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ACUTE ALTITUDE SICKNESS – A REVIEW OF CURRENT UNDERSTANDING AND TREATMENT OPTIONS

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Abstract

Acute altitude sickness usually affects un-acclimatized people travelling to altitudes higher than 2500 meters. There are three forms of altitude sickness; Acute Mountain Sickness, High-Altitude Pulmonary Edema and High-Altitude Cerebral Edema. Acute Mountain Sickness includes headache, dizziness, weakness, insomnia, anorexia, nausea and vomiting with high altitude headache being the most prominent symptom. In few patients, Acute Mountain Sickness may progress to more severe forms which represent with High-Altitude Pulmonary Edema or High – Altitude Cerebral Edema, both of which can be fatal if not diagnosed and treated early. Increased permeability of the cerebral and pulmonary endothelium resulting from hypoxemia also leads to High-Altitude Cerebral Edema and High-Altitude Pulmonary Edema. Acclimatization is the imperative measure and process to prevent these symptoms and the development of Acute Mountain Sickness. Early identification of symptoms and immediate descent prevents the worsening of the sickness. Pharmacological mitigation of Acute Mountain Sickness may also include the use of Acetazolamide, commonly known as Diamox. This drug is a carbonic anhydrase inhibitor which seems to be effective in controlling symptoms of Acute Mountain Sickness and decreasing the occurrence of High-Altitude Pulmonary Edema and High-Altitude Cerebral Edema. Dexamethasone, a synthetic glucocorticoid is an alternative drug, although preferred as an adjunctive therapy rather than prophylactically agent for High-Altitude Cerebral Edema. Nifedipine, a calcium channel blocker is the -drug of choice for both the prophylaxis and treatment for High-Altitude Pulmonary Edema. In conclusion, the prevention of Acute Mountain Sickness must be taken into consideration prior to ascending the mountain and travellers are recommended to consult with a healthcare professional for better management prior to embarking on a trek.

Keywords: *acute altitude sickness, acclimatization, pulmonary edema, cerebral edema.*

Acute altitude sickness

The global adventure tourism market has been estimated to grow at a compound annual growth rate of 45.99% during the period 2016-2020. According to the adventure tourism market report, increased inclination for adventure over other tourism activities will be a key factor for growth in the market. In 2015, the adventure tourism industry generated revenue of $7.88 trillion. However, the definition of tourism is changing rapidly. The beachside holidays or regular sight-seeing holidays are losing its market to adventurous activities such as skydiving, surfing, rock or mountain climbing, caving, and deep-sea diving that involve high risk (Global Adventure Tourism Market 2016-2020: Technavio; Sep-2016).

Mountain climbing and trekking appear to be among those of the more popular activities in adventure tourism in various regions around the world. Therefore guidance must be provided to travellers with regards to the risks and health concerns involved in reaching high altitudes particularly for those not adapted to living in such conditions normally. This review aims to provide the relevant current consideration involved in the development, treatment and prevention of Acute Mountain Sickness (AMS).

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The term "acute mountain sickness" is used to describe the nonspecific symptoms occurring in unacclimatized individuals shortly after ascent to high altitudes which are at approximately greater than 2500 meters. At such altitudes, symptoms may vary in severity among individuals, from a mild headache, nausea, dizziness, to coma and death [Porcelli M et al., 2014]. However, common symptoms have been categorized to a eadache, dizziness, weakness, insomnia, anorexia, nausea and vomiting, among which high altitude headache (HAH) is the most prominent [Yarnell P et al., 2000]. High-altitude cerebral edema is a rare and life-threatening conditions usually preceded by AMS. It is characterized by features of AMS along with rapidly progressive cerebral symptoms, mainly confusion, hallucination, ataxia, visual loss and loss of consciousness. Retinal hemorrhages, papilloedema and focal neurological signs may also be found [Porcelli M et al., 2014]. These changes may be characterized and viewed on magnetic resonance imaging (MRI) as common findings [Hackett P et al., 1998]. High-altitude pulmonary edema, a non-cardiogenic form of pulmonary edema usually occurs in the first 4 days of ascent above 2500meters. More profoundly this may occur without any preceding signs of AMS [Davidson S, 2014]. Concurrently, excessive hypoxic pulmonary vasoconstriction is characterized by irregular respiration, an initially dry cough which later becomes and leads to bloody sputum, decreased oxygen saturation, chest discomfort, breathlessness and extreme fatigue [Davidson S, 2014]. On auscultation, crepitation is present in both the lung fields which is supported by the radiological demonstration of patchy edema of the lungs (Davidson S, 2014). Given these representations by travelers on adventure holidays to high altitude locations each year, acute mountain sickness may become a public health concern and an economic burden if not addressed early. The incidence of mountain sickness is, therefore, increasing due to use of modern means available for rapid ascent [Brundrett G, 2002]. High altitude pulmonary edema and high altitude cerebral edema, though uncommon, are potentially fatal. Among the various scoring systems to diagnose and grade the severity of AMS, Lake Louis self-assessment questionnaire is widely accepted by healthcare professionals and commonly used for diagnosis as shown in table 1 [Dellasanta P et al., 2007; Taylor A, 2011. Roach R et al., 1993].

The table above shows the scoring system used in the diagnosis of AMS based on the LLS. A diagnosis is made based on 1. A rise in altitude within the last 4 days, 2. Presence of a headache plus 3. Presence of at least one other system and 4. A total score of 3 or more from the questions shown in the table above. A total score of 3 to 5 is regarded as mild AMS. A total score of 6 and above is regarded as severe AMS.

The Lake Louise Score provides the basis to determine the severity of AMS in patients on adven-

TABLE 1.

Lake Louise Score (LLS) for the diagnosis of Acute Mountain Sickness (AMS)

HEADACHE	
Symptoms	Score
None	0
Mild headace	1
Moderate headace	2
Severe headhace, incapacitation	3
GASTROINTESTINAL SYMPTOMS	
Symptoms	Score
None	0
Poor appetite or nausea	1
Moderate nausea &/or vomiting	2
Severe nausea &/or vomiting	3
FATIGUE &/OR WEAKNESS	
Symptoms	Score
Not tired or weak	0
Mild fatigure/weakness	1
Moderate fatigure/weakness	2
Severe fatigure/weakness	3
DIZZINESS/LIGHT-HEADEDNESS	
Symptoms	Score
Not dizzy	0
Mild dizziness	1
Moderate dizziness	2
Severe dizziness, incapacitating	3
DIFFICULTY SLEEPING	
Symptoms	Score
Slept as well as usual	0
Did not sleep as well as usual	1
Woke many times, poor sleep	2
Could not sleep at all	3

ture holidays. A total score of 3 to 5 is regarded as mild AMS and a total score of 6 and above is regarded as severe AMS. The diagnosis and level of AMS will then determine the proceeding treatment the traveller will require.

Epidemiology and risk factors

The incidence of AMS increases with the presence of certain risk factors which include the rate of ascent, pre-acclimatization and the altitude attained [Taylor A, 2011; Luks A et al., 2017]. The rate of ascent is the most important factor affecting the development of AMS. Trekkers in the Everest region of Nepal appear to have a slower rate of ascent and a lower prevalence of AMS compared to those climbing Kilimanjaro where the rate of ascent is more rapid [Taylor A, 2011] .

Men and women appear to be equally susceptible to develop AMS. In fact, studies suggest that younger individuals may be at higher risk. People aged >40–60 years tend to develop AMS less than younger individuals [Honigman B et al., 1994].The association between smoking and risk of AMS remains unclear [Vinnikov D et al.,2016; Song P et al., 2014]. On the other hand, alcohol may cause overexertion and dehydration leading to intensifying AMS symptoms. Furthermore, its sedative effect and interaction with drugs may cause respiratory depression [Porcelli M, Gugelchuk G, 1995]. There is some evidence indicating pre-existing lung disease, and obesity may be of relevance, however there is no evidence supporting the underlying medical problems such as asthma, coronary artery disease or diabetes mellitus increase the risk of AMS [Honigman B TM et al., 1994; Ri-Li G et al., 2003; Yang B et al., 2015; Luks A et al., 2017; West J, 2009]. Severe anemia and sickle cell disease are contra-indications to high-altitude travel [Taylor A, 2011; West J, 2009].

Pathophysiology: The exact pathophysiology of acute altitude sickness is not fully understood however the common theme presented in the current literature states Hypoxia as the main contributor to altitude sickness.

The Normal arterial partial pressure of oxygen (PaO_2) at sea level is around 90-95 mmHg. At 6000 meters above sea level, it falls to about 35mmHg (Global Adventure Tourism Market 2016-2020: Technavio; Sep-2016). This dramatic fall in PaO_2 is due to low a barometric pressure of the atmosphere at such heights. This causes diminished alveolar oxygen tension. This decrease in PaO_2 is detected by the chemoreceptors in the carotid body which stimulates the hypoxic ventilatory response (HVR), which then results in water loss, increased PaO_2 and decrease $PaCO_2$. Because of decreased $PaCO_2$ in alveoli, there is respiratory alkalosis, which by suppressing the chemoreceptor signal that detects the dangerous fall in PaO_2, partly masks the ventilatory reaction to hypoxia [Taillie J, 2003]. The rapid ventilator response then results in an increase in the respiration rate and bicarbonate diuresis; the combination of these causes increases the fluid loss from the body leading to dehydration [Yarnell P et al., 2000; Taillie J, 2003].

Low PaO_2 and low blood volume due to dehydration increases the levels of circulating catecholamines, which causes an increased heart rate, blood pressure and venous tone [Taillie J, 2003; Clarke C, 1998]. It also increases sympathetic nervous system activity, causes pulmonary vasoconstriction and increased pulmonary artery pressure, and increase cerebral blood flow resulting in edema [Hackett P, Rennie D, 2002; Tom P et al., 1994]. The active proteins upregulated by tissue hypoxia initiate the angiogenic process by attacking and disintegrating the capillary basement membrane, ultimately weakening the capillaries resulting in the leakage of plasma and/or blood [Severinghaus J, 1995]. There is a loss of endothelial integrity due to the release of a variety of growth factors and cytokines from macrophages; attracted by the angiogenic response, via the active proteins, ultimately resulting in cerebral edema once the compensatory capacity by Cerebrospinal fluid (CSF) is surpassed [Yarnell P et al., 2000]. The rise in pulmonary capillaries pressure resulting from vasoconstriction leads to changes in the alveolar-capillary permeability [Hackett P, Rennie D, 2002; Maggiorini M et al., 2001]. This causes hydrostatic induced leakage of protein rich and hemorrhagic fluid, causing pulmonary edema [Swenson E et al., 2002]. Figure 1 and figure 2 below represent the processes involved.

Prevention: There are pharmacological and non pharmacological approaches to prevent the altitude sickness. These should be taken into consideration prior to and during the adventure holiday and under the strict guidance and recommendations of a

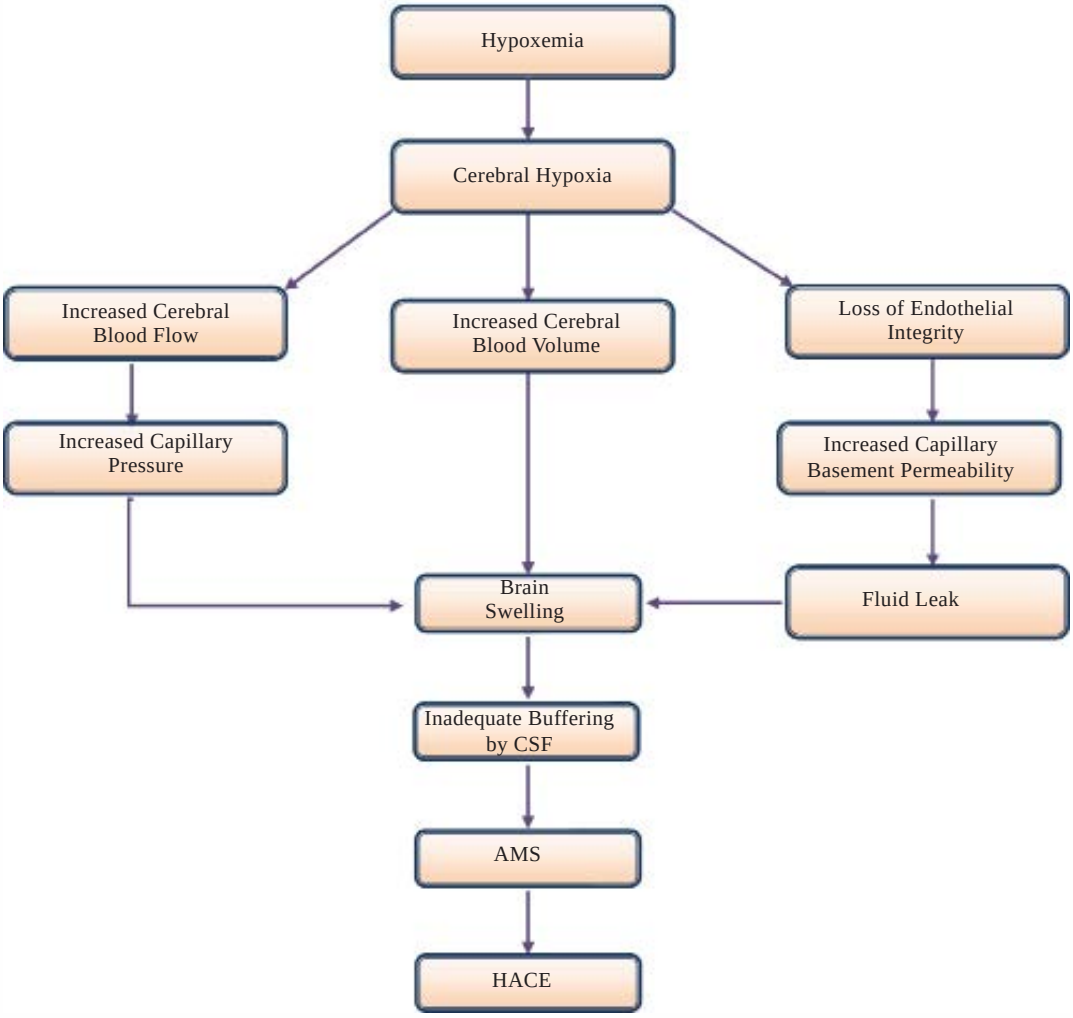

Figure 1 *The pathophysiology of Acute Altitude Sickness demonstrated via HACE . Development of HACE is shown to be through cerebral hypoxia to cause loss of endothelial integrity, increased cerebral blood volume and increased cerebral blood flow. These lead to the swelling of the brain and ultimately to altitude sickness and HACE.*

healthcare professional. The non-pharmacological and pharmacological measures have been outlined.

Non-Pharmacological measures: If possible, climbers should spend at least one night at an "intermediate" elevation below 3000 m. Above 3000 m, the sleeping altitude should be increased by only 300-500 m per day and should take a rest day for every 1000 meters of elevation gained (i.e. spend a second night at the same altitude) . If possible, flying or driving directly to high altitude should be avoided [Bartsch P, Swenson E, 2013; Hackett P, Roach R, 2001; Luks A et al., 2014]. Pre-acclimatizing before ascending to higher altitude has beneficial physiological changes and decreases risk of developing AMS symptoms [Luks A et al., 2017; Beidleman B et al., 2009]**.** Alcohol consumption and use of sedative drugs depress respiration. So, their use before ascend must be avoided [Porcelli M, Gugelchuk G, 1995]. Strenuous exercises after ascent must be avoided. Several studies show varying results linking exertion with increased incidence of AMS [Rupp T et al., 2013; Roach R et al., 2000]. Drink plenty of fluids to prevent dehydration. Furthermore, a high carbohydrate diet, low-fat and low-salt diet should be maintained throughout the trek. These dietary changes increase the performance by decreasing the altitude sickness [Porcelli M, Gugelchuk G, 1995].

With these in mind, patients with preexisting illnesses, however, should undergo a mandatory consultation and physical examination by their healthcare professional prior to departure and be embarking on a high altitude trekking holiday [Porcelli M, Gugelchuk G, 1995].

Pharmacological Measures: Pharmacological prophylaxis is largely directed towards the prevention

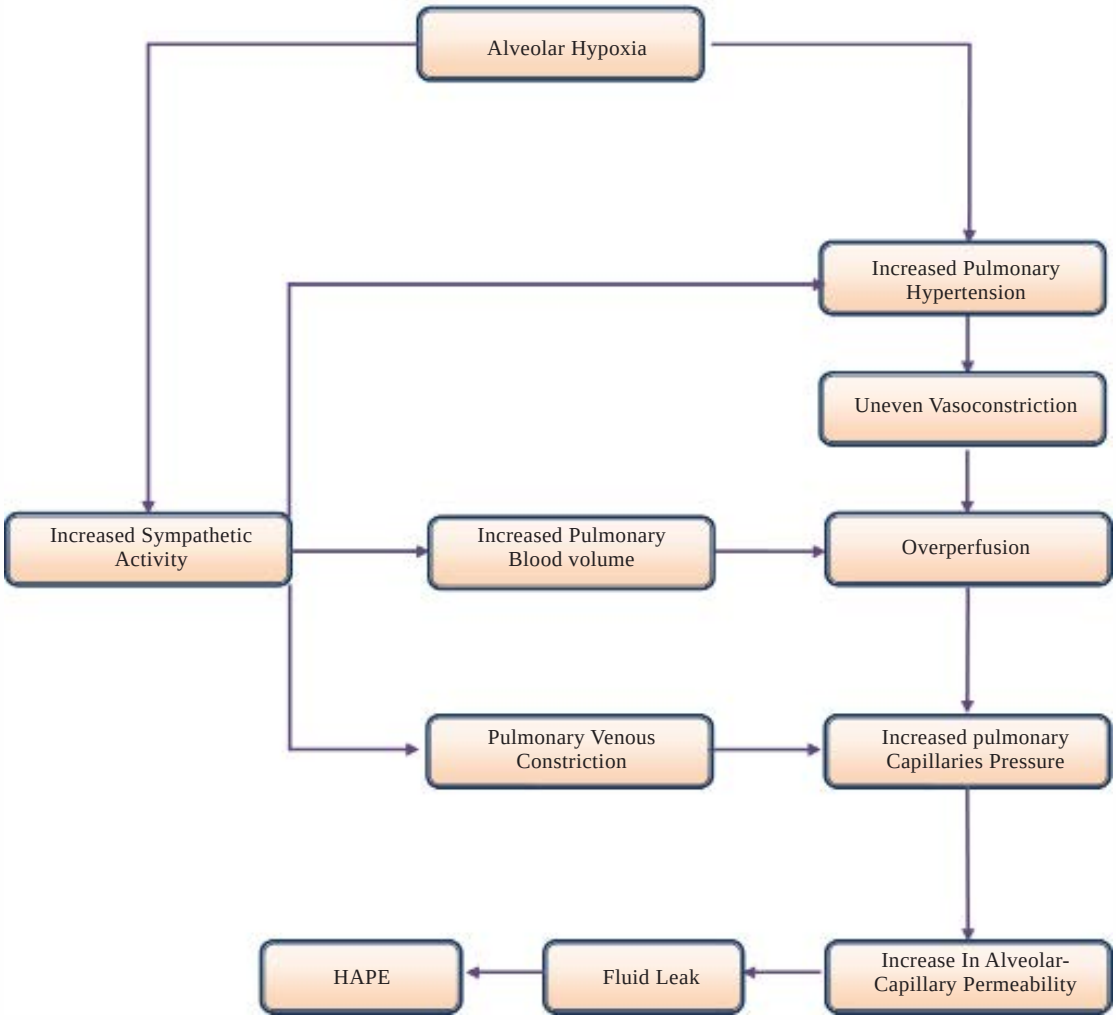

FIGURE 2. *The pathophysiology of Acute Altitude Sickness demonstrated via HAPE. Development of HAPE is shown to be through alveolar hypoxia to cause increased pulmonary hypertension and increased sympathetic activity which then leads to pulmonary venous constriction, increase in alveolar capillary permeability, fluid leakage and HAPE.*

of acute mountain sickness in high risk individuals. HACE and HAPE follow AMS hence preventing AMS will help prevent HACE and HAPE subsequently.

Acetazolamide is the main drug used for AMS prophylaxis. The appropriate dosage for prophylaxis remains debatable [*Dumont L et al., 2000*]. Most of the studies conducted suggests 125 mg twice daily is enough for most of the climbers [*Luks A et al., 2014; Low E et al., 2012*]. However, this dose may be inadequate for individuals on rapid ascents and/or ascents to very high altitudes [*Hackett P et al., 1988*].

Dexamethasone, is an alternative prophylactic drug, if Acetazolamide is intolerant and contraindicated [*Tang E et al., 2014; Ellsworth A et al., 1991, 1987*]. However, it is not routinely advised as a prophylactic drug as it causes dysphoria and increases the risk of recurrence of altitude illness once it is stopped [*Hackett P et al., 1988*].

Use of high-dose systemic corticosteroids for more than seven consecutive days is not advised due to the risk of adrenal suppression [Zell S, Goodman P, 1998]. The dose should be tapered off rather than stopping abruptly when longer use is required [*Luks A et al., 2014*]. For HAPE prophylaxis, Nifedipine 30 mg sustained release every 12 hours can be used [*Luks A et al., 2017; Oelz O et al., 1992*]. Recent studies suggest that both 1800 mg of Ibuprofen/day and inhaled steroid Budesonide also have some benefits in AMS prophylaxis [Lipman G et al., 2012; Chen G et al., 2015; Zheng C et al., 2014]. Some physicians are now using Nifedipine and phosphodiesterase inhibitors, such as Tadalafil, as a combination therapy [*Luks A et al., 2017; Maggiorini M et al., 2006*].

Treatment: Identifying the symptoms early and descending down to lower altitude is the best

known treatment for AMS. Once the symptoms appear, further ascent must be stopped immediately.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDS) like Ibuprofen or Acetaminophen are safe and effective at treating high-altitude headache [Harris N et al., 2003; Broome J et al., 1994]. Antiemetic like Prochlorperazine or Ondansetron is effective against nausea and vomiting [Porcelli M, Gugelchuk G, 1995]. Acetazolamide, Dexamethasone or oxygen therapy can be added in the treatment algorithm for those Individuals with more severe symptoms or whom are not responding to conservative treatment [Hackett P, Roach R, 2001; Grissom C et al., 1992; Hackett P, Roach R,2001; Hackett P et al., 1988; Rodway G et al., 2003]. If no improvement is seen, descend 500–1000 meters or continue descending until symptoms resolve.

Onset of symptoms suggestive of HACE is an indication for immediate descent(20). If descent is not possible, the patient should be placed on supplemental oxygen or in a portable hyperbaric chamber [Keller H et al., 1995; Freeman K et al., 2004]. Initially, 8mg of oral or intramuscular or intravenous Dexamethasone should be administered followed by 4mg every 6 hours until the individual has descended to lower altitude or symptoms have fully resolved [Luks A et al., 2014; Keller H et al., 1995]. There is no evidence of beneficial role of Diuretics or Acetazolamide for HACE.

Supplemental Oxygen, rest and descent is the most effective to treat HAPE in all cases [Hackett P, Roach R, 2001; Koch R, Burtscher M, 2008; Pennardt A, 2013]. If descent is delayed, place the patient in a portable hyperbaric chamber [Freeman K et al., 2004]. Nifedipine 10mg orally initially and then 30mg of the sustained release formulation orally every 12–24 hours are recommended, when patients do not respond to conservative management or when HAPE develops in a remote setting [Luks A et al., 2017; Roach R, 2001] It should be noted, the use of diuretics increases the risk of hypotension in HAPE patients because many patients already have depleted volume at the time of their illness [Luks A et al., 2017].

SUMMARY

The nonspecific symptoms occurring in un-acclimatized individuals shortly after ascent to high altitude is known as Acute Mountain Sickness. Hypoxia is the main supported etiology among all the theories. Rate of ascent, and pre-acclimatization are the major factors that determine the risk of developing AMS. Symptomatic treatment with NSAIDs, antiemetic, rest and delaying further ascent can help relieve symptoms. If symptoms are severe or not responding to conservative treatment, Acetazolamide 125 mg twice daily and oral Dexamethasone 4mg every 6 hours can be added followed by a further descent. Although rare, High-altitude cerebral edema and High Altitude pulmonary edema are life-threatening conditions usually preceded by AMS. Initial management includes Supplemental oxygen and descent for both. For the effective management, Dexamethasone is used in HACE and Nifedipine in HAPE. Maintaining the body in the best state of health before ascent, implementing preventing measures, early recognition of the symptoms and knowing when to descent might help the travellers prevent themselves from the health consequences while travelling to high altitude.

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