High Altitude Medicine

A Case-Based Approach

Jorge Hidalgo
Sabrina Da Re
António Gandra D'Almeida
Editors

Springer

High Altitude Medicine

Jorge Hidalgo • Sabrina Da Re
António Gandra D'Almeida
Editors

High Altitude Medicine

A Case-Based Approach

Springer

Editors
Jorge Hidalgo
Department of General ICU and
COVID-19 Unit
Belize Helthcare Partners Limited
Belize City, Belize

António Gandra D'Almeida
Department of critical care
Portuguese National Institute of Medical
Emergency
Porto, Portugal

Sabrina Da Re
Department of critical care
Hospital Materno Infantil
La Paz, Bolivia

ISBN 978-3-031-35091-7 ISBN 978-3-031-35092-4 (eBook)
https://doi.org/10.1007/978-3-031-35092-4

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

- *Luigi Da Re, Lourdes Gutierrez, and Francesco Da Re for their deep love and understanding.*
- *Salgueiro Casso family.*
- *Health professionals interested in High Altitude pathology.*

Sabrina Da Re

To my parents, my lovely wife Gerhaldine, my daughter Allyson, and my son Benjamin.
—Jorge Hidalgo

I dedicate this book to my family especially to my children. Thank you so much for the love, support, and understanding for all the time that work keeps me away from you.
To Jorge and Geraldine that made this possible.
António Gandra d'Almeida
"The happiest man in the world is the one who knows how to recognize the merits of others and he can rejoice in the good of others as if he were his own."
Johann Wolfgang von Goethe

Foreword

Keen students of high altitude medicine and physiology may recall the exploits of Alexander Kellas on Mt Kamet in 1920. It was in those early years of high altitude exploration that physiology, medicine, and mountains have come together. Since then and over the years giants of high altitude science such as Griff Pugh, Michael Ward, Jim Milledge, John West, and others built the foundations of knowledge we now cherish with the publication of the core text High Altitude Medicine and Physiology in 1989, now in its 6th edition. One could say that a new specialty has been born. In many respects, high altitude medicine is the science of pushing the boundaries. They are boundaries of human endurance—physical and psychological. In 1980, Reinhold Messner conquered Mt Everest without using supplemental oxygen. In 2003, Mr Yūichirō Miura reached the summit of the same mountain aged 80. An American, Jordan Romero succeeded in reaching the summit aged 13. By the age of 15, he became the youngest person to accomplish the prized ascent of Seven Summits. Recently, all 14 eight thousand+ summits have been climbed in marathon succession by Nirmal Purja, who achieved it in under 7 months. From acclimatization, genetic predisposition, endurance training through geriatric and pediatric considerations high altitude medicine is now a vast and growing field. Whilst mountains were and continue to be the domain of professional mountaineers, there is increasing number of people ascending to high altitudes for leisure, taking part in commercial or charity expeditions, as well as heading there for work. It is not surprising that in those austere, remote and physiologically challenging environments, some of them fall ill. Specialists with an interest in mountain medicine are few and resources are not always available in those remote locations. What can be lifesaving is basic knowledge of high altitude medicine. This book, edited by Dr Jorge Hidalgo, aims to introduce concepts from the field in an approachable manner. It is not overbearing with facts and physiology, but at the same time it respects readers' thirst for understanding. The editor's intention has been to use "teaching moments" approach, basing clinical considerations on real cases. This allows to frame the approach to high altitude problems, whilst providing a sketch of the available evidence with regard to treatment. The evidence contours are not exhaustive, but this serves another purpose. Imperfection is an advantage as it fuels growth. A need to revise, reinvent, and

re-appraise evidence means that this book has a potential to grow with time becoming a "living text" that adapts to our understanding of high altitude physiology and medicine. Multinational faculty contributing to this book does so with enthusiasm taking a reader on a journey by providing context to each case. I am hopeful that the book will find place not merely in university libraries, but on rough shelves of mountain shelters and remote health posts. Its format lends itself also to becoming an online resource for medics heading into the mountains, as well as those seeking introduction to an amazing medical specialty. Perhaps the knowledge contained within will help to save a life. "Great things are done when men and mountains meet; this is not done by jostling in the street"—remarked William Blake. Perhaps readers will meet with the book and find inspiration within those pages, to delve deeper into the mountains and mountain medicine, and to catch a breath of fresh air—as this is not done simply by jostling in the street.

Piotr Szawarski

Consultant in Anesthesia and
Intensive Care Medicine
Frimley Health NHS Foundation Trust
Wexham Park Hospital, Slough, UK

Acknowledgments

The preparation of this project *High Altitude Medicine* required the effort of many individuals. We want to thank the authors or collaborators for coming on board on this endeavor, being able to support the pressure of a timeline, taking a moment to satisfy the call for expertise and help, and keeping aside multiple other tasks and, indeed, personal time.

We sincerely appreciate the talent and accomplishments of the Springer professionals, Miranda Finch and in particular, Eugenia Judson, who partnered with us all along and took our manuscript and produced it into this book.

Finally, many thanks to our patients, the ultimate motive of us to be physicians, to whom we must express our gratitude. They trust us with their lives and give us the courage and motive to be consensually learning and actions to make us always keep the utmost attention to details. We welcome all comments, pros, cons, and suggested revisions.

MBBS, MRCPI (Internal Medicine, Dublin),
EDIC, DA (Diploma Anaesthesia, Gold Medal)
Chief Medical Officer and Head Critical Care and
Accident and Emergency
Swami Dayanand Hospital
New Delhi
India

Dr Ranajit Chatterjee

We would like to express our deep gratitude to Professor Ranajit Chatterjee, for his academic contribution, enthusiastic encouragement, and for his useful and constructive recommendations for this project.

Contents

Chapter 1
Introduction to High Altitude Medicine

Jose Alfonso Rubio Mateo-Sidron, Fernando Eiras Abalde, and Jorge Hidalgo

Objectives

Know the pathophysiology of high-altitude diseases (HAI).
Know the clinical presentation of HAI.
Know the preventive measures of HAI.
Know the treatment of HAI.
Know the controversies in HAI.

Case Study

We present the case of a 32-year-old male from Europe (he lives about 2–10 m above sea level). He decided to go on a trip and do mountaineering. He had made several routes throughout his life, but never at such altitude. Its maximum height target was 5790 m. Over the course of 3 days, he progressively climbed, but upon reaching the refuge at 4708 m, he began feeling shortness of breath, fatigue, exhaustion and neurological disorders (improper speech, refusal to eat, incoordination). Nevertheless, he decided continue climbing until his final goal. Due to this progressive clinical deterioration, the team decided to descend to the shelter, where they

J. A. R. Mateo-Sidron
Critical Care Medicine, Hospital Universitario Vithas Arturo Soria, Madrid, Spain

F. E. Abalde (✉)
Intensive Care Unit (ICU), Pontevedra University Hospital Centre, Pontevedra, Spain
e-mail: fernando.eiras.abalde@sergas.com

J. Hidalgo
Critical Care, Belize Healthcare parners, Belize, Belize

J. Hidalgo et al. (eds.), *High Altitude Medicine*,
https://doi.org/10.1007/978-3-031-35092-4_1

began treatment with oxygen. He continued to deteriorate so he was transferred to a hospital.

Upon arrival at the hospital his vital signs were: Tª 35.5 °C HR 110lmp BP 135/85 mmHg FR 36 rpm SatO2 81% with ventimask reservoir. GSC 11/15. Auscultation showed cardiac tachycardia, and pulmonary generalized crackles. In lower limbs, there was mild edema.

Blood test showed: Biochemical: Glucose 113 mg / dl. Urea 34 mg / dl. Creatinine 0.7 mg / dl. Na 145 mEq / L. K 4.2 mEq / L. Arterial blood gas: pH 7.41 pCo2 40 mmHg pO2 51 mmHg SatO2 81% HCO3 26. Hemogram: Hb 13.9 g / dl. Platelets 85 × 109 / L. Leukocytes 7 × 109 / L. Coagulation: Normal. ECG: Sinus tachycardia. Normal QTc. Normal PR. Chest X-ray: bilateral diffuse interstitial infiltrates. Echocardiogram at bedside: No relevant alterations.

Treatment with dexamethasone and broad-spectrum antibiotics were started. Cultures were carried out.

At 24 h of admission, he persisted with progressive clinical deterioration, with worsening on the Glasgow to 7/15 and greater respiratory compromise in terms of mechanics, saturation, and hypoxia; therefore, it was decided to analogous sedation and relaxation, orotracheal intubation and connection to invasive mechanical ventilation. Throughout the days, the patient developed progressive neurological and respiratory improvement, which allowed extubating 5 days after admission to the ICU. Being discharged after 7 days.

Discussion of the Case

In our case, a patient without comorbidity who lives in an area of low altitude with respect to sea level, decides to undertake an ascent to more than 2500–3000 m. In addition, he does not carry out prophylactic measures prior to the ascent.

Based on the beginning of symptoms a few days after starting the ascent. Thorough clinical history, physical examination, and complementary tests, we can make differential diagnoses. The diagnostic hypothesis is: High altitude illness (HAI) which includes Acute Mountain sickness (AMS), High altitude cerebral edema (HACE) and High altitude pulmonary edema (HAPE).

On the one hand, the patient had some respiratory symptoms: cough, dyspnoea which progresses to cyanosis, tachypnoea, orthopnoea, and symptoms compatible with pulmonary edema. X-ray and laboratory tests were not suggestive of infectious disease, and echocardiography showed preserved LVEF.

HAPE is a non-cardiogenic pulmonary edema. Irregular pulmonary vasoconstriction, excessive perfusion in some areas, increased pulmonary capillary pressure and finally failure due to capillary “stress” occurs. Also, endothelial dysfunction due to hypoxia.

On the other hand, there were neurological symptoms: alterations in the level of consciousness, confusion, and ataxia of gait, progressing to further deterioration of the Glasgow.

HACE is produced by alteration of brain autoregulation in the presence of hypoxic cerebral vasodilation and permeability of the blood-brain barrier; all contribute to brain edema.

After starting treatment with corticosteroids and connection to mechanical ventilation, significant clinical improvement began.

Pathogeny

HAI encompasses the syndromes that can occur after an initial ascent to a high altitude, generally>2000-2500 m, or with a new ascent while at a high altitude. HAI includes: AMS, HACE, and HAPE [1].

The main mechanism that triggers these pathologies is hypobaric hypoxia (Hp). Hypoxia is defined as the reduction in the partial pressure of oxygen (PaO2) at the cellular level. This is the main causal agent of height-related diseases [2–4]. As the barometric pressure drops, so does the available oxygen. At high altitudes, especially when tissue oxygen demands are high, the marked reduction in pressure gradient and available oxygen can cause tissue hypoxia. There are other factors that influence barometric pressure, with little influence at low altitudes, but greater at high altitudes such as temperature and latitude [2].

The physiological compensation mechanisms for this Hp are acute or chronic:

Acute compensation mechanisms are divided into two stages (acclimatization and adaptation). The acclimatization stage runs from the ascent until about the fifth day. (a) Acute respiratory adaptation (hyperventilation) is the most immediate response. The hypoxic ventilatory response (HVR) is produced by the stimulation of peripheral chemoreceptors, producing an increase in minute ventilation. Increased ventilation increases alveolar pO2, reduces alveolar pCO2, increases pH. On the other hand, central chemoreceptors in the brain medulla respond to alkalosis in the cerebrospinal fluid (CSF) by inhibiting ventilation, so that the complete hypoxic ventilatory response is attenuated. (b) Acute circulatory adaptation (tachycardia). There is an increase in heart rate and cardiac output, increasing the supply of cellular oxygen. The other acute stage is Adaptation, which is established after the fifth day and produces an increase in haematocrit and improves the capacity to transport oxygen [2, 5–8].

Regarding chronic mechanisms, three are fundamentally three: (a) Erythrocytosis, defined as the increase in the number of red blood cells, which improves the O2 transport, causing an increase in blood viscosity. Increase in the synthesis of erythropoietin (EPO) by the kidney, stimulating the production of red blood cells in the bone marrow, the synthesis of 2,3-Diphosphoglycerate (2,3-DPG) is increased, producing a shift of the haemoglobin dissociation curve to the right. (b) Pulmonary vasoconstriction. HVR causes increased pulmonary vascular resistance, increased pulmonary arterial pressure, all with the aim of maintaining constant blood flow. Secondarily, the right ventricle hypertrophies when it must pump against a higher pressure. Cardiac output is initially elevated, with subsequent normalization. (c) At

the tissue level, hypoxia-inducible factor 1 (HIF-1) is elevated, stimulates vascular endothelial growth factor (VEGF), which stimulates angiogenesis and nitric oxide synthesis. All this produces greater blood flow, greater supply of oxygen to the tissues, improvements in oxidative metabolism and the exchange of tissue gases [2, 6–9].

In the development of AMS and HACE, it is considered a continuum of the same disease by many authors, the mildest forms being AMS and the most serious being HACE. The event that initiates AMS is excessive cerebral vasodilation in response to hypoxemia [2, 3, 5]. There is also mild astrocytic inflammation caused by a redistribution of fluid from the extracellular to the intracellular space without evidence of cerebral edema. All of this can trigger the activation of the trigeminal vascular system, causing headaches and nausea [10, 11]. If it continues to evolve, it will develop HACE. Edema formation occurs in HACE (the relationship between cerebral edema and AMS is less clear), initially cytotoxic (intracellular) edema, later extravascular ionic edema, evolving to vasogenic edema with protein extravasation and, finally, loss of integrity of the BBB with extravasation of red blood cells and microbleeds [12]. Brain edema will cause increased intracranial pressure (ICP), which if not stopped could cause brain herniation and finally evolve to death [13].

HAPE is initiated by an increase in pulmonary arterial pressure, by an initial cascade of physiological responses that seek to compensate the hypoxia but which over time become harmful [5, 7]. This elevated pulmonary pressure, associated with unevenly perfused areas; by regional phenomena of uneven vasoconstriction; they result in a failure of the integrity of the alveolar-capillary barrier and an irregular pulmonary edema throughout the lung. This process continues with the breakdown of the alveolar-capillary barrier, producing leakage into the alveolar space of liquid, proteins and cells. This extravascular fluid in the alveolar spaces will make gas exchange difficult. If this is perpetuated, it will produce alveolar haemorrhage. There is a probable genetic component in the development of HAPE, not yet well studied, due to the interpersonal variability of the response to exposure in height [2, 5, 14].

Clinic

As we discussed earlier, most experts consider AMS and HACE to be different stages of severity of the same process [7, 15].

AMS Clinic

The onset of symptoms is highly variable. It can start very early, 1–2 h after the ascent, although it usually takes 6–12 h or up to 24 h. On the other hand, symptoms usually resolve within a day or two, if there is no further ascent.

Symptoms can be mild or very disabling. Among them mainly are headache, fatigue, light-headedness, anorexia, nausea, vomiting, and sleep disorders [16].

HACE Clinic

What characterizes and makes HACE different from the rest of the pathologies of the HAI spectrum are the neurological symptoms and signs; these include altered level of consciousness, irritability, confusion, drowsiness, stupor, coma, gait disturbance. Ataxia is one of the most characteristic symptoms; they also tend to have tandem gait involvement and much less frequent finger-nose involvement [10, 11, 15].

The appearance of general neurological signs should make us think about the probable evolution from AMS to HACE. This transition may be progressively or abruptly.

HAPE Clinic

Initial symptoms usually appear 2–4 days after the ascent, although sometimes it occurs earlier. It occurs more often at night or after strenuous exertion. Development after a week at the same altitude is very rare.

The most frequent symptoms of HAPE at the beginning are non-productive cough and dyspnoea on exertion. This progresses to dyspnoea at rest or with minimal effort, productive cough (pink, frothy sputum, or frank blood). All of this associated with tachycardia, tachypnoea, tirage, or low-grade fever. Crackles are frequent. The highlight of this pathology is the great dissociation between the patient's great hypoxemia and clinically finding a better patient than expected for this hypoxemia [4, 5].

The association between AMS / HACE and HAPE is frequent, especially as we increase in height [17].

One of the problems that are established to identify this pathology is that the symptoms are frequently confused with an infection of the upper respiratory tract or dyspnoea secondary to altitude or exhaustion.

There are another series of diseases related to altitude that we include in this section, as they are not specific to altitude, although they usually appear in these conditions.

Acute hypoxia. High altitude pharyngitis and bronchitis. Headache at high altitude. High altitude syncope. Organic brain syndrome. Peripheral edema. Periodic sleep breathing. Ultraviolet keratitis. High altitude retinopathy. Hypothermia and frostbite. Deterioration at high altitude. Pulmonary edema. Monge's disease, chronic mountain polycythaemia. High-altitude pulmonary hypertension. Pregnancy problems: pre-eclampsia, hypertension, and low-birth-weight babies. T cell dysfunction [18–20].

Diagnosis

AMS Diagnosis

AMS is diagnosed clinically in those patient who, having recently ascended high altitudes (generally more than 2000 m), initiates typical symptoms referred to in the section (CLINIC SECTION) [21].

Diagnosis is made by physical examination, vital signs, laboratory values, and SpO2 oxygen saturation.

If the symptoms appear more than 2 days after reaching the altitude, there is absence of headache, and there is not an improvement after administration of supplemental oxygen, this should make us consider an alternative diagnosis.

Radiographic or laboratory tests are not warranted unless the diagnosis is unclear [21–23].

There are diagnostic support scoring systems such as the Lake Louise AMS score (Table) [23]. Which is the most widely used standardized method today. There are another series of interesting tools such as Screening for acute mountain sickness.

HACE Diagnosis

The diagnosis is clinical, we must suspect it in a patient who makes an ascent in height and initiates neurological symptoms and signs (CLINICAL SECTION). The complementary tests are only useful to exclude other diagnoses, except brain magnetic resonance imaging (MRI).

In laboratory tests, an increase in the white series stands out. There is usually hypoxemia, respiratory alkalosis, and low saturation in pulse oximetry. CSF biochemistry will be normal, with increased opening pressure. The chest radiograph may reveal pulmonary edema or be normal. Brain computed tomography (CT) may show brain edema and signal attenuation [21, 23, 24].

Finally, in MRI, it is the most useful test, the characteristic pattern of magnetic resonance is observed, consisting mainly of involvement of the corpus callosum - preferably in the splenium (SCC). In FLAIR sequence, a lesion is marked in SCC, confirmed by DWI, with increased values in the apparent diffusion coefficient (ADC), which indicates a greater diffusion of the water compatible with vasogenic edema. The MRI can remain altered for days or weeks, highlighting that hemosiderin deposits could remain for years. There is no correlation between MRI severity and subsequent clinical outcome [25, 26].

2018 Lake Louise acute mountain sickness score

Headache		
	0 points	None at all
	1 points	A mild headach
	2 points	Moderate headache
	3 points	Severe headache, incapacitating
Gastrointestinal symptoms		
	0 points	Good appetite
	1 points	Poor appetite or nausea
	2 points	Moderate nausea or vomiting
	3 points	Severe nausea and vomiting, incapacitating
Fatigue and/or weakness		
	0 points	Not tired or weak
	1 points	Mild fatigue/weakness
	2 points	Moderate fatigue/weakness
	3 points	Severe fatigue/weakness, incapacitating
Dizziness/light-headedness		
	0 points	No dizziness/light-headedness
	1 points	Mild dizziness/light-headedness
	2 points	Moderate dizziness/light-headedness
	3 points	Severe dizziness/light-headedness, incapacitating
AMS clinical functional score		
Overall, if you had AMS symptoms, how did they affect your activities?		
	0 points	Not at all
	1 points	Symptoms present, but did not force any change in activity or itinerary
	2 points	My symptoms forced me to stop the ascent or to go down on my own power
	3 points	Had to be evacuated to a lower altitude

HAPE Diagnosis

It develops in those patients who, after an ascent, start the respiratory symptoms previously referred to (CLINIC SECTION). The diagnosis, as in the other pathologies related to the height, is based on the history and the physical examination.

Outstanding findings on examination include tachycardia, tachypnoea, tracing, low-grade fever, and lung crackles. The oxygen saturation by pulse oximetry is significantly decreased below that expected for altitude. Laboratory tests are not specific for diagnosis. The white series, brain natriuretic peptide (BNP), troponin may be elevated. [27, 28].

Chest X-ray may be helpful with chest X-ray. In it, bilateral alveolar infiltrates - very rare unilateral involvement - are usually observed, patchy predominantly in the right central hemithorax - not always -, which increase in size and converge with the progression of the disease [21, 28–30].

Chest computed tomography (CT) usually shows patchy lobular ground glass and consolidation opacities, reflecting a heterogeneous alveolar filling.

Echocardiography reveals an increase in pulmonary artery pressure and, occasionally, a dysfunction of the right heart. Lung ultrasound detects an increase in extravascular lung water consisting of B lines [31].

Differential Diagnosis (DD)

AMS DD

The AMS generates doubts at the time of diagnosis, since it has a heterogeneous clinic that can be confused with exhaustion or a viral clinic, like influenza, asthenia, generalized fatigue, myalgia, headache, exhaustion. On other occasions it is confused with dehydration - thirst, weakness, headache, and nausea- (the latter with a good response to fluid replacement) [4, 32, 33].

HACE DD

Hypothermia and taking medications can cause neurological alterations, so we must keep them in mind when establishing the diagnosis of HACE. When a focal neurological affectation is present (hemiparesis, speech alteration or a visual deficit) it should make us consider an alternative diagnosis (ischemic stroke, haemorrhage). There is an extensive list of pathologies with which to perform the differential diagnosis.

Ingestion of toxins, carbon monoxide toxicity, anxiety, brain neoplasms, Diabetic ketoacidosis, hypoglycaemia, hyponatremia, hypothermia, brain

abscess, infection, Guillain-Barré syndrome, intracranial haemorrhage, ischemic stroke, transient ischemic attack, migraine, dehydration, King's syndrome [15, 32, 33].

HAPE DD

The main DD of HAPE is infectious. To differentiate it from pulmonary infectious pathology, we can help ourselves with the little clinical expressiveness of the picture in relation to the great hypoxemia and radiological affectation that the patient presents; as well as a good response to the supplementary oxygen therapy administered and the decrease in height. On the other hand, infectious pathology usually lasts longer. Pneumonia, although it can coexist with HAPE, is rare.

DD includes viral upper respiratory infection, pneumonia, bronchospasm, asthma, acute decompensated heart failure, exercise-associated hyponatremia, myocardial infarction, pulmonary embolism and pneumothorax [1, 5, 28, 33]

Treatment

AMS and HACE Treatment

Decrease in height is the best measure for AMS and HACE treatment. It is necessary in cases of progression of AMS, severe disease or HACE. The resolution of symptoms is variable for everyone, but usually improves after the descent from 300 to 1000 m [1].

Administered supplemental oxygen improves AMS symptoms and may serve as an alternative to descent or when symptoms are severe. Its use is necessary in cases of severe AMS progression or HACE [1, 35].

Portable hyperbaric chambers are effective in treating severe AMS or HACE. Symptoms improve significantly, but they usually reappear within 12 h. Its use should not delay the descent [1, 34, 35].

Acetazolamide treatment accelerates acclimatization to high altitudes. Only one study has examined it for the treatment of AMS, most use it in prevention. The dose studied was 250 mg every 12 h (72), although the usual dose is 125–250 mg twice a day (up to 750 mg a day) [1, 34, 36].

Dexamethasone is effective in improving symptoms, but it does not facilitate acclimatization. It should be used in moderate / severe AMS or HACE as soon as it is available. There are few studies, but extensive experience with its use in this pathology. The recommended dose is an 8 mg dose followed by 4 mg every 6 h until symptoms resolve. It can be used alone or in combination with acetazolamide [1, 34, 36].

As in all patients, we must assess ABCDE. Monitor the HACE patient for the probability of a low level of consciousness and the need for airway isolation. In addition, it is vitally important to monitor hypotension that may have repercussions in a probable cerebral ischemia due to alteration of cerebral autoregulation. On the other hand, once in a hospital centre, monitor intracranial pressure (ICP) to initiate general measures to control intracranial hypertension, if necessary, to avoid secondary brain damage.

HAPE Treatment

Although some treatments are the same for HAPE as for AMS / HACE, there are some differences, due to the pathophysiological difference of the disease.

The descent is indicated, when possible or when oxygen therapy treatment does not improve symptoms. It is also important to reduce physical activity to a minimum, as well as increasing the temperature [1, 34].

Supplemental oxygen is the vital part in the treatment of HAPE. When available, it should be given to achieve an SpO2 goal of>90% to relieve symptoms. Decreases hypoxemia, reduces pulmonary artery pressure, reverses capillary leak, and improves symptoms [1, 34].

The use of portable hyperbaric chambers should not delay descent in situations where descent is feasible. It can be combined, if available with oxygen therapy, pharmacotherapy. There are no systematic studies, but if it is collected in the literature. In the hospital environment, being at a lower altitude and having high-flow oxygen therapy; the use of hyperbaric therapy is usually not necessary [1, 34].

There is no systematic evidence that CPAP or EPAP improves patient outcomes compared to oxygen alone or in conjunction with medications [1, 37].

Nifedipine works by reducing pulmonary vascular resistance and pulmonary arterial pressure. Its usefulness is based on a single study, and it is proposed that it can be used as an adjuvant therapy when there is no oxygen available or portable hyperbaric chamber, or when the descent is difficult. Prospective study proposed little utility. Recommended dosages vary, but a common regimen is to administer 30 mg (slow-release formulation) every 12 h [1, 34, 38].

There is little evidence of the use of beta-agonists in HAPE. Although they could be useful [1].

The use of PDE-5 phosphodiesterase inhibitors: Sildenafil and tadalafil produce pulmonary vasodilation and decrease the pressure of the pulmonary artery. No systematic study has evaluated it, but physiologically it seems that they may be useful. Its use is considered as a therapy when there is no available oxygen or portable hyperbaric chamber, or when the descent is difficult and nifedipine is not available. Avoid combined use of nifedipine and sildenafil or tadalafil should be avoided due to risk of hypotension [1, 39].

Regarding the use of dexamethasone, there is discrepancy among the experts. A priori it could be useful (prevention of HAPE, reduction of lung inflammation). No

study has established whether it is effective. There is no recommendation in this regard. If may be useful when coexisting with AMS / HACE [1, 40].

Prevention

Within prevention, it is important to carry out a physical examination, as well as a clinical interview before the ascent; so we can predict those people with a higher risk of developing disease at altitude.

Those people who have been to a high altitude before, knowing the behaviour that they have previously had, will serve as a predictor of behaviour when they are exposed to that same height. We have the biggest problem in those people who have never been exposed to heights; for this, there is a model to identify people at risk of suffering a serious altitude illness, although this model is currently being questioned [22, 41].

AMS/HACE Preventive

Gradual ascent is a very useful measure in preventing disease. A gradual ascent is recommended, planning the ascent speed, and above all, even more importantly the overnight altitude [1, 34].

Acetazolamide should be taken prophylactically, in people at moderate or high risk of AMS with high-altitude ascent. Facilitates acclimatization. The recommended prophylaxis dose for adults is 125 mg every 12 h (up to 750 mg daily) [1, 34].

Dexamethasone does not facilitate acclimatization. There is a benefit in preventing AMS. Doses are 2 mg every 6 h or 4 mg every 12 h (Consider even 4 mg every 6 h in very high-risk situations). It can be used as an alternative to acetazolamide for adult travellers at moderate or high risk of AMS [1, 34].

Acetazolamide and dexamethasone should be started the day before the ascent, but still have beneficial effects if started on the day of the ascent.

Ibuprofen can be used for the prevention of AMS in people who do not want to take other preventive medication.

The use of paracetamol or budesonide inhaled is not recommended [1].

When possible, ascent in stages and pre-acclimatization can be considered as a method of prevention of AMS. In literature it is not studied at all. It seems, is that spending 6–7 days at a moderate altitude (2200–3000 m) before proceeding to a higher altitude reduces the risk of AMS [1, 34].

Hypoxic tents can be helpful in facilitating acclimatization and prevention of AMS, provided sufficiently long exposures are taken regularly.

Products derived from coca or Gingko biloba, reduced AMS in some trials, but in others. No recommendation can be made [1, 42].

Other methods without evidence: antioxidants, iron, dietary nitrates, leukotriene receptor blockers, phosphodiesterase inhibitors, salicylic acid, spironolactone, and sumatriptan, “forced“or “excessive” hydration [1].

HAPE Preventive

Some of the prophylactic methods are the same for AMS / HACE as for HAPE, important differences in pathophysiology establish small changes.

A gradual ascent is the main method of preventing HAPE. Although it is true that no studies have evaluated it prospectively, there is a clear relationship between the rate of ascent and the incidence of diseases [1, 34, 39].

Nifedipine is recommended for the prevention of HAPE in people susceptible to HAPE. The recommended dose is 30 mg prolonged-release every 12 h. It should start the day before the ascent and continue until the descent begins or 4–7 days have passed at the highest elevation [1, 34, 39].

Tadalafil can be used for the prevention of HAPE in known susceptible individuals who are not candidates for nifedipine [1, 34, 39].

Dexamethasone can be used to prevent HAPE in known susceptible individuals who are not candidates for nifedipine and tadalafil [1, 34, 39].

Acetazolamide accelerates acclimatization and should be effective in prevention. If that could be recommended for prevention in people with a history of HAPE [1, 34, 39].

Salmeterol is not recommended for HAPE Prevention [1, 34].

Pre-acclimatization and staggered ascent: No studies have examined this in HAPE. But it seems clear that it would be recommended [1, 34].

Question Discussion

We have already discussed many of the controversies throughout the topic, and we will leave many others behind; but I would like to emphasize the following.

Is there increased cerebral blood flow in patients with AMS?

Hypoxemia produced by AMS may involve increased cerebral blood flow (CBF). The CBS is not clear that there are differences between those with and without AMS. There are controversial results, possibly due to changes in the diameter of the middle cerebral artery (CBS remained unchanged); changes in internal carotid artery diameter were not correlated with high altitude headache [36, 43].

What is the dose of acetazolamide in prophylaxis?

Acetazolamide is important in the prophylaxis of AMS. There is much debate about the appropriate dose. Most studies suggest that 125 mg twice a day is sufficient, but higher doses may be necessary in too rapid ascents and / or ascents to very high final altitudes [1, 36, 44].

Is the use of intermittent hypobaric or normobaric hypoxic exposures useful prior to ascent?

Studies have reported conflicting results regarding intermittent hypobaric or normobaric hypoxic exposures, with some studies showing benefit and others showing no clear effect [45, 46].

Key Points

- Early identification of diseases associated with altitude is important. Especially HACE and HAPE.
- The evaluation of patients prior to the ascent and the implementation of prevention measures play an important role in this type of pathology.
- The most important prevention is gradual ascent, acetazolamide and sometimes dexamethasone or nifedipine.
- Hyperbaric hypoxia is the main trigger mechanism, understanding the pathophysiology allows us to understand how to address it.
- Once the disease is established, administering supplemental oxygen, lowering the height, hyperbaric chambers, and sometimes dexametamethasone are vital for the patient.

References

1. McIntosh SE, Freer L, Grissom CK, Auerbach PS, Rodway GW, Cochran A, et al. Wilderness medical society clinical practice guidelines for the prevention and treatment of frostbite: 2019 update. Wilderness Environ Med. 2019 Dec;30(4S):S19–32.
2. West JB. American College of Physicians, American Physiological Society. The physiologic basis of high-altitude diseases. Ann Intern Med. 2004;141(10):789–800.
3. Anholm JD, Foster GP. Con: hypoxic pulmonary vasoconstriction is not a limiting factor of exercise at high altitude. High Alt Med Biol. 2011;12(4):313–7.
4. Hackett PH, Roach RC. High-altitude illness. N Engl J Med. 2001;345(2):107–14.
5. Gallagher SA, Hackett PH. High-altitude illness. Emerg Med Clin North Am. 2004;22(2):329–55. viii
6. Tinoco-Solórzano A, Nieto Estrada VH, Vélez-Páez JL, Molano Franco D, Viruez SA, Villacorta-Córdova F, Avila Hilari A, Cahuaya Choque CA. Medicina intensiva en la altitud. revisión de alcance. Revista de Medicina Intensiva y Cuidados Críticos. 2020;13(4):218–25.
7. Schoene RB. Illnesses at high altitude. Chest. 2008 Aug;134(2):402–16.
8. Monge C, Leon-Velarde F, Rivera M, Palacios J. Altura: Conocimientos Basicos: Realizacion: Unidad De Diagnostico De Tolerancia A La Altura (Udta) | Hipoxia (médica) | Edema. Inst Investig Altura UPCH. 2000;1(1):1–11.
9. West JB. Physiological effects of chronic hypoxia. N Engl J Med. 2017;376(20):1965–71.
10. Sanchez del Rio M, Moskowitz MA. High altitude headache. Lessons from headaches at sea level. Adv Exp Med Biol. 1999;474:145–53.
11. Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitudes. Lancet Neurol. 2009;8(2):175–91.
12. Meier D, Collet T-H, Locatelli I, Cornuz J, Kayser B, Simel DL, et al. Does this patient have Acute Mountain sickness?: the rational clinical examination systematic review. JAMA. 2017;318(18):1810–9.