Travelling safely to places at high altitude – Understanding and preventing altitude illness

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Background

Increasing numbers of people are travelling to places at high altitude each year. Altitude illness is common in places at high altitude and may be life-threatening. General practitioners (GPs) are best placed to provide evidence-based advice to keep travellers well informed of the possible risks they may encounter in places at high altitude.

Objectives

The aim of this article is to review knowledge on altitude illness in order to help GPs assist patients to travel safely to places at high altitude.

Discussion

Acclimatisation to high altitude is a complex process and when inadequate leads to the pathological changes of altitude illness, including high-altitude headache, cerebral oedema, pulmonary oedema and acute mountain sickness. Higher ascent, faster rate of ascent and a previous history of altitude illness increase the risk of altitude illness. Acetazolamide and other medications used to prevent altitude illness are discussed in detail, including the finding that inhaled budesonide may prevent altitude illness.

Physiology at altitude

High altitude is used in this article to mean altitudes higher than 2500 m at which a traveller sleeps; significant altitude illness is unlikely below this height. As altitude increases, barometric pressure decreases and, consequently, the amount of oxygen in each breath decreases (Figure 1). The decreased oxygen in inspired air in places at high altitude, hypobaric hypoxia, is the central causative factor for the development of altitude illness.

The body responds (acclimatisation) to low oxygen within minutes of the traveller arriving at a place of high altitude and this process continues for weeks. The important initial changes are:

- hyperventilation
- increased sympathetic tone causing increased heart rate, blood pressure and cardiac output
- vasoconstriction of the pulmonary vasculature, which in the extreme situation is responsible for high-altitude pulmonary oedema (HAPE)
- cerebral vasodilation caused by hypoxia, which can lead to cerebral oedema.

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Later changes include:6
• increased erythropoietin secretion,
  increased haemoglobin production
  within three days and diuresis, causing
  increased haematocrit
• decreased muscle mass
• increased vascularity.
Individual and genetic variances exist in this
acclimatisation response,7 and inadequate
responses lead to the pathological changes
of altitude illness. Although the exact
pathogenesis remains unclear, increased
capillary leakage causing cerebral oedema
in acute mountain sickness (AMS) and
high-altitude cerebral oedema (HACE),8  and
similar pulmonary changes in HAPE,9  have
been consistently described. The likely
causes for this are hypoxia-induced blood
flow and pressure increases, and capillary
leakage mediated by chemicals such as
bradykinin, nitric oxide, arachidonic acid and
vascular endothelial growth factor.6

**Clinical conditions found at high altitude**

Altitude illness is a collection of different
conditions that occur at high altitude:
high-altitude headaches (HAH), AMS,
HACE, HAPE and other less common
conditions such as retinal haemorrhage,
high-altitude syncope, cerebral venous
thrombosis and cortical blindness. Altitude
illness varies in severity from being a
nuisance and interfering with a traveller’s
holiday (eg HAH and mild AMS), through
to more severe AMS, and possibly
fatal progression to HACE. HAPE, also
potentially fatal, can develop independently
of the other conditions in places at high
altitude.8 The main manifestations, clinical
information, course and management are
shown in Table 1.

**Risk of developing altitude illness**

Because there is a lack of standardisation
in altitude, ascent rate, outcome and
populations, the reported prevalence of
AMS varies in different studies. AMS has
been reported to affect 40% of visitors
at high-altitude ski resorts and vacation
destinations,10 and up to 80% of people
who rapidly reach moderate heights
(eg those who fly to La Paz).11 About half
of the trekkers who ascend to 5000 m will
develop AMS.12 There are no reports of
AMS in mainland Australia as the highest
peak, Mount Kosciuszko, is only 2228 m;
however, cases of AMS have been
reported in scientists who have flown to
the geographic south pole (2835 m).13

The most important risk factors
identified in the literature are how high
and how quickly one ascends, and whether
travellers previously developed altitude
illness.12,14–16 The risk of developing severe
AMS, HACE and HAPE is more than 12
times as likely in travellers with a previous
history of these conditions.17 AMS is
also related to exercise at altitude,18
and one small study suggests the oral
contraceptive pill may be associated with
an increased risk.13 The incidence of AMS
is unrelated to the level of physical fitness,
gender, previous altitude experience,
load carried, recent respiratory infections,
alcohol intake or cigarette smoking.15,16
Box 1 provides information to assist GPs
in assessing the risk of altitude illness in
travellers. This information is based on
guidelines developed by the Wilderness
Medical Society.19

**Prevention of altitude illness**

Slow ascent and allowing ample time
for acclimatisation are widely advocated
and shown in practice to effectively
prevent AMS,15 although the actual rate of
ascent recommended varies from 300 to
500 m a day at higher than 3000 m. One
meta-analysis reported AMS incidences
of 50–75% when ascending more than
500 m a day at higher than 4000 m.20 The
Wilderness Medical Society developed
the guideline that ascent should not be
higher than 500 m a day at altitudes of
more than 3000 m, and a day’s rest every
three to four days should be included.19
Spending two or more nights at places
of high altitude 30 days before ascending
has been found to be protective against
altitude illness.16 Additionally, resting in
the first 48 hours after arriving at places
of high altitude is advisable to prevent
altitude illness.18

**Medication used to prevent altitude illness**

Medications are a useful adjunct to prevent
altitude illness in travellers who are not
able to follow the recommendations for
prevention, or who may have had altitude
illness before (Table 2).

**Acetazolamide**

Acetazolamide, commonly prescribed
off-label in Australia to prevent AMS, is
the only drug currently shown to facilitate
acclimatisation.19 Although the exact
mechanism remains unclear, it inhibits
carbonic anhydrase, an enzyme found in
many tissues. Acetazolamide decreases

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**Figure 1.** Decreasing oxygen availability due to altitude7
the resorption of bicarbonate in the proximal renal tubule and binds carbon dioxide in the peripheral tissues, resulting in metabolic acidosis. By reducing the metabolic alkalosis of hypocapnia, which normally inhibits the central respiratory drive, hyperventilation can continue for longer. Acetazolamide also acts as a mild diuretic, decreasing oedema. An interesting side effect, not mentioned in Table 2, is decreased effervescence of carbonated beverages because of carbonic anhydrase inhibition in the saliva.

There is difficulty generalising from studies that use two different populations: climbers who are at places of high altitude and going higher, and general travellers who travel from sea level to lesser heights. However, a meta-analysis of 11 randomised control studies concluded that acetazolamide 250 mg daily was strongly associated with a decrease in AMS (combined odds ratio of 0.41; 95% confidence intervals: 0.26, 0.64).11

### Dexamethasone

Multiple trials have shown dexamethasone to be of benefit in preventing AMS.20–22 However, unlike acetazolamide, it only masks the symptoms of AMS by reducing inflammation, has significant side effects and, if stopped early, may lead to rebound AMS. The key role of dexamethasone is in the treatment of altitude illness, with prevention being reserved for those who cannot tolerate acetazolamide.

A more recent trial found that a study group using budesonide 200 µg inhaled twice a day had an AMS incidence of 24%, which was significantly different from the placebo group in which the incidence was 60% (P = 0.0006). Budesonide also had fewer side effects than dexamethasone.23 This is promising if future studies support these results.

### Nifedipine

Nifedipine 60 mg was shown to prevent HAPE,24 but not decrease AMS,25 and is currently the primary agent used for prevention and treatment for HAPE.

### Table 1. Common conditions occurring at altitude

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<tr>
<th>Condition</th>
<th>Clinical features</th>
<th>Course and management</th>
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<tr>
<td><strong>High-altitude headache (HAH)</strong></td>
<td>Most common symptom at high altitude&lt;br&gt;– 25% of travellers at 1920–2956 m31&lt;br&gt;– up to 90% of unacclimatised people who travel to 5000 m36&lt;br&gt;Thought to be due to activation of pain fibres in the trigeminal nerve in response to vasodilation, which in turn is caused by the brain's vulnerability to hypoxia, with some contribution by vascular mediators such as arachidonic acid8</td>
<td>HAH settles with oxygen after 10–15 minutes, and resolves with decrease in altitude and a non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen 600 mg three times a day35</td>
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<td><strong>Acute mountain sickness (AMS)</strong></td>
<td>Headache after a rise in altitude in the past four days, and at least one of the following symptoms: 10&lt;br&gt;– gastrointestinal upset (eg anorexia, nausea, vomiting)&lt;br&gt;– fatigue or weakness&lt;br&gt;– dizziness or light-headedness&lt;br&gt;– difficulty sleeping</td>
<td>Presents within six to 36 hours of high-altitude exposure, is usually benign and commonly resolves in two to four days with simple rest and ceasing further rise in altitude&lt;br&gt;Severe AMS is best treated with oxygen and medical care, including dexamethasone, otherwise progression to HACE is possible</td>
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<td><strong>High-altitude cerebral oedema (HACE)</strong></td>
<td>Rapidly progressing, life-threatening marked elevation of intracranial pressure and cerebral oedema&lt;br&gt;Considered a progression from severe AMS, and is usually preceded by a further decrease in oxygenation in a person with severe AMS&lt;br&gt;– patients with AMS advised not to continue to ascend until symptoms have settled19</td>
<td>Usually develops later than AMS, 24–36 hours after arrival at a place of high altitude.&lt;br&gt;Rare in travellers at altitudes &lt;3500 m,&lt;br&gt;Affects 0.5–1% of travellers at altitudes &gt;3500 m8,17&lt;br&gt;Characterised by symptoms of severe AMS and cerebral symptoms, signs of impaired mental state, and the cardinal symptom and signs of ataxia&lt;br&gt;Rapidly leads to coma and death if untreated&lt;br&gt;– medical emergency requiring immediate reduction in altitude (300 m or more), oxygen and intravenous dexamethasone</td>
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<td><strong>High-altitude pulmonary oedema (HAPE)</strong></td>
<td>Non-cardiogenic form of pulmonary oedema&lt;br&gt;Occurs 0.5–4% of predisposed previously healthy individuals who ascend higher than 3000 m17&lt;br&gt;People with HAPE report dyspnoea, cough, decreased exercise tolerance, or chest tightness, and exhibit signs of pulmonary oedema: pulmonary crepitations, tachypnoea, tachycardia or cyanosis</td>
<td>Usually commences two to four days after arrival at a place of high altitude, Can develop independently of AMS&lt;br&gt;Accounts for most of the deaths related to altitude illness88&lt;br&gt;Urgent treatment by trained medical staff requires rapid descent of about 1000 m, oxygen, and nifedipine with adjunctive drugs</td>
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(Table 2). Nifedipine works by inhibiting the hypoxic pulmonary vasoconstriction, thus preventing or relieving pulmonary oedema.

**Other medications**

Sumatriptan and gabapentin have single studies to support effectiveness, but further research needs to be conducted before these medications can be recommended as prophylaxis for AMS. The use of phosphodiesterase inhibitors (e.g. tadalafil, sildenafil) as adjuncts to prevent and treat HAPE remains debatable. In a systematic review by Dumont et al, there was no evidence that codeine, aspirin, theophylline, spironolactone and antidiuretic hormone reduced the incidence of altitude illness.

**Natural remedies**

Gingko biloba was claimed to have some benefits in preventing AMS; however, the research is inconsistent and conflicting on the association between gingko biloba and AMS. Consequently, it is not advisable to recommend gingko biloba to prevent AMS. Some have suggested cocoa tea, offered at hotels in Cusco, as a prevention against AMS; however, there are currently no systematic studies to support these claims.

**Fitness to travel to high altitude**

With no direct literature to consult, and individual variation and comorbidities, it is difficult to advise about the safety of travel to places at high altitude for people with pre-existing conditions. Generally, people with stable heart conditions, epilepsy and diabetes can safely travel up to 3000 m. Contraindications for travel to places at high altitude include severe chronic obstructive airways disease (COAD), unstable asthma, severe ischaemic heart disease, severe or uncontrolled heart failure, pulmonary hypertension and complicated pregnancy.

**Box 1. Travellers at risk of altitude illness**

Anyone ascending to 2800 m in one day
Anyone with prior history of acute mountain sickness ascending higher than 2800 m
Anyone ascending higher than 500 m/day at altitudes higher than 3000 m
Anyone with a prior history of severe acute mountain sickness, or high-altitude cerebral oedema or pulmonary oedema

**Table 2. Medications for prevention of altitude illness**

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<tr>
<th>Indication</th>
<th>Medication</th>
<th>Side effects or precautions</th>
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<tr>
<td>HAH</td>
<td>Ibuprofen 600 mg tds*</td>
<td>Fluid retention, hypertension, gastro-oesophageal irritation</td>
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<tr>
<td>AMS</td>
<td>Acetazolamide 125 mg bd</td>
<td>Paraesthesia (up to 45%), polyuria (2–5%), rash (3%) and dysgeusia (similar to placebo)11</td>
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<tr>
<td></td>
<td>Paediatric dose: 2.5 mg/kg every 12 hours‡</td>
<td>Contraindications include allergies or previous anaphylactic reactions to sulphur drugs,§ pregnancy, significant renal</td>
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<tr>
<td>HACE</td>
<td>Dexamethasone 2 mg every six hours or 4 mg every 12 hours†</td>
<td>Insomnia, unmasking of diabetes, mood disorder and peptic ulceration with possible gastrointestinal bleeding Avoid long-term use (&gt;2 weeks) because of Cushingoid’s effects and potential suppression of the adrenal glands with possible crisis if the drug is stopped suddenly</td>
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<tr>
<td>HAPE</td>
<td>Nifedipine, sustained release 30 mg every 12 hours or 20 mg every eight hours</td>
<td>Headache, swollen ankles and constipation (AMS-like symptoms) Many significant interactions, especially with drugs that are metabolised via the cytochrome P450 3A4 pathway</td>
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*Also for treatment, including the headache in AMS15
†For children old enough to travel to altitude, refer to section on fitness to travel
‡Not be used for prophylaxis in children
§Risk of cross-sensitivity is low in people with other sulphur allergies (up to 10%), so a supervised trial could be considered prior to travelling29
∥Estimated glomerular filtration rate <10 mL/min/1.73 m²
AMS, acute mountain sickness; bd, twice a day; HACE, high-altitude cerebral oedema; HAH, high-altitude headache; HAPE, high-altitude pulmonary oedema; tds, three times a day
delay after an uncomplicated dive, and at least a week after recompression therapy.32

Women with uncomplicated pregnancies can safely travel up to 2500 m and, similarly to air travel, should do so before 36 weeks’ gestation. Older people without any of the above-mentioned comorbidities have no increased risk of altitude illness. There is minimal information about the incidence of altitude illness in children. One study suggests a higher incidence;33 however, most authorities agree that the incidence of altitude illness is similar to that in adults.34 Diagnosing altitude illness in children is more difficult, and the best advice would be to travel to altitude with children who can adequately communicate symptoms they are experiencing.

Conclusion

As clinicians, we are involved with the care of people who are increasingly entering the challenging environment of high altitude. This article provides scientific information for clinicians to assess the risk and provide information and interventions to prevent altitude illness as part of our role to facilitate a safe journey for our patients.

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Competing interest and funding: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

References


