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# Prevention and Treatment of High-Altitude Pulmonary Edema

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**Abstract** We distinguish two forms of high altitude illness, a cerebral form called acute mountain sickness and a pulmonary form called high-altitude pulmonary edema (HAPE). Individual susceptibility is the most important determinant for the occurrence of HAPE. The hallmark of HAPE is an excessively elevated pulmonary artery pressure (mean pressure 36-51 mm Hg), caused by an inhomogeneous hypoxic pulmonary vasoconstriction which leads to an elevated pulmonary capillary pressure and protein content as well as red blood cell-rich edema fluid. Furthermore, decreased fluid clearance from the alveoli may contribute to this noncardiogenic pulmonary edema. Immediate descent or supplemental oxygen and nifedipine or sildenafil are recommended until descent is possible. Susceptible individuals can prevent HAPE by slow ascent, average gain of altitude not exceeding 300 m/d above an altitude of 2500 m. If progressive high altitude acclimatization would not be possible, prophylaxis with nifedipine or tadalafil for long sojourns at high altitude or dexamethasone for a short stay of less then 5 days should be recommended. (Prog Cardiovasc Dis 2010;52:500-506)
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High-altitude pulmonary edema (HAPE) presents within 2 to 5 days after arrival at high altitude.[1-3] It is rarely observed below altitudes of 2500 to 3000 m and after 1 week of acclimatization at a particular altitude. Early symptoms of HAPE include exertion dyspnea, cough, and suddenly reduced exercise performance. As pulmonary edema progresses, orthopnea, breathlessness at rest, and gurgling in the chest develop, cough worsens and pink frothy sputum reveals overt pulmonary edema.[1-3] Râles are discrete at the beginning, typically located over the middle lung fields.[1-3] Chest radiographs and computed tomographic scans of early HAPE show a patchy, peripheral distribution of edema.[4] In advanced cases of HAPE observed at the altitude of 4559m arterial $P_{O_2}$ usually drops below 35 mm Hg. In the early stage of HAPE bronchoalveolar lavage (BAL) reveals a protein- and red blood cell–rich edema fluid without signs of inflammation,[5] whereas in a more advanced stage, proinflammatory mediators and granulocytes add to the initial changes.[3,6]

Hemodynamic measurements in HAPE indicate that the development of pulmonary hypertension within hours after rapid exposure to high altitude is a hallmark of this disease. Characteristically, mean pulmonary artery pressure in HAPE ranges between 36 and 51 mm Hg.[1,7-11] Using the arterial occlusion method,[11] which is likely to measure pressures in vessels close to 100 $\mu$m in diameter,[12] we demonstrated that the pulmonary capillary pressure is elevated in HAPE, being on average 22 mm Hg (range, 20-26 mm Hg).[11] An impaired nitric oxide production in the lungs is probably the leading underlying mechanism of elevated pulmonary artery pressure in these individuals[5,13,14]; BAL performed in HAPE-susceptible adults within a day after ascent to 4559 m revealed elevated red blood cell counts and serum-derived protein

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**Abbreviations and Acronyms**

**AMS** = Acute mountain sickness

**BAL** = bronchoalveolar lavage

**ENaC** = amiloride-sensitive Na-channels

**HAPE** = High-altitude pulmonary edema

concentration in BAL fluid, but the number of alveolar macrophages/$\mu$L and neutrophiles/$\mu$L, and the concentration of proinflammatory mediators, interleukin-1, tumor necrosis factor $\alpha$, interleukin-8, thromboxane, prostaglandin $E_2$ and leukotriene B4 were not increased. Thus, HAPE in its early stage is a high-pressure-mediated permeability type of pulmonary edema.

In addition, it was found that hypoxia inhibits nasal epithelial Na-transport in both HAPE-resistant and susceptible mountaineers[15,16] and that, at low altitude, compared to those HAPE-resistant, HAPE-susceptible adults present with a lower activity of the amiloride-sensitive Na-channels (ENaC),[15-17] suggesting a possible contribution of alveolar epithelial cells ENaC to the pathophysiology of HAPE.

The current concepts for the prevention and treatment of HAPE are based on its pathophysiology and include progressive adaptation of the pulmonary circulation to the hypoxic environment (acclimatization), prevention and treatment of excessive hypoxic pulmonary vasoconstriction and improvement fluid clearance from the alveolar space (Fig 1).

## Prevention

### *Slow ascent*

Slow ascent is the major measure of prevention and is effective even in susceptible individuals. Indirect evidence came from the observation, that even subjects who developed HAPE more than once upon rapid ascent in the Alps successfully reached altitudes up to 7000 m when the average daily ascent rate above 2000 m does not

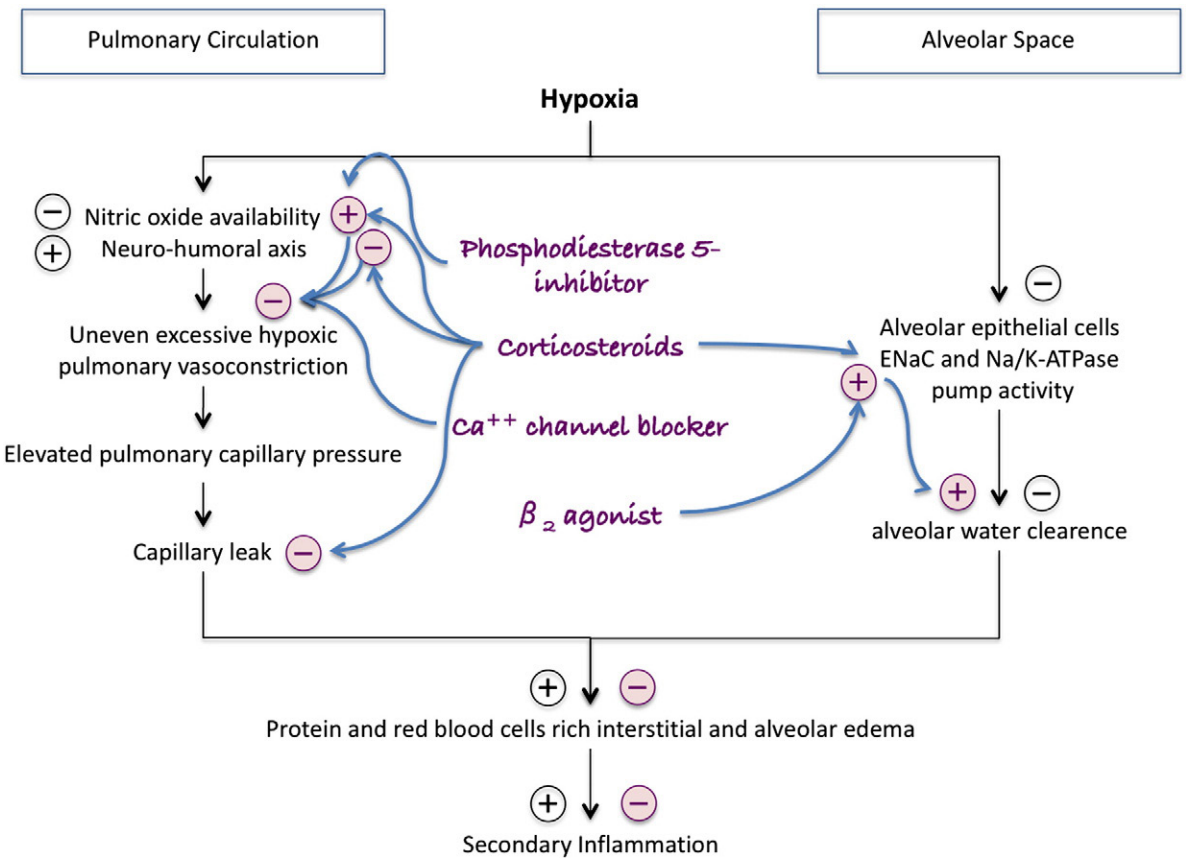


Fig 1. Action mechanisms of the different drugs used for prevention and treatment of high altitude pulmonary edema. Phosphodiesterase 5-inhibitors such as sildenafil and tadalafil increase nitric oxide availability in the pulmonary circulation leading to a decrease in pulmonary vascular tone; hence, pulmonary capillary pressure and fluid leakage in to the interstitial and alveolar space. Corticosteroids increase nitric oxide availability in the pulmonary circulation leading to a decrease in pulmonary vascular tone, decrease hypoxia associated neurohumoral activation and pulmonary capillary permeability, and enhance hypoxia-associated decrease in alveolar water clearance. $\beta_2$ agonists enhance alveolar water clearance by stimulating ENaC.

exceed 350 to 400 m/d.[18] The experience of the Indian Army that up to 15% of its soldiers, if airlifted to extreme altitudes, developed HAPE[19] but, if acclimatized during several weeks before the stay at extreme altitude, did not develop HAPE. However, after several weeks, some of these soldiers developed signs of right ventricular failure with tachypnea, tachycardia, jugular vein distention, enlargement of the liver and ascites, and on chest radiographs an enlargement of the heart and prominent vascular pedicules but no pulmonary infiltrates.[20] Echocardiography showed pericardial effusion, enlargement of the right ventricle and normal dimensions and ejection fraction of the left ventricle. Thus, this experience of the Indian army is highly suggestive for the persistence of pulmonary hypertension during stay at high altitude and for an acclimatization-associated rapid remodeling of the pulmonary precapillary vessels within days after ascent to high altitude that protect the capillaries from exposure to high hydrostatic pressure or blood flow.[21] The observation that high altitude induced changes of the pulmonary vasculature and right heart are reversible upon moving to low altitude and that some high altitude residents when returning to high altitude develop HAPE,[22] are further arguments in favor of a rapid remodeling process of the pulmonary vessels in response to changes in ambient oxygen content. Thus mountaineers susceptible to HAPE should be advised to progressively acclimatize to high altitude with an ascent rate not to exceed 300 m per day. Moreover, people should not ascend further if they develop any symptoms of acute mountain sickness (AMS) or beginning HAPE (exertion dyspnea, cough, and suddenly reduced exercise performance) and avoid vigorous exercise during the first days of exposure to altitudes above 3000 m, since exercise may enhance or cause pulmonary edema.[23,24] Furthermore, susceptibility to HAPE may be increased during and shortly after infection.[25]

### *Drug prevention*

Prevention of excessive rise in pulmonary artery pressure is the standard of care for the prevention of

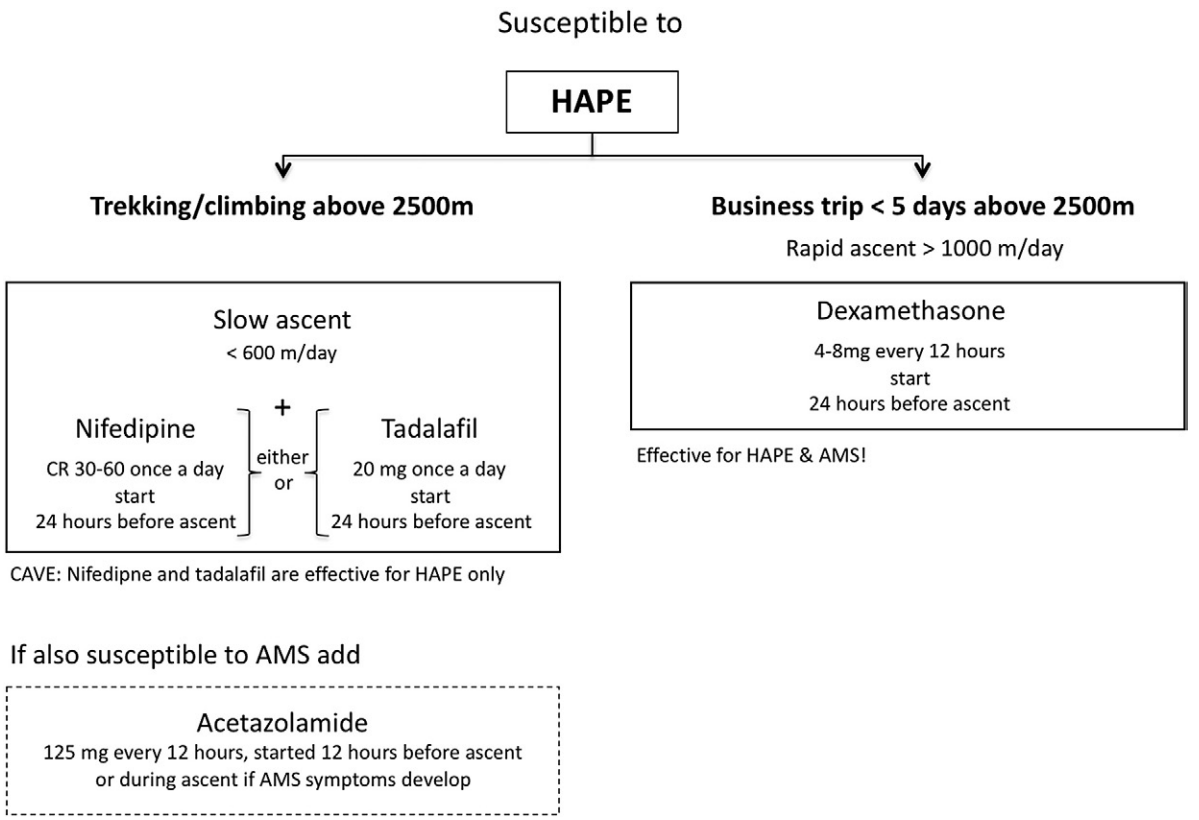


Fig 2. Algorithms for the prevention of HAPE: we suggest to differentiate between a short stay at an altitude above 2500 m (business trip) and mountaineering (trekking/climbing) at altitudes above 2500 m for more the 4 days. Dexamethasone prophylaxis is warranted for a business trip to a location at an altitude above 2500 m because acclimatization is not possible following time constrain and if not contraindicated dexamethasone represent an effective and safe treatment option if taken for a short period of time. In all other situations slow ascent and the use of a pulmonary vasodilator are recommended because it has been proven to be effective and safe. CAVE, neither nifedipine nor tadalafil prevent AMS; therefore, the acetazolamide may be added as a prophylaxis or treatment for mild AMS symptoms.

HAPE in individuals with a history of unquestionable HAPE when slow ascent is not possible (Fig 2). For almost 20 years, it has been known that 20 mg of the slow-release formulation of nifedipine taken every 8 hours starting 24 hours before ascent to 4559 m and continued until descent decreases the incidence of HAPE from 63% to 10%.[26] A few years ago, these results could be reproduced using 10 mg tadalafil bid, a phosphodiesterase-5 inhibitor.[27] The incidence of HAPE was 74% in the placebo and 10% in the tadalafil group. However, it should be emphasized that neither nifedipine not tadalafil are effective in preventing AMS,[27,28] and that in some susceptible individuals, phosphodiesterase-5 inhibitors may possibly exacerbate AMS by an unknown mechanism.[29] No other significant side effects were reported for either drug.[26,27] Thus, pulmonary vasodilators should be given for HAPE prevention only, starting with the ascent and ending when acclimatization is completed, a time point being not defined yet for HAPE-susceptible individuals. If, despite pulmonary vasodilator prophylaxis, AMS is present, additional acclimatization or AMS prophylaxis with acetazolamide is recommended.[30-32] Whether acetazolamide prophylaxis prevents HAPE is unclear yet. In acute hypoxia acetazolamide inhibited hypoxic pulmonary vasoconstriction in animals[33-35] and non-HAPE susceptible persons.[36] However, acetazolamide failed to decrease pulmonary artery pressure in a double-blind placebo-controlled study performed in trekkers traveling in Nepal from 4300 to 5000 m.[37]

The use of the $\beta_2$-agonist salmeterol has been suggested as an alternative for the prophylaxis of HAPE in susceptible adults. Salmeterol inhaled at the high-dose of 125 $\mu$g bid during rapid ascent and stay for two nights at 4559 m decreased the incidence of HAPE from 74% to 33%,[17] thus slightly less effective than a pulmonary vasodilator, suggesting that preventing excessive increase in pulmonary artery pressure is possibly more effective. Therefore, the routine use of salmeterol for HAPE prophylaxis cannot be recommended until a clinical trial proves equivalence between salmeterol and a pulmonary vasodilator.

Recently, we have shown that dexamethasone prophylaxis, which has been proven effective for the prevention and treatment of AMS,[38,39] taken 1 day prior to ascent and continued during ascent and stay at 4559 m, prevents HAPE in susceptible adults.[27] Dexamethasone prevented pulmonary artery pressure to increase, its effect being comparable to that of tadalafil. This effect can tentatively be explained by a dexamethasone mediated stimulation of cGMP production in hypoxia,[40] an increase in the activity of nitric oxide synthase,[41] and a favorable modulation of the increased sympathetic activity in these individuals.[42-44] However, other mechanisms may also account for the effect of dexamethasone such as an improvement of the alveolar transepithelial Na and water transport,[45] tightening of the pulmonary capillary endothelium[46] possibly by inhibition of hypoxia-induced inflammation,[47] and improvement of surfactant production.[48,49] Recently, at the Hypoxia Symposium in Lake Louise 2009, we presented the result of a follow-up study in HAPE-susceptible persons testing the effect of dexamethasone early vs late prophylaxis. We found that dexamethasone taken 1 day prior to ascent (early) prevented HAPE but not if taken after the first night at 4559 m (late). These results confirm that dexamethasone taken 1 day prior to ascent is effective for HAPE prophylaxis, but not if started after the first night at high altitude. This is in line with previous case reports indicating that HAPE may develop despite treatment of AMS with dexamethasone.[50,51] In both studies, during the observation period of 3 and 5 days respectively, AMS score was significantly lower in the dexamethasone than in the placebo group, the blood glucose levels and systemic blood pressure being not different between groups.[27] Thus, for individuals susceptible to HAPE who plan to be exposed to an altitude above 3000 m for less then 5 days, in the absence of contraindications, a prophylaxis with dexamethasone appears highly attractive and safe, particularly if the use of a calcium antagonist or a phosphodiesterase 5 inhibitor is contraindicated.[52] However, before general recommendation can be given, particularly for those mountaineers planning a prolonged exposure to high altitude, further studies are needed to determinate the minimal effective dose and its safety profile in the setting of trek or expedition.

## Treatment

Immediate improvement of oxygenation either by supplemental oxygen, hyperbaric treatment,[53,54] or by rapid descent is the treatment of choice for HAPE. For the mountaineer in a remote area without medical care, descent has first priority, whereas the tourist with HAPE visiting a high-altitude plateau in the Andes, Himalayas, or Rocky Mountains may stay at altitude if medical facilities are available. If unable to reach lower altitude for a few days, treatment with nifedipine or sildenafil is strongly recommended (Fig 3). In mountaineers with HAPE at 4559 m, treatment with 20-mg slow-release nifedipine taken every 6 hours led to a persistent relief of symptoms, improvement of gas exchange, and radiographic appearance over an observational period of 34 hours.[55] In this study, nifedipine therapy was not associated with hypotension.

Today, there are only anecdotal reports[56] but not clinical trials on the use of sildenafil or other phosphodiesterase 5 inhibitors in the high-altitude setting, this despite strong evidence that in both normobaric[57,58] and

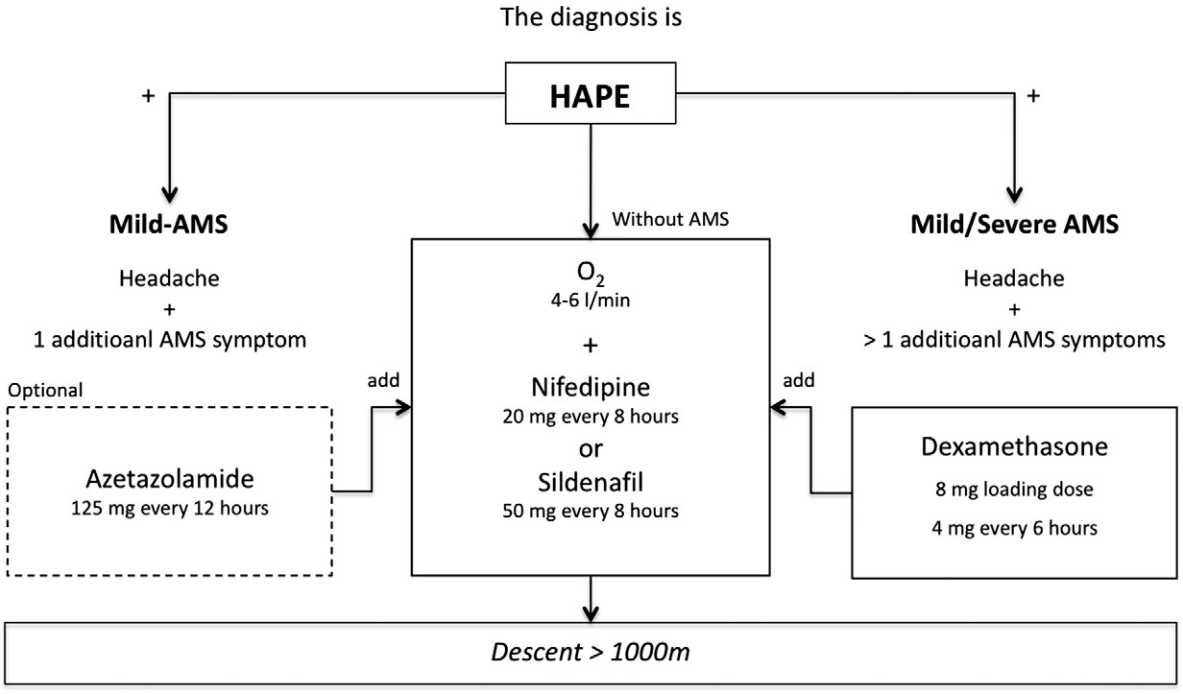


Fig 3. Algorithms for the treatment of HAPE: HAPE may present with or without AMS symptoms. The primary treatment of HAPE without AMS symptoms is oxygen and either nifedipine or sildenafil. This treatment restores exercise capacities to allow decent, which remains the only causative treatment of HAPE. If HAPE is associated with mild AMS, it is likely that improving arterial oxygenation AMS symptoms resolve spontaneously; therefore, the addition of acetazolamide in this situation is considered as optional. Conversely, if HAPE is associated with moderate to severe AMS, the coadministration of dexamethasone is strongly recommended.

hypobaric hypoxia[29,59,60] phosphodiesterase 5-inhibitors significantly decrease pulmonary artery pressure. Moreover, recently, it has been found that sildenafil enhances recovery from hypoxia-mediated endothelial cells leakiness.[61] The use of sildenafil, compared to nifedipine, is attractive because it is primarily a pulmonary and not a systemic vasodilator,[58,62] which significantly decreases the risk of a systemic hypotension. However, it has been reported that sildenafil more then nifedipine may exacerbate AMS.[27,29] In the setting of the high-altitude research laboratory Capanna Regina Margherita (4559 m), we treated successfully several patients with HAPE giving them 25 to 50 mg sildenafil every 8 hours and 8 mg dexamethasone bid. The coadministration of dexamethasone rapidly resolved AMS symptoms and may have contributed to tighten pulmonary capillaries and improve alveolar water clearance (Fig 1). In all patients, HAPE resolved 24 to 48 hours. None of them needed evacuation by helicopter.

When medical assistance is available, vasodilatory treatment is not absolutely necessary because with bed rest and supplemental oxygen for 24 to 48 hours, relief of symptoms can be achieved within hours, and complete clinical recovery within several days is possible. Whether the combined regimen of bed rest, supplemental oxygen, and nifedipine or a phosphodiesterase 5-inhibitor is superior to bed rest and oxygen alone has not been investigated yet. In adults with advanced HAPE, intermittent continuous positive end-expiratory airway pressure has been shown to improve $Sa_{O_2}$ by 10% to 20%[63-66]; however, one should be aware that if used at high altitude, it might cause high-altitude cerebral edema by increasing central venous pressure.[67]

## Statement of Conflict of Interest

The author declares that there are no conflicts of interest.

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