end stage AMS and involves severe AMS symptoms as well as ataxia, confusion, and gross neurological dysfunction. HAPE is considered a separate entity than AMS or HACE but is found congruently with HACE in 50 percent of cases. Symptoms include dyspnea at rest, a productive cough and weakness.

The mainstay of prevention for all types of altitude illness includes a slow ascent rate, plenty of rest and fluids. Acetazolamide and dexamethasone are the current recommended medications for prophylaxis, however the herbal remedy Ginkgo biloba have all been shown to be effective in some studies. Once symptoms develop treatment is largely based on descent, limiting further exertion and providing supplemental oxygen. Acetazolamide, Dexamethasone, Nifedipine, and Phosphodiesterase-5 inhibitors are all shown to be effective treatments although some are still in the developmental stage in terms of recommendations and dosing. Hyperbaric therapy is also indicated in severe cases when available.

The altitude illnesses of Acute Mountain Sickness, High Altitude Cerebral Edema, and High Altitude Pulmonary Edema are diagnoses that need to be taken seriously, although most cases are minor in nature and will improve significantly with time, rest or descent. Humans have a significant variability in terms of ones ability to adapt to high altitude due to mechanisms that are still not fully understood. However it is inevitable that many visitors will develop symptoms as they visit high altitude and it is imperative that clinicians providing care in these environments be educated on this relatively common condition and how to best treat it.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/183
First Advisor
Latha Reddy PA-C

Second Advisor
Jonathon W Gietzen MS PA-C

Keywords
acutemountain sickness, altitudeillness, high altitude pulmonary edema, high altitude pulmonary edema, acclimatization

Subject Categories
Medicine and Health Sciences

Rights
This work is licensed under a Creative Commons Attribution 3.0 License.

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/183
NOTICE TO READERS

This work is not a peer-reviewed publication. The Master’s Candidate author(s) of this work have made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author(s) nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author(s) and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student authors attest that this work is completely their original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
ACUTE MOUNTAIN SICKNESS, HIGH ALTITUDE CEREBRAL EDEMA AND HIGH ALTITUDE PULMONARY EDEMA

By:

VAHEED SEVVOM

A Clinical Research Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Forest Grove, OR

For the Masters of Science Degree August, 2008

Faculty Advisor: Latha Reddy PA-C
Clinical Project Advisor: Jonathon W Gietzen MS PA-C
STATEMENT OF ACCEPTANCE:

This project is hereby accepted as a requirement for completion of the degree of:
Masters of Science in Physician Assistant Studies at Pacific University School of Physician Assistant Studies on this day the sixteenth of August, 2008.

Vaheed Sevvom, PA-S                      Date
Author

Jonathon W Gietzen MS, PA-C               Date
Clinical Project Coordinator

H. F. Randolph III, PA-C, MPAS           Date
Program Director
Biography

Vaheed Sevvom is a native of Colorado and majored in Kinesiology and Applied Physiology at the University of Colorado at Boulder. Prior to PA school he had experience as a medical assistant and as a physical therapy aide. He became interested in a career as a Physician Assistant after his aspirations of playing professional soccer in Europe were thwarted by three knee surgeries and by the realization that he needed to pursue gainful employment that was actually realistic. He has always loved biology and medicine and his primary interest is acute care. He is moving back to Colorado where he is eager to start his first job in Emergency Medicine at a level one trauma center in Denver.

Acknowledgements

To Amanda Primm, Thank you for your patience, teamwork, understanding and continued love throughout this wonderfully rewarding and tireless journey that we have been on together. You carried me when I felt too tired to stand. I know this will all be worth it in the end.

To my parents and brother, Thank you for your continued emotional encouragement and enthusiasm for this undertaking over these last two years. You all continue to inspire me with your love and support. I could not have done this without you.

To my classmates, Thanks for everything all of you have done. I started this only expecting an education and walk away with so much more than that. Your friendship is invaluable and I aspire to equal your intelligence and compassion.
Abstract

Recreation and business draw countless visitors to high altitude locations across the country every year. Many people coming from low land elevations are unacclimatized to the lower oxygen levels at higher altitude and develop symptoms of altitude illness. The most common type of altitude illness is Acute Mountain Sickness (AMS), followed by the more rare conditions of High Altitude Cerebral Edema (HACE) and High Altitude Pulmonary Edema (HAPE), both of which can be life threatening. The purpose of this literature review was to use information from various internet search engines, online medical journals, research articles, and textbooks to compile the latest information on the pathophysiology, signs and symptoms, treatment and prevention of AMS, HACE, and HAPE.

AMS and the other altitude illnesses are clinical diagnoses in relation to recent arrival to altitude in a person who is otherwise unacclimated to high elevation. The clinical criteria for diagnosing AMS involves the following findings in the context of recent arrival to high altitude; a headache with one or more of the following: anorexia, nausea or vomiting, fatigue or weakness, dizziness or lightheadedness, or difficulty sleeping. HACE is considered end stage AMS and involves severe AMS symptoms as well as ataxia, confusion, and gross neurological dysfunction. HAPE is considered a separate entity than AMS or HACE but is found congruently with HACE in 50 percent of cases. Symptoms include dyspnea at rest, a productive cough and weakness.

The mainstay of prevention for all types of altitude illness includes a slow ascent rate, plenty of rest and fluids. Acetazolamide and dexamethasone are the current recommended medications for prophylaxis, however the herbal remedy Ginkgo biloba have all been shown to be effective in some studies. Once symptoms develop treatment is largely based on descent, limiting further exertion and providing supplemental oxygen. Acetazolamide, Dexamethasone, Nifedipine, and Phosphodiesterase-5 inhibitors are all shown to be effective treatments although some are still in the developmental stage in terms of recommendations and dosing. Hyperbaric therapy is also indicated in severe cases when available.

The altitude illnesses of Acute Mountain Sickness, High Altitude Cerebral Edema, and High Altitude Pulmonary Edema are diagnoses that need to be taken seriously, although most cases are minor in nature and will improve significantly with time, rest or descent. Humans have a significant variability in terms of ones ability to adapt to high altitude due to mechanisms that are still not fully understood. However it is inevitable that many visitors will develop symptoms as they visit high altitude and it is imperative that clinicians providing care in these environments be educated on this relatively common condition and how to best treat it.

Keywords: acute mountain sickness, altitude illness, high altitude pulmonary edema, high altitude pulmonary edema, acclimatization
## Table of Contents

Statement of Approval ........................................................................................................ 1

Biography .......................................................................................................................... 3

Acknowledgements........................................................................................................... 3

Abstract ........................................................................................................................... 4

Table of Contents ............................................................................................................. 5

List of Tables .................................................................................................................... 6

List of Abbreviations ........................................................................................................ 6

Introduction and Background ......................................................................................... 7

Methods ........................................................................................................................... 7

Results ............................................................................................................................. 8

Discussion ......................................................................................................................... 8

Conclusion ......................................................................................................................... 24

Tables ............................................................................................................................... 26

References ....................................................................................................................... 27
List of Tables

Table I: Factors predisposing infants and young children to hypoxemia
Table II: Differential Diagnosis for the various altitude related illnesses
Table III: Specific Treatment Recommendations

List of Abbreviations

AMS………………………………………………………………Acute Mountain Sickness
HACE………………………………………………………………High Altitude Cerebral Edema
HAPE………………………………………………………………High Altitude Pulmonary Edema
Introduction and Background

Every year thousands of people in the United States alone visit high terrain environments, often for recreational activity. Many of those people are unacclimatized to elevation and some of those people develop symptoms of altitude sickness, medically known as Acute Mountain Sickness (AMS), or its related illnesses High Altitude Pulmonary Edema (HAPE) and High Altitude Cerebral Edema (HACE). In recreational or tourist destinations located at high altitude, Acute Mountain Sickness is deemed a public health problem. It also has economic consequences, primarily for the ski industry, but also hospitals and patients. Emergency Departments in Denver, Colorado commonly care for patients transferred from nearby ski areas with symptoms of AMS and a significant amount of time, money and resources are spent on caring for these patients. Every year visitors to high altitude are at risk of developing this common and potentially serious illness without ever knowing it \(^1\), \(^3\).

The purpose of this literature review is to identify the signs and symptoms, pathophysiology and treatment of Acute Mountain Sickness in unacclimatized visitors to high altitude environments. This information should include risk factors and prevention. Furthermore, an understanding of the prevalence and incidence as well as the geographic areas where AMS is more likely to occur should be understood. The current literature should describe the underlying physiology that is related to altitude acquired hypoxemia as well as suggest proper management of this illness.

Methods

An exhaustive search was used to compile the available medical literature into the most relevant and up to date information. Ovid and Pub Med search engines were the primary sources for collecting medical research articles. “Up to Date”, an objective online medical database that also compiles the latest research information into a concise format was also used for both
information and to find the most current articles that may have been missed during the initial search in Ovid and Pub Med. The following search terms were used to identify acceptable literature articles: acute mountain sickness, mountain illness, altitude sickness, mountain sickness, high altitude cerebral edema, high altitude pulmonary edema and altitude acclimatization. Emphasis was placed on articles that discussed pathophysiology, signs and symptoms, treatment and prevention. The world wide web was utilized to access information regarding the various geographic terrains mentioned within the body of this article, primarily the specific elevations of states and ski resorts.

**Results and Discussion**

Over 18 articles were found that met the specific search criteria. The articles were investigated for information on signs and symptoms, risk factors, definitions and criteria of high altitude, pathophysiology, treatment, and prevention of high altitude related illness.

**Definitions**

“High altitude” is considered a terrestrial elevation over 1500m (4921 ft), “very high altitude” is 3500-5500m (11,483-18,045 ft) and “extreme altitude” is 5500-8850m (18,045-29,035 ft). Patient encounters at “very high” and “extreme” altitudes are rare because of limited clinical access and most persons recreating at these altitudes are prepared for and knowledgeable regarding self treatment. Therefore, this dialogue will largely discuss “high altitude” elevation as this is the most commonly encountered in medical or hospital settings and most pertinent in terms of discussing treatment for most clinicians. It is of critical importance for clinicians working in or near high altitude terrain to be familiar with Acute Mountain Sickness, especially because “high altitude” is surprisingly not as high or as far away as one may initially think. For example, the entire state of Colorado is considered “high altitude”. Most of the destination ski
resorts in Colorado also allow visitors to easily access “very high altitude” on the ski slopes. Breckenridge ski resort in Colorado is 9,600 feet at the base and offers lift access up to 13,000 feet. In other lower elevation states, there is still easy access to “high altitude” terrain. Portland, Oregon for example is situated at 50 feet above sea level, but the nearby ski resort of Mount Hood Meadows varies between 4,500 at the base and 7,300 feet at the summit. Slightly further away Mount Bachelor Ski Resort in central Oregon varies between 6,300 and 9,000 feet of elevation. It’s easy to see how the ski industry alone provides almost instant access to “high altitude” and often to “very high altitude” environments.\(^1,3,10\)

Acute Mountain Sickness is a constellation of symptoms that occurs within hours to days in an unacclimatized person who visits high altitude. The primary mechanism for this is hypoxia due to a decrease in barometric pressure and a decrease in the partial pressure of ambient oxygen.\(^4\) A more progressive and debilitating form of AMS is referred to as High Altitude Cerebral Edema (HACE) which results in more severe AMS symptoms, as well as varying stages of encephalopathy. Another variation of AMS is also known as High Altitude Pulmonary Edema (HAPE), which in the realm of high altitude medicine is considered a separate entity than AMS and HACE.\(^1,2,3\) The signs and symptoms, as well as the pathophysiology of all these conditions will be discussed below.

Altitude acclimatization occurs when one’s body adjusts to lower levels of oxygen and typically takes anywhere from 1-3 days to occur.\(^4\) Several mechanisms are involved in this process and some occur immediately while others take much longer. Depth of respiration and ventilation will increase immediately to compensate for hypoxemia, as detected in the peripheral chemoreceptors in the carotid arteries. This process is referred to as the hypoxic ventilatory response (HVR). Cardiac output and pulmonary artery pressure will increase to ensure adequate
perfusion in the lungs, even in parts of the lungs that are underutilized at lower elevations. A fairly quick hypoxia induced cerebral artery vasodilatation occurs to maintain perfusion to the brain. The kidneys will immediately start producing more erythropoietin to stimulate bone marrow production of red blood cells, but this process takes weeks to produce a significant effect and does not help much in the short term. Another long-term adaptation involves increasing intracellular mitochondria to improve oxygen carrying capacity and efficiency, but this also does take some time and is unhelpful in a relatively acute altitude change. These multiple processes are incompletely understood and are highly variable among different individuals. It is thought that genetic differences account for the large variation in anatomic and physiologic responses and this in turn influences ones intrinsic ability to adjust to hypoxemia. However, it is known that allowing enough time to acclimatize is the primary factor in how well one will adjust to high altitude 1,2.

Prevalence, Incidence and Risk Factors

Variables that determine if one will develop AMS while at altitude include ascent rate, maximum altitude, sleeping altitude, duration at altitude, amount of exertion, temperature, and barometric pressure. Risk factors include pre-existing medical conditions, especially cardiopulmonary conditions, and residence below 900 meters of altitude. The most important predictor of developing AMS is a previous history of such 1.

Interestingly, there does not appear to be any correlation with gender or age. Some studies report a high incidence of AMS, HAPE, and HACE in men, but as the researchers admit, this is largely due to the study population. All types of acute mountain sickness occur less often in people over age 50 regardless of sex. The “tight fit” hypothesis suggests cranial capacity plays a role in developing AMS and HACE such that those individuals with more room for expansion
of cerebral spinal fluid are at decreased risk of developing symptoms. This hypothesis is relatively new and conclusive research is limited, but perhaps the normal decrease in brain volume with age accounts for a lower incidence in those over 50 years old \(^4\). It is suggested that HAPE occurs more frequently and with greater severity in children and young adults, but other research suggests that incidence in children is the same as adults \(^1,^3\). However, it is known that infants and young children are more susceptible to hypoxemia for various reasons (table 1), so although the data is inconclusive caution is still advised when traveling to higher elevations with young children \(^20\).

Due to study design limitations it is difficult to determine the incidence of illness related to high altitude. However, it is estimated that AMS occurs between 20 and 25 percent in the general tourist population at elevations above 2500 m (8202 ft). It is known to occur in 40 to 50 percent of lowland living individuals who ascend to 4250 m (14,000 feet). The incidence of High Altitude Cerebral Edema in this same population is estimated at below 0.01%. High Altitude Pulmonary Edema is only slightly more common at an estimated rate of 0.01% to 0.1%. The occurrence rate and severity for all these conditions increases with altitude and ascent rate and is therefore more common in high altitude skiers, trekkers and climbers \(^1,^8\).

One particular study estimated that tourists traveling to the Rocky Mountains at elevations between 1920-2957 meters developed AMS 25% of the time within the first 1-3 days of their arrival to elevation \(^2\). Another study in 1991 reported that the incidence of Acute Mountain Sickness in visitors to Summit County, Colorado was 22% at altitudes of 1850 – 2750 meters (7000-9000 ft) and 42% at altitudes of 3000 m (10,000 ft) \(^3\).

Winter Park Ski Resort in Winter Park, Colorado reported that between November 1\(^{st}\), 2007 and March 22\(^{nd}\), 2008 they had 50 cases of AMS. Winter Park also estimates they have
almost 1 million skiers each ski season, which is roughly the same as the date range when these
50 cases occurred. Unfortunately there is no information available as to how many of these skiers
are out of state visitors versus those that are from Colorado and other high elevation areas who
would be acclimated to some degree of elevation. However, a gross interpretation of this data
suggests that this is relatively rare as only 50 cases were reported during the length of the ski
season at a location where it is suspected that these diagnoses would be more frequent. On the
other hand, for a clinician practicing in this type of location, this averages to one case every three
days during ski season. Although raw, this data does suggest a high potential for altitude related
patient encounters in certain geographic areas even though the total incidence may be low in
those same areas 9.

**Signs and Symptoms**

In essence, Acute Mountain Sickness is a clinical diagnosis. In 1991 the International
Hypoxia Symposium held in Lake Louise, Alberta, Canada came up with criteria for diagnosing
acute mountain sickness with input from the International Society for Mountain Medicine and
many other groups involved in cardiac or pulmonary physiology. The Lake Louise Consensus
committee has defined AMS as a headache with one or more of the following: anorexia, nausea
or vomiting, fatigue or weakness, dizziness or lightheadedness, or difficulty sleeping in the
context of recent arrival to high altitude. These symptoms typically occur 6-10 hours after assent
to high altitude, but may begin as early as one hour or as late as 48 hours. Other diagnoses are
likely if these symptoms occur beyond 3 days after accent or with lack of headache. In children
the symptoms are less specific but the Lake Louis Consensus proposes that fussiness, decreased
appetite, poor sleep, vomiting and changes in playfulness in relation to recent arrival to a higher
altitude suggest the diagnosis 20, 21. The Lake Louise Consensus is considered the gold standard
for diagnosing AMS and all other subsidiaries of altitude illness and has remained largely unchanged since its conception in 1991.

Considered the end stage of AMS, HACE can develop in hours to days in a person with AMS, most commonly occurring within 3 to 5 days. It can occur at elevations as low as 2750m (9022 feet), but often occurs at much higher elevations. It is thought that HACE develops due to a hypoxia induced increase in cerebral blood flow as well as diminished integrity of the blood brain barrier. MRI of the brain shows that reverse white matter edema occurs, most prominently in the splenium callosum. Patients typically have the symptoms of AMS described above, especially headache, but then develop other symptoms such as mental status changes, confusion, lethargy, and possibly coma. Truncal ataxia, papilledema, retinal hemorrhage and focal neurological deficits may occur. However, global encephalopathy, not focal findings, characterizes High Altitude Cerebral Edema and it tends to present as drowsiness followed by stupor. Seizures are a rare occurrence. When fatal, death occurs due to brain herniation. One particular study in China determined that ataxia, as measured with heel-to-toe walk, finger-nose pointing and Rhomberg’s tests, was the best objective clinical indicator of AMS progressing to HACE. They also found that ataxia and mild confusion were the most common symptoms and often occurred together. Their research found a 96% correlation between ataxia and cerebral edema as confirmed by MRI or CT in the diagnosis of HACE. It was concluded that providers should be highly suspicious of HACE in patients who are new to altitude and present with symptoms similar to alcohol intoxication, even if very mild and if no headache is present.

The Lake Louise Consensus definition of HAPE requires at least two symptoms such as dyspnea at rest, cough, weakness, chest tightness or congestion and two signs such as crackles or wheezing, central cyanosis, tachypnea or tachycardia. Severe cases may have cough with sputum
Production or hemoptysis and respiratory distress, sometimes so severe it may lead to death in rare circumstances. Severe HAPE is suggested when a patient fails to achieve 90% oxygen saturation within five minutes of being placed on oxygen supplementation. HAPE typically presents itself within 1-3 days after arrival to high altitude. Other diagnosis such as pneumonia, pulmonary embolism, CHF or other cardiogenic edema and pneumothorax must be ruled out if symptoms develop beyond 4 days after arrival to high altitude. Diagnostic signs include right sided midlung rales or decreased O2 saturation. Chest X-ray may show infiltrate in the midlung fields bilaterally in moderate HAPE, but will initially be only on the right in more mild cases. CT scan will confirm the X-ray findings but is most often unnecessary. High Altitude Pulmonary Edema accounts for the majority of deaths that are related to high altitude illness 1, 3.

At high altitude a condition known as “Periodic Breathing of Sleep” is considered a subset of HAPE and occurs almost exclusively during non-REM sleep. It causes hyperventilation that is sometimes so severe it can awaken persons from their sleep. Sleeplessness at altitude is relatively common in unacclimatized individuals and it is thought that this is fully, or at least in part, caused by periodic breathing of sleep. It is thought it may be a result of exaggerated carotid receptor stimulation due to alkalosis and hypoxia. This condition tends to improve with rest and time, but may indicate an increased likelihood of developing HAPE 11, 12.

It is estimated based on current literature that 50 percent of those with HAPE also have AMS and 14 percent have HACE. Fifty percent of those that die of HAPE are found to have HACE at autopsy 7.

Differential Diagnosis

A plethora of conditions may mimic or present like Acute Mountain Sickness, but the onset of symptoms after three days of arrival to altitude, absence of a headache, a rapid response
to fluids or rest and a failed response to descent, oxygen or dexamethasone require further investigation. Other disease states which may mimic AMS, HACE are HAPE can be found in table 2, although this list is not conclusive of all the differential diagnoses.

**Conditions that Exacerbate Signs and Symptoms**

All of the variants of Acute Mountain Sickness are made worse with exercise and increase in severity as altitude increases. Interestingly, physical fitness does not play a part in determining if one develops altitude illness nor does it affect one’s ability to acclimatize. Nonetheless, physical fitness does tend to allow one to perform more vigorous exertion at high altitude and because of this more fit individuals may be at an increased risk of developing symptoms because they are more likely to be more active at elevation. These individuals may also think physical fitness will have a protective effect, which it does not, and may push themselves harder when at elevation or may ignore the initial symptoms and will continue activities that will worsen the mild initial symptoms.

Many pre-existing illnesses may be exacerbated by exposure to elevation, but Acute Mountain Sickness may be more likely to occur in patients with defects in cardiopulmonary function such as congestive heart failure and pulmonary hypertension. Patients who have undergone carotid endarterectomy or other carotid surgery which has destroyed or removed the carotid bodies will also predispose one to high altitude illness. Any medication or drug, including alcohol, which decreases ventilation and/or alters sleep patterns, will possibly exacerbate symptoms of altitude illness.

The presence of High Altitude Pulmonary Edema or a previous history of HAPE not only increases the likelihood of repeat HAPE but also increases the probability of developing Acute Mountain Sickness and/or High Altitude Cerebral Edema.
Pathophysiology

High altitude illness will occur when a person has an uncompensated hypoxemia at high elevation that is a result of acclimatization being exceeded for that particular individual. The fraction of inspired oxygen (FiO2) is constantly 21% throughout all altitudes of inspired air and therefore this is not responsible for hypoxia at altitude. However, the barometric pressure of oxygen does decrease with elevation gain which leads to a decrease in the partial pressure of oxygen. Partial pressure is the driving force getting oxygen to the tissue and this decrease is what initially causes hypoxemia at elevation 4,7.

The exact process of Acute Mountain Sickness is not well understood. It is known that hypoxia elicits neurohumoral and hemodynamic responses that result in overperfusion of microvascular beds which leads to increased capillary pressure, capillary leakage and ultimately edema. One hypothesis is that the cerebral vasodilatation results in the headache, which is responsible for other symptoms such as nausea and malaise. Another theory suggests that mild cerebral edema itself causes all the symptoms of AMS. Research indicates that upon ascent to high altitude all persons have some degree of cerebral edema. A newer theory hypothesizes that it may be ones ability to compensate or adapt to this swelling that determines if they become symptomatic AMS 3,5.

Treatment

Treatment is largely the same for all types of altitude illness. Treatment may vary based on the availability of medical care and articles and research tend to differentiate treatment options based on “wilderness care” versus “hospital care”. The primary focus of this article is hospital or clinic based care although some options will be discussed for care when hospital care is not available.
Far and away the best treatment for any of the high altitude illnesses is descent to a lower altitude. Symptoms will resolve in correspondence with how quickly one descends such that the faster one descends the faster their symptoms will improve. A descent of 500-1000 meters will usually lead to resolution of AMS but HACE may require further descent. The mechanism behind this is an increase in partial pressure of oxygen which reverses hypobaric hypoxia. However, in mild cases this may be inconvenient. Tourists with mild symptoms are likely to continue going about their vacation activities and are at risk for developing more severe forms of AMS because of this 1, 3.

If descent is not an option then cessation of further ascent and physical exertion are the next most beneficial options. Limiting exertion and halting ascent is therapeutic for all types of altitude illness. This allows an individual time to acclimatize and prevents further hypoxic stress. This is the primary treatment for mild to moderate AMS and with mild illness symptoms will resolve in 1-2 days. Once again, this may be inconvenient for many visitors to high altitude 1, 4, 7.

Medically speaking, providing oxygen at 1-2 liters per minute has been shown to be extremely helpful in decreasing symptoms and minimizing severity of all degrees of Acute Mountain Sickness, High Altitude Cerebral Edema and High Altitude Pulmonary Edema. This is largely due to compensating for the hypoxemia that is the underlying cause for all types of altitude illness. Specifically this occurs as a result of a rapid return to normal capillary pressure in the microvascularization in response to adequate oxygenation 1, 3.

Acetazolamide is a carbonic anhydrase inhibitor that is clinically indicated for a variety of medical conditions. Carbonic anyhdrase is an enzyme that catalyzes the conversion of carbon dioxide and water to bicarbonate and hydrogen ion (CO2 + H2O → carbonic anhydrase → HCO3- + H+). Physiologically this is used to maintain acid-base balance in the tissues and to
help transport carbon dioxide out of the body. This promotes release of bicarbonate (HCO3-) through respiration and diuresis. Acetazolamide is used for treatment of glaucoma because it decreases fluid level and relieves intra-ocular pressure. It is also used in seizure disorders and in situations where a patient has an elevated CSF or intracranial pressure. Most important for this discussion, it is the primary medication to prevent and treat Acute Mountain Sickness. It works by speeding acclimatization due to its effects on promoting diuresis of bicarbonate. As bicarbonate is lost the blood pH lowers and this stimulates a natural increase in ventilation. Prophylaxis is recommended for those who ascend quickly to altitude and plan on staying at a sleeping altitude over 3000 m. Current recommendations from EverestER.org only recommend prophylaxis for those who are flying into Tibet or Bolivia, those who are forced to rapidly ascend (as in a mountain rescue mission) or those with a previous history of AMS. Acetazolamide is also the primary drug for treatment of AMS. One study suggests that acetazolamide reduces the severity of symptoms by 74% within 24 hours. The recommended dose is 125-250 mg PO BID starting the day before ascent and through the time where maximum altitude is achieved. Treatment dose is the same and should be taken until symptoms resolve. This drug has a sulfa component and should be avoided in patients who have an allergy to sulfonamides. It is also a pregnancy category C. Lesser side effects patients should be made aware of are polyuria, parasthesias, and that the drug will alter the taste of carbonated beverages. The benefits of this medication, aside from being an effective treatment, are that there is no rebound effect and that it may be combined with dexamethasone for treatment of severe altitude illness.

The glucocorticoid dexamethasone is also indicated for prevention and treatment of AMS and HACE, although it is second line to acetazolamide. This may change as a result of multiple studies suggesting that it is as effective, or in some cases superior, to acetazolamide and often
works within 12 hours. The exact mechanism of how this works is unknown, but theories suggest that it may work by reducing blood brain volume or blocking brain capillary leakage. This drug has a very rapid onset of action and may be lifesaving in severe cases of AMS or when HACE develops. Unfortunately dexamethasone has no use in HAPE due to the mechanism of action. Side effects include hyperglycemia, mood changes, irritability and dyspepsia. It is also a pregnancy category C. It does not aide in acclimatization and may sometimes cause symptoms when discontinued due to a rebound effect. For prevention of AMS the recommended dose is 2 mg every 6 hours or 4 mg every 12 hours by mouth. Treatment of AMS is 4 mg every 6 hours PO, IV, or IM and the treatment of HACE is 8 mg initially and then 4 mg every 4 hours thereafter by PO, IV or IM. One study did suggest that a combination of dexamethasone and acetazolamide is more effective than either alone, although other research in this area is limited. However, the current recommendations include the use of either acetazolamide or dexamethasone individually first before adding the other agent if the first is not effective \(^1, 3, 7, 14\).

Nifedipine is a dihydropyridine calcium channel blocker that is typically used for treatment of angina and or hypertension. It has also been shown useful in prevention and treatment of HAPE. In High Altitude Pulmonary Edema it works by relaxing smooth muscle thereby reducing pulmonary artery pressure. This reduction allows for better hemodynamic flow, better oxygenation and a decrease in pulmonary edema. For prevention of HAPE the recommended dose is a 20-30 mg extended-release tablet twice daily starting the day prior to ascent and continuing throughout while at maximum elevation. For treatment of HAPE the suggested regiment is 10mg initially, then 20-30 mg extended release tablets twice daily. However, this is often not necessary if oxygen is available. The side effects include hypotension
and reflex tachycardia. It is also pregnancy category C. Because of its role strictly in cardiopulmonary physiology Nifedipine has no role in treatment of AMS or HACE \(^1, 3, 7, 14\).

A new and promising area of research in treatment of HAPE is the use of Phosphodiesterase-5 Inhibitors such as tadalafil (Cialis) and sildenafil (Viagra) due to their pulmonary vasodilatation effects which ultimately improve pulmonary gas exchange. These may ultimately be preferable to Nifedipine pending further research \(^14\). Preliminary investigations are showing that these medications may improve exercise tolerance at high altitude by attenuating the effects of alveolar hypoxia on pulmonary artery pressure. In general these medications are well tolerated, although the major side effect is worsening headache. In the future this medication may be helpful for treatment and perhaps even prevention of HAPE or potentially all types of altitude illness \(^15, 16\).

Drugs such as albuterol and salmeterol which are Beta 2 Agonists have been shown effective in prevention and anecdotally in the treatment of HAPE. These drugs work by blocking the beta receptors within the pulmonary tree, resulting in relaxation of the smooth muscle and dilation of the airways. They also cause an increase in the clearance of the alveolar fluid. The recommended dose for prevention is 125 mcg inhaled twice daily starting two days prior to ascent and through two days while at peak altitude. No specific research was found indicating a dose for treatment of HAPE, but use if a beta-agonist should be considered with Nifedipine in the treatment of HAPE if oxygen and or descent are not viable options. Side effects include insomnia, anxiety or tremor but these are usually mild and self limited \(^1, 3, 4\).

Hyperbaric therapy reverses the effect of hypoxia by increasing the pressure of inspired O2, thus raising the oxygen saturation. This is an excellent addition to other treatments due to its rapid action and because it is useful, although not always practical, in treatment of all types of
acute mountain sickness. Unfortunately many hospitals do not have this capability. For those adventure seekers who plan on achieving significant altitude, such as mountaineers or climbers, there are portable hyperbaric chambers for sale. These have been shown to be highly effective in HAPE and HACE if oxygen and or descent are not immediate options 1, 2, 3.

The herbal extract of the Ginkgo leaf has many reported uses, primarily for aide in memory and concentration, as well as for treatment of vertigo. The scientific evidence supporting these claims is highly variable and continues to be a topic of debate. There is suggestion that it is also useful for prevention of AMS. It is thought that this may be due to antioxidant effects, but this is pure speculation in the literature. The dose and side effects are also unknown. Two trials have shown that Ginkgo biloba prevented AMS during a gradual ascent to 5000 meters and reduced the symptoms and incidence of AMS by 50% during rapid ascent to 4100 meters 1, 6. EverestER.org also is touting Ginkgo biloba as a promising medication to prevent altitude illness 19.

Prochlorperazine (Compazine) stimulates the hypoxic ventilatory response and because of this it is thought to be superior to other anti-emetics in treating the nausea and vomiting associated with AMS. Other anti-emetics such as promethazine (Phenergan) and ondansetron (Zofran) will also be helpful. However, for any person who is experiencing nausea or vomiting that is severe enough to potentially cause dehydration absolutely needs to consider descent as the primary treatment measure 14.

Specific Treatment Regimens

Mild AMS should be treated conservatively. Patients should be encouraged to descend or at least stay at the same elevation for 24-48 hours with minimal exertion to allow for some degree of acclimatization. Oxygen at 1-2 L/min should resolve symptoms. Acetazolamide 125 –
250 mg PO BID can also be considered but is not paramount. Analgesics for headache and antiemetics, particularly prochlorperazine, for nausea should be given as needed. For moderate AMS descent is again the primary focus, as well as the other measures for mild AMS. If the patient is unable to descend they need to be consistently monitored for deterioration to HACE. One to two doses of dexamethasone 4 mg PO every 6 hours has been shown to be helpful and is recommended by experts in acute mountain sickness. Acetazolamide 125 – 250 mg PO is optional but may help speed acclimatization and will especially be helpful if the patient plans on staying at altitude. When AMS turns into HACE it is considered an emergency as it can be life threatening. Patients must descend, and in some cases depending on location and severity, may need to be evacuated emergently. Supplemental oxygen should be given to maintain O2 sat above 90%. The guidelines suggest dexamethasone 8 mg initially followed by 4 mg every 6 hours. Hyperbaric therapy is recommended if available and if the patient is unable to descend \(^1,3,4,19\).

For HAPE descent again provides the quickest recovery but oxygen and rest will help in almost all cases except those that are severe or complicated by HACE. Increasing alveolar and arterial oxygenation is the highest priority in patients with HAPE and supplemental oxygen will reduce pulmonary artery pressure between 30 and 50 percent which is sufficient to reverse the effects of HAPE rapidly. The oxygen goal should be to maintain O2 saturation above 90% with O2 flow starting at 2-4 liters per minute and then titrating as needed to maintain. Often these patients will do well with this regiment but in some cases may require outpatient oxygen in recalcitrant cases where the patient feels better but does not maintain oxygen saturation above 90% on room air. Patients with concomitant HACE, other co-morbid conditions, children and elderly, or those that require oxygen at more than 4 liters per minute need to be admitted to the
hospital for consistent monitoring. Medications and hyperbaric therapy have not been found to be helpful if the patient is maintaining O2 saturation. In an outdoor setting these patients need to get oxygen, stay warm and hydrated and minimize exertion. They need to descend if at all possible and if their case is severe will require evacuation. If unable to descend portable hyperbaric therapy may be lifesaving. These patients are likely to benefit from Nifedipine 10 mg PO. Beta 2 agonists such as albuterol and salmeterol should be considered. Dexamethasone should be withheld unless the patient also develops HACE. Patients should not be discharged unless they are able to maintain an O2 saturation above 90% on room air with clinical and radiographic evidence of improvement 1,3,14. Table 3 summarizes treatment recommendations for AMS, HACE, and HAPE.

Diuretics are contraindicated in treatment of AMS, HACE, and HAPE. In HACE this may lead to hypovolemia which can lead to cerebral ischemia. Perhaps even more tempting is to diurese a patient that clinically presents with symptoms of High Altitude Pulmonary Edema that is clearly visualized on chest radiographs. The wet cough, cyanosis, oxygen desaturation and obvious pulmonary infiltrate lead one to believe the patient is volume overloaded and would benefit from fluid reduction. However, they are usually euvolemic and diuretics will cause severe hypovolemia and dehydration 1,2,3,14,19.

**Prevention**

As discussed above, the single best method of prevention for any type of altitude related illness is a slow ascent. It is recommended that those individuals who live at low elevation or those that are making extreme changes in elevation (such as mountain climbers) ascend no more than 300 meters (1000 feet) per day. This recommendation is of critical importance and should be tightly monitored in those who have already experienced AMS, HACE or HAPE. Although
no studies have proven that hydration is a significant player in developing AMS it is known that altitude can cause diuresis. This may be mediated by an increased release of atrial natriuretic peptide and increases fluid loss due to increased ventilation. Adequate hydration is always recommended and those who regularly engage in high altitude activity routinely try to stay well hydrated. The medical team at the Mount Everest Base Camp suggests drinking enough fluids through the day to keep one’s urine clear. Acetazolamide is the standard medication for prevention, but other medications are being researched for the potential effectiveness for prevention of AMS and other types of altitude illness. Dexamethasone has been proven effective as a second line prophylactic agent in those that have a sulfa allergy (Acetazolamide is a sulfa drug).

There are some limitations in the studies because this is a condition that typically occurs where medical care is not immediately accessible. However, with over 30 years of research available numerous search engines, the various components of the pathophysiology, treatment and prevention are well covered and would seemingly uncover any flaws or conflicting evidence within the research articles.

Conclusions

Acute Mountain Sickness is the most common type of altitude related illness and is usually mild in nature and can easily be prevented with the right precautions such as rest, slow ascent, hydration and in some cases medical intervention. Both acetazolamide and dexamethasone are proven effective for both prevention and treatment and various other medications and herbal supplements are currently being researched. Oxygen, rest, a slow ascent and descent continue to be the mainstays of treatment. High Altitude Cerebral Edema and High
Altitude Pulmonary Edema are severe forms of altitude illness and are considered a medical emergency, with immediate descent being the primary treatment.

The continued desire for people to visit high altitude destinations along with the inherent physiologic limitations of the human species to adapt to hypoxemia at increased elevation indicates that AMS and its subsidiaries will probably not be a disorder that is easily eradicated. Nonetheless, current literature and future research will continue to aide in the accuracy of the diagnosis and the precision of treatment. As the population continues to seek out recreation at high altitude it is important for providers to educate patients on the symptoms and prevention of altitude illness. It is also important for providers working at high elevation, even in urban environments, be aware of the clinical presentation and treatment of the unacclimatized person with Acute Mountain Sickness as it is far more common than one might think in the tourist population. Patients who have already experienced AMS, HACE or HAPE should be advised to slow their descent, recognize the early symptoms and to utilize preventive medications.
Tables and Figures

Table 1. Factors predisposing infants and young children to hypoxemia

<table>
<thead>
<tr>
<th>Predisposition for inhibition of respiratory drive</th>
</tr>
</thead>
<tbody>
<tr>
<td>More compliant rib cage</td>
</tr>
<tr>
<td>Reduced surfactant in pre-term infants</td>
</tr>
<tr>
<td>Increased airway reactivity in response to hypoxia</td>
</tr>
<tr>
<td>Reduced upper and lower internal diameter of airways</td>
</tr>
<tr>
<td>Fewer alveoli in early infancy</td>
</tr>
<tr>
<td>Presence of fetal hemoglobin until 4-6 months</td>
</tr>
</tbody>
</table>

Table 2. Differential Diagnosis for the various altitude related illnesses

<table>
<thead>
<tr>
<th>DDX for AMS/HACE</th>
<th>DDX for HAPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Psychosis</td>
<td>Asthma</td>
</tr>
<tr>
<td>Carbon Monoxide Poisoning</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Diabetic Ketoacidosis</td>
<td>Hyperventilation Syndrome</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Mucous Plugging</td>
</tr>
<tr>
<td>Electrolyte Abnormalities</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>Ingestion of toxins, drugs or alcohol</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Migraines</td>
<td>Pulmonary Embolus</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Specific Treatment Recommendations

<table>
<thead>
<tr>
<th>Mild AMS</th>
<th>Descent or rest for 1-2 days to allow acclimatization. Consider acetazolamide 125-250 mg PO BID and or oxygen 1-2 L/min NC. Analgesics and anti-emetics as needed for specific symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate AMS</td>
<td>Same as mild except consider dexamethasone 4mg PO/IM Q 6 hrs in addition to or in place of acetazolamide. Acetazolamide helps acclimatize and better option if remaining at altitude. Monitor for deterioration to HACE.</td>
</tr>
<tr>
<td>HACE</td>
<td>Immediate descent or evacuation. O2 to maintain O2 sat above 90%. Give dexamethasone 8mg PO/IM/IV initially then 4 mg Q 6 hrs. Hyperbaric therapy if unable to descend.</td>
</tr>
<tr>
<td>HAPE</td>
<td>Descent for quickest recovery. O2 2-4 L/min to maintain O2 sat above 90%. Consider Nifedipine 10 mg PO if no concomitant HACE. Consider Beta 2 agonists or EPAP mask. Dexamethasone only if HACE develops. Consider admitting if other concomitant conditions, failure to maintain O2 sat above 90% or if requiring more than 4L/min to maintain O2 sat.</td>
</tr>
</tbody>
</table>
References


10. Wikipedia.com (2008); Breckenridge, CO, Winter Park, CO, Summit County, CO, Mt. Hood Meadows, OR, Mt. Bachelor, OR.


14. Rosen JM. “High Altitude Disease in Adults” Up to Date 2008: www.uptodate.com/


20. Endom EE. “High Altitude Disease in Children” Up to Date 2008: www.uptodate.com/