

Recent Advances in High Altitude Illness

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Learning objectives:

Following this presentation, participants will be able to:

1. Discuss the current concepts of the pathophysiology of acute mountain sickness and high altitude cerebral and pulmonary edema.
2. Understand the critical role of the blood brain barrier in altitude illness.
3. Approach the treatment and prevention of altitude illness based on an understanding of the deranged physiology.

Recent advances in high altitude illness have to do with understanding of the pathophysiology as well as prevention and treatment. I will focus on the new concepts of pathophysiology, but will also provide in this syllabus a more general overview of the altitude illnesses. AMS and HACE represent the main neurological pathology of altitude, while HAPE reflects the pulmonary pathophysiology.

I ACUTE MOUNTAIN SICKNESS (AMS) AND HACE

The **incidence of AMS** varies with location, depending on both absolute altitude reached, and rate of ascent to altitude. 15-40% of Colorado resort skiers (depending on altitude of resort) develop AMS, and studies have shown an incidence of 40% in McKinley climbers, 70% in Rainier climbers, and 70-100% if flown directly to 14,000 ft. Given the huge numbers of Colorado tourists (25 million a year), this is not a trivial problem. HACE is defined as the progression of cerebral symptoms and findings of **ataxia** and change in consciousness, in persons with AMS or HAPE.

Sleeping altitude is the critical factor, with 9,000 ft being a significant threshold for illness (>20% incidence), and 8 to 9,000 ft less of a problem (perhaps 10-15% incidence), while below 8,000 ft AMS is uncommon. Susceptibility to AMS is **not** related to physical fitness or gender, although women have less pulmonary edema. Older adults (>50) are a bit less susceptible, while limited data suggest that children probably have the same incidence as the general adult population.

Risk factors include: fast rate of ascent, such as going from below 4000 ft to over 9000 ft in one day; the sleeping altitude reached; no exposure to altitude in the previous 2 months; living below 3000 ft; overexertion; and especially genetic predisposition. Exposure to 10,000 ft for 4 nights or more in the previous 2 months **is protective**, as is a slow rate of ascent.

Individual susceptibility and reproducibility are well documented. Contributing factors include low vital capacity, low hypoxic ventilatory response (HVR), and exaggerated pulmonary hypertension in response to hypoxia. Cerebral circulatory responses and an individual's

intracranial dynamics play an important role, but can't be tested at sea-level. Currently, past history of AMS is the most significant risk factor and best predictor.

Early **diagnosis** is the key to successful management and a high index of suspicion is critical. The **setting**: rapid ascent to a higher altitude in unacclimatized persons. The **symptoms**: headache (the cardinal symptom), anorexia, dizziness, nausea, insomnia, lassitude, dyspnea. Note that these are mostly neurologic symptoms. Periodic breathing is common, but not a sign of AMS. **Early AMS feels exactly like a hangover.** In the early stages, **physical findings** are lacking. When advanced, the findings are those of pulmonary and cerebral edema. **Ataxia**, change in mental status and cyanosis are the most useful indicators of serious illness. **Differential diagnosis** includes dehydration, exhaustion, CO poisoning, infections of lung or brain, viral syndromes, migraine events, TIA's, hypothermia, drugs, and psychiatric problems.

The **pathophysiology** of moderate to severe AMS and high altitude cerebral edema is clearly related to **brain swelling**. Whether early AMS, especially the headache, is due to brain swelling is not yet established. Factors contributing to brain swelling include:

a. The degree and rate of onset of hypoxemia.

Atmospheric hypoxia leads to alveolar hypoxia and arterial hypoxemia, which initiates the pathophysiologic changes. New evidence suggests that most persons at high altitude will have some degree of brain swelling, but the greater and the more acute the hypoxemia, the more deranged the physiology. Rapid onset of hypoxemia overwhelms the body's adaptive responses, while gradual onset permits improvement in oxygenation, displacement of CSF to accommodate swelling, and changes in CSF production and absorption.

b. Hypoventilation

Inadequate ventilation (breathing) can be due to low HVR, respiratory depressant drugs, or ascent too rapid for adequate acclimatization. This causes greater hypoxemia and therefore greater hypoxic stimulus. Coupled with the relatively higher CO₂, cerebral blood flow is augmented, favoring brain edema.

c. Impaired gas exchange

Arterial PO₂ is determined by alveolar PO₂ and A-a oxygen difference. Interstitial edema is common in those with AMS, causing increased alveolar-arterial oxygen difference and therefore greater hypoxemia.

d. Fluid retention

Those acclimatizing well have a diuresis secondary to re-set of osmolarity center in the brain, with suppression of ADH and aldosterone, while those with AMS have an antidiuresis (fluid retention) with elevated ADH and aldosterone. Overhydration of the brain contributes to cerebral edema, while those with diuresis keep the brain drier.

e. Individual anatomy.

The ability to accommodate increased brain volume depends upon relative proportion of brain volume to CSF volume in the cranium, as well as proportion of spinal cord to CSF in the spinal canal. (The first compensation for brain swelling is displacement of CSF into the spinal canal.) These values are highly variable and may help explain the essentially random nature of AMS. They are also relatively constant in an individual, which may help explain individual reproducibility. This factor, in contrast to the ones above, is rather speculative.

Mechanisms of brain swelling include:

- a. **Cytotoxic edema**, due to a shift of fluid into cells was the classic explanation, but now doubted. May play a role in severe end-stage illness, but role in early illness is unclear.
- b. **Vasogenic edema** can be a true permeability defect or due to increased capillary filtration. The new finding of white matter edema on MRI T-2 images confirms vasogenic mechanism, but exact pathophysiology is not clear. These are possible factors: 1) Increased microvascular pressure with increased capillary filtration secondary to vasodilatation and overperfusion (evidence in animals). 2) Central noradrenergic mechanism - shown to regulate brain water and permeability in monkeys. 3) Permeability mediators, such as eicosanoids from lipid peroxidation, bradykinin or other kinins, oxygen and hydroxyl radicals, or **angiogenesis** (the process by which new blood vessels are formed, as in wound healing and tumor growth). Angiogenesis is stimulated by hypoxia, and blocked by dexamethasone. TGF- β stimulates macrophages to release vascular growth factors (**VEGF**) that increase permeability as

endothelial cells start to bud. **Nitric oxide** also has an important role in blood brain barrier permeability. 4) Theory of generalized "capillary leak syndrome" in which vasodilating leukotrienes, endothelin or other endothelial-related permeability factors are thought to be liberated, which induce a systemic capillary leak. This fits with retinal hemorrhage, proteinuria, and interstitial lung edema, but little experimental data.

Intracranial dynamics

a. As brain volume increases, **ICP rises**, although very little until a critical threshold is reached. This can be described by the pressure-volume curve, or the pressure-volume index (PVI), the volume required to raise the ICP ten-fold. Mean is 26ml, but quite variable, and related to diameter of spinal canal. Intracranial compliance refers to the change in pressure for a unit change in volume. A dehydrated brain is much more compliant than a "wet" brain.

b. **Cerebral vasodilation** causes increased cerebral blood flow and increased cerebral blood volume, engorging the brain and making it stiffer and less compliant. Rapid changes in CBF, such as the marked decrease in CBF with giving oxygen, or the increase in CBF in the apneic phase of periodic breathing, can rapidly change ICP.

c. The initial compensation for increased brain volume is **displacement of CSF** through the foramen magnum into the spinal subarachnoid space. Cerebral ventricular volume and intracranial subarachnoid CSF volume diminish, which can be measured on MRI. This is followed by increased CSF absorption and decreased CSF formation. (Diamox decreases CSF formation.)

d. As brain edema continues, ICP rises beyond perfusion pressure, cerebral blood flow stops, causing death. Localized compression of brain structures or ischemia may produce focal neurologic findings, but usual picture is encephalopathy, not localized signs.

Treatment is directed toward reducing brain volume and stopping the BBB leak.

1. Reduce hypoxia/increase oxygenation

- a. Descent--1,000 ft may be adequate--as far as necessary for results.
- b. Oxygen if available, especially good for headaches and encephalopathy.
- c. Hyperbaric therapy if available (portable pressure bag)

- d. Oxygen plus hyperbarics if patient in extremis.
2. Speed the process of acclimatization
 - a. Acetazolamide, 125-250mg every 12 hours. 5 mg/kg/day in 2 divided doses for children. Promotes diuresis, stimulates ventilation, decreases CSF formation. (a sulfhydryl drug, occasional cross-reactivity with sulfa).
 - b. Acclimatization at same altitude okay for self-limited illness--sick person never left behind alone.
3. Treat symptoms
 - a. Analgesics--acetaminophen, aspirin, ibuprofen, etc., codeine.
 - b. Anti-emetics—Ondansetron (Zofran) or promethazine (Phenergan).
Benadryl for extrapyramidal reactions.
4. Reduce brain capillary leak
 - a. Dexamethasone 4mg PO, IM, IV every 6 hours. May need to continue until patient evacuated to lower altitude, since rebound may occur with cessation, and drug does not improve acclimatization.
5. Reduce brain edema
 - a. Renal diuretics: acetazolamide, furosemide, others
 - b. Osmotic diuretics: glycerol or mannitol (rarely used)
 - c. Hyperventilation: voluntary HV helps while awake. Caution with intubation and forced hyperventilation since patient already alkalotic, and CBF markedly reduced if oxygen given. Can render subject ischemic.
6. Patient may re-ascend with staged acclimatization, with or without acetazolamide.

II. HIGH ALTITUDE PULMONARY EDEMA (HAPE)

A. General

1. Strikes 1-2% above 12,000 ft. sleeping altitude, occur in 1:10,000skiers at 9,000ft.
2. Most common on 2nd night.
3. Related to rate of ascent, exertion, use of sleeping medications, cold.
4. Some evidence for transient, milder forms of illness (subclinical).

B. Diagnosis

Early: dry cough, increased heart rate, decreased exercise performance, shortness of breath with exercise and increased exercise recovery time.

Late: dyspnea at rest, tachycardia, tachypnea, cyanosis, productive cough, rales.

Atypical presentations: sudden death, cerebral manifestations only (esp. ataxia), acclimatized person, mixed with respiratory infection, bronchospasm.

C. Management

1. Rest, keep victim warm. Exercise and cold increase pulmonary artery pressure (PAP).
2. **Oxygen.** Lifesaving. Raises SaO₂%, reduces PAP, stops leak.
3. Descent with minimal exertion, exercise raises PAP and decreases SaO₂%.
4. CPAP mask. Adjunctive therapy, improves gas exchange.
5. Medications which may be helpful (usually not necessary)
 - a. **Nifedipine** 10 mg PO stat, 20 or 30 mg extended release 2 to 3 times a day. Drug of choice if oxygen or descent not available. Reduces PAP 30-50%, only slightly increases SaO₂%.
 - b. **Nitric oxide**, 40 to 80 ppm in air or oxygen, rarely available. NO plus oxygen superior to oxygen alone in terms of hemodynamic response, but not yet shown superior clinically.
 - c. **Inhaled Iloprost** (prostaglandin), not yet approved by FDA. Will undoubtedly be helpful and fast acting, but expensive.
 - d. **Viagra** and other PDE-5 inhibitors block hypoxic pulmonary vasoconstriction, will probably be useful in HAPE; studies are pending. Viagra 50 mg every 8 hrs, or Cialis 10 mg every 12 hrs.
 - e. **Acetazolamide** 5 mg/kg/day. Has not been studied in HAPE, but starting to be used. Not advisable in markedly dyspneic patients with good respiratory drive; better for those with relative hypoventilation, and early in illness.
 - f. **Albuterol or salmeterol** inhaler. Not yet studied for RX, but why not try it? Safe, cheap, easy to use; recently shown to prevent HAPE in those very

susceptible. Increases alveolar fluid clearance, reverses bronchospasm, reduces PAP.

6. Victim may re-ascend when HAPE is resolved, preferably with acetazolamide or other agent.

D. Pathophysiology

Non-cardiogenic; with normal wedge pressures, normal LV function. High pulmonary artery pressure is *sine qua non*, but another factor must be present, since not all those with pulmonary hypertension have edema. The key is high microvascular pressure. Uneven pulmonary arteriolar constriction may cause high microvascular pressures in areas not constricted, leading to failure of the capillary membrane. Pulmonary venous constriction, mediated by the sympathetics via stellate ganglion, also might be important. Chemical mediators may play a role in causing a permeability defect. Inflammation, as evidenced by presence of leukotrienes, thromboxane, and others factors in the edema fluid, is probably secondary to leak, but might play a prominent role in a person with a viral infection (viral priming of the microcirculation).

- E. **Prevention** same as for AMS--acetazolamide empirically effective (but not studied), also nifedipine shown good for prophylaxis, 20mg slow release every 8 hours. Other agents are: salmeterol (Serevent), sildenafil (Viagra), tadalafil (Cialis) 10 mg every 12 hrs during ascent, and dexamethasone. I recommend acetazolamide (Diamox), since it prevents both AMS and HAPE as well, although not yet proven for HAPE.

III Prevention of altitude illness

1. Slow ascent; climb high, sleep low. Ideal rate of ascent difficult to establish because of marked individual variation in ability to acclimatize. Reasonable recommendation is not to sleep 2000ft higher than previous night once above 8000ft. An extra day for acclimatization every 3-4000ft is prudent.
2. High carbohydrate diet (>70%) controversial. Reduced AMS by 30% in one study.
3. Avoid respiratory depressants (esp. benzo-type sleeping pills; Ambien is safe) and use of alcohol in small amounts only.

4. Chemoprophylaxis:

- a. Indications are forced rapid ascent or history of recurrent illness.
- b. **Acetazolamide** up to 5mg/kg/day divided into 2 or 3 doses, for one day prior and one to two days after ascent. 125 mg bid may be sufficient for most. Sulfa drug cross-reactivity possible but not common.
- c. **Dexamethasone** 4mg every 6 to 12 hours--for those intolerant of acetazolamide, or for insertion to extreme altitude. May have to continue for three or four days, since drug does not speed acclimatization. Commonly used on "summit day." Recently shown to prevent HAPE by reducing PAP, mechanism is unknown.
- d. Use of both drugs promoted by some, acetazolamide to speed acclimatization and dexamethasone to prevent brain swelling, but only in first few days.
- e. **Ginkgo biloba** in three studies reduced AMS from 35 to 100%, other studies negative. More effective with moderate rate of ascent. Dose: 100 mg bid starting 2-3 days before and while at altitude. Safe, cheap.

How to Prevent Altitude Illness in Your Patients

- A. Take time to acclimatize
 1. Keep sleeping altitude gain less than 2,000ft per night once above 8,000ft
 2. One extra night for acclimatization every 2-3,000ft above 8,000ft
 3. Climb high, sleep lower
 4. Avoid abrupt transport to above 10,000ft. If unavoidable, acclimatize for three nights before going any higher.
- B. Help, not hinder body's natural acclimatization
 1. Avoid overexertion
 2. No alcohol, only safe sleeping medications
 3. Modest exercise on acclimatization days
 4. Avoid CO exposure. Ventilate tents and snow shelters when cooking.
 5. Encourage good hydration, high carbohydrates
- C. Recognize signs of poor acclimatization/early AMS

1. Teach clients about what to expect--normal versus abnormal.
2. Encourage clients to monitor how they feel and report to you if headaches, etc.
3. Make inquiries about symptoms and observe appetites, energy levels, skin color, behavior of clients.

D. Judicious use of acetazolamide, or if necessary, dexamethasone (see above text).

Consider ginkgo biloba.

BIBLIOGRAPHY

1. Anand S, Prasad B, Chugh S, et al. Effects of inhaled nitric oxide and oxygen in high-altitude pulmonary edema. *Circulation* 1998;98:2441-5.
- 1a. Bartsch, P., Maggiorini. M., Ritter, M., Noti, C., Vock, P., Oelz, O. Prevention of high-altitude pulmonary edema by nifedipine. *N Engl J Med* 1991;325:1284-1289.
2. Hackett PH, Roach RC. High-altitude medicine. In: Auerbach PA, ed. *Wilderness Medicine*. St. Louis: Mosby, 2007:2-43.
3. Hackett P, Roach RC. High-Altitude Illness. *New England Journal Medicine* 2001;345:107-14.
4. Hackett P. Many climbers and trekkers find acetazolamide 500 mg/day to be useful. *BMJ* 2001;322:48.
5. Hackett P. High altitude and common medical conditions. In: Hornbein T, Schoene R, eds. *High Altitude: An Exploration of Human Adaptation*. Vol. 161. NY, NY: Dekker, 2001:839-86.
6. Hackett PH; Roach RC. High altitude pulmonary edema. *J. Wilderness Med* 1990;1:3-26
7. Hackett PH, Roach RC, Wood RA, et al. Dexamethasone for prevention and treatment of acute mountain sickness. *Aviat Space Environ Med* 1988; 59:950-954.
8. Hackett PH. The cerebral etiology of high-altitude cerebral edema and acute mountain sickness. *Wild Environ Med* 1999; 10:97-109
9. Keller HR, Maggiorini M, Bartsch P, Oelz O. Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. *Br Med J* 1995; 310:1232-1235.
10. Maggiorini M, Melot C, Pierre S, et al. High altitude pulmonary edema is initially a hydrostatic, not a permeability edema. *Circulation* 2001; 103:2078-2083.

11. Oelz O; Maggiorini M; Ritter M; Waber U; Jenni R; Vock P; Bartsch P. Nifedipine for high altitude pulmonary edema. *Lancet* 1989;2:1241-1244
12. Roach RC, Houston CS, Honigman B, et al. How well do older persons tolerate moderate altitude? *West J Med* 1995; 162:32-36.
13. Maggiorini, M., H. Brunner-LaRocca, et al. (2006). "Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema; a randomized trial " *Ann Intern Med* 145: 497-506.