The major health implications of ascent to high altitude

2: Clinical aspects of the exposure to chronic hypoxia

Air Commodore Bruce H Short, RFD, MB BS, FRACP, FCCP, FACP

Acute mountain sickness (AMS)

In 1913, Ravenhill first described AMS, referring to it by the Bolivian name *puna*.[1] In 1982, Dickinson described two broad syndromes: the first is the benign simple acute mountain sickness and the second is the more serious malignant form of mountain sickness.[2] The malignant form is further divided into the pulmonary syndrome and the cerebral syndrome. In recent times the terms "high altitude pulmonary oedema" (HAPE) and "high altitude cerebral oedema" (HACE) have been applied to these two types of malignant AMS.

Dickinson has emphasised the continuity between benign and malignant AMS (ie, HAPE or HACE may readily follow benign AMS) and the coexistence of both pulmonary and cerebral presentations in the one individual.

AMS must be distinguished from the entirely different diseases of subacute mountain sickness and chronic mountain sickness (Monge's disease).

Simple benign AMS requires no specific therapy and any treatment that is needed may be administered at altitude, but both forms of malignant AMS are potentially life threatening and descent is the mandatory therapeutic measure. Heath et al stress that oedema is not the sole pathophysiology in HAPE and HACE: pulmonary and cerebral thromboses with haemorrhages are frequently identified.[3]

Air Commodore Bruce Short is the Assistant Surgeon General ADF (Air Force) and the Consultant in General Medicine to the Surgeon General ADF. He is in private practice as a specialist general physician in Sydney. For recreation he has trekked into the mountain ranges of Nepal, Sikkim, Bhutan, Peru and Bolivia.

Synopsis

- Acute mountain sickness (AMS) is classified as benign or malignant.
- AMS can be avoided by limiting ascent to 300 m per day, with a rest day after every third day of ascent, and by following the maxim "climb high, but sleep low".
- Simple benign AMS (typically headache with disturbance of sleep and appetite) requires no specific therapy and can be managed at altitude.
- Acetazolamide 250 mg twice daily or 500 mg slow release preparation once daily can prevent AMS and aid acclimatisation to altitude. Dexamethasone 4 mg every six hours is equally effective in preventing AMS but does not aid acclimatisation.
- Malignant AMS has two forms: high altitude pulmonary oedema (HAPE) and high altitude cerebral oedema (HACE).
- Symptoms suggestive of either or both HAPE and HACE demand immediate escorted descent to an altitude lower than where symptoms began.

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Benign AMS

Benign AMS is a self-limiting condition affecting healthy people following their rapid ascent to altitude and is due to hypobaric hypoxia. Symptoms appear from 6 to 12 hours after ascent, but occasionally as late as 96 hours, peak between 48 and 72 hours, abate usually by the fifth day and are not recurrent at that altitude. Altitude exposure of 1–2 hours by tourists is associated with a negligible incidence of AMS. Both the rapidity of ascent and the absolute altitude, particularly the altitude during sleeping, dictate symptom onset. Symptom duration also correlates with the altitude during sleeping.

A few individuals experience benign AMS at altitudes as low as 2500 m. In the Mount Everest region, some 50% of trekkers who walk above 4000 m over five or more days develop AMS.[4]

Many of the contemporary clinical descriptions of benign

AMS followed the study of Indian military forces by Singh.[5] During the 1960s, the Indian Armed Forces documented the military, medical and logistical problems of the air and road transportation of large numbers of unacclimatised personnel to high altitude. It was noted that the symptoms were more severe in those moved by air rather than road. The acclimatisation protocols used by the IAF were as follows:[5]

- Rest for seven days at 8000 feet acclimatised for altitudes between 8000 and 11 000 feet (2400–3300 m).
- Rest for seven days at 11 000 feet acclimatised for altitudes between 11 000 and 14 000 feet (3300–4200 m)
- Rest for seven days at 14 000 feet acclimatised for altitudes between 14 000 and 18 000 feet (4200–5400 m).

There is no clinical test available to assess which individual will develop AMS, but the presence of extreme hyperventilatory dizziness and a hypersensitive gag reflex has been suggested to correlate with an increased susceptibility to benign AMS.[6] There is no sex difference in susceptibility and athletic fitness is no protection; indeed, fitter individuals may achieve altitude more rapidly and thereby precipitate symptomatic benign AMS. Thus the young are more likely than the older person to develop benign AMS. One study suggested obesity is a risk factor for developing benign AMS.[7]

Similarly, there are no reliable clinical signs useful in the diagnosis of benign AMS, and the clinical assessment is based on a constellation of symptoms. A diagnosis of benign AMS is tenable with the the finding of headache together with at least one other symptom in an individual recently arrived at altitude (Box). The typical sufferer is sleepless, eating poorly and complaining of headache. For investigators there exists a self report questionnaire developed at the Lake Louise Symposium in 1991 to attempt a standardisation of terms in AMS research.[8]

Signs are absent in mild benign AMS; however, evidence of fluid retention may be observed as periorbital and pedal oedema with decreased urine output. Localised pulmonary rales may be observed, but when associated with respiratory symptoms more correctly denote HAPE. Resting tachycardia, normotension and tachypnoea are associated with benign AMS.

The exact mechanism of benign AMS is unclear. The precipitant is hypobaric hypoxia and there is always a time lag before symptom onset. There is a uniform antidiuresis in benign AMS with a retention of sodium and water and consequent decreased urinary output. Plasma vasopressin levels, while increased in HAPE, are more the result rather than the cause of that malignant AMS, and are not increased in benign AMS.[9]

In man at altitude, a rise in levels of atrial natriuretic peptide (ANP) has been observed.[10] ANP is released from atrial myocytes, stimulated by atrial stretch following a rise in right atrial pressure secondary to hypoxic pulmonary artery vasoconstriction. ANP increases urinary sodium excretion and thereby fluid excretion. The asymptomatic human response to altitude is to exhibit a mild diuresis, rather than to retain fluid and thereby develop symptoms of AMS. Further studies have shown significant variability in plasma ANP levels in people with benign AMS, so the aetiology of benign AMS continues to remain speculative. Associated with the fluid retention seen in benign AMS there is also a mild cerebral oedema and this probably accounts for the cerebral symptoms.[11]

A Quechuan Indian cairn in the Peruvian Andes. The Quechuan Indians are acclimatised to living at altitudes above 3000 m. Rapid ascent above such altitudes will commonly result in acute mountain sickness.

Box Symptoms of benign acute mountain sickness

Headache (may be severe; typically throbbing, bitemporal or occipital; commonly worse during the night and on awakening; stooping or the Valsalva manoeuvre typically exacerbate the pain)

Fatigue	Dyspnoea*
Dry cough	Dizziness
Tinnitus	Anorexia
Nausea and vomiting	Irritability
Sleep disruption	Incoordination
Reduced urine output	

*Dyspnoea on exertion and sleep disruption are almost universal at high altitude and do not themselves indicate AMS. Dyspnoea at rest, with or without a dry cough more commonly signifies HAPE than AMS.

Background: Mount Salcantay, 6402 m, in the Peruvian Andes

Managing benign AMS

Prevention: This embraces both a graded ascent and pharmacological prophylaxis. Avoidance of smoking, alcohol, sedatives and overexertion assists the acclimatisation mechanism and thereby reduces the likelihood of benign AMS.

Present recommendations suggest that when ascending above 3000 m, the sleeping altitude should not exceed 300 m above the previous night's altitude, with a rest day every three days (or after 1000 m climbed). The golden dictum of *climb high, sleep low* emphasises the importance of a descent before sleeping to avoid all forms of AMS. In some parts of the world there is the increasing problem of mechanical transport assisted ascents, whereby the individual loses control of the ascent rate and may additionally suffer enforced sleeping at altitude. This has particular military significance with the widespread employment of helicopters for transporting troops to altitude.

Acetazolamide therapy is beneficial for use in rapid ascents during emergencies, including military deployments to altitude, for personnel with a known increased susceptibility to benign AMS, and perhaps for those with more marked symptomatic benign AMS.

Acetazolamide induces a metabolic acidosis which directly stimulates ventilation and thereby increases arterial partial pressure of oxygen. Additionally, the associated weak diuresis may help counter fluid retention. The recommended regimen is either 250 mg twice daily or 500 mg slow release preparation once daily commencing at least 24 hours before an ascent to greater than 2500 m. Therapy is continued until maximal ascent is attained or when acclimatisation is achieved.[12] The drug improves effort performance, reduces sleep disturbance and decreases periodic breathing.

Therapy with acetazolamide, a non-bacteriostatic sulphonamide, is commonly associated with side effects. These include polyuria, paraesthesiae in hands and feet, nausea and dysgeusia. Acetazolamide-induced dysgeusia is typified by carbonated beverages tasting flat due to the inhibition of the enzyme carbon anhydrase in the lingual papillae, so that carbon dioxide is not converted to the taste-sensing carbonic acid. The related diuretic drugs, benzolamide, which does not cross the blood–brain barrier, and methazolamide, with a longer half life, have fewer side effects than acetazolamide.

For those intolerant of the sulphur-containing acetazolamide, dexamethasone has also been used for prophylaxis of benign AMS, given in a dose of 4 mg every six hours.[13] This regimen has been shown to be as effective as acetazolamide. Unlike acetazolamide, dexamethasone does not aid acclimatisation, and consequently symptoms of AMS may reappear if dexamethasone is discontinued before the completion of the acclimatisation process.

One study demonstrated a reduction of the cerebral symptoms of benign AMS with the combined therapy of acetazolamide and dexamethasone, and this effect was greater than using acetazolamide alone.[14]

Treatment: Most cases of benign AMS will improve within 48 hours without intervention, and rest alone relieves most symptoms. The duration of rest should be from two to four days while acclimatisation proceeds. Further ascent in the presence of benign AMS is contraindicated; indeed, descent will be required if symptoms increase or fail to settle after 24 hours of rest and hydration.

Simple analgesia may be effective for the headache of benign AMS. For centuries lowlanders have been exhorted to chew coca leaves and drink coca tea by native highlanders in the Andes to ameliorate the effects of the *soroch,* with variable effectiveness.

Oxygen use, while often impractical for trekkers, can reduce symptoms (results are variable) but will temporarily inhibit the acclimatisation process. Voluntary hyperventilation may temporarily relieve symptoms by increasing arterial partial pressure of oxygen.

Acetazolamide has been shown to be as effective in treatment as in prophylaxis. One treatment study used a regimen of acetazolamide 250 mg every 8 hours with optimum benefit.[15] As yet there are no studies of the effect of acetazolamide in benign AMS in small children.

Dexamethasone, in the absence of contraindications, may be combined with acetazolamide to hasten symptom relief. In particular, the combination may be used adjunctively to assist the severely incapacitated patient during escorted descent.

The use of antiemetic medications is contraindicated, as their sedative effect may induce significant respiratory depression, particularly during sleep, thereby impeding the acclimatisation process and adding to the hypoxic burden.

The only definitive management for all forms of mountain sickness remains descent, at times to only a few hundred metres lower in altitude.

The presence of HAPE and/or HACE is an absolute indication for immediate escorted descent to an altitude lower than where the symptoms commenced.

High altitude pulmonary oedema (HAPE)

HAPE rarely occurs below 2500 m, but above this altitude it is the most common cause of death from altitude illness, accounting for up to 20 deaths annually worldwide in trekkers, climbers, skiers, and particularly mountaineers. About 10% of those making rapid ascents to 4500 m will develop HAPE.[16] Dr Charles Houston, a mountaineering doctor, first reported this noncardiac pulmonary oedema in 1960.[17]

Young athletic men and children are at increased risk of

HAPE. This risk is enhanced by individual susceptibility, cold exposure, strenuous exertion at altitude and recent respiratory tract infections. Interestingly, the increased pulmonary artery flow to the left lung seen with isolated absent right pulmonary artery and increased pulmonary artery pressure in the pulmonary hypertension syndromes are all associated with an increased susceptibility to HAPE.[18]

Studies from Leadville, Colorado, at 3100 m have shown that highlanders who reascend to altitude after spending time at lower altitudes can develop so-called "re-entry HAPE", sometimes with less than one-week exposure at lower altitudes. The susceptible individuals are often children.[19]

The onset of HAPE is sometimes abrupt, most commonly occurring at night, usually between the second and fourth day following rapid ascent. The sleeping altitude is important in precipitating symptoms. HAPE may be preceded by AMS or occur *de novo*.

In 1991 the International Hypoxia Symposium recommended a clinical definition of HAPE. The criteria consisted of:

- at least two symptoms occurring after recent ascent to altitude: dyspnoea at rest, cough (dry or productive, often with blood-staining), decreased exercise performance, and chest restriction;
- at least two signs, including rales and crackles in at least one lung field, central cyanosis, tachycardia and tachypnoea.[20]

Radiographic findings may show patchy infiltrates, either localised or distributed throughout both lung fields. There is no cardiomegaly and the hilar pulmonary vasculature is pronounced. Typically, clear areas of the lung are seen, especially at the apices and lung bases; Kerley B lines and effusions are rarely seen.

The pathophysiology of HAPE is not entirely clear. HAPE is characterised by hypoxia-induced pulmonary artery hypertension together with a normal pulmonary–capillary wedge pressure. The pulmonary oedema fluid is rich in protein, erythrocytes and macrophages. As a rule, those prone to HAPE have higher pulmonary artery pressures both at rest and in response to hypoxia, altitude and exercise than those who are resistant to HAPE.[21]

Presently no satisfactory animal model of HAPE exists and therefore no general mechanism has been elucidated. A theory devised by West et al suggested that disruption of the capillary junctions was the basis of human HAPE. Maximally exercising humans may achieve a pulmonary capillary wedge pressure of 40 mmHg at the lung bases, a level shown in rabbits to cause this capillary "stress failure".[22]

Scherrer et al noted that in subjects with HAPE, the selective pulmonary vasodilatation induced by the inhalation of nitric oxide (40 ppm) is associated with a diversion of pulmonary blood flow from oedematous regions to non-oedematous regions in the lung. This effect was not seen in subjects resistant to HAPE. For this study, Doppler echocardiographic measurements of pulmonary artery pressures and lung perfusion scintigraphy were performed on mountaineers at a high altitude research laboratory at 4559 m.[23] Scherrer et al hypothesised that excess hypoxic pulmonary vasoconstriction is an important mechanism of HAPE and that reversing this vasoconstriction is important in treating and preventing HAPE. Nevertheless, the common finding in other studies[24] of pulmonary capillary thrombi also suggests the possibility that thrombus-obstructed flow may be responsible for the increase in pulmonary artery pressure and may thereby cause regional differences in blood flow.

Treatment of HAPE

HAPE is almost entirely preventable by a cautious rate of ascent, particularly in those with a known predisposition. If HAPE is recognised promptly, descent will provide complete relief. The response to descent is rapid, and often seen with descent by as little as 500 m to 1000 m. Sufferers are often asymptomatic within 24 hours and may resume cautious reascent in two or three days.

As cold and exertion are known to raise pulmonary artery pressures and thereby exacerbate HAPE, applying warmth and minimising exertion are first-aid measures to be commenced in all suspected cases. Many sufferers are additionally dehydrated from either severe dyspnoea or vomiting and therefore benefit from fluids. Descent is mandatory in all but minor cases and the patient should be kept upright during the escorted descent. Sufferers should descend to below the altitude at which they were last free of any altitude-related symptoms.

At moderate altitudes, such as in ski resorts, patients may be treated with warmth, bed rest and oxygen at high flow rates (>6 L/min) sufficient to keep oxygen saturation above 90%. The beneficial response to oxygen is usually dramatic and seen within 0.5 to 2 hours, although it is not evident in all cases of HAPE. Treatment at maintained altitude demands regular monitoring to ensure patient improvement.

In the absence of oxygen and as an aid to assist descent, portable hyperbaric bags are available to temporarily simulate descent. Like other treatments, the bags are not a substitute for descent, but facilitate clinical stabilisation if descent is not immediately possible, such as during adverse weather conditions. There are two types available, the Gamow bag weighing (with foot pump) 6.5 kg, and the CERTEC bag, weighing (with hand pump) 4.8 kg, and both may be dropped by aircraft. Logistical problems exist with their use. The head of an orthopnoeic patient must be raised and a relay of personnel is required to provide regular pumping to ensure continuous bag pressure.

Pharmacological agents used in the treatment of HAPE should be regarded as secondary lines of treatment, given the excellent clinical responses to both descent and oxygen.

Nifedipine has been shown to lower pulmonary artery pressure and the alveolar arterial pressure gradient, preventing symptoms when given prophylactically to HAPE-susceptible people. HAPE was prevented in nine of ten susceptible subjects who began taking the drug on ascent (20 mg slow release nifedipine every eight hours), and who went on to four days of continued exercise at an altitude of 4590 m.[25]

Dexamethasone is often additionally administered since HAPE is often complicated with either HACE or AMS. The place of frusemide in the management of HAPE is controversial. Original work by Singh et al suggested a role in management,[24] but careful reviews have questioned the benefits of the high doses used in their study. Indeed, the major complication of systemic hypotension has occasionally been reported in association with only limited improvement in respiratory symptoms.

High altitude cerebral oedema

This condition is a progression of the cerebral symptoms of AMS, thus headache alone does not signify HACE. It is less frequent than the other high altitude syndromes, although it is frequently accompanied by some evidence of HAPE. Infrequently, it may commence *de novo* with severe headache, neck stiffness and drowsiness, followed rapidly by coma.

In Indian troops deployed by air transportation to 3500 m, the incidence of HACE was 1.25%, with an incidence of HAPE of 5.7% within the same group. The incidence of HACE rises above altitudes of 3500 m. and the mean altitude for the development of HACE is 4700 m. It is unusual below 2500 m.

The mean duration of altitude exposure for the development of HACE is five days, with cases reported as early as the first day at altitude. A history of HACE is found in 20% of sufferers.

In the setting of recent increase in altitude, the clinical criteria for HACE include:

- a change in mental status and/or ataxia in a person with AMS, or
- both a change in mental status and ataxia in a person without AMS.

The progression from AMS to HACE is usually gradual. Early warning signs of the development of HACE include an increasing lassitude, such as a member unable to keep up with the group, through to mild mental confusion, especially if associated with minor clumsiness and unsteadiness. Lethargy and increasing drowsiness precede an early onset coma. Truncal ataxia is especially prominent and hemiparesis, cranial nerve palsies, seizures and hallucinatory disorders have all been reported. The combination of severe headache, disturbed consciousness and ataxia appearing after recent altitude acquisition is clear evidence of HACE. Engorged retinal veins are commonly seen with exposure to altitude; however, papilloedema, when present, is a clear marker of HACE.

Computed tomography and post-mortem evidence discloses cerebral oedema and increased intracranial pressure as present in nearly all cases of HACE. Petechial haemorrhage, focal tissue destruction and spongiosis occur frequently.

Treatment of HACE

Untreated HACE is fatal. Early recognition, prompt escorted descent, and if available, high flow oxygen therapy are the basis of management. Prompt escorted descent may necessitate movement at night by torchlight, the patient carried on the back of local porters or on pack animals. Evacuation delay to the hours of first light may prove fatal at worst, or at best, transform a walking sufferer to a comatose state, possibly requiring stretcher evacuation with relays of four stretcher-bearers to effect the descent. In remote mountainous areas, descent by foot should not be delayed while awaiting the arrival of air transportation, which may suffer both from erratic service scheduling and adverse local flying conditions. Alternative landing zones at lower altitude may be prearranged for helicopter-assisted evacuations to permit the immediate escorted foot descent of the HACE sufferer.

Dexamethasone administered orally or parenterally in a dose of 4 mg every six hours is a suitable adjunct to immediate descent. If descent has to be delayed, the use of a portable hyperbaric chamber together with oxygen and dexamethasone is beneficial.

Frusemide is not indicated since any induced hypotension will exacerbate the ataxic gait. The data are presently unclear as to the place of acetazolamide in the treatment of HACE and thus it is currently not recommended.

At the hospital receiving facility, comatose patients should be treated as head-injured cases with intubation and hyperventilation. Most patients recover rapidly after descent, but cognitive impairment, weakness and ataxia may persist for many months.

Summary — preventing and managing altitude sickness

The adverse health outcomes associated with ascent to high altitude can be avoided by following a few basic rules. Ascent should be gradual, averaging no more than 300 m per day, punctuated by regular rest periods every 1000 m or third day. The appearance of any symptoms should suggest an altitude-related cause until otherwise proven. If the symptoms suggest AMS, the climber should rest and cease the ascent. If there is no improvement or if a deterioration ensues,

descend immediately to an altitude lower than where symptoms began. The use of acetazolamide both as prophylaxis and for treatment of significant AMS is now accepted. Abide at all time by the dictum of *climb high, sleep low*. Persons with a past history of altitude-related diseases should be especially careful to ascend slowly and to use, where indicated, pharmacological prophylaxis.

Symptoms suggestive of either or both HAPE and HACE demand immediate escorted descent to an altitude lower than where symptoms began.

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A history of courage

Book review: *Neville Howse — Australia's first Victoria Cross winner* by Michael Tyquin

($39.95 Oxford University Press, Melbourne, 1999. ISBN 0 19 551190 5)

NEVILLE HOWSE was not only the first Australian to win the VC, he remains the only Australian medical officer to win the award. He was decorated after his gallant rescue of a wounded soldier under shellfire at Vredefort on 24 July 1900 in the Boer War. Howse went on to serve in World War One, rising to the rank of Surgeon General, and subsequently had a distinguished career as a rural doctor and government minister.

Captain Michael Tyquin's biography of Howse fills a serious gap in the history of Australian military medicine. The book was launched in Canberra in November 1999, on the occasion of the Centenary Symposium of the Boer War, an international seminar hosted by the Australian War Memorial. Captain Tyquin is a professional historian and career soldier within the Royal Australian Army Medical Corps. He has particular interests in Australian heritage and military medical history and has previously published *Gallipoli: the medical war.*

Howse played a key role in the conception and development of Colonel A G Butler's *Official history of the Australian Medical Services in the Great War* and one sees in this new biography the story behind much of that official history.

Major General John Pearn

Surgeon General