High altitude and its effect on lung
26-8-16

Kodati Rakesh
Senior resident
Pulmonary medicine
• High Altitude physiology
• Acute high altitude illness
• Chronic high altitude illness
• High altitude in pre-existing lung disease
HIGH ALTITUDE PHYSIOLOGY
## High altitude

<table>
<thead>
<tr>
<th></th>
<th>High altitude</th>
<th>Very high altitude</th>
<th>Extreme altitude</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ht (m)</strong></td>
<td>1500 - 3500 m</td>
<td>3500 - 5500 m</td>
<td>5500 - 8500 m</td>
</tr>
<tr>
<td><strong>PaO2 (mm Hg)</strong></td>
<td>55 - 75</td>
<td>40 - 60</td>
<td>28 - 40</td>
</tr>
<tr>
<td><strong>SpO2 (%)</strong></td>
<td>Atleast 90</td>
<td>75 - 85</td>
<td>58 - 75</td>
</tr>
<tr>
<td><strong>High altitude illness</strong></td>
<td>&gt; 2500 m</td>
<td>HAI</td>
<td>Severe HAI</td>
</tr>
<tr>
<td><strong>Physiology</strong></td>
<td>Increased ventilation prevents hypoxia</td>
<td>Extreme hypoxia during sleep, exercise</td>
<td>Progressive deterioration of physiologic functions</td>
</tr>
</tbody>
</table>

*Hackett, PH, Roach, RC. High-Altitude Medicine. In: Wilderness Medicine, 5th ed*
High altitude

• Hypobaric hypoxia
• Low environmental temperature
  – temperature falls by 1°C per 150m gain in altitude
• Low absolute humidity
  – increases the insensible water loss from the body
  – predispose to dehydration
• Increased solar and ionizing radiation
  – harmful effects especially in the eye and skin

A.M. Luks and E.R. Swenson, ERJ 2007
Hypoxia at high altitude

<table>
<thead>
<tr>
<th>Altitude, m (ft)</th>
<th>Barometric Pressure, mm Hg</th>
<th>Inspired Po₂, mm Hg (% of sea level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (0)</td>
<td>760</td>
<td>149 (100)</td>
</tr>
<tr>
<td>1000 (3281)</td>
<td>679</td>
<td>132 (89)</td>
</tr>
<tr>
<td>2000 (6562)</td>
<td>604</td>
<td>117 (79)</td>
</tr>
<tr>
<td>3000 (9843)</td>
<td>537</td>
<td>103 (69)</td>
</tr>
<tr>
<td>4000 (13 123)</td>
<td>475</td>
<td>90 (60)</td>
</tr>
<tr>
<td>5000 (16 404)</td>
<td>420</td>
<td>78 (52)</td>
</tr>
<tr>
<td>8848 (29 028)</td>
<td>253</td>
<td>43 (29)</td>
</tr>
</tbody>
</table>

John B West, Ann Intern Med 2004
High altitude
Oxygen cascade

- O₂ diminishes as oxygen moves from air to the tissues.
- Ventilation
- Regional matching of ventilation and blood flow
- Diffusion of oxygen from the air to the blood
- Transport within the circulation
- Diffusion of oxygen from the blood into the tissue
- Metabolism in the mitochondria
Pulmonary Hypertension

Pulmonary Vasoconstriction

Systemic Vasodilatation

Acute Hypoxia

Peripheral Chemoreceptor

Ventilation ↑

Respiratory Alkalosis

Inhibition

Sympathetic Activation

Cold, Exercise

Heart Rate ↑

Cardiac Output ↑

Blood Pressure ↑

Myocardial contraction Velocity ↑

Peter Bärtsch et al; Circulation. 2007;116:2191-2202
Hypoxic ventilatory response

- Hypoxic stimulation of the peripheral chemoreceptors
- Genetically determined and quite variable
- Correlate positively with physical performance at high altitude and inversely with the susceptibility to AMS
- Extrinsic factors
  - respiratory depressants (alcohol and sedative/hypnotics)
  - fragmented sleep
  - respiratory stimulants (progesterone) and sympathomimetics (coca, caffeine)
Hypoxic ventilatory response

• Respiratory alkalosis blunts the HVR by acting on central medullary chemoreceptors
• However ventilation gradually increase – ‘ventilatory acclimatization’
  – compensatory metabolic acidosis by kidney
  – Movement of $\text{HCO}_3$ out of CSF
  – increased sensitivity of carotid body
  – erythropoietin signalling in brain
Hypoxic ventilatory response

Lenfant C, Sullivan K: Adaptation to high altitude; NEJM 1971;284:1298
Blood gases at 8848 m

<table>
<thead>
<tr>
<th>Barometric pressure, mm Hg</th>
<th>Inspired PO2, mm Hg</th>
<th>PA O2 mm Hg</th>
<th>PaO2 mm Hg</th>
<th>Pa CO2 mm Hg</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>253</td>
<td>43</td>
<td>35</td>
<td>28</td>
<td>7.5</td>
<td>&gt; 7.7</td>
</tr>
<tr>
<td>760</td>
<td>149</td>
<td>100</td>
<td>95</td>
<td>40</td>
<td>7.4</td>
</tr>
</tbody>
</table>

West JB. Science, 1984
Gas exchange

<table>
<thead>
<tr>
<th>Decrease $O_2$ delivery</th>
<th>Increase $O_2$ delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low alveolar – arterial oxygen gradient</td>
<td>Haemoconcentration by a mild diuretic effect of hypoxia</td>
</tr>
<tr>
<td>Effective diffusion limitation during exercise (↑CO ↓capillary transit time)</td>
<td>Hypoxia-mediated EPO secretion - increased RBC production</td>
</tr>
<tr>
<td>Increased extravascular lung water</td>
<td></td>
</tr>
</tbody>
</table>
Gas exchange

Intra erythrocytic alkalosis

↑alkalosis very high altitudes (>5000 m)

Increased 2, 3 DPG
Pulmonary mechanics

• Fall in vital capacity
  – pulmonary vascular engorgement
  – subclinical interstitial oedema
  – increased abdominal distension
  – decreased respiratory muscle strength

• No change in FEV1

• Increase in PEFR
  – decreased air density

Hypoxic pulmonary vasoconstriction

- Small pulmonary arterioles and veins with a diameter of < 900 µm
- Venous changes ~20% of the total increase in pulmonary vascular resistance
- Intrinsic to muscle cells of pulmonary arteries
- Endothelin and sympathetic activation

Peter Bärtsch et al; Circulation. 2007;116:2191-2202
Hypoxic pulmonary vasoconstriction

• Normally inhomogenous
  – baseline ventilation-perfusion ratio (V/Q) inhomogeneity
  – regional differences in endothelial release of NO
  – uneven distribution of smooth muscle cells in pulmonary arterioles

• Inhomogeneity increases with the magnitude of HPV

• Exaggerated HPV – risk of HAPE

Peter Bärtsch et al; Circulation. 2007;116:2191-2202
Cardiovascular response

- Unchanged or slightly decreased systemic BP
  - hypoxic vasodilation
- BP and SVR rise over at least 3 to 4 weeks
  - increasing sympathetic activity
  - reduced tissue hypoxia a/w acclimatization
- ↑ HR (both at rest and on exercise), myocardial contractility & ↑ cardiac output
Hematologic response

• Hb % increases within 1 to 2 days of ascent and continue to increase
• Initially – hemoconcentration
  – great insensible fluid loss by large ventilation of cold dry air
  – hormonal effects
• Later – EPO production (within 24 -48 hrs starts raising )
• Increased viscosity sufficiently impair cardiac output and limit microvasculature perfusion
Tissue adaptation

- Diminished muscle fiber size
- Increased myoglobin concentration
- Increased activity of enzymes in oxidative metabolism
- Up regulation of cytoglobins (heme proteins similar to myoglobin)
HIF

Cellular adaptation to hypoxia

Physical performance

- Decreased VO$_2$ max
- Decreased work capacity
- Reduced alveolar arterial oxygen gradient
- Shortened pulmonary capillary transit time
- V/Q mismatch due to non uniform HPV
- Elevated PAP during exercise

Exercise limitation at high altitude

*John B West, Ann Intern Med 2004*
Mental performance

• At an altitude above 4000 m people experience
  – an increased arithmetic errors
  – reduced attention span
  – increased mental fatigue
  – decision making

John B West, Ann Intern Med 2004
Sleep

- **Subjective features**
  - poor quality with sensation of occasional awakenings
  - sense of suffocation
  - restless sleep on awakening

- **Objective features**
  - shift from deeper to lighter sleep stages
  - fragmentation of sleep (frequency of arousals)
  - periodic breathing
  - duration of sleep maintained

*John V Weil, High Alt Med Biol 2004*
Periodic breathing

• Waxing and waning breathing pattern in sleep
• Instability in the control system
• Stimulation by hypoxia alternates with inhibition by hypocapnic alkalosis
• Declines during acclimatization at moderate altitude (< 4500 m)
Periodic breathing

• Acetazolamide – reduction of alkalosis and possible lowering of apneic threshold

• Low doses of BZDs - shortened sleep latency, decreased arousals, increased sleep efficiency, increased REM, and produced subjectively better sleep

John V Weil, High Alt Med Biol 2004
ACUTE HIGH ALTITUDE ILLNESS
Acute high altitude illness

- Acute mountain sickness (AMS)
- High altitude cerebral edema (HACE)
- High altitude pulmonary edema (HAPE)
Clinical pictures of altitude illness

Pathophysiology of altitude illness

AMS

HAPE

HACE
Epidemiology of HAI

• Up to 50–70% of mountaineers develop symptoms of AMS
• HACE and HAPE - incidence of 0.1–4%
• AMS  > 2500 m
  HAPO  > 3000 m
  HACO  > 4000–5000 m
• Susceptible individuals can be affected below these altitudes also

Tom Smedley & Michael PW Grocott, British J pain 2013
Risk factors HAI

• Genetic susceptibility
• Degree of hypoxic stress
  – Rate of ascent
  – Elevation attained
  – Lack of acclimatisation
  – Vigorous exertion or substance consumption
• Occur in any subject if the altitude is sufficiently high or the rate of ascent is sufficiently rapid, regardless of the person's capacity to acclimatize

Tom Smedley & Michael PW Grocott, British J pain 2013
HAPE – susceptibility

• Susceptible individuals
  – abnormal increase in pulmonary artery pressure (PAP) during brief or prolonged hypoxic exposure
  – Greater PAP rise during exercise in normoxia

• Polymorphisms of RAAS pathway, the nitric oxide pathway and the hypoxia inducible factor pathway
Risk factors HAI (HAPE)

- Cold ambient temperature
- Respiratory tract infection
- Preexisting abnormalities with ↑ pulmonary blood flow - predispose to HAPE, even at altitudes below 2500 m
  - Primary pulmonary hypertension
  - Congenital absence of one pulmonary artery
  - Left-to-right intra cardiac shunts

Joshua O. Stream et al; Wilderness & environmental medicine, Dec 2008 : Vol. 19
Risk factors HAI (HAPE)

- PFO - reverses the direction of blood flow, shunting blood from right to left and further exacerbates hypoxemia.

- PFO is 4 times more common among HAPE-susceptible individuals.

- Larger PFOs correlate directly with increased arterial hypoxemia, and a increased risk of developing HAPE.

<table>
<thead>
<tr>
<th>Frequency of PFO, No. (%)</th>
<th>HAPE-Susceptible Participants (n = 16)</th>
<th>HAPE-Resistant Participants (n = 19)</th>
<th>P Value (Odds Ratio [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 550 m</td>
<td>9/16 (56)</td>
<td>2/19 (11)</td>
<td>.004 (10.9 [1.9-64.0])*</td>
</tr>
<tr>
<td>At 4559 m</td>
<td>11/16 (69)</td>
<td>3/19 (16)</td>
<td>.001 (11.7 [2.3-59.5])*</td>
</tr>
<tr>
<td>P value (550 vs 4559 m)†</td>
<td>.16</td>
<td>.32</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency of HAPE, No. (%)</th>
<th>HAPE-Susceptible Participants (n = 16)</th>
<th>HAPE-Resistant Participants (n = 19)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 4559 m</td>
<td>8/16 (50)</td>
<td>0/19 (0)</td>
<td>.001*</td>
</tr>
</tbody>
</table>

Yves Allemann et al; JAMA, Dec 2006
## Risk factors HAI

<table>
<thead>
<tr>
<th>RF</th>
<th>Odds ratio</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior h/o HAI</td>
<td>12.82</td>
<td>6.95 -23.66</td>
</tr>
<tr>
<td>Ascent &gt; 400 m/day</td>
<td>5.89</td>
<td>3.78-9.16</td>
</tr>
<tr>
<td>Migraine</td>
<td>2.28</td>
<td>1.28-4.07</td>
</tr>
<tr>
<td>Low Ventilatory response to hypoxia at exercise</td>
<td>6.68</td>
<td>3.83-11.63</td>
</tr>
<tr>
<td>Desaturation at exercise in hypoxia ≥ 22%</td>
<td>2.50</td>
<td>1.52-4.11</td>
</tr>
</tbody>
</table>

Jean-Paul Richalet et al; Am J Respir Crit Care Med 2012
Pathophysiology – AMS/HACE

• Cerebral edema
  – *Vasogenic edema* - increase in permeability of BBB due to increase in intravascular pressures or the effect of hypoxemia per se
• MRI showed intense T2 signals in the white matter, particularly in the splenium and corpus callosum with no gray matter edema*
  – *Cytotoxic edema* - rare
  – Increased CBF and the loss of autoregulation of ICP
  – Chemical factors (VEGF, NO & cytokines) alter the endothelial permeability

*Hackett PH et al; JAMA 1998*
Pathophysiology – AMS/HACE

• Tight fit hypothesis
  – not the amount of swelling that matters
  – person's ability to tolerate such swelling
  – Individuals with a greater brain to cranial vault ratio become more symptomatic than individuals with a smaller ratio but with the same degree of cerebral edema
Pathophysiology - HAPE

Maladaptive responses to the hypoxia

• *Exaggerated and uneven pulmonary vasoconstriction*

• Poor ventilatory response

• Increased sympathetic tone

• Hypoxia induced endothelial dysfunction (↓NO & ↑endothelin)

*Joshua O. Stream et al; Wilderness & environmental medicine, Dec 2008 : Vol. 19*
Criteria for HAI

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mountain sickness</td>
<td>Headache and at least one of the following symptoms: fatigue or weakness;</td>
</tr>
<tr>
<td></td>
<td>dizziness or lightheadedness; gastrointestinal symptoms (nausea or vomiting,</td>
</tr>
<tr>
<td></td>
<td>anorexia); difficulty sleeping</td>
</tr>
<tr>
<td>High-altitude cerebral edema</td>
<td>Change in mental status or ataxia in a person with acute mountain sickness,</td>
</tr>
<tr>
<td></td>
<td>or change in mental status and ataxia in a person without acute mountain</td>
</tr>
<tr>
<td></td>
<td>sickness</td>
</tr>
<tr>
<td>High-altitude pulmonary edema</td>
<td>At least two of the following symptoms: dyspnea at rest; cough; weakness or</td>
</tr>
<tr>
<td></td>
<td>decreased exercise performance; chest tightness or congestion and</td>
</tr>
<tr>
<td></td>
<td>At least two of the following signs: crackles or wheezing in at least one</td>
</tr>
<tr>
<td></td>
<td>lung field; central cyanosis; tachypnea; tachycardia</td>
</tr>
</tbody>
</table>

*Criteria based on The Lake Louise consensus on the definition of altitude illness. [Link](http://www.high-altitude-medicine.com/AMS-LakeLouise.html).
## Risk assessment HAI

<table>
<thead>
<tr>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow ascent (≤500 m/day above 2500 m) and taking 1 day for acclimatisation for every addnl 1000m ascent</td>
<td>Fast ascent (&gt;500 m/day above 2500 m) &amp; taking 1 day for acclimatisation for every addnl 1000 m ascent</td>
<td>Fast ascent (&gt;500 m/day above 2500 m) without a extra day for acclimatisation</td>
</tr>
</tbody>
</table>

No h/o high altitude illness with previous exposure to similar altitude

History of high altitude illness with previous exposure to similar high altitude

Fast ascent (>500 m/day above 2500 m) for persons who are partially acclimatized

Ascent > 3000 m in less than 2 days

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*Peter Bärtsch; Acute high altitudinal illnesses; NEJM 2013*
AMS

- Head ache - cardinal symptom
- Anorexia, nausea, dizziness, malaise, sleep disturbances or combination of these
- Sense of oppression in the chest
- Delayed for 6 to 12 hours following arrival at high altitude

*Peter Bärtsch; Acute high altitudinal illnesses; NEJM 2013*
AMS

• Within 6 to 12 hours after ascent to 2500 m or more
• Resolve in one day if there is no further ascent, and do not recur at the same altitude
• Prevalence and severity increase with increasing altitude
  – 10 to 25% of who ascend to 2500 m
  – 50 to 85% of who ascend to 4500 to 5500 m

Peter Bärtsch; Acute high altitudinal illnesses; NEJM 2013
D/D - AMS

• Clinical history
• No confirmatory laboratory tests
• Supplemental oxygen may be used to support the clinical diagnosis
• Differentials:
  – dehydration
  – hypothermia
  – exhaustion
  – alcohol hangover
  – carbon monoxide poisoning
  – respiratory or cerebral infections
HACE

• Truncal ataxia
• Progressive decline of mental function & consciousness
• Coma followed by death from brain herniation within 24 hours
• After at least 2 days at altitudes above 4000 m
• 0.5 to 1.0% among persons at 4000 to 5000 m
• Headache not responding to NSAIDs and associated vomittings indicates probable progression of AMS to HACE
Lake Louise Score for the Dx of AMS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Severity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Headache</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe/incapacitating</td>
<td>3</td>
</tr>
<tr>
<td>2. Gastrointestinal</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Poor appetite or nausea</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate nausea or vomiting</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe nausea or vomiting/</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>incapacitating</td>
<td></td>
</tr>
<tr>
<td>3. Fatigue/weakness</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe/incapacitating</td>
<td>3</td>
</tr>
<tr>
<td>4. Dizziness/lighthead</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe/incapacitating</td>
<td>3</td>
</tr>
<tr>
<td>5. Difficulty sleeping</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Not as well as usual</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Poor night’s sleep</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Unable to sleep</td>
<td>3</td>
</tr>
</tbody>
</table>

A diagnosis of acute mountain sickness (AMS) requires (a) score > 3, (b) presence of headache and (c) recent ascent.

High-altitude cerebral oedema

<table>
<thead>
<tr>
<th>With AMS</th>
<th>Without AMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered mental status or/and ataxia</td>
<td>Altered mental status and ataxia</td>
</tr>
<tr>
<td></td>
<td>AMS</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Descent</strong></td>
<td>Not mandatory except in the setting of intractable symptoms or suspicion that illness is progressing</td>
</tr>
<tr>
<td><strong>Supplemental O₂</strong></td>
<td>Can serve as an alternative to descent</td>
</tr>
<tr>
<td><strong>Hyperbaric therapy</strong></td>
<td>Effective temporizing measure awaiting descent or benefits of medical therapy</td>
</tr>
<tr>
<td></td>
<td>Practically challenging for use in patients with severe nausea, vomiting or decreased conscious level</td>
</tr>
<tr>
<td><strong>Drugs Rx</strong></td>
<td>Acetazolamide Dexamethasone – severe AMS</td>
</tr>
</tbody>
</table>

*Tom Smedley & Michael PW Grocott, British J pain 2013*
Descent

• Descent remains the single best treatment for AMS and HACE

• Should descend until symptoms resolve

• Symptoms resolve following descent of 300 to 1000 m

• Required descent vary between persons

Tom Smedley & Michael PW Grocott, British J pain 2013
Acetazolamide

- 125 to 250 mg orally every 12 hours
- Continue for 24 hours after symptoms resolve or descent accomplished
- Relieves symptoms, improves arterial oxygenation, and prevents further impairment of pulmonary gas exchange
- Accelerates acclimatisation process

Dexamethasone

- Does not facilitate acclimatization and further ascent should be delayed until the patient is asymptomatic while off the medication
- 8-mg dose (IM/IV/PO) followed by 4 mg q6h until symptoms resolve
- False sense of security when symptoms diminish

Tom Smedley & Michael PW Grocott, British J pain 2013
# Dexamethasone

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Methods</th>
<th>Assessment AMS</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine et al; NEJM 1989 RCT</td>
<td>6</td>
<td>Simulated altitude of 3700m for 48 hrs 4 mg PO/IM q6h</td>
<td>Symptom score</td>
<td>Reduction of symptoms by 63 %</td>
</tr>
<tr>
<td>Hackett et al; Aviat space Environ Med 1988</td>
<td>11</td>
<td>4400 m after 1 hr flight 4 mg PO/IM q6h</td>
<td>Symptom score</td>
<td>Improvement at 12 hrs in symptom score</td>
</tr>
<tr>
<td>Ferrazini et al; BMJ 1987 RCT</td>
<td>35</td>
<td>altitude of 4559m above sea level Placebo (18) vs Dexa(17)</td>
<td>Symptom score  O2 saturation FEV1 &amp; FVC Resting MV</td>
<td>No change in MV, rest all improved in dexa group</td>
</tr>
</tbody>
</table>
Dexamethasone vs hyperbaric chamber

- Randomised trial among AMS subjects (n = 31)
- Altitude of 4559m above sea level

Keller HR et al; BMJ 1995
## Prevention

<table>
<thead>
<tr>
<th>High Altitude acclimatization</th>
<th>International Society of Mountain Medicine</th>
<th>Wilderness Medical Society</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Once above 3000m, sleeping altitude should not increase by more than 500m per day</td>
<td>• First night at altitude should be spent below an altitude of 2400m</td>
</tr>
<tr>
<td></td>
<td>• One day of rest should be catered after every 3-4 days of ascent</td>
<td>• Once above 2400m, sleeping altitude should not increase by more than 600m per day</td>
</tr>
</tbody>
</table>
Prevention of AMS

- Acetazolamide
- Dexamethasone
  - prior h/o intolerance
  - allergic reaction to acetazolamide
  - rapid ascent higher than 3000 m
- Acetazolamide & dexamethasone – very rapid ascent
- Gingko biloba
- NSAIDs
  ✓ Prophylaxis may be stopped after 2 to 3 days at the target altitude, if stays for several days
  ✓ Should be stopped once descent is initiated
Prevention of AMS by Acz

Prevention of AMS by Acz

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of subjects</th>
<th>Paresthesia</th>
<th>Polyuria</th>
<th>Taste disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. with event/ total No. (%)</td>
<td>Acetazolamide</td>
<td>Placebo</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>250 mg day⁻¹</td>
<td>130/191 (68.1)</td>
<td>40/186 (21.5)</td>
<td>34/62 (54.8)</td>
<td>28/53 (52.8)</td>
</tr>
<tr>
<td>Risk ratio [95% CI]</td>
<td>3.04 [2.31 to 4.01]</td>
<td>1.04 [0.74 to 1.46]</td>
<td>0.86 [0.13 to 5.88]</td>
<td></td>
</tr>
<tr>
<td>500 mg day⁻¹</td>
<td>113/187 (60.4)</td>
<td>17/190 (8.9)</td>
<td>14/138 (10.1)</td>
<td>9/139 (6.5)</td>
</tr>
<tr>
<td>Risk ratio [95% CI]</td>
<td>6.44 [4.09 to 10.1]</td>
<td>1.56 [0.72 to 3.40]</td>
<td>3.05 [1.19 to 7.78]</td>
<td></td>
</tr>
<tr>
<td>750 mg day⁻¹</td>
<td>76/84 (90.5)</td>
<td>16/58 (27.6)</td>
<td>66/136 (48.5)</td>
<td>32/117 (27.4)</td>
</tr>
<tr>
<td>Risk ratio [95% CI]</td>
<td>3.15 [2.09 to 4.75]</td>
<td>1.59 [1.18 to 2.14]</td>
<td>3.39 [0.77 to 15.0]</td>
<td></td>
</tr>
</tbody>
</table>

Prevention of AMS by Dexa

Enjie Tang et al; International Journal of Cardiology 2014
# NSAIDS - AMS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>86 participants Ascending from 1,240 m to 3,810 m</td>
<td>294 trekkers 4280 or 4358m (183 completed)</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Ibuprofen 600 mg or placebo TID, starting 6 hours before ascent</td>
<td>Ibuprofen 600 mg or placebo TID, before ascent to 4928 m</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>44 ibuprofen, 42 placebo</td>
<td>232 ITT (123 vs 109) 183 APP (110 vs 73)</td>
</tr>
<tr>
<td><strong>Outcome (study vs control)</strong></td>
<td>AMS 43 % Vs 69 % (OR 0.3, 95% CI 0.1 to 0.8) AMS severity also lower in NSAID group</td>
<td>(ITT) AMS (24.4% vs 40.4%; P = 0.01) (APP) AMS (32.9% vs 22.7%; P =0.129) (ITT) Severity (8.9% vs 11.9%; P =0.45) (APP) Severity (9.6% vs 8.2%; P =0.74)</td>
</tr>
</tbody>
</table>

Lipman et al; Annals of Emergency Medicine 2012  
Gerstch et al, Wilderness & environmental medicine, 2012
NSAIDs

- Aspirin or ibuprofen may be useful for preventing the headache associated with AMS
- Role in high risk situation is unclear
- The limitations of trials involving NSAIDs make such determinations difficult
## Gingko biloba

<table>
<thead>
<tr>
<th></th>
<th>Chow T et al; 2005, California</th>
<th>Moraga FA et al, 2007, Ollague, Chile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>57 subjects Elevated to 3800 m to 24 hrs</td>
<td>36 subjects Elevated to 3696 m</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>LLS used for AMS Dx 120 mg BD G biloba 250 mg BD ACZ 5 days before the ascent</td>
<td>G biloba 80 mg/12 h ACZ 250 mg/12 h or Placebo 24 hours before ascent and during their 3-day stay</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>20 acetazolamide 17 Ginkgo biloba 20 placebo</td>
<td>12 G biloba 12 ACZ 12 placebo</td>
</tr>
<tr>
<td><strong>Outcome AMS incidence</strong></td>
<td>30 % ACZ 65 % G biloba 60 % placebo</td>
<td>36 % ACZ 0 % G biloba 56 % placebo</td>
</tr>
<tr>
<td><strong>Conclusion</strong></td>
<td>No benefit of G Biloba</td>
<td>Support the use of G Biloba</td>
</tr>
</tbody>
</table>

*Tony Chow et al; Ann Intern Med 2005
Moraga FA et al, Wilderness and Environmental Medicine, 18, 251 257 (2007)*
## Prevention of HAI trial, Mt Everest Himalayas, Nepal

### Participants
487 healthy trekkers assigned to receive ginkgo, acetazolamide, combined acetazolamide and ginkgo, or placebo, initially taking at least three or four doses before continued ascent.

### Methods
Randomised in a double blind fashion to receive twice daily either ginkgo 120 mg, acetazolamide 250 mg, combined ginkgo 120 mg and acetazolamide 250 mg, or placebo.

### Outcome measure
Incidence of AMS by LLS.

### Results
- 14 (12%) ACZ
- 43 (35%) G biloba
- 18 (14%) ACZ + biloba
- 40 (34%) placebo

### Conclusion
When compared with placebo, ginkgo is not effective at preventing AMS. Acz 250 mg twice daily afforded robust protection against symptoms of AMS.
Clinical features HAPE

• Usually 2 - 4 days after arrival at a new altitude
• Subtle, non productive cough → pink, frothy sputum to frank blood
• Dyspnea on exertion and difficulty walking uphill with early progression to dyspnea at rest
• Restricted exercise tolerance
• Deterioration in gas exchange also increases the risk of high-altitude cerebral edema

Peter Bartsch et al; N Engl J Med 2013;368:2294-302
Clinical features HAPE

- Inspiratory crackles
- Appears better than expected for the severity of hypoxemia
- Rapid correction of the SpO2 and clinical status with supplemental O2 in the setting of a severe infiltrative lung process seen on radiograph is virtually pathognomonic for HAPE

Peter Bartsch et al; N Engl J Med 2013;368:2294-302
Diagnosis HAPE

• History and physical examination
• CXR - patchy alveolar infiltrates, predominantly in the right central hemithorax, which become more confluent and bilateral as the illness progresses
• USG – Ultrasound lung comets caused by air fluid interface in the presence of EVLW
• Differentiating HAPE from ADHF or pneumonia can be difficult, particularly in older patients with comorbidities

Wimalasena Y et al; Wilderness Environ Med, 2013
Oxygen therapy

- Supplemental O₂ and rest while remaining at high altitude are sufficient treatment for mild to moderate HAPE
- Supplemental O₂ is *first-line therapy*
  - reduces pulmonary artery (PA) pressure
  - reverses capillary leak
  - reduces both the heart and respiratory rates
Descent / Hyperbaric chamber

- Atleast 500 to 1000 m
- Passive descent recommended
- Also treats acute mountain sickness
- Portable hyperbaric chamber
  - good temporizing measure before definitive therapy
  - if oxygen is not available
  - descent is unsafe or impossible
PAP therapy

- Improves gas exchange by providing positive airway pressure
- Temporary measure
- Considered as an adjunct to O\textsubscript{2} administration
- No studies have established its role in HAPE

Larson EB; Lancet 1985; 1(8425):371-3
Pharmacologic therapy

• Nifedipine

• PDE5 inhibitors
  – Sildenafil
  – Tadalafil
  – Strong physiologic rationale present, but no studies have evaluated therapeutic benefit
Nifedipine - HAPE

- Decreased systolic PAP
- Narrows the alveolar-arterial oxygen gradient
- Improves radiographic scores of PE
- 30 mg SR formulation every 12 hours
- Unlikely to cause significant hypotension in previously healthy persons
- Should not be relied on as the sole therapy unless descent is impossible and access to supplemental oxygen or portable hyperbaric therapy cannot be arranged

Oelz O et al; Lancet 1989 Nov 25;2(8674):1241-4
Nifedipine - HAPE

- Prospective study among 110 patients in a military hospital in Sikkim
- Alternately received nifedipine or placebo along with reduction of altitude, bed rest and nasal oxygen therapy
- Nifedipine appears to provide no additional benefit in the resolution of HAPE

Rajesh Deshwal et al; Wilderness Environ Med, 2012 Mar;23(1):7-10
Nifedipine – prevention HAPE

Nifedipine Vs placebo in prevention of HAPE
20 mg SR Nifedipine every 8 hrly during the ascent and following 3 days at high altitude

<table>
<thead>
<tr>
<th></th>
<th>Nifedipine (n =10)</th>
<th>Placebo (n= 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary edema</td>
<td>1</td>
<td>7</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic PAP (mm Hg)</td>
<td>41 ± 8</td>
<td>53 ± 6</td>
<td>0.01</td>
</tr>
<tr>
<td>A-a O2 gradient</td>
<td>6.6 ± 3.8</td>
<td>11.8 ± 4.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Prevention HAPE

- RCT of 29 adult with previous HAPE
- 4559 m within 2 days ascent

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=9)</th>
<th>Tadalafil (n=10)</th>
<th>Dexamethasone (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS</td>
<td>8</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Mean sPAP</td>
<td>28 mm Hg</td>
<td>13 mm Hg</td>
<td>16 mm Hg P =0.012</td>
</tr>
</tbody>
</table>

Both dexamethasone and tadalafil decrease systolic PAP
May reduce the incidence of HAPE in adults with a history of HAPE

Maggiorini M et al; Ann Intern Med 2006
Prevention HAPE

Salmeterol 125 mcg vs placebo
Beta agonists up regulate clearance of alveolar fluid

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>SALMETEROL GROUP</th>
<th>PLACEBO GROUP</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.6±10.2</td>
<td>46.0±12.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (no.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>No. of previous episodes†</td>
<td>2.4±1.0</td>
<td>1.9±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>94.1±11.1</td>
<td>89.1±13.5</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic pulmonary-artery pressure (mm Hg)</td>
<td>60.9±15.5</td>
<td>63.6±13.9</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>73.5±11.5</td>
<td>67.0±7.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Partial pressure of arterial oxygen (mm Hg)</td>
<td>33.9±7.3</td>
<td>30.0±5.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Incidence of HAPE
74 % (placebo) vs 33 % (Rx)
P = 0.02

Satori et al; NEJM 2002
CHRONIC HIGH ALTITUDE ILLNESS
CMS

- Maladaptation among high altitude residents
- Altitudes above 2500 m
- First described by Carlos Monge 1928 in Peru
CMS

- Excessive erythrocytosis
  (> 2 SD above the mean Hb % of the population at altitude of residence)
- Severe hypoxemia
- Moderate to severe PH
- Gradually disappears after descent to low altitude & reappears after return to high altitude

Léon-Velarde et al; High Alt Med Biol Vol 6, 2005
CMS

- Blunted HVR
  - Relative hypoventilation
- Exaggerated hematopoietic response
- More HPV
- Polycythemia blunting ventilatory response
CMS - prevalence

- 83 individuals
- Eight towns across the HP districts (mean altitude 3281 m)
- Overall prevalence of CMS – 6.17 %

<table>
<thead>
<tr>
<th>Altitude group (m)</th>
<th>N</th>
<th>CMS score</th>
<th>prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3000</td>
<td>31</td>
<td>1.03 ± 0.20</td>
<td>0 %</td>
</tr>
<tr>
<td>≥ 3000</td>
<td>50</td>
<td>1.85 ± 0.25</td>
<td>13.73 %</td>
</tr>
</tbody>
</table>
CMS

- Headache, tinnitus, vertigo, dizziness, lethargy, impaired memory and mentation
- Burning in the palms and soles
- Dilatation of veins
- Plethoric appearance with ↑hematocrit & Hb
- Normal respiratory function confirmed by lung function tests
CMS

• Erythrocytosis
  – Increased production of pro-inflammatory markers
  – oxidative stress
  – damage to the vascular endothelium
  – development of atherosclerosis
  – consequent increment in the risk of cardiovascular events such as vascular occlusion, myocardial ischemia and stroke
The Qinghai CMS score

- Breathlessness and/or palpitations
- Sleep disturbance
- Cyanosis
- Dilatation of veins
- Paresthesias
- Headaches and
- Tinnitus
- Hb  
  - Males: 18 - 21 g/dl (0), ≥ 21 g/dl (3)  
  - Females: 16 - 19 g/dl (0), ≥ 19 g/dl (3)

- Value of 0, 1, 2, and 3 (absent, mild, moderate, and severe respectively)
- Absent Score 0 - 5
  Mild Score 6 - 10
  Moderate Score 11 - 14
  Severe Score > 15

Léon-Velarde et al; High Alt Med Biol Vol 6, 2005
CMS - therapy

• Periodic travel to low altitude levels
• Severe cases – to be shifted permanently
• Phlebotomy with / without isovolumic hemodilution
  – reduces hematocrit
  – improves oxygenation
  – relief of symptoms
• Safety and efficacy not established
CMS - therapy

• Iron deficiency – leading to increased pulmonary artery pressures and aggravation of PH
• Rebound rise if the person continue to stay at high altitude
• Subjects concern on blood letting
CMS - therapy

• Physical exercise – non pharmacological Rx
• Aerobic exercise might play a beneficial role in decreasing the erythrocytic mass and in reducing CMS symptoms
• Exercise has to be performed with care due to the development of severe PH
• Reduction of Hb concentration is consequence of improved oxygenation due to training & increased exercise-related hemolysis
CMS - therapy

- Respiratory stimulants
  - Medroxy progesterone
  - Almitrine
- ACE Inhibitors
  - Enalaprilat
- Adrenergic blockers
- Safety and efficacy not established

Peripheral stimulant for ventilation
1.5 mg/kg/day
Decrease in Hct, CMS symptoms

Increased renal blood flow, oxygen availability, suppressing EPO, direct antagonism also
Reduced renal nerve activity
Reduced hypoxia mediated sympathetic stimulation

Mariia Rivera-Ch et al; Respirol Physiol Neurobiol 2007;158(2-3):251-65
CMS - therapy

• **Acetazolamide**
  – decreased serum erythropoietin
  – decreased hematocrit
  – decreased serum soluble transferrin receptors
  – increased arterial pO2
  – reduced the number of apnea–hypopnea episodes and pulmonary vascular resistance

• Prolonged treatment with 250 mg acetazolamide (6 months) is well tolerated and efficient for CMS

*Marina Rivera-Ch et al; Respirol Physiol Neurobiol 2007
Richalet et al, Am J Respir Crit Care Med, 2008*
<table>
<thead>
<tr>
<th>Location</th>
<th>Altitude</th>
<th>N of cases</th>
<th>Disease</th>
<th>TX</th>
<th>Target</th>
<th>Outcome</th>
<th>Level of evidence</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>3008-4888</td>
<td>13</td>
<td>CMS</td>
<td>Isovolemic hemonilution</td>
<td>Decrease Hct</td>
<td>Improved signs and symptoms</td>
<td>NR controlled single group</td>
<td>Wu, 1979</td>
</tr>
<tr>
<td>USA</td>
<td>3100</td>
<td>5</td>
<td>CMS</td>
<td>Medroxy-progesterone</td>
<td>Improve oxygenation, decrease Hct</td>
<td>Decreased Hct</td>
<td>P-D double-blind crossover trial</td>
<td>Kryeger et al., 1978b</td>
</tr>
<tr>
<td>China</td>
<td>3300</td>
<td>129</td>
<td>CMS</td>
<td>Rhodiola, a Tibetan herb</td>
<td>Decrease erythrocyte deformability and lipid peroxidation</td>
<td>Improved signs and symptoms</td>
<td>P-D double-blind controlled R-trial</td>
<td>Xi et al., 2000</td>
</tr>
<tr>
<td>Bolivia</td>
<td>3600</td>
<td>31</td>
<td>CMS and HAPH</td>
<td>Nifedipine</td>
<td>Decrease HAPH (D.E.)</td>
<td>Decrease &gt;20% in Ppa in 2/3 of the subjects</td>
<td>NR case-control series</td>
<td>Antezana et al., 1998</td>
</tr>
<tr>
<td>Bolivia</td>
<td>3600</td>
<td>40</td>
<td>CMS</td>
<td>Almitrine</td>
<td>Increase ventilation, decrease Hct</td>
<td>Increased PaO₂, decreased PaCO₂</td>
<td>P-D double-blind controlled R-trial</td>
<td>Villena et al., 1985</td>
</tr>
<tr>
<td>Bolivia</td>
<td>3600</td>
<td>8</td>
<td>CMS</td>
<td>Isovolemic hemonilution</td>
<td>Increase C.O. and ventilation, decrease Hct, decrease HAPH (H.C.)</td>
<td>Decreased VE/Q m, improved PaO₂</td>
<td>NR controlled single group</td>
<td>Manier et al., 1988</td>
</tr>
<tr>
<td>Location</td>
<td>Altitude</td>
<td>N of cases</td>
<td>Disease</td>
<td>TX</td>
<td>Target</td>
<td>Outcome</td>
<td>Level of evidence</td>
<td>Ref.</td>
</tr>
<tr>
<td>----------</td>
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<tr>
<td>China</td>
<td>3658</td>
<td>60</td>
<td>CMS</td>
<td>Medroxy-progesterone</td>
<td>Improve oxygenation, decrease Hct</td>
<td>Improved signs and symptoms</td>
<td>NR controlled single group</td>
<td>Zhou et al., 1983</td>
</tr>
<tr>
<td>Perú</td>
<td>3700</td>
<td>155</td>
<td>CMS</td>
<td>Bloodletting</td>
<td>Decrease Hct</td>
<td>Improved signs and symptoms</td>
<td>NR controlled single group</td>
<td>Sedano et al., 1988b</td>
</tr>
<tr>
<td>Perú</td>
<td>3700</td>
<td>36</td>
<td>CMS</td>
<td>Isovolemic hemodilution</td>
<td>Decrease Hct</td>
<td>Improved signs and symptoms</td>
<td>NR controlled single group</td>
<td>Sedano and Zaravia, 1988</td>
</tr>
<tr>
<td>Perú</td>
<td>4430</td>
<td>1</td>
<td>CMS</td>
<td>Isovolemic hemodilution</td>
<td>Decrease Hct</td>
<td>Improved oxygen transport</td>
<td>NR prepost series</td>
<td>Winslow et al., 1985</td>
</tr>
<tr>
<td>Perú</td>
<td>4430</td>
<td>10</td>
<td>CMS</td>
<td>(O_2) supplementation and breathing technique</td>
<td>Improve oxygenation, decrease Hct</td>
<td>Improved signs and symptoms</td>
<td>NR case-control series</td>
<td>Bernardi et al., 2003</td>
</tr>
<tr>
<td>Perú</td>
<td>4430</td>
<td>10</td>
<td>CMS</td>
<td>Acetazolamide</td>
<td>Increase ventilation, decrease Hct</td>
<td>Increased (Sa_O_2), decreased Hct</td>
<td>P-D double-blind controlled R-trial</td>
<td>Richalet et al., 2004</td>
</tr>
</tbody>
</table>
HAPH

- Subset of CMS (PH and Cor pulmonale without polycythemia)
- Mean PAP > 30 mm Hg or Systolic PAP > 50 mmHg measured at the altitude of residence
- Right ventricular hypertrophy, heart failure, moderate hypoxemia
- Absence of excessive erythrocytosis

Léon-Velarde et al; High Alt Med Biol Vol 6, 2005
HAPH

- Reduction of NO production
- Vascular remodelling of pulmonary arterioles
  - endothelial dysfunction
  - smooth muscle proliferation
  - adventitial thickening
- Hypoxia associated smooth muscle proliferation in originally weakly muscularised arterioles and normally non-muscular pulmonary vessels

X-Q. Xu and Z-C. Jing; Eur Respir Rev 2009; 18: 111, 13–17
HAPH

- Non specific presentation
- Exertional dyspnea – m/c
- Signs related to right heart failure
- Echocardiography – screening tool
- Right heart catheterisation – gold standard

X-Q. Xu and Z-C. Jing; Eur Respir Rev 2009; 18: 111, 13–17
HAPH

• Ideal management for HAPH is migration to low altitude
• PDE 5 Inhibitors – relatively selective pulmonary vasodilatation with little systemic hypotension
• Endothelin antagonists
• Rho kinase inhibitor fasudil

Aibek E. Mirrakhimov, The Open Cardiovascular Medicine Journal, 2016
HAPH

• PDE 5 inhibitors – meta analysis

Bo Jin et al; Clin Drug Investig 2010 30 (4): 259-265
### Treatment group SBP

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment group SBP [mean (SD)]</th>
<th>Control group SBP [mean (SD)]</th>
<th>WMD (fixed) [95% CI]</th>
<th>Weight (%)</th>
<th>WMD (fixed) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghofrani et al.</td>
<td>120.00 (17.30)</td>
<td>120.00 (13.00)</td>
<td>12.98</td>
<td>0.00</td>
<td>-11.34, 11.34</td>
</tr>
<tr>
<td>Aldashev et al.</td>
<td>124.00 (17.00)</td>
<td>123.00 (13.00)</td>
<td>8.16</td>
<td>1.00</td>
<td>-13.30, 15.30</td>
</tr>
<tr>
<td>Cornolo et al.</td>
<td>136.80 (7.80)</td>
<td>135.30 (8.10)</td>
<td>20.60</td>
<td>1.50</td>
<td>-7.50, 10.50</td>
</tr>
<tr>
<td>Hsu et al.</td>
<td>126.00 (11.00)</td>
<td>129.00 (10.00)</td>
<td>19.65</td>
<td>-3.00</td>
<td>-12.21, 6.21</td>
</tr>
<tr>
<td>Bernheim et al.</td>
<td>128.00 (10.00)</td>
<td>137.00 (13.00)</td>
<td>14.53</td>
<td>-9.00</td>
<td>-19.72, 1.72</td>
</tr>
<tr>
<td>Reichenberger et al.</td>
<td>133.00 (59.90)</td>
<td>136.00 (41.20)</td>
<td>1.15</td>
<td>-3.00</td>
<td>-41.08, 35.08</td>
</tr>
<tr>
<td>Snyder et al.</td>
<td>103.00 (11.00)</td>
<td>106.00 (12.00)</td>
<td>22.94</td>
<td>-3.00</td>
<td>-11.53, 5.53</td>
</tr>
</tbody>
</table>

Total (95% CI): 76 [75]  
Test for heterogeneity: $\chi^2 = 2.60$, df = 6 (p = 0.86), $I^2 = 0\%$  
Test for overall effect: $Z = 1.07$ (p = 0.28)

### Treatment group HR

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment group HR [mean (SD)]</th>
<th>Control group HR [mean (SD)]</th>
<th>WMD (fixed) [95% CI]</th>
<th>Weight (%)</th>
<th>WMD (fixed) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghofrani et al.</td>
<td>84.00 (21.70)</td>
<td>83.50 (19.90)</td>
<td>4.23</td>
<td>0.50</td>
<td>-14.92, 15.92</td>
</tr>
<tr>
<td>Aldashev et al.</td>
<td>62.00 (9.00)</td>
<td>62.00 (8.00)</td>
<td>15.40</td>
<td>0.00</td>
<td>-8.08, 8.08</td>
</tr>
<tr>
<td>Ricart et al.</td>
<td>93.70 (14.00)</td>
<td>87.90 (13.70)</td>
<td>9.55</td>
<td>5.80</td>
<td>-4.46, 16.06</td>
</tr>
<tr>
<td>Richale et al.</td>
<td>76.50 (6.40)</td>
<td>81.30 (4.60)</td>
<td>25.28</td>
<td>4.80</td>
<td>-11.11, 15.11</td>
</tr>
<tr>
<td>Hsu et al.</td>
<td>73.00 (13.00)</td>
<td>68.00 (10.00)</td>
<td>9.73</td>
<td>5.00</td>
<td>-5.17, 15.17</td>
</tr>
<tr>
<td>Bernheim et al.</td>
<td>83.00 (13.00)</td>
<td>81.00 (11.00)</td>
<td>8.12</td>
<td>2.00</td>
<td>-9.13, 13.13</td>
</tr>
<tr>
<td>Faoro et al.</td>
<td>111.00 (52.40)</td>
<td>89.00 (15.00)</td>
<td>1.23</td>
<td>22.00</td>
<td>-6.55, 50.55</td>
</tr>
<tr>
<td>Reichenberger et al.</td>
<td>78.00 (15.00)</td>
<td>73.00 (15.00)</td>
<td>8.14</td>
<td>5.00</td>
<td>-6.11, 16.11</td>
</tr>
<tr>
<td>Snyder et al.</td>
<td>71.00 (10.00)</td>
<td>67.00 (10.00)</td>
<td>18.32</td>
<td>4.00</td>
<td>-3.41, 11.41</td>
</tr>
</tbody>
</table>

Total (95% CI): 104 [103]  
Test for heterogeneity: $\chi^2 = 7.92$, df = 8 (p = 0.44), $I^2 = 0\%$  
Test for overall effect: $Z = 0.88$ (p = 0.38)

---

Bo Jin et al; Clin Drug Investig 2010 30 (4): 259-265
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seheult RD et al, 2009, RCT 3800 m</td>
<td>8</td>
<td>Bosentan vs placebo 5 days before ascent and continued for 2 days at altitude</td>
<td>PASP increased in both the groups</td>
</tr>
<tr>
<td>Kozonazarov et al, 2012 3200–4000 m</td>
<td>15</td>
<td>sPAP before and 3 h after a single oral dose of bosentan (125 mg)</td>
<td>systolic PAP decreased from $46 \pm 1.9$ to $37 \pm 2.2$ mm Hg ($p &lt; 0.01$)</td>
</tr>
<tr>
<td>Kozonazarov et al, 2012 3200-3500 m, RCT</td>
<td>19</td>
<td>Fasudil or placebo IV in a dose of 1 mg·min$^{-1}$ for the following 30 min (total dose of fasudil 30 mg)</td>
<td>systolic $P_{AP}$ by decreased by $-10.37 \pm 0.97$ mmHg ($p&lt;0.001$) compared with placebo</td>
</tr>
</tbody>
</table>
HAPH

• No long-term data available on the management of HAPH
• All patients with HAPH should be advised to descend to a lower altitude
• Limitations of the data on pharmacological correction

Aibek E. Mirrakhimov, The Open Cardiovascular Medicine Journal, 2016
HIGH ALTITUDE ON PRE-EXISTING LUNG DISEASE
COPD

- Increased mortality and higher incidence of cor pulmonale among high altitude residents
- Impaired gas exchange with fall in PaO2 (difficult to predict the fall in paO2 in individuals)
- May not be symptomatic due to hypoxia due to partial acclimatization

AM Luks & Swenson, Eur Resp J 2007
COPD

• No studies in subjects with severe disease / resting hypercapnia or altitude above 3048 m
• Lower air density should improve airflow dynamics but effects in studies are variable
• At risk of HAPE and acute right heart failure if PH present

AM Luks & Swenson, Eur Resp J 2007
COPD

- Assess the need for supplemental O2 for patients with FEV1 < 1.5L
- Continue baseline medications and carry supply of rescue inhalers and prednisone for potential exacerbations
- Counsel patients with pre-existing PH against high-altitude travel
- Prophylaxis with nifedipine SR 20 mg bid if PH present
- Avoid travel till 2 wks after radiographic resolution in cases of spontaneous pneumothorax

AM Luks & Swenson, Eur Resp J 2007
Asthma

• Decreased allergen burden
• Exposure to cold air
• Variable effects of hypoxia and hypocapnia
• Reduced air density
• Variable response noted in different field studies

AM Luks & Swenson, Eur Resp J 2007
Asthma

- Mild intermittent or mild persistent disease may ascend to altitudes as high as 5000 m
- Caution in cases of more severe disease
- Continue baseline medications and carry peak flow meter and supply of rescue inhalers and prednisone for potential exacerbations
- Consider using balaclava or bandana over mouth to warm and humidify air

AM Luks & Swenson, Eur Resp J 2007
Pulmonary hypertension

• No systematic studies examining the outcomes in known PH
• Counsel patients about the risks, symptoms and signs of HAPE
• Administer supplemental oxygen for trips above 2000 m even in patients not on supplemental oxygen at baseline
• For patients not on pre-existing medical therapy, prophylaxis with nifedipine SR 20 mg BD

AM Luks & Swenson, Eur Resp J 2007
Pulmonary thromboembolic disease

- Prospective study of 20,257 hospital admissions

<table>
<thead>
<tr>
<th>Low altitude (n = 18565)</th>
<th>High altitude (n = 1692)</th>
<th>$p$</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>46</td>
<td>&lt; 0.001</td>
<td>30.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI: 17.06-51.67</td>
</tr>
</tbody>
</table>

- Long term stay at high altitudes is associated with a 30 times higher risk of spontaneous vascular thrombosis

*Anand et al, Natl Med J India, 2001*
Pulmonary thromboembolic disease

- Conflicting results in literature about the effects of hypoxia on platelet function and coagulation parameters
- Many case reports which documented arterial or venous thromboembolic events at high altitude occurred in people with underlying coagulopathy
- Most marked rise in thrombin-antithrombin complexes during hypobaric hypoxic exposure was seen in those with the factor V Leiden mutation or oral contraceptive use

Schreijer AJ et al, Lancet 2006
Pulmonary thromboembolic disease

- Continue any pre-existing anticoagulation regimen during high-altitude sojourn with close follow-up of INR before and after trip
- Do not initiate new anticoagulation prescription in patients not on a pre-existing regimen
- Discontinue oral contraceptives in females with pre-existing coagulopathy
- Avoid immobility and dehydration
OHS

• Risk of right ventricular decompensation
• Avoid high-altitude travel
• Administer supplemental oxygen for day- and night-time use
• Prophylaxis with ACZ as they are at high risk for AMS
• Use CPAP unit and make necessary adjustments in set pressure for machines lacking pressure compensation

AM Luks & Swenson, Eur Resp J 2007
OSA

- Obstructive apneas markedly decreased
- Related to changes in air density, increased respiratory drive and upper airway tone
- May have increase in central apneas
- CPAP machine and make necessary adjustments in set pressure for machines lacking pressure compensation
- Acetazolamide therapy for central apneas

*AM Luks & Swenson, Eur Resp J 2007*
ILD

• Alteration in the gas exchange
• Assess need for supplemental oxygen and administer during stay at high altitude if predicted Pa O₂ < 50–55 mmHg
• Screen for pre-existing PH and, if present administer supplemental oxygen and prophylax with nifedipine
Pneumothorax

• Bullae communicate with the airways to a greater extent than expected, allowing for pressure equalisation

• Patients with pneumothorax or recent chest surgery should wait 2–3 weeks after successful drainage of the pneumothorax prior to air travel

• With persistent pneumothorax or BPF, travel to altitude with chest tube or Heimlich valve in place

• Screening patients at high risk for SSP for the presence of occult pneumothorax with CXR / CT scan prior to travel

AM Luks & Swenson, Eur Resp J 2007
Take home message

• Prior h/o AHI - strong risk factor to develop AHI
• Descent - single best treatment for AHI
• Slow ascent < 500 m/day is preventive
• Acetazolamide – Rx of choice in AMS, CMS & sleep disordered breathing
• Oxygen therapy – Rx of choice for HAPE