High Altitude Illness in Annapurna Circuit Trek

Behrouz Moghaddasi, MD[1]

Abstract

After 3-4 *days at any point* 1-16 *days trekking in Annapurna circuit (max altitude*=5416*m), individual may show clinical manifestation of altitude illness. Despite a slow and gradual ascent, we recorded a wide range of clinical symptoms and signs. There is risk of developing high altitude illness especially at altitude above 1900m. The most common forms of high altitude illness are: Acute Mountain Sickness typically consists of headache variably accompanied by loss of appetite, nausea, vomiting, disturbed sleep, fatigue, and dizziness; High Altitude Cerebral Edema is likely a continuum of AMS, a potentially fatal illness characterized by ataxia and decreased consciousness; and High Altitude Pulmonary Edema a potentially fatal consequence of rapid ascent to high altitude characterized by incapacitating fatigue, dyspnea with minimal effort that advances to dyspnea at rest. We found out, High altitude illness will occur in non-acclimatized individuals not only after rapid ascent but also some times after slow ascent to high altitude. By slowing down the ascent and resting more we tried to prevent serious high altitude illness. Most of Symptoms and signs will be relieved by slowing ascent and rest. But descent is mandatory, for the treatment of the potentially fatal illnesses of high-altitude pulmonary and cerebral edema. This research provides detailed information about clinical manifestation (symptoms and signs) of altitude illnesses. After reviewing the clinical features, we will investigate the chance of occurrence of these symptoms and signs. In addition to the above, we had interesting observations and findings that we will explain.*

Keywords: Acute mountain sickness, high-altitude pulmonary edema, high-altitude cerebral edema, altitude acclimatization, incapacitating fatigue, exertional dyspnea, Annapurna circuit trek.

Aims and objective

The aim of this research was to find out clinical manifestation of altitude illness

1 Doctor of Medicine, Emergency Medicine Specialist, Iran

and risk of developing high altitude potentially fatal syndromes (HACE & HAPE), during a slow and gradual ascent in Annapurna circuit trek (210km, max altitude 5416m, 16 days). The ultimate aim being, better understanding and early appropriate management of the entity.

Methodology

This is a field research with direct and participant observation methods. In another words this is a prospective, multidisciplinary study. 128 mountaineers were monitored in Annapurna circuit trek (nine trips 2016-2018). We focused on recording the details of clinical manifestations, symptom and signs and managing high altitude illnesses on the way. We followed a graded ascent with the planned travel itinerary in all of our trips. All mountaineers were healthy, male and female with 20–40 years old. All of them had experiences of climbing around 5000m. We evaluated them in a buddy system step by step. We were curious about any symptom and signs of high altitude illnesses. Research diagnostic instruments is Lake Louise Questionnaire Score (LLQS; score of ≥ 3) and physical examination. We completed a Lake Louise self-assessment questionnaire on a twice per day basis for each member of the expedition. In physical examination we do and look for signs that indicate a deterioration in the individual's condition (mental status, ataxia and peripheral edema). In addition to the above respiratory rate, heart rate, and SaO2 (pulse oximetry) readings were obtained twice per day, when needed and recorded. Indeed we design an *AMS & PHYSICAL EXAMINATION WORKSHEET* and collect data to evaluate them.

Introduction

Every year greater numbers of people travel to Himalaya and Nepal. High altitude illness is common among these travelers and is sometimes life threatening. At high altitude there is a drop in barometric pressure, which causes a decrease in the partial pressure of oxygen. This hypobaric hypoxia triggers a series of physiological responses, which, in most cases, help the individual adapt to the low oxygen conditions and high altitude. However, in some cases, maladaptive responses occur, and it causes high altitude illness.

Actually, high altitude illness caused by acute exposure to low partial pressure of oxygen at high altitude. It presents as a collection of nonspecific symptoms and signs. Spectrum of illness varies from mild to severe and is inclusive of acute mountain sickness (AMS), high altitude cerebral edema (HACE) and high altitude pulmonary edema (HAPE), and several other rare forms. Slow ascent and allowing ample time for acclimatization are widely advocated and shown in practice to effectively prevent high altitude illness, but 100% is not a guarantee.

In most previous studies and researches, have talked about the incidence of high

altitude illnesses after fast ascent. The overall incidence of high altitude illness was 53% (Peter Hackett; Drummond Rennie; Harry D. Levine, 1976). In another study (Jill Jin, 2017), high altitude illness occurs in more than 25% of people traveling to above 3500m. AMS may progress from nonspecific symptoms to life-threatening high-altitude cerebral edema in less than 1% of patients (David Meier; Tinh-Hai Collet; Isabella Locatelli, 2017).

In this study, we talk about the incidence of high altitude illnesses and clinical manifestations after graded ascent with the planned travel itinerary. The purpose of this research is to answer the research questions: what is the incidence of clinical symptoms and signs of high altitude illnesses after gradual ascent? Is there any chance for the potentially fatal syndromes (HACE & HAPE) with graded ascent?

High altitude illness affects more than 18% of individuals ascending to above 1900m. More than 65% of people traveling to above 3500m have one or more of AMS symptoms. HACE occurs rarely at altitudes <3500m, and its incidence between 3500m and 5500m is estimated to be 4–5%. We found in a graded ascent with the planned travel itinerary, the likelihood of developing HAPE is less than 1% (78).

The paper has many part. In this introduction, it`s essential to know Annapurna Circuit Trek. Of course we will review the literature relevant to high altitude illness. Then the research methodology and data analysis are simply discussed. And next, the findings are discussed and summarized. The findings of this research are expected to assist high altitude medicine specialists, practitioners and mountain guides in designing and developing successful plan and increasing mountaineers awareness of high altitude illness for a safe and successful plan.

Annapurna Circuit Trek is one of the most popular treks in Nepal and one of the world's popular classic walks. It is a long trek, 210 Km hike around Annapurna massif. We need average 4-6 hrs walking per day. The route allows us to design a proper plan for good acclimatization before tackling the *Thorong-La-pass* at 5416m, however a good basic physical fitness is recommended. We started from Besisahar (740m), then we followed a slow and gradual ascent, and on the 11th day we reached the highest point of our trek and on the 16th day we finished at Nayapul (Table 1). In all of our nine trip we had a similar plan (Figure 1), but sometimes it was necessary to make some brief changes to treat patients.

Detail itinerary:

Day 1: Kathmandu to Besisahar (760m) 5 hrs Drive + Hiking to Bhulbhule 2h (840m)

Day 2: Hiking up to Jajat village 5hr (1300m)

Day 3: Hiking up to Dharapani 3hrs (1900m)

Day 4: Hiking up to Danakyu 2hr (2300m)

Day 5: Hiking up to Chame 5hr (2710m)

Day 6: Hiking up to Pisang 5hr (3310m)

Day 7: Hiking up to Manang 5hr (3540m)

Day 8: Acclimatization Day at Manang

Day 9: Hiking up to Ledar 4hr (4200m)

Day 10: Hiking up to High Camp 4hr (4750m)

Day 11: Hiking up to **Thorung -La pass** 8hr (5416m) trek down to Muktinath

Day 12: Trek down to Jomsom 5hr (2700m)

Day 13: Trek to down to Lete 7 hr (2535m)

Day 14: Trek down to Tatopani 5hr (1200m)

Day 15: Trek to Ghorepani (2870m) 6 hr

Day 16: Trek down to Nayapul (1100m) 6h + Drive to Pokhara

Figure 1: *Annapurna Circuit Trek*

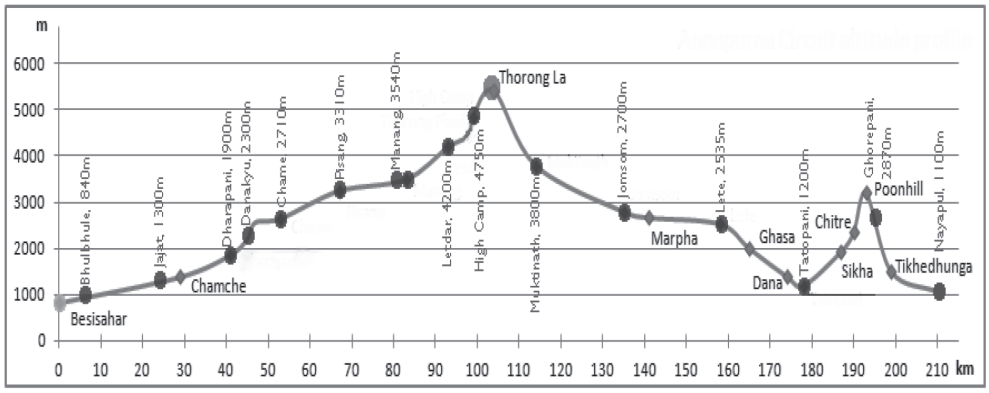

Table 1: *Annapurna Circuit Altitude Profile*

High Altitude Illness, every year, a big numbers of people are ascending to high altitudes for the purposes of climbing, work and other concepts. In 2013, more than 100 million people visited altitudes that could lead to altitude illness[1]. Trekkers are generally well prepared and usually have good support from the companies they trek with; however, recent illnesses, disabilities and deaths on high altitudes remind us of the dangers of altitude illness. High altitude illness is the collective term for acute mountain sickness (AMS), high altitude cerebral edema (HACE), and high altitude pulmonary edema (HAPE) and several other rare forms.

High Altitude is used in this article to mean altitudes higher than 1500m at which significant altitude illness is unlikely below this height (Table 2). As altitude increases, among other important changes, such as decreases in temperature and ambient humidity, barometric pressure decreases and, consequently the amount of oxygen in each breath decreases[2] (Table 3), which causes a decrease in the partial pressure of oxygen at every point along the oxygen transport cascade from ambient air to cellular mitochondria. This hypobaric hypoxia triggers a series of physiological responses, which, in most cases, help the individual tolerate and adapt to the low oxygen conditions.

Altitude	Meters	Feet
High altitute	1,500-3,500	5,000-11,500
Very high altitude	3,500-5,500	11,500-18,000
Extreme altitude	above 5,500	above 18,000

Table 2: *Definitions of High, Very High, and Extreme Altitude*

In simple words, the concentration of oxygen at sea level is about 21% and the barometric pressure averages 760 mmHg. As altitude increases, the concentration remains the same but the number of oxygen molecules per breath is reduced. At

4000 meters the barometric pressure is only 475 mmHg, so there are roughly 40% fewer oxygen molecules per breath. In order to properly oxygenate the body, your breathing rate (even while at rest) has to increase. This extra ventilation increases the oxygen content in the blood, but not to sea level concentrations. Since the amount of oxygen required for activity is the same, the body must adjust to having less oxygen.

Altitude, m (ft)	Barometric Pressure, mm Hg	Inspired Po2, mm Hg (% of sea level)
0 (0)	760	149 (100)
1000 (3281)	679	132 (89)
2000 (6562)	604	117 (79)
3000 (9843)	537	103 (69)
4000 (13 123)	475	90 (60)
5000 (16 404)	420	78 (52)
8848 (2 9028)	253	43 (29)

Table 3: *Barometric Pressure and Inspired Po2 at Various Altitudes*

The decreased oxygen in inspired air in places at high altitude, hypobaric hypoxia, is the central causative factor for the development of altitude illness. [3]

Acclimatization to low oxygen within minutes of the trekker arriving at a place of high altitude and this process continues for weeks.

The important initial changes are: [4]

- 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 Edema (HAPE)
- Cerebral vasodilation caused by hypoxia, which can lead to cerebral edema.

Later changes include: [5]

- Increased erythropoietin secretion, increased hemoglobin production within three days and diuresis, causing increased hematocrit
- Decreased muscle mass
- Increased vascularity.

Individual and genetic variances exist in this acclimatization response,[6] and inadequate responses lead to the pathological changes of altitude illness. Although the exact pathogenesis remains unclear, increased capillary leakage causing

cerebral edema in acute mountain sickness (AMS) and high-altitude cerebral edema (HACE),[7] and similar pulmonary changes in HAPE,[8] 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.[5] The major cause of altitude illnesses is rapid ascending, but sometimes it happens with slow and gradual ascent too.

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 *high altitude retinopathy, retinal hemorrhage, high-altitude syncope, cerebral venous thrombosis and cortical blindness*. Altitude illness varies in severity from high-altitude headaches, 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.[7]

High Altitude Headache (HAH) is an acute process due to acute hypobaric hypoxia caused by rapid ascending to high altitude. HAH is caused by the brain's vulnerability to hypoxia in 25% of trekkers at 1900–3000m 9 , up to 90% of un-acclimatized people who climbed to 5000m.[10]

Acute Mountain Sickness (AMS) consists of nonspecific symptoms, it is typically headache after a rise in altitude in the past four days, and at least one of the following symptoms:[11]

- Gastrointestinal upset (eg anorexia, nausea, vomiting)
- Fatigue or weakness
- Dizziness or light-headedness
- Difficulty sleeping

Because there is a lack of standardization in altitude, ascent rate, outcome and populations, the reported prevalence of AMS varies in different studies. The most important risk factors are how high and how quickly one ascends, 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. [12, 13]

Acute mountain sickness is a clinical diagnosis based on symptoms in the context of ascending to high altitudes. Several questionnaire-based diagnostic tools can be used to diagnose acute mountain sickness. The Lake Louise Questionnaire Score (LLQS) is common is use and valuable (Table 4)[14]. Physical examination is usually normal, but we do and look for signs that indicate a deterioration in the individual's condition (Table 5).

Table 5. Lake Louse self-assessment AMS scoring system

1.	Headache	None (0) to incapacitating (3)
2.	Gastrointestinal symtomes	None (0), poor appetite or nausea (1), moderate nausea or vomiting (2) incapacitating severe nausea or vomiting (3)
3.	Fatigue/weakness	None (0) to severe or incapacitating (3)
4.	Dizziness/lightheadedness	None (0) to incapacitating (3)
5.	Difficulty sleeping (last night)	None or slept as well as usual (0) to could not sleep at all (3)

* Each symptom is graded on a scale of 0-3; the presence of headache plus a score greater than or equal to 3 is usually considered positive for AMS.

Table 5: *Physical Examination*

This scoring system is not linearly correlated and do not give equivalent results; for this reason, study results are often dependent on the scoring system and cut-off points used to determine the presence or absence of AMS.

High Altitude Cerebral Edema (HACE) is a potentially fatal altitude illness, considered a progression from severe AMS, and is usually preceded by a further decrease in oxygenation in a person with severe AMS. Usually develops 24–36 hours after arrival at a place of high altitude. Physical examination is abnormal (Table 5). HACE Characterized by symptoms of severe AMS and cerebral symptoms, signs of impaired mental state, and the cardinal symptom and signs of ataxia. Rapidly it can leads to coma and death if untreated. Patients with AMS advised not to continue to ascend until symptoms have settled.15

High Altitude Pulmonary Edema (HAPE) occurs in healthy individuals at altitudes >2500–3000 m within 2–5 days after arrival16, can develop independently of AMS. It is potentially fatal and accounts for most of the deaths related to altitude illness.17 Early symptoms include excessive exertional dyspnea in relation to the patient's companions, mild cough, chest tightness, reduced exercise performance, incapacitating fatigue. As edema progresses, cough and dyspnea worsen and orthopnea develops. Gurgling in the chest and pink frothy sputum indicate advanced cases. Examination reveals cyanosis, tachypnea, tachycardia, mildly elevated temperature and crackles upon auscultation.

Acclimatization, The major cause of high altitude illnesses is going too high too fast. Altitude acclimatization is the process of adjusting to decreasing oxygen levels at higher elevations, in order to avoid altitude illness. Given time, your body can adapt to altitude. This process generally takes 2-5 days at that altitude.

Prevention of High Altitude Illness, Slow ascent and allowing time for acclimatization are widely advocated and shown in practice to effectively prevent AMS,[11] although the actual rate of ascent recommended varies from 300 to 500m

a day at higher than 3000m. One meta-analysis reported AMS incidences of 50–75% when ascending more than 500m a day at higher than 4000m.[18] The Wilderness Medical Society developed the guideline that ascent should not be higher than 500m a day at altitudes of more than 3000m, and a day's rest every three to four days should be included. 15 Spending two or more nights at places of high altitude 30 days before ascending has been found to be protective against altitude illness.[19] Additionally, resting in the first 48 hours after arriving at places of high altitude is advisable to prevent altitude illness.[20] Some trekker have a higher risk of high altitude illness (Table 6).

Table 6. Trekkers at risk of high 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 3000m.
- Anyone with a prior history of severe acute mountain sickness or high altitude cerebral cedema or pulmonary oedema.

Arterial Oxyhemoglobin Saturation, Early hypoxemia, a decrease in the SaO2 greater than that expected for a given altitude, is a risk factor for developing AMS.[21, 22] Individuals with early hypoxemia should be advised to avoid strenuous exercise and, if continuing to ascend, to ascend slowly. Pulse oximeters are relatively inexpensive and are commonly carried by trekking companies to monitor SaO2 in individuals with worsening symptoms of AMS, HACE and HAPE. Early hypoxemia can be monitored with a pulse oximeter (Figure 2).

Figure 2: *Pulse Oximeter*

Study design and outcomes

In this field research prospective study 128 mountaineers were assigned to ascent Annapurna Circuit Trek profile (Table 1, Figure 1). All ascent groups started the trek at Besisahar (870m), then slowly continued to Thorong_La Pass (5416m), and to the Nayapul (1100m) within 16 days. We followed a graded ascent

according to our profile with a fluctuation 1-2hrs/d. Average trekking 4-5hrs/d rates, respectively (Fig. 1). Included were healthy, physically fit, experienced mountaineers of either gender and between 20 to 40 years of age without any disease. We completed our designed AMS & PHYSICAL EXAMINATION WORKSHEET on a twice per day basis for each member. This worksheet is a modified Lake Louise Questionnaire (Table 4)[14] plus physical examination (Table 5) that we do and look for signs that indicate a deterioration in the individual's condition (mental status, ataxia and peripheral edema). In addition to the above respiratory rate, heart rate were obtained twice per day. Twice per day oximetry was performed in the morning and evening during rest in a standing position with a finger pulse oximeter. Stable values after at least 2 minutes were recorded.

Acute mountain sickness (AMS) scores were assessed daily utilizing the Lake Louise Questionnaire. A score of ≥ 5 reliably identifies a person with AMS. The severe AMS score reflects symptoms of altered cerebral function in conjunction with the experience of being ill. Diagnosis of HACE was made when headache and an AMS score of ≥ 7 were present either with change in mental status or with ataxia. Physical examination score of ≥ 3 suggest HACE and more assessment. Diagnosis of HAPE was made clinically when excessive exertional dyspnea with others pulmonary symptom and signs in conjunction with low arterial oxyhemoglobin saturation (SaO2).

Results

We emphasize that all climbers had a gradual and slow ascent according to our ascent profile (Fig. 1).

- Of 128 mountaineers, 16 (12.5%) at 1900-3310m complained of a pure headache (High Altitude Headache) and resolves with a non-steroidal anti-inflammatory drug (Ibuprofen 600 mg).
- 24 (18.75%) mountaineers at 1900-3540m exhibited positive for AMS (LLQS; score of ≥ 3). They treated with slow ascending and simple medication (Ibuprofen or Acetaminophen).
- At altitudes above 3540m, 84(65.625%) mountaineers exhibited AMS (LLQS; score of ≥ 3). They treated with rest, slow ascending and simple medication. A significant number of this group develop to HACE.

The most common symptoms in order of frequency were: headache, weakness, anorexia and disturbed sleep.

- 31 (24.219%) out of 84 mountaineers with AMS, exhibited sever AMS (LLQS; score of ≥ 5) and resolves with rest, slow ascending, simple medication and acetazolamide. Of these numbers, 13 were involved

below 3500m and 18 above 3500m.

- Of 128 mountaineers, 6 (4.688%) exhibited HACE (LLQS; score of ≥7 + Physical Exam score of ≥4). One of these involved at an altitude lower than 3500m, and the rest was at altitudes above 3500m and one remarkable point was that we had a HACE after Thorong La Pass in descending time (Jomsom, 2700m). All of them show an acute progress from severe AMS(less than 24 hrs). We treated them with rapid descent + medication.
- Of 128 mountaineers, 1 (0.781%) exhibited HAPE at 3310m (Pisang). Chief complaint was excessive exertional dyspnea and incapacitating fatigue continued by pulmonary symptoms and signs. Pulse oximeter detected SaO2: 61(Chart 1).

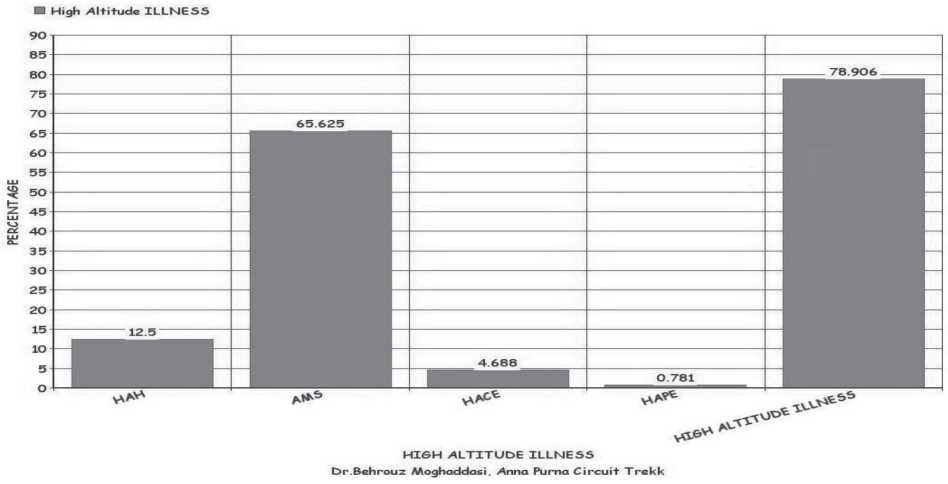

Chart 1: *High Altitude Illness*

Our Guidelines for Field Treatment of Altitude Illness, to manage and treat the patients we acted as follows:

High Altitude Headache; Non-steroidal anti-inflammatory drug (Ibuprofen 600 mg) or Acetaminophen.

AMS; more rest and slow ascent, symptom therapy medication, Acetazolamide 250 mg BID

HACE; Descent as soon as possible, Dexamethasone 8 mg load then 4 mg q6 hours, Acetazolamide 250 mg BID, symptom therapy medication.

HAPE; Rapid descent as soon as possible(Helicopter Rescue), Nifedipine 10 mg po then 30mgSR q12-24 hours, Acetazolamide 250 mg BID, symptom therapy medication.

Discussion

A vast majority of mountaineers, namely 78.9%, exhibited high altitude illness during the Annapurna Circuit Trek. We recorded a wide range of high altitude illness, a simple altitude headache to potentially fatal altitude illnesses such as HACE & HAPE. Our novel findings are important since they indicate that despite a slow and gradual ascent the risk of developing high altitude illness is high. Furthermore, the data suggest that the incidence of high altitude illness may have been underestimated in previous studies. Our mountaineers with delayed AMS and those who have AMS above 3500m showed more possibility of HACE throughout the trekking. This means, the higher the ascent and the longer the duration at high altitudes, the higher was the occurrence of high altitude illness. On the other hand, the chance of HACE was less in those who involved in AMS at lower altitude. The results strongly suggest a correlation between the time of exposure to high altitude with high altitude illness even with a slow and graded ascent. One remarkable point was that we had a HACE in descending time (2700m), it shows an acute progress from AMS within 6-8hrs without any findings in the previous days. Another considerable case was a HAPE at 3300m, she was a 40 years fit mountaineer without past history of high altitude illness. Her complaint was exertional dyspnea that intensified during night and we used of helicopter for rapid descending.

Conclusion

When closely observed and evaluated, a large amount of mountaineers exhibit high altitude illness during trekking to high altitudes. There are a wide range of clinical manifestations with risk of developing a potentially fatal altitude illness. The typical symptoms of AMS include headache, loss of appetite, disturbed sleep, nausea, weakness, and dizziness, beginning shortly after rapid ascent to high altitude but it`s not impossible after slow ascent. Symptoms can usually be relieved by rest, slow ascending and by delaying further ascent until symptoms have resolved; if symptoms are severe, they can be rapidly relieved by descent to a lower elevation. AMS may progress to high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE) in most cases occurs in the absence of AMS. Both of these conditions are potentially fatal; if possible, initial management should include rapid descent, supplemental oxygen, and, in the case of HACE, dexamethasone. Nifedipine may be effective in the management of HAPE. A person suspected of either of these conditions should never descend alone.

Recommendation

No doubt slow ascent and allowing time for acclimatization are widely advocated and shown in practice to effectively prevent altitude illness. But if we assume

that slow and graded ascent is a guarantee for prevention of high altitude illness, it is an unforgivable sin! *We need a proper planning to climb mountains and its essential always be prepared to manage and treat high altitude illnesses.*

•

References

1. Burtscher M, Netzer N, Strohl K, Faulhaber M, Gatterer H. (2013). Hypoxia-related altitude illnesses. J Travel Med; 20(4):247–55.
2. Bailie K, Simpson A, Thompson AAR, et al. Altitude air pressure calculator. Edinburgh: Altitude, 2010. Accessed at www.altitude.org [8 September 2015].
3. Hevroni A, Goldman A, Kerem E. (2015). High altitude: Physiology and pathophysiology in adults and children: A review. Clinical Pulmonary Medicine; 22(3):105–113(9).
4. Ivan Parise. (2017). Travelling safely to places at high altitude – Understanding and preventing altitude illness. J AFP; 46(6): 380-384
5. Hevroni A, Goldman A, Kerem E. (2015). High altitude: Physiology and pathophysiology in adults and children: A review. Clinical Pulmonary Medicine; 22(3):105–113(9).
6. MacInnis MJ, Wang P, Koehle MS, et al. The genetics of altitude tolerance: The evidence for inherited susceptibility to acute mountain sickness. J Occup Environ Med 2011;53(2):159–68.
7. Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitudes. Lancet Neurol 2009;8:175–91.
8. Maggiorini M. Prevention and treatment of high-altitude pulmonary edema. Prog Cardiovasc Dis 2010;52(6):500–06.
9. Gertsch JH, Lipman SH, Holck PS, et al. Prospective, double-blind, randomized, placebo-controlled comparison of acetazolamide versus ibuprofen for prophylaxis against high altitude headache: The Headache Evaluation at Altitude Trial (HEAT). Wilderness Environ Med 2010;21(3):236–43.
10. Burtscher M. High altitude headache: Epidemiology, pathophysiology, therapy and prophylaxis. Wien Klin Wochenschr 1999;111(20):830–36.
11. Hackett PH, Roach RC. High-altitude illness. N Engl J Med 2001;345:1279–81.
12. Hackett PH, Rennie D, Levine HD. (1976). The incidence, importance, and

prophylaxis of acute mountain sickness. Lancet:1149–55.

13. Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. Lancet 1976;2:1210–12.

14. Roach RC, Bärtsch P, Oelz O, Hackett PH. The Lake Louise Acute Mountain Sickness Scoring System. In: Sutton JR, Houston CS, Coates G, editors. Hypoxia and Molecular Medicine. Burlington, VT: Queen City Press; 1993. pp. 272–4.

15. Luks AM, McIntosh SE, Grissom CK, et al. Wilderness Medical Society practice guidelines for the prevention and treatment of acute altitude illness: 2014 Update. Wilderness Environ Med 2014;25(4 Suppl):S4–14.

16. Bärtsch P, Swenson ER. Clinical practice: acute high-altitude illnesses. N Engl J Med 2013; 368: 2294–2302.

17. Bhagi S, Srivastava S, Singh SB. High-altitude pulmonary edema: Review. J Occup Health 2014;56(4):235–43.

18. Dumont L, Mardirosoff C, Tramer M. Efficacy and harm of pharmacological prevention of acute mountain sickness: Quantitative systematic review. BMJ 2000;321(7256): 267–72.

19. Schneider M, Bernasch D, Weymann J, et al. Acute mountain sickness: Influence of susceptibility, preexposure, and ascent rate. Med Sci Sports Exerc 2002;34:1886–91.

20. Roach RC, Maes D, Sandoval D, et al. Exercise exacerbates acute mountain sickness at simulated high altitude. J Appl Physiol 2000;88(2):581–85.

21. Burtscher M, Flatz M, Faulhaber M. Prediction of susceptibility to acute mountain sickness by Sa(O2) values during short-term exposure to hypoxia. High Alt Med Biol. 2004;5:335–40.

22. Karinen HM, Peltonen JE, Kähönen M, Heikki Tikkanen HO. Prediction of acute mountain sickness by monitoring arterial oxygen saturation during ascent. High Alt Med Biol. 2010;11:325–32. doi: 10.1089/ham.2009.1060.