High altitude medicine for family physicians

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SUMMARY
High altitude medicine deals with a continuum of diseases ranging from a mild discomfort to serious ailments affecting all organ systems, including the lungs, brain, and eyes. Decreased oxygen tension is the primary cause. The main principles of prevention are staging and graded ascent to allow acclimatization. Adventure travel to high altitude destinations is becoming increasingly popular; family physicians should be informed of the medical problems associated with such travel.

RÉSUMÉ
La médecine des hauteurs altitudes traite d’un continuum de maladies allant de l’inconfort léger à des troubles graves affectant tous les organes, incluant poumons, cerveau et les yeux. La baisse de la pression d’oxygène en est la cause principale. Les principes de prévention reposent en tout premier lieu sur l’ascension graduelle et par étapes, laquelle permettra l’acclimatation. Les voyages à l’aventure vers des destinations de haute altitude deviennent de plus en plus populaires. Les médecins de famille doivent être informés des problèmes médicaux associés à de tels voyages.

IN THE 403 YEARS SINCE FATHER Acosta published the first documented reports of altitude sickness that occurred as he crossed the Andean divide near Mount Pariacaca, high altitude medicine has been the domain of exercise physiologists and a few physicians who themselves ventured to high altitude destinations. However, the increasing popularity of worldwide travel and adventure holidays now suggests that family physicians should become familiar with the pathophysiology, signs and symptoms, prevention, and treatment of the spectrum of diseases that are collectively referred to as altitude illness.

Tourists with no training, experience, or knowledge can now fly from sea level to the plateau of Llasa at 4000 m and then hike to Everest Base Camp at 5400 m. Family physicians will be called upon in their day-to-day practice, regardless of geographic location or altitude, to counsel patients who are contemplating such extreme activities and to answer the questions of patients who have returned from high altitude destinations with an array of symptoms that they do not understand.

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Some of us will travel ourselves to fairly high altitudes to ski or trek and will be asked by family and friends to explain minor and troublesome symptoms. A few of us will be involved in high altitude expeditions as experts and will be required to diagnose and treat serious high altitude illnesses with the most up-to-date knowledge available. This review aims to provide a comprehensive summary of the pathophysiology, signs and symptoms, prevention, and treatment of high altitude illness from a family physician’s perspective.

Physiology of altitude exposure
As human beings ascend to altitudes above sea level, changes in atmospheric pressure lead to decreased oxygen tension of inspired air, such that at 4500 m arterial oxygen tension is less than half (44 mm Hg) what it is at sea level (94 mm Hg). Hypoxia then causes a sequence of physiologic changes that help the body, in some cases and under certain circumstances, to adapt or acclimatize to the conditions. Successful acclimatization allows an individual to carry on with the intended activity for the intended time. The physiologic changes are both acute (immediate to hours) and delayed (hours to days or more).
The immediate effect of hypoxia is to stimulate the hypoxic ventilatory response (HVR) of the peripheral chemoreceptors in the carotid bodies. This leads to an increase in respiratory rate and volume, resulting in an increase in minute ventilation. This increased ventilation decreases the partial pressure of carbon dioxide (pCO₂) and increases the partial pressure of hydrogen (pH). These changes in turn inhibit the central chemoreceptors in the choroid plexus and cause a subsequent decrease in minute ventilation. This fluctuation and balance between the peripheral chemoreceptors and the central chemoreceptors ultimately determines the rate of renal bicarbonate excretion. Studies have shown that individuals with a strong HVR are least likely to develop altitude illness. As acclimatization occurs, the increase in minute ventilation persists as long as the individual remains at that altitude.

The fluctuation between the central chemoreceptors and the peripheral chemoreceptors results in a pattern of breathing referred to as periodic breathing, or Cheyne-Stokes respiration. Above 2500 m, periodic breathing is almost universal during sleep, resulting in even greater oxygen desaturation at night. The periodic breathing and nocturnal oxygen desaturation diminish as acclimatization occurs. Renal bicarbonate excretion improves, resulting in a decrease in serum pH. This mild metabolic acidosis is thought to stimulate respiration at the level of the central chemoreceptors of the choroid plexus. This increases minute ventilation and thus improves the periodic breathing pattern.

Exposure to high altitudes increases the heart rate and increases stroke volume, with a resultant increase in cardiac output. This further enhances oxygen delivery to the tissues. As acclimatization occurs over the first
week, cardiac output declines to sea-level values (although heart rate remains higher) and stroke volume is reduced.\(^5\)

Hypoxia leads to increased contractility of the pulmonary arterioles. This physiologic response improves the ventilation-to-perfusion mismatch and results in an increase in pulmonary artery pressure.\(^7\)

Similarly, cerebral blood flow responds to hypoxia with cerebral vasodilation and increased cerebral blood flow. The hypocapnia from hyperventilation then causes cerebral vasoconstriction. Hence, a fluctuating balance between hypoxic hyperperfusion and hypocapnic hypoperfusion is maintained.\(^9\)

Hematocrit and hemoglobin undergo acute and chronic changes with increasing altitude. Initial fluid shifts cause immediate hemoconcentration. Erythropoietin- and hypoxia-stimulated erythropoiesis results in increased red cell mass, hematocrit, and hemoglobin levels days later. Hematocrit and viscosity measurements increase linearly with altitude until 0.60, when viscosity begins to increase exponentially.\(^6\) Thrombotic complications above a hematocrit level of 0.60 are common at extremely high altitudes.

In summary, as the oxygen tension of inspired air decreases with increasing altitude, physiologic changes take place both immediately and over time as the body attempts to maintain homeostasis. An individual’s ability to undergo these changes effectively determines whether he or she can carry on with the planned activity. Failure to acclimatize leads from the physiology of altitude exposure to the pathophysiology of altitude illness.

Pathophysiology and clinical presentation
Altitude illness develops when the normal physiologic responses to altitude exposure fail to maintain homeostasis. Although this review discusses acute mountain sickness (AMS), high altitude pulmonary edema (HAPE), high altitude cerebral edema (HACE), and high altitude retinal hemorrhage (HARH) separately, they all share a causative factor: decreased oxygen tension of inspired air and subsequent hypoxia. The separate clinical entities are actually manifestations of the same altitude illness on a continuum from mild to severe. They can occur together, or one can predominate. The many and complicated signs and symptoms of altitude illness (Table 1) led Bezruzhka to say, “An illness at altitude is altitude illness until proven otherwise.”\(^5\)

**Acute mountain sickness.** This mildest and most common form of altitude illness affects approximately 25% of travelers to 2500 m. The percentage increases with altitude such that, at 4500 m, 75% of people are affected.\(^10\) Symptoms consist of nausea, lethargy, headache, sleep disturbance, and mild cough. A rapid rate of ascent, more than 300 m/d, contributes to its development. Men and women seem to be equally susceptible;\(^10\) children more so.\(^11\) Symptoms develop within hours and last approximately 24 to 48 hours. Acclimatization occurs in most cases.

Headaches are very common among those affected by AMS. They are thought to be due to a mild increase in intracranial pressure that might be accounted for by two mechanisms. First, hypoxia results in cerebral vasodilation and increased cerebral blood flow; and second, hypoxia results in fluid shifts that can cause mild cerebral swelling. The mild headache of AMS might progress to more serious HACE.

Sleep disturbance can be the most troubling symptom of AMS; many studies have shown it to be caused by periodic breathing. At 2500 m such breathing is very common, and by 4500 m 75% of people are affected.\(^12\) This pattern of breathing can be explained by the oscillating response between the peripheral chemoreceptors and the central chemoreceptors.

<table>
<thead>
<tr>
<th>Table 1. Symptoms of altitude illness</th>
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<tbody>
<tr>
<td><strong>ACUTE MOUNTAIN SICKNESS</strong></td>
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<tr>
<td>• Nausea</td>
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<tr>
<td>• Lethargy</td>
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<tr>
<td>• Insomnia</td>
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<tr>
<td>• Headache</td>
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<tr>
<td>• Anorexia</td>
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<tr>
<td>• Cough</td>
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<tr>
<td><strong>HIGH ALTITUDE PULMONARY EDEMA</strong></td>
</tr>
<tr>
<td>• Cough</td>
</tr>
<tr>
<td>• Shortness of breath at rest</td>
</tr>
<tr>
<td>• Cyanosis</td>
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<tr>
<td>• Frothy sputum</td>
</tr>
<tr>
<td><strong>HIGH ALTITUDE CEREBRAL EDEMA</strong></td>
</tr>
<tr>
<td>• Headache</td>
</tr>
<tr>
<td>• Ataxia</td>
</tr>
<tr>
<td>• Abnormal behaviour</td>
</tr>
<tr>
<td>• Decreasing level of consciousness</td>
</tr>
<tr>
<td>• Seizures</td>
</tr>
<tr>
<td>• Coma</td>
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<tr>
<td><strong>HIGH ALTITUDE RETINAL HEMORRHAGE</strong></td>
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<tr>
<td>• Asymptomatic unless the macula is involved</td>
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As hypoxia stimulates increased rate and depth of respiration, pCO₂ falls and pH rises, stimulating the central receptors to decrease respiration. The oxygen saturation falls dramatically as apnea occurs. This stimulates the peripheral receptors and again increases respiration. The result is a restless sleep with many wakenings and longer wakeful periods. Headache and cough also interfere with sleep. Although some controversy exists, it is widely accepted that those individuals with a strong HVR have fewer symptoms of AMS, including sleep disturbance.

Weight gain, fluid retention, and decreased urination are all signs of AMS and have been attributed to disturbances in the sodium-potassium pump at the cell membrane caused by hypoxia. This leads to increased intracellular sodium, increased intracellular fluid, extracellular volume depletion, and decreased glomerular filtration. The observation that individuals resistant to AMS appear to urinate more is likely because they have less disturbance in the sodium-potassium pump from less hypoxia.

**High altitude pulmonary edema.**
This ailment develops in a few individuals with AMS and is characterized by cough, shortness of breath at rest, frothy sputum, cyanosis, and progression to acute respiratory failure and respiratory arrest. Exertion exacerbates the symptoms. Clinically, tachypnea, tachycardia, and cyanosis can be seen, and diffuse crepitations and occasionally wheezing can be heard. Chest x-ray examinations show a patchy edema similar to that seen in adult respiratory distress syndrome. The alveolar fluid has high protein levels, suggesting a capillary leak.

The universal finding in HAPE is marked increase in pulmonary artery pressure. Right heart catheterization and Doppler flow studies, conducted in Operation Everest II, have confirmed these findings. Increased pulmonary artery pressure, ventilation-to-perfusion mismatch, and cellular hypoxia contribute to fluid shifts, first into the interstitial spaces and then into the alveoli, further impairing gas exchange and increasing hypoxia.

**High altitude cerebral edema.**
This is the advanced stage of the AMS headache and is characterized by increasingly severe headache; ataxia; abnormal, irrational behaviour; decreasing level of consciousness; and progression to seizures and coma. Focal neurologic findings are common, as are permanent neurologic sequelae in survivors. The death rate for this disorder is extremely high.

The pathophysiologic mechanisms contributing to HACE are not entirely clear. However, researchers suggest that, as hypoxia leads to cerebral vasodilation and increased cerebral blood flow, cerebral autoregulation is lost, combined with hypoxic cell damage leading to cerebral swelling and ultimately to increased intracranial pressure, In addition, microthrombi and microhemorrhage can complicate the picture. Again, a strong HVR appears to protect against the development of HACE.

**High altitude retinal hemorrhage.**
Such hemorrhage is rarely seen below 5500 m, but, above that level, up to 30% of people are affected. It consists of intraretinal hemorrhages, vitreous hemorrhage, and rarely, nerve fibre layer infarcts and central retinal vein occlusion. High altitude retinal hemorrhage is thought to be primarily a result of increased retinal blood flow secondary to hypoxia associated with increased capillary fragility and capillary leak. People using nonsteroidal anti-inflammatory drugs are at increased risk. The hemorrhages are usually of no clinical significance, unless they involve the macula, and in most cases resolve with time and acclimatization.
Prevention
Altitude illness, like any other medical condition, is best treated by prevention. Some basic measures can prevent or lessen to a large degree many of the sequelae of this illness (Table 2).

The main preventive techniques are staging and graded ascent, which allow acclimatization to occur naturally. Part of the explanation for the apparent increased incidence of altitude illness we see today stems from the ease and rapidity with which we now ascend to high altitudes. Before air and motor travel, the gradual ascent by foot to high altitudes allowed sufficient time for acclimatization to occur effectively.

Staging is traveling to an intermediate altitude and camping for several nights before continuing the ascent to the target elevation. Staging is most important for those undertaking very high altitude treks (>4000 m) and has become a standard part of trek preparation. The duration of the staging depends on the goal elevation, and, with intermediate heights (up to 4000 m), 2 days at 3000 m would suffice. Extreme altitude treks, such as Mount Everest, would require several stages and take many weeks.

Graded ascent is another way to minimize altitude illness. A generally accepted rate of ascent is 300 m/d. It is important to sleep at lower altitudes than you have trekked during the day. “Climb high, sleep low” is a well-known saying in trekking circles.

Other important preventive measures include avoiding strenuous exertion for the first 48 hours, consuming large volumes of fluids, and avoiding alcoholic beverages.

Acetazolamide, a potent carbonic anhydrase inhibitor, has proved very effective prophylaxis for AMS at a dose of 250 mg orally two to three times daily, started 24 hours before ascent. The mechanism of action will be discussed later. Acetazolamide should be administered only to individuals who have had previous troubling AMS or to those, such as rescue teams, who must ascend rapidly. The side effects of acetazolamide are somewhat bothersome, though not severe, and include paresthesias, nausea, and altered taste of carbonated beverages.

Dexamethasone, 4 mg orally every 6 hours, starting 12 hours before ascent and continuing throughout the ascent and stay at altitude, is also very effective prophylaxis for AMS. One study showed it surpassing acetazolamide in effectiveness. Again side effects limit its general use to those who are intolerant of acetazolamide. It is also important to note that, although prophylactic benefits are proven, symptoms develop rapidly upon cessation of the drug at high altitudes, suggesting that the normal acclimatization process is altered. This is in contrast to acetazolamide, which can be stopped after 48 hours with no recurrence of symptoms.

Treatment
If preventive measures are unsuccessful, the illness must be treated. For simplicity the diseases are discussed separately, although in the field considerable overlap occurs.
Acute mountain sickness. This is by far the most common ailment, ranging from very mild to incapacitating. Most travelers to ski resorts at 2500 to 3000 m will experience mild symptoms, such as headaches and insomnia. Simple measures, such as fluids, acetaminophen, rest, avoidance of alcohol, and time will help in most cases. Acclimatization occurs over 24 to 48 hours and symptoms subside. Decreasing the sleeping altitude by as little as 150 to 300 m often will eliminate the sleep disturbance. If AMS symptoms are severe, more aggressive measures might be necessary. Descent is often mandatory, and other treatments, such as acetazolamide, dexamethasone, supplemental oxygen and a portable hyperbaric bag, can be used.

Acetazolamide, 250 mg two to three times daily, alleviates most of the symptoms of AMS within hours. Periodic breathing and nocturnal oxygen desaturation improve, as do daytime oxygen saturation, cerebral blood flow, and minute ventilation. The exact mechanism of action is still debated, but both renal carbonic anhydrase inhibition to enhance bicarbonate excretion (producing a mild metabolic acidosis with a compensatory hyperventilation) and choroid plexus carbonic anhydrase inhibition (producing cerebrospinal fluid acidosis and central respiratory stimulation) are thought to play a role.

Dexamethasone has also proved highly effective for treating AMS at a dose of 4 mg orally every 6 hours, although its mechanism of action is less clear. Researchers think that, because it has a membrane-stabilizing effect, it reduces cerebral capillary leakiness and brain swelling. Notably, as in prophylaxis, cessation of treatment at high altitudes results in rapid return of symptoms.

Physicians are becoming interested in portable hyperbaric bags for treating AMS. These nylon, pressure-sealed cylinders are inflated with a foot pump to pressures that effectively reduce the altitude by 25% to 33% and diminish symptoms within 1 to 2 hours. Hyperbaric bags are as effective as supplemental oxygen and might have a longer-lasting effect. They do, however, have some technical drawbacks, including carbon dioxide retention, claustrophobic feeling, recumbent position required, and fatigue of the operator, that limit their usefulness.

Supplemental oxygen is clearly an effective treatment, but the cylinders are cumbersome to carry on a trek.

Treating sleep disturbance with benzodiazepine sedative hypnotics should be avoided because they aggravate the periodic breathing pattern, increasing apneic time and lengthening the oxygen desaturation troughs.

High altitude pulmonary edema. People with this serious, life-threatening condition must be immediately evacuated to a lower altitude. Even going down 300 m will often effectively diminish the signs and symptoms and allow the trek to proceed in a day or so. If evacuation is impossible because of weather conditions, condition of the patient, or lack of evacuation facilities,
then other measures, such as oral nifedipine, supplemental oxygen, and a hyperbaric bag, should be used.

Nifedipine, a calcium ion antagonist with potent vasodilating effects on the pulmonary artery, is extremely effective for reducing the symptoms of HAPE, as well as improving oxygen saturation and x-ray findings. Symptoms can be relieved within an hour of administering 10 mg of sublingual nifedipine immediately followed by 20 mg of slow release nifedipine three times daily. In some cases, relief is so dramatic that the person can continue the trek symptom free.28-30

Previously susceptible individuals might benefit from prophylactic use of nifedipine. Use of acetazolamide and dexamethasone for HAPE has not been studied widely, but the hyperbaric bag has shown some promise. Again, HAPE is a potentially life-threatening disease, and emergency descent and evacuation must be considered the first line of action.

High altitude cerebral edema. Less frequently seen than HAPE, HACE too must be considered a potentially life-threatening condition requiring immediate descent and evacuation. Few controlled studies have examined the treatment for this condition; however, dexamethasone (8 mg immediately followed by 4 mg every 6 hours) is thought to help by decreasing cerebral vascular leakiness and edema. Supplemental oxygen and the hyperbaric bag can be tried along with supportive measures, such as airway management and seizure control.

Conclusion As family physicians, now and in the future, we will be increasingly called upon to use our expertise to counsel, diagnose, and treat patients with altitude illness. Intelligent, concerned patients will come to seek our advice before traveling to high altitude destinations.

We must try to advise goal-oriented, highly driven individuals, who book adventure holidays trekking to Everest and who are unlikely to have the time or inclination to go through staging and acclimatization, of the risks they face. When they start to falter with symptoms of altitude illness and hold up the group, all of whom are also highly driven individuals, they will be loaded onto donkeys to ascend even higher. The results will be disastrous.

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References

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A LOGICAL FIRST CHOICE

ACTIONS:
Acetaminophen is an analgesic and antipyretic.

INDICATIONS:
TYLENOL® acetaminophen is indicated for the relief of pain and fever. Also as an analgesic/antipyretic in the symptomatic treatment of colds.

CONTRAINDICATION:
Hypersensitivity to acetaminophen.

ADVERSE EFFECTS:
In contrast to salicylates, gastrointestinal irritation rarely occurs with acetaminophen. If a rare hypersensitivity reaction occurs, discontinue the drug. Hypersensitivity is manifested by rash or urticaria. Regular use of acetaminophen has shown to produce a slight increase in prothrombin time in patients receiving oral anticoagulants, but the clinical significance of this effect is not clear.

PRECAUTIONS AND TREATMENT OF OVERDOSE:
Resuscitation and supportive care must proceed for any other potentially serious overdose. In acetate overdose, serum levels of acetaminophen are meaningful in predicting those patients likely to develop serious hepatic toxicity. They must be drawn between 4 and 24 hours post overdose and the values plotted on the Matlow-Rumack Nomogram. N-acetylcysteine (NAC) is a highly effective antidote to acetaminophen poisoning. Do not delay administration of N.A.C. either by parenteral or oral routes if the ingested dose is likely to be toxic (> 150 mg/kg ingested) or if serum levels are in the toxic range on the Nomogram. N.A.C. must be administered prior to the 24th hour post overdose to be protective. Further details on therapy of acetaminophen overdose are available by calling your regional Poison Control Centre.

DOSAGE:
Adults: 650 to 1000 mg every 4 to 6 hours. not to exceed 4000 mg in 24 hours.

SUPPLIED:
TYLENOL® Caplets 325 mg. Each white caplet, scored on one side and engraved "TYLENOL®" on the other side, contains 325 mg acetaminophen. Available in bottles of 24t, 50t and 100t caplets.

TYLENOL® Tablets 325 mg. Each round, white tablet, scored on one side and engraved "TYLENOL®" on the other side, contains 325 mg acetaminophen. Available in bottles of 24t, 50t, 100t and 500t tablets.

TYLENOL® Caplets 500 mg. Each white caplet, engraved "TYLENOL®" on one side and "500" on the other side, contains 500 mg acetaminophen. Available in bottles of 24t, 50t and 100t caplets.

TYLENOL® Tablets 500 mg. Each round, white tablet, engraved "TYLENOL®" on one side, and "500" on the other side, contains 500 mg acetaminophen. Available in bottles of 30t, 50t and 100t tablets.

TYLENOL® Gelcaps 500 mg. Each solid capsule-shaped tablet, coated with red gelatin on one end and yellow on the other, printed "TYLENOL®/500" on each gelatin coated end, contains 500 mg acetaminophen. Available in bottles of 24t and 50 gelcaps.

ªPackage is child-resistant.

REFERENCES:

MCNEIL
MCNEIL CONSUMER PRODUCTS COMPANY
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