

High Altitude Illness: A Clinical Summary

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Seminar Topic Lecture

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Oral Seminar Topic Presentation

Honors College

Laramie, WY

High altitude illness is a group of symptoms caused by decreased oxygen levels and lower air pressure at high altitudes. There are four types of high altitude illness that include acute mountain sickness (AMS), chronic mountain sickness (CMS), high altitude cerebral edema (HACE), and high altitude pulmonary edema (HAPE) with AMS being the most common. Diagnosis of high altitude illness is based on symptomatology and history of high altitude exposure. Most patients with AMS present with headache, fatigue, dizziness, and gastrointestinal problems such as nausea and vomiting. HACE and HAPE are more severe and can develop as a result of untreated AMS. Populations with underlying medical conditions related breathing and pulmonary hypertension are more susceptible to AMS, and HAPE specifically. Non-pharmacologic treatments are preferred, including slowed rate of ascent and descent in cases where symptoms do not resolve quickly. Pharmacologic treatment is based on the type of high altitude illness. High altitude illness is a common disease state that allows pharmacists to counsel patients and provide symptom management in inpatient and outpatient settings.

High Altitude Illness

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Objectives

At the completion of this presentation, participants should be able to:

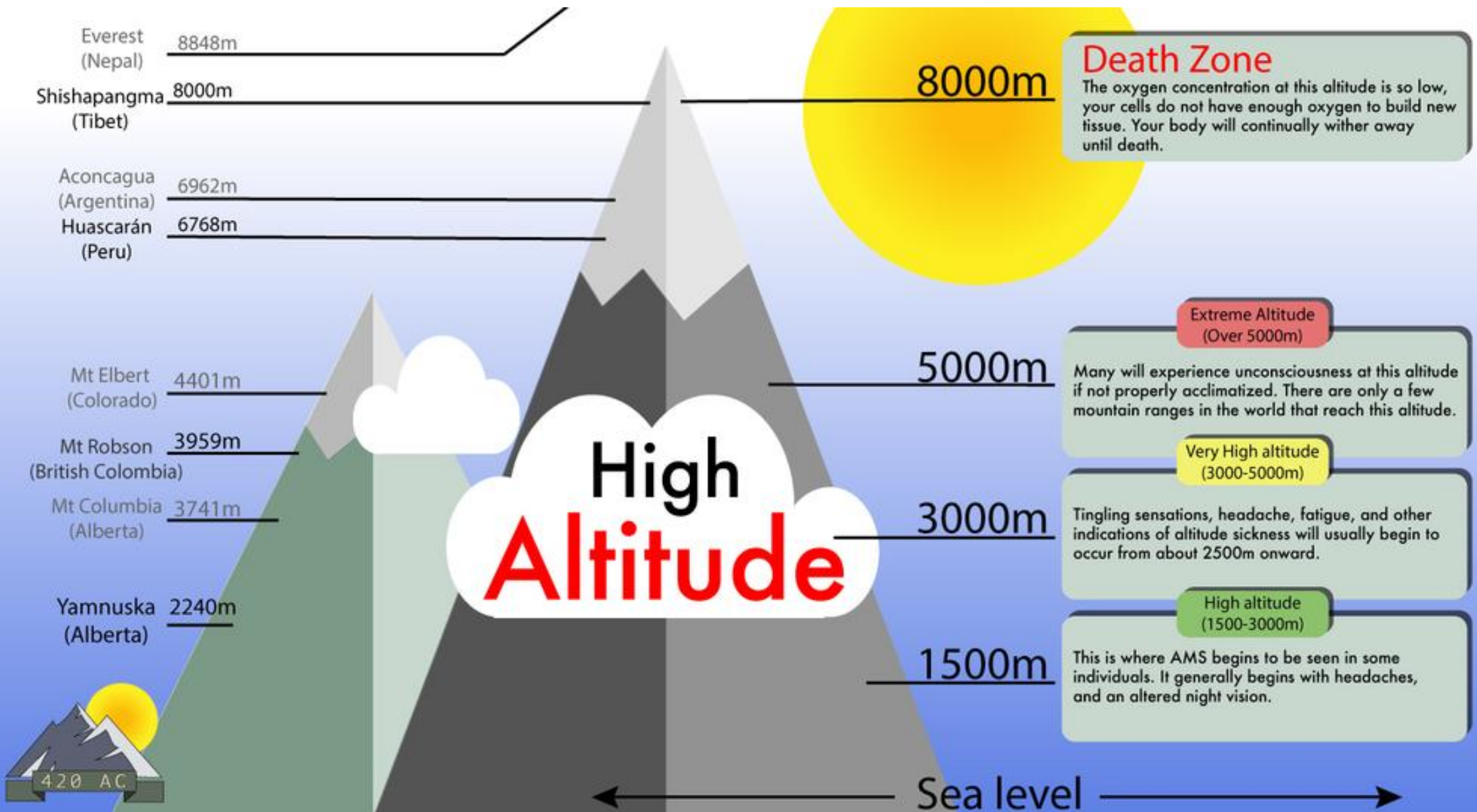
- Differentiate types of high altitude illness
- Identify the signs & symptoms of high altitude illnesses
- Recommend prevention strategies for high altitude illnesses
- Recommend non-pharmacologic and pharmacologic therapies for high altitude illnesses
- Understand the role of the pharmacist in prevention and treatment of high altitude illness

High Altitude Illness

- Group of symptoms caused by decreased oxygen levels and lower air pressure at high altitudes
- Acute Mountain Sickness (AMS) – most common
- Chronic Mountain Sickness (CMS)
- High Altitude Cerebral Edema (HACE)
- High Altitude Pulmonary Edema (HAPE)

Epidemiology

- Men and women equally affected
- AMS occurs in 25% of visitors to Colorado ski areas, 50% visiting Himalayas, and 84% of those traveling directly to Mt. Everest region
- 13% increase in prevalence of AMS with every 1000m increase in altitude above 2500m
- Incidence of AMS in children varies



Risk Factors

- Rapid ascent
- Higher final altitude
- Overexertion
- Cold temperatures
- Normally resides at lower altitudes
- Previous history of altitude sickness
- Underlying medical conditions associated with increased risk of pulmonary hypertension

Pathogenesis

- Generally unknown
- Hypoxia may lead to:
 - Increased rate/depth of ventilation □ increased CO₂ elimination □ respiratory alkalosis and increased pH of blood
 - Increased cerebral blood flow and volume □ headache
 - Increased sympathetic activity □ elevated heart rate and BP
 - Altered permeability of blood brain barrier □ cerebral edema
- HAPE may be due to hypoxic pulmonary vasoconstriction □ increased pulmonary capillary pressure
 - Impaired sodium and water transport within lung may also lead to HAPE

Diagnosis

- Based on symptoms mostly
- Recent ascent to areas of (relative) high elevation
- Rule out alcohol or drug use, dehydration
- Primary vs Secondary HAI
 - Chronic pulmonary disease – conditions that worsen hypoxemia
- Lake Louise Scores: headache and 1+ other symptoms

Lake Louise Scoring System

Symptom	Severity	Score
Headache	None	0
	Mild	1
	Moderate	2
	Severe/Incapacitating	3
Gastrointestinal	None	0
	Poor appetite/Nausea	1
	Moderate N/V	2
	Severe N/V	3
Fatigue/Weakness	Not Tired/Weak	0
	Mild	1
	Moderate	2
	Severe	3
Dizziness/Lightheaded	None	0
	Mild	1
	Moderate	2
	Severe	3

Diagnosis

- AMS symptoms appear first, usually 6-12 hours after arrival at altitude and resolve in 1-3 days
- CMS: excessive erythrocytosis (2 standard deviations above the mean hemoglobin (Hb) value of the population at the altitude of residence)
- HACE symptoms typically develop as a result of untreated AMS
- HAPE develops 1-4 days after arrival at altitudes >2500m and may or may not be accompanied by AMS symptoms

Schafermeyer, Dynamed, 2020

Gallagher, UpToDate, Acute Mountain sickness, 2020

Gallagher, UpToDate, High altitude pulmonary edema, 2020

Gallagher, UpToDate, High Altitude Illness, 2020

Hackett, N Engl J Med, 2001, 345, 107-114

Villafuerte, High Alt Med Biol, 2016

Signs & Symptoms

- AMS/CMS
 - Headache, fatigue, dizziness, nausea/vomiting, reduced appetite
- HACE
 - Altered mental status, ataxia
 - Usually preceded by AMS or HAPE but can be isolated
- HAPE
 - Decreased exercise tolerance, dyspnea, dry cough, crackles on chest auscultation
 - Fever is common
 - ~50% also have AMS symptoms

Associated Conditions

- Severe cough
- High altitude bronchitis
- High altitude retinopathies
- Optic disc swelling
- High altitude sleep apnea

Treatment

Prevention and Therapies

Goals of Therapy

- Prevent High Altitude Illness with non-pharmacologic and pharmacologic measures
- Minimize symptoms associated with high altitude illnesses
- Treat severe cases of high altitude illnesses

Non-Pharmacologic Options

- Slow ascent (<500m /day above 3000m)
- Hydration
- Pre-acclimatization
- Avoiding excessive alcohol consumption and opioid pain medications
- Avoiding overexertion
- Evacuation/Descent
- Hyperbaric chambers
- CMS: phlebotomy

Medications for HAI

- AMS/HACE:
 - Ibuprofen
 - Acetazolamide
 - Dexamethasone
- HAPE:
 - Nifedipine
 - Sildenafil/Tadalafil
 - Salmeterol

Ibuprofen

- Mechanism: NSAID
- Use: AMS prevention
- Dosing: 300 mg PO TID, starting 4-6 hours before ascent
- Contraindications: Severe renal impairment
- Side Effects: GI effects, decreased Hb, increased ALT/AST
- Monitoring: CBC, hepatic function, renal function, BP, GI effects
- Slightly inferior to acetazolamide for AMS prevention but has some evidence compared to placebo

Acetazolamide

- Mechanism: carbonic anhydrase inhibitor □ bicarbonate diuresis □ decreases pH
- Use: AMS, CMS, HACE
- Prevention: 125 mg PO BID beginning the day before ascent
 - May be discontinued after staying at the same elevation for 2-3 days or upon descent
 - In situations of rapid ascent – 1000 mg/day as recommended by the manufacturer
- Treatment: 250 mg PO BID
- Pediatrics: 2.5 mg/kg/dose PO BID
 - Not recommended unless severe prior history of altitude illness

Acetazolamide

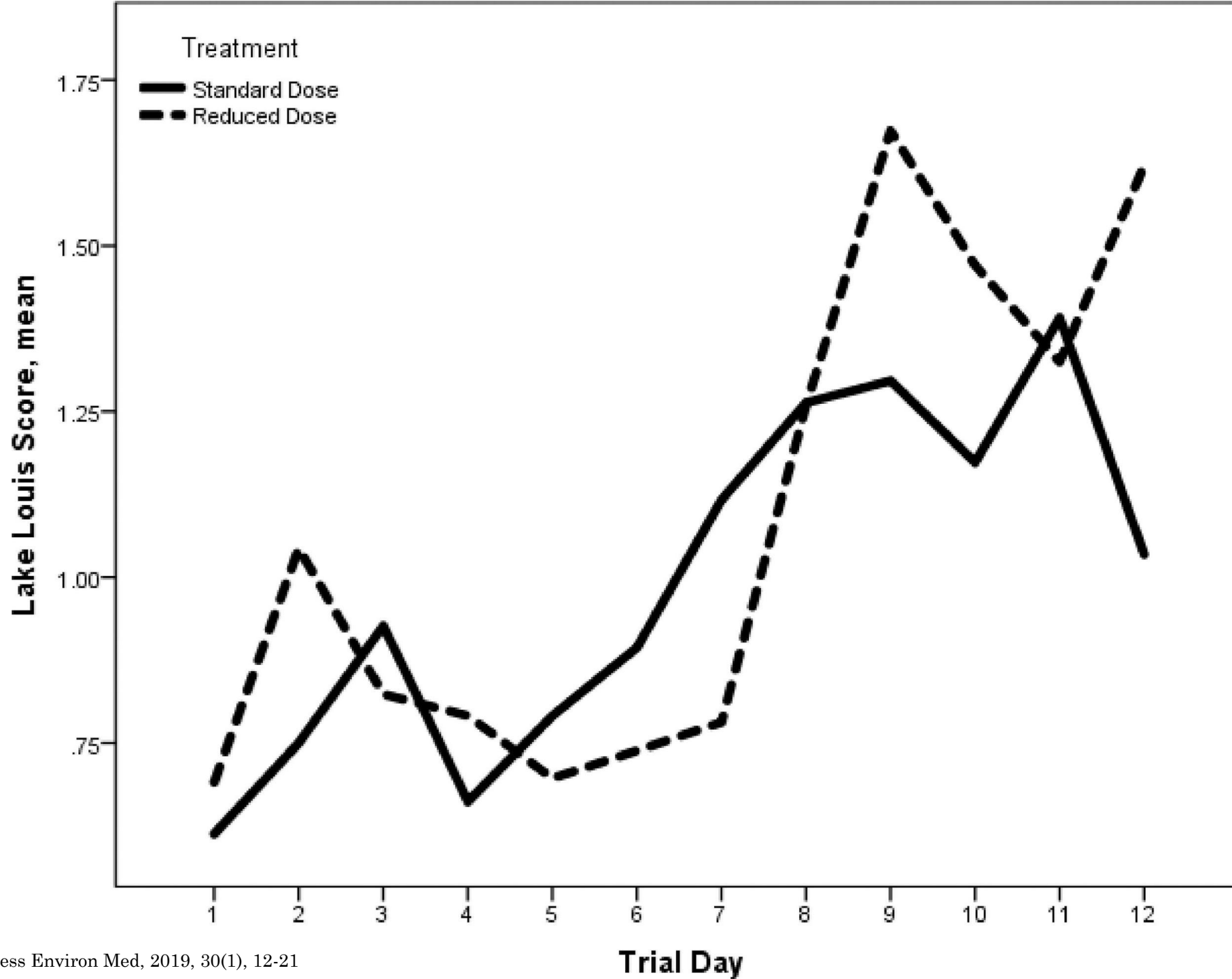
- **Contraindications:** severe renal impairment, severe hepatic impairment, decreased sodium and/or potassium levels, sulfa allergy
- **Side Effects:** excessive fatigue, malaise, skin photosensitivity, confusion, increased urination
- **Monitoring:** serum electrolytes (Na^+ , K^+), blood glucose if diabetic, excessive fatigue
- **Counseling:** Take with or without food, check for sulfa allergy

RADICAL Trial

- Noninferiority trial to compare standard dose (125 mg BID) acetazolamide with reduced dose (62.5 mg BID) acetazolamide
- Primary Outcome: incidence of AMS
 - Secondary Outcomes: severity of AMS and side effects of acetazolamide
- 73 total participants included in analysis – must have reached an altitude of at least 3000m
- Limitations: small study, non-uniform rate of ascent, low incidence of AMS in study

RADICAL Trial

- Found reduced dose to be noninferior to standard dosing
 - AMS incidence in reduced dose: 55.3% (21 of 38 participants)
 - AMS incidence in standard dose: 60.0% (21 of 35 participants)
- Also found similar Lake Louise scores and side effects between groups
 - Mean LLS for reduced and standard dose was 1.014 and 0.966, respectively
 - Side effects included frequent urination, beverage taste change, toe tingling, and finger tingling – similar severity and frequency in both groups
- Impact on Practice: With further study, could potentially use lower doses of acetazolamide for prevention of AMS/HACE – may reduce incidence of side effects



Dexamethasone

- Mechanism: long-acting corticosteroid – reversal of increased capillary permeability
- Use: HACE, alternate therapy for AMS
- Prevention: 2 mg PO every 6 hours or 4 mg PO every 12 hours
 - Start day of ascent
 - May discontinue if at same elevation for 2-4 days or upon descent
- Treatment:
 - AMS – PO, IM, IV - 4 mg every 6 hours – continue for 24 hours after symptom resolution or descent completed
 - HACE – PO, IM, IV – 8 mg initial dose, followed by 4 mg every 6 hours until descent is complete and symptoms resolve

Dexamethasone

- Pediatrics: PO, IM, IV – AMS/HACE treatment
 - 0.15 mg/kg/dose every 6 hours, max 4 mg/dose
 - Can consider for HAPE
- Side Effects: adrenal suppression, immunosuppression, mask hyperglycemia, decreased bone density
- Monitoring: BP, potassium, blood glucose, Hb, weight/height in children
- Counseling: take with food
- Interactions: CYP3A4 inhibitors/inducers

Nifedipine

- Mechanism: calcium channel blocker – increases myocardial oxygen delivery, lowers blood pressure
- Use: HAPE
- Prevention: extended release – 30 mg every 12 hours
 - Starting 24 hours prior to ascent
 - Continue for 5 days after reaching max altitude
 - Not routinely recommended
- Treatment: extended release – 30 mg every 12 hours

Nifedipine

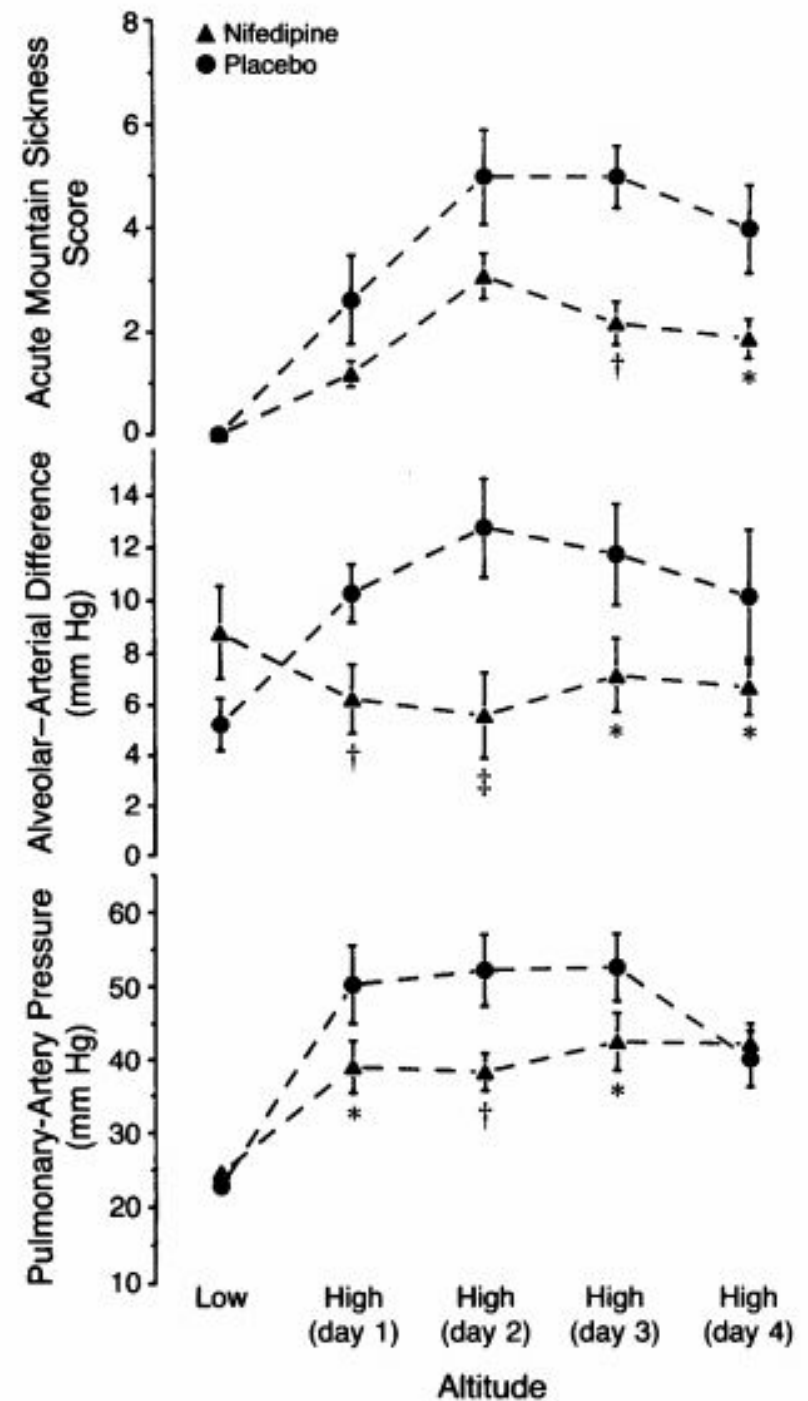
- Pediatrics: reserve for patients with unsatisfactory response to oxygen and/or altitude descent
 - IR – 0.5 mg/kg/dose every 8 hours, max 20 mg/dose
 - ER – 1.5 mg/kg/day once daily or divided (BID), max 40 mg/dose
 - Preferred
- Side Effects: hypotension, peripheral edema, headache, flushing
- Monitoring: heart rate, BP, peripheral edema, signs/symptoms of HF
- Counseling: tablet shell in stool
- Interactions: CYP3A4 inhibitors/inducers

Prevention of HAPE by Nifedipine

- Small placebo controlled, double blind trial using nifedipine doses of 20 mg every 8 hours
- 21 participants – previous, documented history of HAPE
- Primary Outcome: incidence of HAPE
- Incidence of HAPE:
 - Placebo – 7 of 11 participants
 - Nifedipine – 1 of 10 participants

Nifedipine Trial Results

- Decreased incidence of HAPE
- Decreased AMS score
- Lower pulmonary artery pressure
- PaO₂ and SaO₂ higher



PDE-5 Inhibitors

- Tadalafil, Sildenafil
- Mechanism: pulmonary vasculature relaxation
- Alternate prevention therapy for HAPE if nifedipine and other non-pharmacologic treatments are unavailable
- Dosing for Prevention:
 - Tadalafil – 10 mg every 12 hours
 - Sildenafil – 50 mg every 8 hours
- Lack of Data – has shown evidence to be useful for prevention and treatment so only recommended if other therapies unavailable
- Should not be used in combination with nifedipine
- Interactions: CYP3A4 inducers/inhibitors; to a lesser extent – CYP1A2, 2C19, 2C9, 2D6, and 2E1

Salmeterol

- Mechanism: long acting beta agonist – relaxes bronchial smooth muscle
- Use: has shown efficacy for HAPE prevention but lack of data bars recommendation
 - Not recommended for treatment
- Main trial looking at salmeterol for prevention used high doses resulting in side effects – tachycardia, tremors
 - 125 mcg every 12 hours
- Monitoring: serum potassium, BP, HR, pulmonary function
- Can be used with acetazolamide
- Interactions: CYP3A4 inhibitors/inducers

Monitoring & Re-ascent

- AMS:
 - Re-ascent can be attempted within days of symptom resolution
 - Recommended to slow ascension rate
 - Depending on severity of AMS, pharmacologic prophylaxis may be recommended
- HACE
 - Recommended to slow ascension rate
 - Pharmacologic prophylaxis is recommended
- HAPE
 - Likely to re-occur
 - Must be symptom free
 - Pharmacologic prophylaxis is recommended

Role of the Pharmacist

- Educate patients on symptoms and prevention strategies of high altitude illnesses
- Assess risk and recommend prophylaxis as needed
- Recommend treatment medications for each type of high altitude illness
- Counsel patients on use of these medications and side effects

Conclusion & Future Direction

- In all cases of high altitude illness – non-pharmacologic prevention and treatment
- Acute & Chronic Mountain Sickness
 - Acetazolamide, Dexamethasone
- High Altitude Cerebral Edema
 - Dexamethasone (can add acetazolamide)
- High Altitude Pulmonary Edema
 - Nifedipine, PDE5 inhibitors, Salmeterol
- Future Direction:
 - Possible lower doses of acetazolamide, salmeterol for HAPE



Questions??

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