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High altitude pulmonary edema in mountain climbers

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ABSTRACT

Every year thousands of ski, trekking or climbing fans travel to the mountains where they stay at the altitude of more than 2500–3000 m above sea level or climb mountain peaks, often exceeding 7000–8000 m. High mountain climbers are at a serious risk from the effects of adverse environmental conditions prevailing at higher elevations. They may experience health problems resulting from hypotension, hypoxia or exposure to low temperatures; the severity of those conditions is largely dependent on elevation, time of exposure as well as the rate of ascent and descent. A disease which poses a direct threat to the lives of mountain climbers is high altitude pulmonary edema (HAPE). It is a non-cardiogenic pulmonary edema which typically occurs in rapidly climbing unacclimatized lowlanders usually within 2–4 days of ascent above 2500–3000 m. It is the most common cause of death resulting from the exposure to high altitude. The risk of HAPE rises with increased altitude and faster ascent. HAPE incidence ranges from an estimated 0.01% to 15.5%. Climbers with a previous history of HAPE, who ascent rapidly above 4500 m have a 60% chance of illness recurrence. The aim of this article was to present the relevant details concerning epidemiology, pathophysiology, clinical symptoms, prevention, and treatment of high altitude pulmonary edema among climbers in the mountain environment.

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1. Introduction

More than 140 million people worldwide, mainly from Asia, North, Central and South America live in regions lying 2400 m above sea level, i.e. in high-mountain areas (Bhagi et al., 2014). A substantial number of people live permanently in low-land areas but work at higher altitudes, e.g. in astronomical observatories (Hawaii, 4200 m) or in mines (The Andes, 4500 m) (Richalet, 1995). Hostilities along the Indian and Pakistani border have been conducted for many years at an altitude of 5000 m above sea level (Singh and Roy, 1969) and the international forces military operation in Afghanistan is often carried out at the elevation exceeding 3000 m above sea level (Korzeniewski, 2008). Every year thousands of ski, trekking or climbing fans travel to the mountains where they go skiing at an altitude of more than 2500–3000 m, or climb summits exceeding 7000–8000 m. All of these people are, either temporarily or permanently, exposed to environmental conditions characterized by low air pressure, low oxygen concentration, low ambient temperature and increased solar radiation. The lack of basic knowledge on the risk factors prevailing in high-mountain areas may have disastrous consequences which can be potentially health- or life-threatening. High mountain climbers are at a serious risk from the effects of adverse environmental conditions prevailing at higher elevations. The illnesses they experience may be classified into four categories: diseases resulting from hypotension and hypoxia, diseases resulting from the exposure to low temperatures, diseases associated with the effects of solar radiation, exacerbation of previously asymptomatic medical conditions. Illnesses associated with hypotension and hypoxia form a category of diseases which are particularly dangerous and potentially deadly for mountain climbers. They cover a wide range of medical conditions from mild to life-threatening ones (Korzeniewski, 2014). The severity of these illnesses is largely dependent on elevation (the higher the altitude, the lower the air pressure and oxygen concentration), time of exposure to high mountain conditions (hours, days, weeks) as well as the rate of ascent and descent. Additionally, the intensity of exertion, psychophysical condition of a climber, age as well as co-existing health problems contribute to the development of pathological

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changes. Acute mountain sickness (AMS), a condition associated with the effects of low air pressure and low oxygen concentration, is the most common health problem in mountain climbers. AMS presents as a collection of different symptoms (headache, nausea, vomiting, general malaise, fatigue) and typically affects unacclimatized lowlanders who have quickly changed elevation. It needs to be pointed out that high fitness level does not prevent the onset of AMS (Advisory Committe Statement, 2007). The symptoms usually appear 3–24 h after ascent above 1800 m in less than 24 h and subside 3–7 days following the arrival at higher altitudes. The symptoms may reappear (even after undergoing acclimatization) any time the climber quickly changes the elevation. 10–20% of people who have climbed to 1800–2400 m in less than 24 h develop the symptoms of AMS. The majority of climbers who ascended to a height of 3600–4300 m suffer mild symptoms of AMS, 50% experience moderate symptoms while 12–18% may develop a severe form of AMS. A rapid ascent to the altitude of over 5300 m produces serious pathological symptoms in the majority of climbers. The disease can affect both those who climbed from low to high altitude within a short period of time, as well as those who, being at high altitude, climbed even higher. Thus, the cause of AMS is not high altitude itself, but rather rapid changes in elevation within a short period of time (Korzeniewski, 2014). In the great majority of cases AMS is a minor affliction resolving in a few days. However in a small proportion of people (2–3%) going to high altitude there develops the potentially lethal condition of high altitude cerebral or pulmonary edema or a mixture of these two (Milledge, 2006).

High altitude pulmonary edema (HAPE) is yet another disease resulting from hypotension and hypoxia. HAPE is a life-threatening non-cardiogenic pulmonary edema which typically occurs in lowlanders who ascend rapidly to altitudes above 2500–3000 m (Paralikar, 2012). It is the most common cause of death resulting from the exposure to high altitude (Pennardt, 2013). High altitude pulmonary edema manifests in two forms. It can occur in mountaineers returning from a sojourn at a low altitude, also known as "reentry" HAPE, and in rapidly climbing unacclimatized lowlanders. It usually occurs within 2–4 days of ascent above 2500–3000 m (Hackett and Roach, 2001). The illness rarely occurs after more than 4 or 5 days at the same altitude, most likely because of remodeling and adaptation (West and Mathieu-Costello, 1999).

The aim of this article was to present the relevant details concerning epidemiology, pathophysiology, clinical symptoms, prevention, and treatment of HAPE in mountain climbers.

2. Epidemiology

The prevalence of high altitude pulmonary edema depends on the degree of mountaineers' susceptibility, the rate of ascent, and the final altitude (Bärtsch et al., 2005). In 1970s, the incidence of HAPE was reported in 3% of adults trekking in Peru at 3782 m (Hultgren and Marticorena, 1978). Sophocles (1986) estimated the incidence of HAPE in visitors to ski resorts in the Rocky Mountains, Colorado (2500 m) to be 0.01–0.1%. His study also reported that men are more susceptible to HAPE as compared with women. A lower incidence of pulmonary edema in women was also reported in the study of Hultgren et al. (1996), where 84% of the HAPE patients at an altitude 2500 m were men as compared with women. In the same study, the average arterial oxygen saturation in patients with HAPE was 74% as compared with a normal average oxygen saturation of 92% at such altitude, showing the occurrence of hypoxemia in HAPE patients.

At an altitude of 4500 m, the prevalence of HAPE may vary, depending on the rate of ascent, between 0.2 and 6% in an unselected population (Bärtsch et al., 2002) and at 5500 m between 2 and 15% (Hackett et al., 1976). The reported incidence of HAPE ranges from an estimated 0.01% of skiers traveling from low altitude to 2500 m, to 15.5% of Indian soldiers rapidly climbing to altitudes of 5940 m (Hackett and Roach, 2012). According to Hochstrasser et al. (1986), the prevalence of HAPE in a general mountaineering population in Alps is <0.2% (Hochstrasser et al., 1986). Among trekkers in the Himalayas (Maggiorini et al., 1990) and climbers in the Alps (Hackett and Rennie, 1979) ascending at a rate >600 m/day HAPE incidence is around 4%. The risk of HAPE rises with increased altitude and faster ascent. The incidence among persons with an unknown history of high-altitude pulmonary edema is 0.2% if they ascend to 4500 m in 4 days and 2% if they ascend to 5500 m in 7 days. The incidence increases to 6% and 15%, respectively, when these altitudes are reached within 1–2 days (Bärtsch and Swenson, 2013).

Climbers with a previous history of HAPE, who ascend rapidly above 4500 m, have a 60% chance of HAPE recurrence (Bärtsch et al., 2002). Susceptible individuals can avoid HAPE if they ascend slowly with an average gain of altitude not exceeding 300–350 m/day above an altitude of 2500 m (Bärtsch et al., 2003). When an altitude of 4559 m is reached within 22 h, the HAPE incidence increases to 7% in mountaineers without, and to 62% in those with a history of radiographically documented pulmonary edema (Bärtsch et al., 2002). Susceptibility to HAPE may increase in mountaineers with unrecognized underlying illness; some individuals may have developed diastolic heart failure rather than HAPE, which was due to hypertensive heart disease (Bärtsch et al., 2003).

The HAPE mortality rates in previous years varied between 4% (Menon, 1965) and 11% (Lobenhoffer et al., 1982), depending on the rate of descent or oxygen treatment. HAPE had a reported mortality of 44% if untreated, compared with 6% among those who receive supplementary oxygen, descend to a lower altitude, or both (Lobenhoffer et al., 1982). Nowadays, largely due to a spectacular increase in the number of skiing, trekking and climbing tours, HAPE mortality rates in places where there is limited access to medical care can even reach 50% (Bärtsch and Swenson, 2013).

3. Pathophysiology

There are two typical settings for high altitude pulmonary edema. The first setting involves high-altitude inhabitants returning from sojourns at low altitude, while the second includes unacclimatized lowlanders rapidly ascending to high altitudes. The two forms most likely share the same pathophysiology (Bärtsch et al., 2003). HAPE is associated with pulmonary hypertension and elevated capillary pressure (Maggiorini et al., 2001).

3.1. Hypoxic pulmonary vasoconstriction

Mechanisms of high-altitude pulmonary edema include uneven hypoxic pulmonary vasoconstriction (HPV) that exposes pulmonary capillaries to high pressure, damaging their walls and leading to a high-permeability form of edema (Bhagi et al., 2014). The classical concept of a characteristic increase in HPV is proposed as an important pathogenic factor in the development of HAPE (Hackett et al., 1992; Scherrer et al., 1996). Alveolar hypoxia leads to an adaptive vasomotor response in the form of HPV, which is non-homogenous in nature (Bhagi et al., 2014). The pulmonary capillary pressure increases as a result of HPV, which occurs mainly in smaller pulmonary arteries (Archer and Michelakis, 2002). Recent studies strongly suggest non-uniform regional hypoxic arteriolar vasoconstriction as an explanation for how HPV occurring predominantly at the arteriolar level causes leakage. In areas of high blood flow due to lesser HPV, edema develops due to pressures that exceed the dynamic and structural capacity of the alveolar capillary barrier to maintain normal fluid balance (Swenson and Bärtsch,

2012). The location of fluid leakage caused by hypoxia-induced pulmonary vasoconstriction is not known. Pulmonary vasoconstriction during HAPE is heterogeneous and unevenly distributed. It is evident by asymmetric distribution of rales and infiltrates, as seen during clinical examinations performed early in the course of edema (Bhagi et al., 2014).

3.1.1. Increased pulmonary artery pressure

HAPE pathophysiology is considered to be initiated by the increased pressure in the pulmonary capillaries during prolonged altitude exposure (Bärtsch et al., 2005). This pressure is the force driving fluid out of the pulmonary capillaries due to interstitium leakage, which can be a contributing factor to edema formation (Ganter et al., 2006). An abnormally high pulmonary artery pressure and capillary pressure lead to a non-inflammatory and hemorrhagic alveolar capillary leak that secondarily may evoke an inflammatory response in HAPE (Swenson et al., 2002). Persons who are considered to be susceptible to high altitude pulmonary edema because of two previous episodes of HAPE have abnormally high systolic pulmonary artery pressure (>40 mmHg) under hypoxic conditions (12% oxygen in ambient air at sea level) (Dehnert et al., 2005). As a result of the constriction of small pulmonary arteries, blood gets diverted away, causing elevated blood flow and raising the pressure, which consequently leads to an increase in capillary permeability. Individuals developing HAPE have an abnormal rise in pulmonary artery pressure (PAP) during brief or prolonged exposure to hypoxia (Bhagi et al., 2014). The abnormally high PAP associated with HAPE is most likely due to multiple factors, including increased sympathetic activity, decreased nitric oxide, and elevated endothelin-1 levels (Stream and Grissom, 2008). Nitric oxide is a mediator of exaggerated hypoxic pulmonary vasoconstriction, and its decreased availability may play a major role in the susceptibility to and the development of HAPE (Pennardt, 2013). HAPE-susceptible individuals demonstrate significantly reduced levels of exhaled nitric oxide with a resultant elevation in PAP at high altitude (Busch et al., 2001; Duplain et al., 2000). HAPE-susceptible individuals also exhibit higher levels of endothelin-1, which is a potent endothelium-derived pulmonary vasoconstrictor. Endothelin-1 antagonism decreases pulmonary artery pressures in healthy volunteers at high altitude (Modesti et al., 2006) and HAPE-sensitive individuals exposed to hypoxia (Pham et al., 2012). Climbing to high altitude is often associated with strenuous exertion and exposure to cold weather, both of which result in an exaggerated increase in sympathetic activity in HAPE-susceptible persons that directly correlates with a rise in pulmonary artery pressure.

3.2. HAPE susceptibility

HAPE susceptibility is associated with a blunted hypoxic vascular response (Hohenhaus et al., 1995). While HAPE often affects healthy individuals, the risk for this disorder may be elevated in persons with underlying pulmonary hypertension (Stream and Grissom, 2009). Susceptible individuals develop exaggerated HPV and a large rise in PAP when exposed to hypoxia. As these changes are distributed unevenly within the pulmonary vascular bed, regional overperfusion of capillaries occurs, leading to stress failure of the blood-gas barrier, increased permeability and pulmonary edema (Swenson et al., 2002). This process, which is non-inflammatory in nature, may be accelerated by impaired alveolar fluid clearance (Sartori et al., 2002).

3.3. Non-inflammatory process

Swenson et al. (2002), in their study using broncho-alveolar lavage (BAL) performed within a day of ascent to 4559 m, showed that early HAPE is characterized by a protein-rich fluid containing albumin in high concentrations and an elevated red blood cell count. They demonstrated that this leakage in early HAPE is non-inflammatory and a unidirectional breach of the alveolar capillary barrier in the absence of inflammation. Pulmonary edema in HAPE was thus concluded to be hydrostatic with altered alveolar-capillary permeability. The number of alveolar macrophages, neutrophils and the concentration of pro-inflammatory mediators, such as IL-1, TNF-α, IL-8, thromboxane, prostaglandin E_2, and LTB_4, was not increased. They occurred at a later stage of HAPE. The mechanism which may contribute to the pathophysiology of HAPE is diminished capacity for alveolar fluid reabsorption. Removal of alveolar fluid is driven by the active reabsorption of Na^+ that enters the cells via Na^+ channels and Na^+-coupled transport (Na^+/X) and is extruded by Na^+ K^+ ATPases. Thus active Na^+ reabsorption generates the osmotic gradient for the reabsorption of water (Paralikar, 2012). Another factor which should be taken into consideration in HAPE pathophysiology is genetic predisposition (e.g., HLA-DR6, HLA-DO4) (Hanaoka et al., 1998), especially among HAPE susceptible individuals having an abnormal rise in pulmonary artery pressure with hypoxic breathing (Yagi et al., 1990).

3.3.1. Alterations in pulmonary mechanics and gas exchange

Clarenbach et al. (2012) demonstrated that clinically overt HAPE is preceded by a pattern of alterations in pulmonary mechanics and gas exchange that are consistent with reduced compliance and respiratory muscle strength, uneven distribution of ventilation and gas exchange impairments that are caused by interstitial fluid accumulation.

3.4. Asymptomatic HAPE

HAPE can also take an asymptomatic form and to be transiently present in some fast-ascending climbers. The potential relationship between the presence of asymptomatic HAPE during high altitude exposure and changes in cardiac function needs to be clarified. The lack of correlation between the number of ultrasound lung comets and cardiac changes suggest that non-cardiogenic mechanisms may underlie this transient increase in lung fluid (Bouzat et al., 2013).

4. Clinical symptoms

High altitude pulmonary edema is rarely observed below altitudes of 2500–3000 m and after 1 week of acclimatization at a particular altitude (Paralikar, 2012). The symptoms of HAPE may appear over the course of several hours or days, sometimes even after a night's sleep at a high altitude (Bhagi et al., 2014). Although HAPE can occur without preceding acute mountain sickness (Benner, 2007), it is commonly found to develop in association with AMS (Bärtsch and Roach, 2001). Risk factors that increase the incidence of HAPE include a prior history of the condition, rapid ascent rates, higher altitudes achieved, heavy exertion, cold ambient temperatures, and preexisting respiratory infection. The presence of conditions or anatomic abnormalities that increase pulmonary blood flow or pressure, including primary pulmonary hypertension, intracardiac shunts such as an atrial septal defect or patent foramen ovale, and congenital absence of a pulmonary artery, also increases the risk of HAPE (Pennardt, 2013). Early symptoms of HAPE include a subtle nonproductive cough, shortness of breath, dyspnea on exertion and reduced exercise performance. As HAPE progresses, cough worsens and the person may have a debilitating degree of dyspnea, even at rest. Orthopnea may also occur. Gurgling sounds from the chest and pink frothy sputum indicate advanced cases. Physical examination typically reveals tachycardia, tachypnea, cyanosis, and elevated body

temperature, generally not exceeding 38.5 °C. The heart rate is generally more than 120 beats/min and the respiratory rate more than 20 breaths/min (Richalet, 1995). Rales are discrete initially and located over the middle lung fields (Bhagi et al., 2014; Paralikar, 2012). In the chest X-ray patchy opacities with inconsistent predominance of location are seen, as well as infiltrates in the region of the right middle lobe (Zhou, 2011; Schoene, 2008). There is often a discrepancy between the minor findings on auscultation compared with the degree of alveolar infiltration on chest X-ray (Bärtsch et al., 2003). The radiographic appearance of HAPE is more homogeneous and diffuse in advanced cases and during recovery (Vock et al., 1993). The electrocardiogram may show right axis deviation and ventricular strain or even hypertrophy (Basnayat, 2005). Hypoxemia and respiratory alkalosis are revealed by arterial blood gas measurements (Hackett and Roach, 2001). Individuals who develop HAPE at altitudes of 4000 m show an abnormal increase in pulmonary artery pressure during brief or prolonged hypoxic exposure (Bärtsch et al., 2005; Grünig et al., 2000). Most HAPE-susceptible individuals have a low hypoxic ventilatory response (Hackett et al., 1988), which leads to a low alveolar PO_2 and thus a greater stimulus to HPV at any given altitude. HAPE-susceptible individuals also have 10–15% lower lung volumes (Eldridge et al., 1996), which may contribute to increased PAP in hypoxia or exercise by causing greater alveolar hypoxia.

Subclinical HAPE probably occurs and causes no or minimal symptoms which can be ignored or attributed to other factors (Bärtsch et al., 2003). The true incidence is unknown, although some studies have suggested that more than 50% of persons may have subclinical fluid accumulation in the lungs, consistent with occult edema which resolves spontaneously even though subjects remain at high altitude (Cremona et al., 2002; Mason et al., 2003). In advanced cases, HAPE may be associated with HACE, high altitude cerebral edema (characterized by swelling of brain tissue due to fluid leakage) and show symptoms such as ataxia and decreased levels of consciousness (Bhagi, 2014). According to the Lake Louise criteria (Roach et al., 1993) HAPE can be diagnosed if a person at high altitude has at least two of these symptoms (chest tightness, cough, dyspnea at rest, and markedly decreased exercise performance) and two signs (central cyanosis, pulmonary crackles, tachycardia >110/min and tachypnea >20/min). HAPE is most often misdiagnosed or mistreated as pneumonia (Netzer et al., 2013). The main differential diagnoses are also pulmonary embolism, pulmonary infarction and hyperactive airway disease. In addition, HAPE may be complicated by infection, cerebral edema, pulmonary thrombosis, frostbite or trauma from pressure points during immobilization (Advisory Committe Statement, 2007).

5. Prevention

The main steps to preventing HAPE include graded ascent and time for acclimatization, low sleeping altitudes, avoidance of respiratory infections, avoidance of exercise, alcohol and sleeping pills (Paralikar, 2012). The most effective method of prevention and one that is effective especially in susceptible individuals is slow ascent, 300–350 m/day. An extra acclimatization day with rest should be added for every 600–1200 m above 2500 m (Pennardt, 2013). Vigorous exercise should be avoided during the first days of altitude exposure especially by individuals with a history of HAPE (Bärtsch et al., 2003). Pharmacologic prophylaxis is recommended as adjunctive therapy for individuals who must ascend more than 2500–3000 m in a 24 h period, e.g. in some rescue or military operations or for subjects with a prior history of HAPE (Hackett and Roach, 2012; Stream and Grissom, 2008). If slow ascent is not possible, nifedipine (calcium channel blocker and an inhibitor of hypoxic pulmonary vasoconstriction), which minimizes pulmonary hypertension, should be used among climbers. 60 mg daily of a slow-release preparation in two doses should be given, starting with the ascent and ending on 3rd–4th day after arrival at the final altitude, if the stay is to be prolonged, or after returning to an altitude below 3000 m. It should be emphasized that nifedipine prevents HAPE, but is not effective for the treatment of acute mountain sickness (Paralikar, 2012). Similarly, acetazolamide is used for prophylaxis and treatment of AMS, but it has no established role in the prevention and treatment of HAPE (Shrestha et al., 2014).

Sildenafil (long-acting, inhaled beta$_2$-agonist), which reduces hypoxic pulmonary vasoconstriction, is effective for prevention of HAPE at a high dose of 125 μg twice daily (Bhagi et al., 2014). However, this medication is not recommended as a single agent prophylactic measure and should be considered as a supplement to nifedipine in patients with a history of recurrent HAPE (Luks et al., 2010). The increase in pulmonary artery pressure at high altitudes is significantly attenuated by dexamethasone (Maggiorini, 2006). The suggested dose of dexamethasone is 8 mg initially, followed by 4 mg every 6 h. Study of Maggiorini et al. (2006) demonstrated that both tadalafil (a phosphodiesterase-5 inhibitor, 10 mg twice daily) and dexamethasone (8 mg twice daily) are also effective in preventing HAPE in susceptible individuals to reduce the risk of HAPE. Prevention of an excessive rise in PAP is necessary for prevention of HAPE as well (Bhagi et al., 2014). Nitric oxide inhalation has been shown to improve arterial oxygenation and reduce the hypoxia-induced rise in PAP in HAPE subjects and to rapidly improve arterial oxygenation (Archer and Michelakis, 2002). Persons with mean pulmonary artery pressures greater than 35 mmHg or systolic pulmonary artery pressures greater than 50 mmHg should avoid sojourns to altitudes greater than 2500 m and ensure the availability of supplemental oxygen and/or nifedipine prophylaxis if such travel must be undertaken (Hackett and Roach, 2012; Luks and Swenson, 2007). Since the inflammation associated with respiratory infections may predispose to alveolar capillary leaks and the development of pulmonary edema, patients with such illnesses should avoid high altitude until fully recovered (Pennardt, 2013).

6. Treatment

The treatment of choice for high altitude pulmonary edema in hypoxic conditions is immediate improvement of oxygenation by supplemental oxygen and rapid descent to a lower altitude (in mild HAPE, early descent of only 500–1000 m leads to rapid recovery). When descent and supplemental oxygen administration is not possible, simulated descent with the use of a portable hyperbaric chamber (e.g., Gamow bag, Certec bag) should be used at 2–4 lb in^{-2} for several hours to simulate a descent of 1500 m or more as a temporizing measure until real descent can be effected (Hackett and Roach, 2012; Luks et al., 2010). When neither descent nor hyperbaric treatment is possible, administration of the calcium-entry blocker nifedipine is recommended (Paralikar, 2012). In climbers with HAPE at 4559 m, treatment with 20 mg slow-release nifedipine taken every 6 h led to a persistent relief of symptoms, improvement of gas exchange, and radiographic clearance over an observational period of 34 h (Oelz et al., 1989). Phosphodiesterase inhibitors, such as tadalafil or sildenafil, cause pulmonary vasodilation and decrease pulmonary artery pressure, providing a strong physiological rationale for their use in the treatment of HAPE (Pennardt, 2013). In areas where medical assistance is available, vasodilatory treatment is not strictly necessary, because with supplemental low-flow oxygen (2–4 l/min) for 24–48 h to maintain arterial saturation above 90% and bed-rest from strenuous physical activity, relief of symptoms is achieved within hours and complete clinical recovery within several days while staying at the same

altitude (Maggiorini, 2006). Discharge criteria include resolution of clinical dyspnea, arterial partial pressure of oxygen greater than 60 mmHg or saturation greater than 90% on room air, and radiographic improvement of pulmonary edema (Hackett and Roach, 2012). Medications play only a secondary role in the treatment of HAPE because of the effective results of descent and treatment with oxygen. Drug therapy should be considered only as an adjunct to these two modalities and not as a replacement (Advisory Committe Statement, 2007).

7. Summary

HAPE is a life threatening, non-cardiogenic form of pulmonary edema afflicting some individuals after rapid ascent to high altitude above 2500 m. It usually occurs within 2–4 days of ascent above 2500–3000 m and rarely after more than 4–5 days at the same altitude, most likely because of remodeling and adaptation. In most cases, it is preceded by symptoms of acute mountain sickness. HAPE diagnosis at high altitude is based on the presence of dyspnea, tachypnea, cough, pulmonary crackles, and cyanosis. A chest radiograph demonstrates pulmonary infiltrates but this technique is rarely available in the mountains. Exposure to hypobaric hypoxia causes important physiological changes in the respiratory system, the most important of which are hypoxic pulmonary vasoconstriction and the hypoxic ventilatory response. HAPE associated with pulmonary hypertension and elevated capillary pressure manifests in two forms: it can occur in mountain inhabitants returning from a sojourn at a low altitude, also known as reentry HAPE, and in rapidly climbing unacclimatized healthy lowlanders. Individuals with a previous history of HAPE, who ascend rapidly above 4500 m, have a 60% chance of HAPE recurrence. In advanced cases, HAPE may be associated with HACE. Most deaths from high-altitude illness occur with high-altitude pulmonary edema, the risk of which is related to the rate of ascent, individual susceptibility, and the level of exertion.

HAPE is most often misdiagnosed or mistreated as pneumonia. The differential diagnosis of HAPE except of pneumonia includes pulmonary embolism, pulmonary infarct and hyperactive airway disease. In addition, HAPE may be complicated by infection, cerebral edema, pulmonary thrombosis, frostbite or trauma from pressure points during immobilization. Inadequate acclimatization remains the most significant risk factor for developing HAPE. The main steps to preventing HAPE include graded ascent and time for acclimatization, low sleeping altitudes, avoidance of respiratory infections, and avoidance of strenuous exercise. The most effective method of prevention and one that is effective especially in susceptible individuals is slow ascent, 300–350 m/day. An extra acclimatization day with rest should be added for every 600–1200 m above 2500–3000 m. Immediate descent and administration of supplemental oxygen to raise saturation levels above 90% is a treatment of choice for HAPE. The use of portable hyperbaric chambers may be an effective temporizing measure, when descent and oxygen administration are impossible. Nifedipine may be considered as an additional treatment but must not be used as monotherapy, unless descent, supplemental oxygen, and the use of portable hyperbaric chambers are not feasible.

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