Review Article

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High Altitude Pulmonary Edema, High Altitude Cerebral Edema, and Acute Mountain Sickness: an enhanced opinion from the High Andes – La Paz, Bolivia 3,500 m

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Abstract: Traveling to high altitudes for entertainment or work is sometimes associated with acute high altitude pathologies. In the past, scientific literature from the lowlander point of view was primarily based on mountain climbing. Sea level scientists developed all guidelines, but they need modifications for medical care in high altitude cities. Acute Mountain Sickness, High Altitude Pulmonary Edema, and High Altitude Cerebral Edema are medical conditions that some travelers can face. We present how to diagnose and treat acute high altitude pathologies, based on 51 years of high altitude physiology research and medical practice in hypobaric hypoxic diseases in La Paz, Bolivia (3,600 m; 11,811 ft), at the High Altitude Pulmonary and Pathology Institute (HAPPI – IPPA). These can occasionally present after flights to high altitude cities, both in lowlanders or high-altitude residents during re-entry. Acute high altitude ascent diseases can be adequately diagnosed and treated in high altitude cities following the presented guidelines. Treating these high-altitude illnesses, we had no loss of life. Traveling to a high altitude with sound medical advice should not be feared as it has many benefits. Nowadays, altitude descent and evacuation are not mandatory in populated highland cities, with adequate medical resources.

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Keywords: high altitude; high altitude illnesses; high altitude physiology; hypobaric hypoxia; mountain climbing; physiologic adaptation.

Background

Planet Earth is not a smooth sphere, it has geographic spikes that include: the Himalayas [max. elevation 8,848 m; 29,029 ft], the Andes [max. elevation 6,962 m; 22,841 ft], the Alps [max. elevation 4,809 m; 15,776 ft], the Transatlantic mountains [max. elevation 4,528 m; 14,856 ft], the Rocky Mountains [max. elevation 4,528 m; 14,856 ft], and several others. Not all mountains are inhabitable, being the Andes among the most populated. Some high altitude destinations include Lhasa – Tibet, China (3,650 m; 11,975 ft), Cusco, Peru (3,300 m; 11,000 ft), La Paz, Bolivia (3,100 m – 4,100 m; 10,170 ft – 13,451 ft), and Potosi, Bolivia (4,100 m; 13,451 ft). Cities with over 1,000,000 inhabitants include the following: La Paz and El Alto, Bolivia (3,100 m – 4,100 m) "the Capital of Hypoxia" followed by Quito, Ecuador (2,784 m), Toluca, Mexico (2,648 m), Cochabamba, Bolivia (2,621 m), Bogota, Colombia (2,601 m), Addis Ababa, Ethiopia (2,362 m) Mexico City, Mexico (2,316 m), Xining, China (2,299 m), Sana'a, Yemen (2,316 m), and Puebla, Mexico (2,176 m) (https://www.visualcapitalist.com/the-50-highest-cities-in-the-world).

Originally, Acute Mountain Sickness (AMS), High Altitude Pulmonary Edema (HAPE), and High Altitude Cerebral Edema (HACE) were described based on mountain climbing. Due to the alarming symptomatology, travel to high altitudes for entertainment purposes or residence is still feared by most people. Mainly because classically, no apparent cause of the disease was found other than the exposure to the hypobaric hypoxic environment. However, our experience for over half a century at the High Altitude Pulmonary and Pathology Institute (HAPPI – IPPA) in Bolivia, living and working in La Paz and El Alto cities with >2.3 million inhabitants between 3,100 m and 4,100 m of

altitude, provides us with a different point of view. High altitude should not be feared and should be understood instead in its risks and even in its benefits, particularly when traveling to high altitude cities. It is important to note that the normal arterial partial pressure of oxygen (PaO_2) in La Paz is 60 mmHg, 1/3 less than at sea level. Under certain circumstances, upon arrival at high altitude, children and adults (newcomers or native residents re-entry) can sometimes suffer AMS, HAPE, or HACE.

Reports from sea-level refer that HACE and HAPE have mortality rates up to 40% where there is little medical care [1]. This is not our experience at 3,500 m, in our medical practice. Nobody should die from these diseases in a high altitude city.

We previously published "Acute Mountain Sickness, High Altitude Pulmonary Edema, High Altitude Cerebral Edema, a view from the High Andes" [2] that unfortunately was not fully understood by some experts in the field. La Paz (4,100 and 3,100 m) is considered the "Capital of Hypoxia" and the 51-years-old medical experience from our Institute is expressed in this article. Making use of Peter Bartsch's altitude classification [2], we classified 76% of the specialists who criticized our paper as sea-level residents (13), two were low altitude dwellers <1,600 m, one was from moderate altitude 2,200 m, and only one was a high altitude dweller 3,500 m (who apparently has no first author publications in this field and seems to just follow sea level publications). Their influence resulted in a Retraction of the article despite our disagreement, and support from multiple distinguished international doctors and scientists (http://altitudeclinic.com/blog/2021/07/ams-hape-hace-a-view-from-the-high-andes/). Some of their observations were answered in a previous article [3]. This new "Enhanced" version comes to light responding to several trivial observations from them. Retraction watch contacted us, and an informative publication in their blog followed: (https://retractionwatch.com/2021/09/10/misleading-and-inaccurate-information-rocky-tenure-for-high-mountain-paper-as-complaints-prompt-retraction/).

We find a conflict with the belief that high altitude hypoxia is normally deleterious, implying that people living at high altitude gradually "deteriorate", as most sea-level scientists believe. They appear to be highly fearful of hypobaric hypoxia, as hypoxia has been historically associated with illness and death in their living habitat at sea level. During the International Consensus on high altitude diseases, there was an extensive discussion of the use of "Loss of Adaptation" in reference to Chronic Mountain Sickness, where our team as the only ones living and practicing at high altitude, opposed its use from the medical and pathophysiological point of view [4]. We understand comparative studies of life over millions of years in other non-medical-practitioner fields consider the concept of "adaptation" referring to genetic observations, but as high altitude medical practitioners, we find contradictions in the words used to describe certain population differences, as over 200 million people live at high altitude worldwide. We believe that if life was not adapting in some way at high altitude, it would lead to the loss of life and possibly to the end of entire populations. We personally find the concept of "acclimatization" inaccurate and exclusive as it implies a value judgement of certain populations as more adapted or as having a higher right to live under certain environments. Although not originally defined as such, it leads to great confusion among highlanders. As high altitude dwellers, with Spanish ancestry and belonging to long-lived and healthy families, we do not find high altitude as a disadvantage in any way. We believe the establishment of certain wording used for describing our human capacity or non-capacity to "adapt" to high altitude requires further discussion and the inclusion of all international experts in the health sciences field, particularly those who live and work at high altitude. Moreover, in this paper, we use the word "adaptation" as referring to the process of being able to physiologically adapt to the given circumstances in the environment. We do not refer to the genetic wording established by other fields or experts.

Accordingly, based on our human studies, we have postulated the theory of the tolerance to hypoxia formula, where we show that paradoxically the higher humans go, the more tolerant they are to hypoxia [5]. This attempts to explain why Messner and Habeler were able to reach the summit of Mt. Everest without oxygen, a feat previously thought impossible. The application of this formula needs further population studies, particularly in other species as rodents studies consider mice were able to adapt to the highlands better than rats [6]. A man on the summit of Mount Everest breathing ambient air is over six times more tolerant to hypoxia than a sea-level dweller [5] (PaO_2=25 mmHg at 8,400 m) [7]. We have previously described extended longevity at high altitude [8]. Would people live longer at high altitudes than in the lowlands if they were continuously "deteriorating"? We find a contradiction here. Rats may be scarce in the highlands but humans are not. Better scientific explanations are required to explain these differences in species. Rats' studies may have limitations regarding certain physiological aspects pertaining to the human-kind. What we wrote in 1989, in our book entitled "High Altitude Pathology at 12,000 ft", regarding HAPE and other high altitude diseases stands solidly to the test of time [9].

Some observations made on our work have been already published in a widely read paper [10]. We hereby respond to the rest of the observations made on our work with further evidence-based comments to explain our points of view. By following these guidelines, we have been 100% successful in treating the acute high altitude pathologies. Most observations in this paper refer to adults although some, as specified throughout the paper, apply to children. Furthermore, we present our view regarding "physiologic adaptation" and the most common high altitude-related illnesses based on our experience. Their prevention, treatment, and high altitude recommendations are discussed to ensure the well-being of all those traveling to a high altitude city.

High altitude physiology

High altitude physiology and biology follow the laws of physics and gases in lower barometric pressure (Figure 1). Life depends on water, carbon, multiple minerals, adequate temperature, and oxygen, with its end-product carbon dioxide playing a fundamental role in high altitude acid-base balance [11]. Partial pressure of oxygen of inspired air (PIO_2) is defined as: $PIO_2 = FiO_2 \times (Pb - 47\ mmHg)$, or $0.21 \times (760–47) = 149$ mmHg at sea level [12]. The barometric pressure and PIO_2 decrease exponentially with increasing altitude, where at 3,500 m: PB = 495 mmHg, PIO_2 = 94 mmHg [13].

The Oxygen Transport Triad (Pneumo-dynamic pump, Hemo-dynamic pump, and hemoglobin) plays a fundamental role in high altitude physiological adaptation [3, 14]. The gases in the Earth's atmosphere mainly composed of Oxygen 20.9% and Nitrogen 78% at any altitude, come in contact with the alveoli transported by the pneumo-dynamic pump that ventilates the lungs. Oxygen transfer across the alveolo-capillary membranes responds solely to diffusion [15]. At high altitude, the alveolar-arterial PO_2 difference ($A\text{-}aPO_2$) is reduced, from the sea level value of 5 mmHg to 2.7 mmHg in La Paz, Bolivia (3,500 m), due to the lower barometric pressure and physiological adaptation [16].

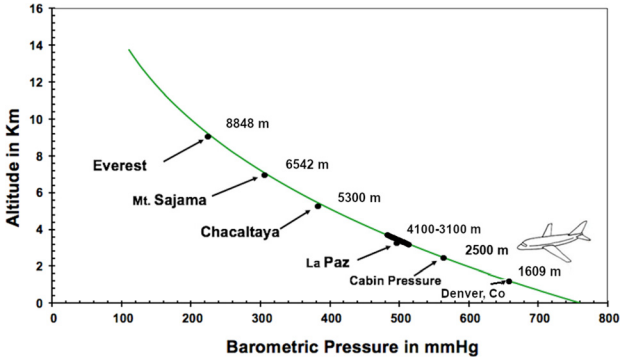

Figure 1: Barometric pressure – altitude relationship showing important high altitude landmarks. The cities of La Paz and El Alto (contiguous). Mount Chacaltaya (5,270 m or 17,290 ft, IPPA's high altitude glass pyramid laboratory location). Mt. Sajama (6,542 m or 21,463 ft, the highest Bolivian mountain and the world's highest soccer match field). IPPA.

The respiratory cascade is flatter at high altitude. At 5,230 m, in Chacaltaya, the Bolivian Aymara natives present an $A\text{-}aPO_2$ of 1 ± 1.4 mmHg where a lower ventilation/perfusion mismatch level is presumed [17], and a 173% higher diffusion capacity was observed [18]. These changes possibly represent fundamental physiologic adaptation mechanisms as reduced oxygen pressure at high altitudes needs to be optimized in the respiratory cascade.

Hemoglobin plays a crucial role in the capture and transport of oxygen. Dissolved oxygen is practically insignificant in the transport of oxygen itself, playing the role of maintaining the equilibrium of oxygen saturation in hemoglobin. The Oxygen Content in arterial blood is (CaO_2) $=(SaO_2 \times 1.34 \times Hb) + (0.003 \times PaO_2)$. The hemo-dynamic pump (cardiovascular system) plays the role of transporting hemoglobin loaded with oxygen (and all other plasma constituents) from the lungs to the capillaries in the tissues. Oxygen is then transported to the mitochondria by diffusion. In summary:

Pneumo-dynamic pump → alveolar-capillary oxygen diffusion → Hemoglobin oxygen capture → Hemo-dynamic pump → tissue capillary-mitochondria diffusion.

As blood returns to the lungs, circulation transports CO_2 to the lungs for partial exhalation, maintaining adequate levels for an optimal acid-base status containing a pH of 7.4. The arterial partial pressure of oxygen (PaO_2) is around 100 mmHg at sea level, and the SaO_2 is 95%–99%. In La Paz (3,500 m), PaO_2 = 60 mmHg, and SaO_2 = 88%–92%.

High altitude physiologic adaptation

Many authors use the term "acclimatization" to high altitudes. We believe that this term's use should be referred only to climatic changes, not barometric changes. Instead, we differentiate adaptation into two types: Genetic and Physiologic. The first takes many millions or thousands of years, whereas the latter includes (within one lifetime) short to long-term essential survival change. In our criteria, epigenetic phenotypic expressions are within the physiological adaptation scope, as they are "functional adaptations" as also referred to by others [19, 20]. As Frisancho pointed out back in 2013, there is a developmental

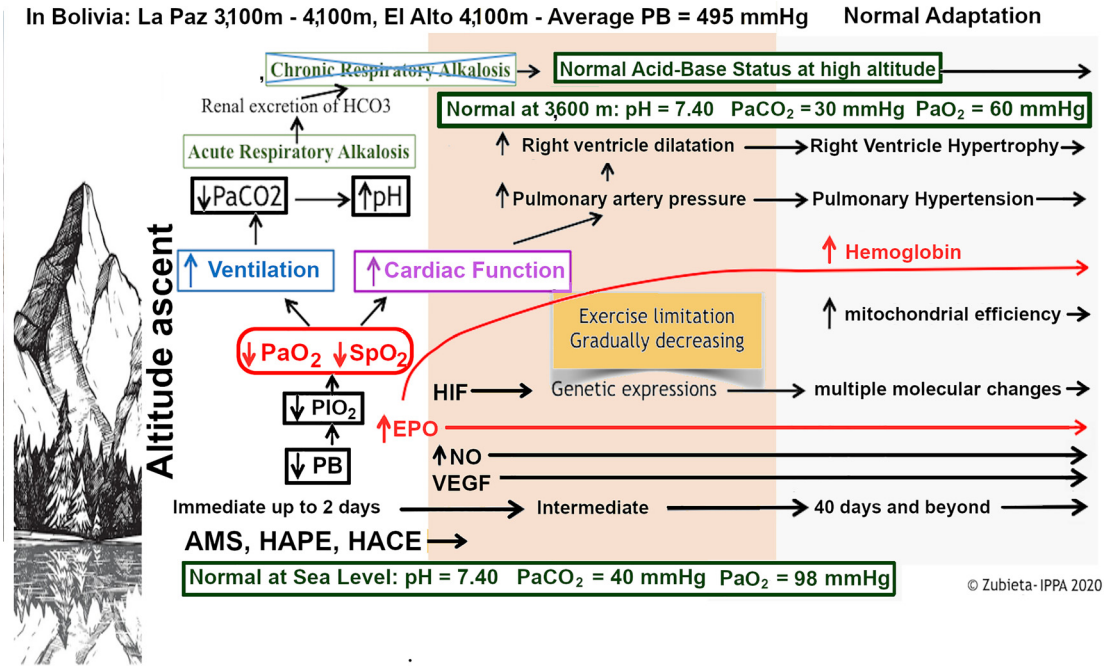

Figure 2: Time related physiological adaptation to high altitude. Starting from the bottom left side. Red ascending line: 40 days logarithmic hemoglobin increase to reach a plateau upon arrival to 3,600 m. PB = barometric pressure; PIO_2 = partial pressure of inspired oxygen; PaO_2 = arterial partial pressure of oxygen; SpO_2 = pulse oximetry saturation; $PaCO_2$ = arterial partial pressure of carbon dioxide; HIF = hypoxia inducible factor; NO = nitric oxide gas; EPO = Erythropoietin. The acid-base status should be interpreted according to the high altitude correction factors [11]. IPPA.

functional adaptation to high altitude [21], which we interpret as physiological adaptation. Storz and Scott also write about "physiological adaptation to high altitude hypoxia" [22]. Anthropologists now have a modern concept called "climate change adaptation" in reference to the changes humans make in response to or in anticipation of the adverse effects of climate change [23].

Acute symptomatic physiologic adaptation to high altitude resolves, in most cases, within 2 or 3 days, provided there is an adequate kidney and cardiovascular function. Ventilation (pneumo-dynamic pump) and Circulation (Hemo-dynamic pump) increase upon arrival and play the initial fundamental role of physiologic adaptation. Subsequently, optimal hematologic adaptation is achieved following the High Altitude Adaptation Formula = Hemoglobin/time [13]. The article, where this formula is explained, has 73 citations referred to as "a classic" by some scientists. The sentence we coined, "Full hematological adaptation to high altitude is achieved when the increase of red blood cells reaches a plateau and stops", can be found in multiple publications and books. Upon arriving at a high altitude from sea level, there is a logarithmic increase in hemoglobin (Figure 2). At 3,500 m, this curve takes approximately 40 days to reach the top plateau, where the final optimal adaptation is achieved [13].

Initial hyperventilation on arrival at high altitude is said to reduce the arterial partial pressure of carbon dioxide ($PaCO_2$) [24]. The resulting increase of pH above normal values referred to as acute respiratory alkalosis brings forth impaired metabolic function. Hypoxia is associated with Hypoxia-inducible factor (HIF) and Vascular endothelial growth factor (VEGF) production, and increases Erythropoietin (EPO) and nitric oxide gas (NO), all fundamental favorable mechanisms. However, the alkalosis cannot be sustained permanently, and the kidney eliminates bicarbonates returning the pH to normality (Figure 2). Maintaining a normal arterial pH is fundamental for survival in all species, as well as in high altitude physiological adaptation, and for optimal cellular function [25]. Once pH is restored, there is no chronic respiratory alkalosis at high altitude, but rather an optimal adaptation. The correct interpretation of acid-base balance requires altitude adjustments and corrections as previously published [11, 25, 26]. At extreme altitudes like Chacaltaya at 5,260 m, where we have our Glass Pyramid Chacaltaya laboratory (the highest in the world), the pH has been reported to be mildly alkalotic (pH=7.47) after 9 or 10 weeks [27]. However, this needs further studies and interpretation. Furthermore, reaching the Mount Everest summit requires an optimal pH following our acid-base high altitude correction factors of the Van Slyke Formula

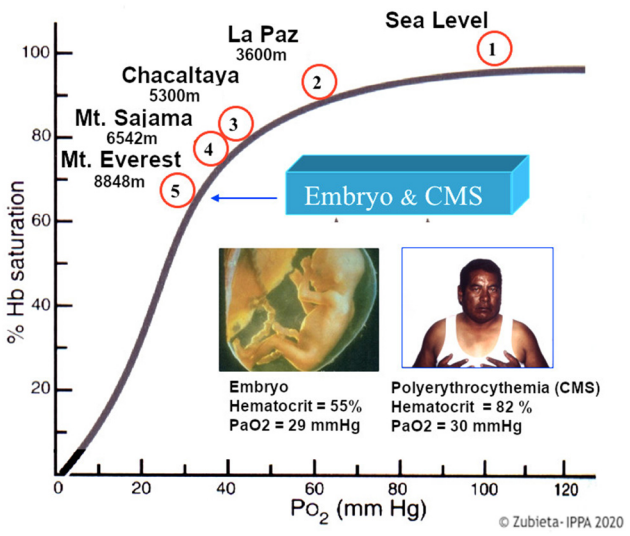

Figure 3: Hemoglobin dissociation curve showing different PaO_2 – SpO_2 levels in Bolivia in locations described in Figure 1. Embryo present a PaO_2 of 29–30 mmHg (similar to those at Mt. Everest). IPPA.

[26]. The SpO_2 reduces as the altitude increases following the hemoglobin oxygen dissociation curve (Figure 3). It is important to note that there are significant variations in SpO_2 upon breath-holding at high altitude (Figure 4) [28]. This explains why when measuring SpO_2 at high altitude at rest, even minor breathing changes make the values oscillate. Arterial blood gases at high altitudes have a lower PaO_2, a lower $PaCO_2$, and a normal pH range [25].

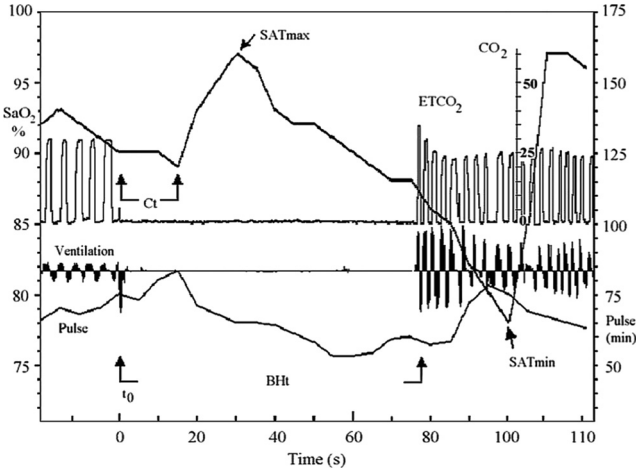

Figure 4: Breath-holding test developed at IPPA: From top to bottom on the left: SpO_2, $ETCO_2$, pneumotachograph ventilation and pulse. The black line shows SpO_2 variation during breath-holding in adults in La paz. The resting SpO_2 (SaO_2) from pulse oximetry is 90–92%. SATmax reached 97% (sea level values) and decreased to SATmin 78% until breathing reinstated. BHt = breath-holding time; $ETCO_2$ = end-tidal CO_2.

According to Prof. Dr. Gustavo Zubieta-Castillo Sr (1926–2015), "*The organic systems of human beings and all other species tend to adapt to any environmental change and circumstance within an optimal period of time, and never tend towards regression which would inevitably lead to death*". This sentence was originally inspired by the questionable concept of "Loss of adaptation" (mentioned as "regression" above) in reference to Chronic Mountain Sickness (CMS), which is not in the scope of this paper. However, its implications are immense as we believe adaptation is the process of being able to adapt to change be it acute or chronic, each in its own terms, and it can be applied even to the physiologic epigenetic adaptation to life in space that we refer to as "**BioSpaceForming**" [29].

High altitude acute pathologies

Acute mountain sickness (AMS)

The 2001 Consensus Statement of experts concluded, "AMS is as frequent in childhood as in adulthood" (Pollard et al. 2001). AMS is not present below 2,000 m. Few reports specify AMS incidence in childhood: 19% in Colorado at 3,109 m and 34% in Tibet at 4,550 m. Its frequency increases with the ascent rate and altitude reached. Upon arrival at a high altitude, the two pumps of the Oxygen Transport Triad are activated [3]. The sudden breathlessness on minimal exercise is associated with hyperventilation and tachycardia, a perfectly normal response. Nevertheless, AMS may develop within 6–24 h in some individuals.

AMS can manifest with headaches (cardinal symptom), sleeping disorders, uneasiness, dehydration from hyperventilation and diminished thirst sensation, loss of appetite, fatigue upon physical activities, and digestive gas expansion (an essential factor of digestive discomfort, poorly described in the current publications). HAFE (High Altitude Flatus Expulsion) has been described before [30].

We propose to use HAGE (High Altitude Gas Expansion) instead of HAFE. A detailed explanation of the physical behavior of intestinal gases at high altitudes can be read at [3].

Due to their dramatic effect, other significant symptoms are nausea and vomiting, which naturally worry parents. Initial vomiting can often be quite alleviating for children, not so if the symptom persists. We base this observation in acknowledging that both metabolism and digestion are disturbed after acute exposure to high altitude. The acute physiological adaptation mechanisms consume energy and oxygen, and the organism may

prioritize their usage by the vital organs: brain, heart, and possibly kidneys [31]. Furthermore, it allows for a better diaphragmatic expansion, essential for adequate ventilation. Persistent vomiting is a different story, where children can enter dehydration that may require adequate IV rehydration, mainly when there is anorexia.

Some patients present infectious superimposed diarrhea, further aggravating dehydration and malaise. Symptoms observed in preverbal children include increased fussiness, decreased appetite, poor sleep patterns, and reduced playfulness.

The diagnosis is primarily clinical, based on the fundamental fact of a recent arrival at a high altitude. However, other pathologies must be discarded. Exposure to high altitudes should be regarded as a test of cardio-pulmonary fitness [9]. Recent or chronic concurrent pathologies (sometimes silent at sea level) are common, e.i. Viral infections [32]. Most children and adults evolve favorably from AMS in 1 or 2 days.

Treatment

The treatment is based on the symptomatology, concomitant and base pathologies in each case. All concomitant diseases require treatment along with the derived symptoms and the hypoxemia observed. Mild headaches can be treated with aspirin (except in children younger than 15, and specific cases such as the presence of allergies or other contraindications). Acetaminophen can be used instead. Ibuprofen has also been reported to be helpful in adults [33]; however, we very rarely have used it. If the symptoms persist, oxygen administration at 2 L/min via nasal cannula for a few hours can be helpful. Most evolve favorably, however, a chest X-ray and laboratory tests should be performed if symptoms persist. Many physicians use acetazolamide, a diuretic, and a ventilatory stimulant. However, we hardly ever use it due to its side effects: dehydration and tingling sensation in the limbs. Although others recommend its use [34], it is controversial [35]. An additional recommendation is to use loose clothes for easy expansion of gastric and intestinal gases facilitating their unrestricted evacuation. Milk and its derivatives should be avoided on the first day of arrival except for babies, but lactose-free could help. Aspirin taken ½ hour before the arrival to high altitude in those older than 15 years of age can be helpful in our experience. Upon arriving at high altitude, hyperactivity in children and adults can be a risk factor to develop acute high altitude pathologies, as shortness of breath becomes more evident under intense physical activity.

However, very few travelers may present the most feared scenarios: HAPE, and very rarely HACE, the day after arrival and up to 3 days later. These two pathologies must be immediately diagnosed and treated as they can evolve to deadly consequences.

High Altitude Pulmonary Edema (HAPE)

Among the first to describe HAPE was Charles Houston. Overall, the incidence of HAPE in travelers climbing to an altitude of 4,550 m was reported to be 1.5% [32]. In general, HAPE incidence is around one in 10,000 visitors [36]. Noteworthy is that arriving by plane or bus to a high altitude city like La Paz and going to a comfortable hotel or lodging may most probably reduce the incidence compared to mountain climbers. Although the incidence is low, it is a high-risk pathology that can lead to a fatal outcome if not diagnosed and treated promptly. Hence, it becomes crucial that pediatricians and physicians treating children and adults at high altitudes be adequately informed.

Up-to-date, there is no conclusive scientific evidence determining the cause of HAPE. Noteworthy is Hultgren's hypothesis for the etiology of HAPE, where hypoxic pulmonary vasoconstriction can be extensive but uneven. The non-uniform response would expose the micro-vasculature to higher pressures in the less constricted areas giving rise to the typical patchy edema [37]. We also proposed a concomitant flue viral infection (such as catching a cold) that could aggravate or trigger uneven lung inflammation that would explain this patchy phenomenon, as altitude changes are often accompanied by climate changes and patients often catch common colds [9, 32]. This becomes more important now as what we described as the HAPE tongue is very similar to COVID-19 viral tongues and the irregular patchy distribution in lungs (see below).

Hypoxia [38], is a potent factor increasing microvascular permeability [39–43]. Claiming that HAPE is due to increased capillary pressure remains a highly questionable point. Only few data support this contention [44]. The strong criticism relies on estimating capillary pressure from occlusion pulmonary artery pressure and wedge pressure [45, 46]. Furthermore, if such were the case, no patchy isolated areas of pulmonary edema would be present but rather within the whole lung.

HAPE is considered to be characterized by exaggerated and unevenly distributed pulmonary vasoconstriction that results in a significant increase in the pulmonary artery and capillary pressure. No model has been developed thus

far to confirm this fluid dynamic hypothesis. Based on computational modeling [47, 48], capillary de-recruitment (the consequence of vasoconstriction) was found to be a potent factor in decreasing microvascular filtration and capillary pressure, and accordingly, it would represent strong protection against the development of edema. Vasoconstriction was also documented at a systemic level (forearm blood flow) in HAPE-S mountaineers (High-Altitude Pulmonary Edema Sensitive) following hypoxia exposure, unlike in non-HAPE-S subjects. This was ascribed to decreased bioavailability of NO, leading to impaired vascular endothelial function [49]. A decrease in exhaled NO was also found in HAPE-S subjects on exposure to hypoxia as well as in patients with HAPE.

The use of vasodilators possibly requires some tuning. One shall agree that vasodilators would decrease peripheral resistance leading to capillary recruitment, and this would, in turn, inevitably cause an increase in microvascular filtration. In other words, vasodilators might vanish the anti-edemagenic role of vasoconstriction. It remains challenging to explain how vasodilators are useful to treat HAPE, although it is clear that they can alleviate the work of the right ventricle. It remains true that vasodilators at the lung level favor increased maximum oxygen uptake in healthy subjects. The reason is that increasing the capillary vascular bed decreases blood velocity and this allows a more efficient alveolar-capillary equilibration [50].

Risk factors

It is important to note that the rate of ascent and altitude reached are associated with a higher HAPE incidence. Commonly, it presents after 24 h but can present itself up to several days later. It can also be repetitive on several entries and is termed re-entry HAPE in apparently normal high-altitude residents returning from lower altitude travel. The time of stay at sea level is a transcendental aggravating factor. Based on our studies, in adult residents of La Paz (3,100–4,100 m), descending to sea level, it has been observed that there is a linear decrease in hemoglobin, hematocrit, and the number of red blood cells over 20 days. This complicates re-entry adaptation upon returning to high altitude [13].

Consequently, it can be assumed that children going to sea level for less than a week should have a lower probability of suffering HAPE when returning to high altitude. Hultgren observed that the time of sea-level stay was 10–14 days for re-entry HAPE to appear [37]. Children from Colorado have been found to present re-entry-HAPE even after less than a week's stay at sea level [51]. Unfortunately, no hematological studies in those publications are reported.

Conversely, hematological adaptation upon arriving to a high altitude takes twice the length of time than adaptation to sea level. It takes 40 days to build an optimal hematocrit upon arrival to the city of La Paz [13]. However, further studies on children need to be carried out. Aggravating factors fundamentally include the altitude reached, the exertion, exposure to cold, congenital heart disease, individual susceptibility, perinatal pulmonary hypertension, and viral infections [9]. HAPE can appear in children that present some congenital heart anomaly such as Patent Ductus Arteriosus (P.D.A.), Interatrial Communication (I.A.C.), and others [52]. Co-morbidities should always be considered.

Diagnosis

HAPE diagnosis results from a clinical interpretation of the symptoms and signs: coughing, insomnia, cyanosis, tachycardia, tachypnea, shortness of breath at rest, and marked lassitude. Physical examination reveals: rales on chest auscultation, the "HAPE tongue", bloody sputum (advanced cases), very low pulse oximetry (SpO_2), and low arterial partial pressure of oxygen (PaO_2) in arterial blood gases [53]. The normal values for SpO_2 in the city of La Paz are 88%–92%. Children and adults with lower values than 85% should be closely observed and followed up at this altitude. This varies in children according to the altitude [54]. The "HAPE tongue", previously described by us, is present in children and adults. It is of great importance as it can aid significantly in the diagnosis. However, it is not always present and could also be attributed to other diseases. Nevertheless, if someone just arriving at high altitude presents cough, it would most probably be pathognomonic [9]. The tongue is white, suggesting local desquamation and irregularly distributed bright red areas (Figure 5). There seems to be a similarity of irregular presentation of the focal edema patchy infiltrates in the chest X-ray, surrounded by correctly functioning normal lung areas, sometimes present only on one side.

Interestingly, as in COVID-19 patients, the Chest X-ray and/or Chest CAT scan is conclusive in the diagnosis in most cases (Figure 6). Likewise, in COVID-19, a disease with a different etiology generated by a virus, the tongue can have a similar presentation to the "HAPE tongue" as previously described. In 2001, we contributed to the standing that HAPE could also have a concomitant viral origin [9, 32]. It is also advisable to perform arterial blood gases and hemograms considering each altitude's average values. The normal blood gases ranges for the city of La Paz at 3,500 m are: PaO_2 = 58–61 mmHg, $PaCO_2$ = 28–32 mmHg, and pH = 7.37–7.43. PaO_2 in HAPE is always reduced. The $PaCO_2$ is generally decreased but can increase above normal levels in

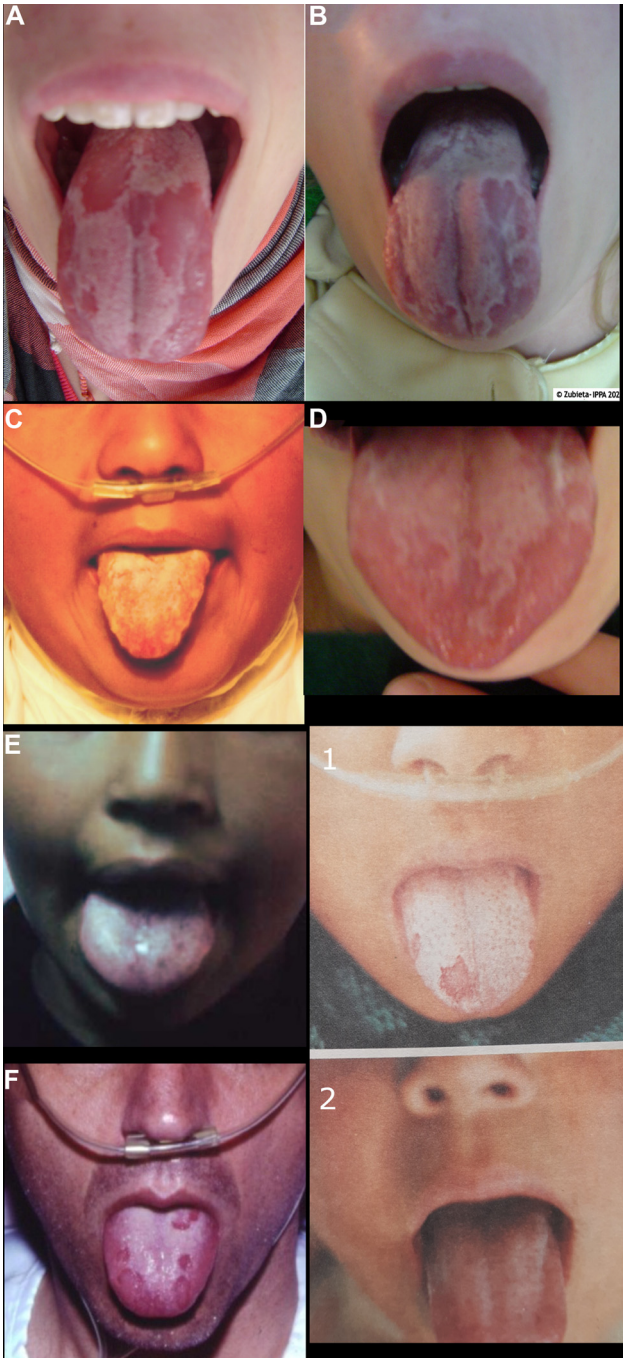

Figure 5: HAPE tongue (local desquamation with irregularly distributed bright red areas) at 3,500 m. A to E: Photos in five children. F: Adult photo. 1: Child with HAPE, and 2: The same child after recovery.

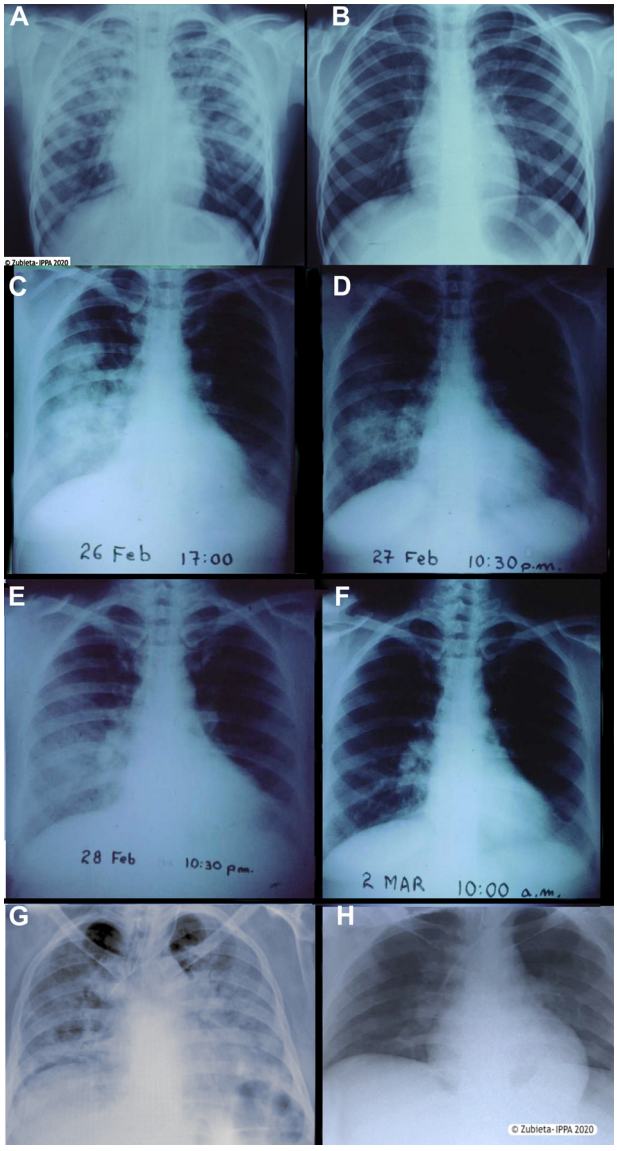

Figure 6: A: HAPE chest X-rays in a child with bilateral irregular focal cotton-like edema areas surrounded by functioning lung areas. B: Recovery of the child after 2 days following our treatment showing complete clearance without sequelae. C to F: HAPE in an adult showing unilateral big cotton-like images with a favorable evolution in 4 days. G to H: Severe HAPE in an adult evolving favorably (3,500 m) in spite of a cardiomegaly.

more severe cases. The pH is mostly alkalotic but can be acidotic in the more severe cases or with other co-morbidities, which should induce further testing. Proteinuria, hemoglobinuria, Elevated Leukotriene E4 in urine analyses can also be present. Inflammatory markers such as elevated Erythrocyte Sedimentation Rate and Reactive C-Protein can also be present. As appreciated, these pathophysiological mechanisms are similar to those present in COVID-19 [55]. Interestingly, in one recent case of a woman with HAPE, we found D-Dimer elevated (2,906 µg/L), but she fully recovered after a couple of days.

Pulmonary hypertension and a dilated right ventricle

The electrocardiogram reports sinus tachycardia, usually a high pointed P-wave along with a right axis deviation of QRS, and a modified T-wave reflecting right ventricular overload [56]. High-pointed P-waves imply right atrial enlargement generally associated with pulmonary hypertension. Pulmonary hypertension is a hallmark reaction in HAPE [44] and hence the focus of treatment as described below. Blood circulation is shunted away from poorly oxygenated lung zones towards healthy alveoli to minimize V/Q mismatch upon exposure to high altitude hypoxia [57]. Echocardiography can present a dilated right ventricle and right atrium, as well as increased pulmonary artery pressure [58]. Chest X-rays can often show a convex pulmonary artery in the P-A projection. In the city of La Paz, Bolivia at 3,100–4,100 m, the Mean Pulmonary Artery Pressure (MPAP) is 23 mmHg [59]. Hence, some pulmonary hypertension is a normal physiologic favorable response at high altitudes. Nevertheless, some individuals who previously presented HAPE were shown to have an excessive pulmonary vascular constriction not wholly responsive to oxygen administration [60], yet oxygen is helpful and should result in a favorable evolution.

Treatment

Oxygen administration is the first-line medication. Most of the symptoms can be treated adequately: headaches with analgesics and shortness of breath with bed rest in semi-fowler or fowler position. When children present HAPE when going with their parents to higher altitudes for entertainment, the best solution is to administer oxygen via nasal cannula (2–3 L/min) if tolerated or in oxygen tents or in oxygen enriched rooms, which is much more comfortable. Oxygen can reduce pulmonary artery pressure in most patients. Bed rest alone at high altitude has been shown to resolve HAPE in children going to La Oroya, Peru, at 3,750 m [61]. Nevertheless, to avoid any risks, we always use oxygen, as we work in a city with all the necessary resources. International societies such as the International Society for Mountain Medicine or the Medical Committee of the UIAA (International Union of Alpinists), or the Wilderness Medical Society recommend using glucocorticoids, nifedipine, other calcium blockers, sildenafil, or other PDE5 inhibitors [62]. However, we do not recommend the routine use of antibiotics, corticoids, calcium-channel blockers, nifedipine and/or diuretics like furosemide, except under exceptional circumstances such as the emergencies presented when mountain climbing. In our medical practice at a fixed high altitude city of La Paz (3,100–4,100 m), they are unnecessary in most cases as they can aggravate dehydration, resulting from vomiting, hyperventilation, and anorexia. Each patient should be diagnosed and treated based on his/her characteristics. Excessive use of medication can also irritate the gastric mucosa and perhaps aggravate inflammation but this requires further studies. It is also important to note that these patients and others suffering from AMS have a diminished thirst sensation. Consequently, adequate oral rehydration with electrolytes is recommended unless there is vomiting, where IV infusions become mandatory. The Gamow bag on the mountain has been proven useful.

Prognosis

The resolution of HAPE in children is quite fast between 24 h and 48 h, not so in adults where it can last several days (Figure 6). This implies that children can be discharged promptly without suffering the inconvenience of a lengthy hospitalization. Children going to lower altitudes can evolve favorably likewise within 24 h. However, in high-altitude cities like La Paz (3,100–4,100 m), there is adequate medical care based on know-how and advanced hospital resources, making it unnecessary to evacuate and descend in altitude. HAPE resolution leaves no sequelae (Figure 6) [3]. Nevertheless, HAPE can have a significant death toll in the mountain or in cities if the patients are undiagnosed or untreated [63]. In our 51 years of practice at the High Altitude Pulmonary and Pathology Institute (HAPPI–IPPA) in La Paz, we have never had a fatal outcome resulting from any high-altitude pathology. This is the fundamental reason that drives us to communicate our experience. We have all the diagnostic resources available, including the Hyperoxic/Hypoxic Adaptation Chamber Version 2.

Awareness and education of pediatricians and physicians at high altitude has reduced the incidence. Better habitat conditions, adequate nutrition, long flights in pressurized airplane cabins at a comparative altitude of 2,500 m (8,200 ft) also positively influence physiologic adaptation to high altitudes. Short flights of less than 1 h from sea level airports can result in a higher incidence of acute high altitude disease.

High Altitude Cerebral Edema (HACE)

HACE presents with headaches, ataxia, behavioral changes, hallucinations, confusion, altered mental status, disorientation, decreased level of consciousness, focal neurological signs, and can evolve into a coma, but it is quite rare [32]. Symptoms include ataxia, confusion, or altered mental status. HACE may also occur in the presence of HAPE [64].

Most cases can be diagnosed clinically. A brain CAT scan or MRI can be performed, as they can aid in the diagnosis, but it is not always evident. With a predilection for the splenium of the corpus callosum, white matter edema has been found in HACE [65], nevertheless, it can be reversible with adequate treatment. Laboratory tests should be practiced routinely in search of some co-morbidities that could complicate the evolution. The treatment should be carried out as soon as possible, as with all high altitude diseases. Time is the worst enemy due to progressive dehydration, and increasing hypoxia, accumulating fatigue, and a probable Hypoxic Ventilatory Decline (HVD) [66]. Additionally, some degree of an adverse effect of HIF and/or VEGF under some circumstances has been described [67, 68]. HIF plays a vital role in the ventilatory response to high altitude hypoxia [24].

Descent from high-altitude cities in order to treat these pathologies is unnecessary but essential for those that come to the city of La Paz and climb the surrounding mountains. They must return promptly to the city of La Paz to be successfully treated. Dexamethasone can be used, 10 mg (Oral), or intramuscularly (I.M.), particularly in the mountain. The administration of oxygen should be permanent, maintaining SpO_2 >90%. CPAP with oxygen use may prove to be beneficial. Some physicians have used the Gamow bag, a portable, manually inflated hyperbaric chamber, which has been said to be life-saving for those hiking in the mountains and presenting HAPE or HACE. In our Institute, we utilize the Hyperoxic/Hypoxic Adaptation Chamber Versions 1 and 2, which have resulted in a 100% favorable evolution in all the cases we treated over the years. Although some patients were quite severe and symptomatic, there was no loss of conscience or coma in those we treated at 3,500 m.

Conclusions

The adjacent cities of La Paz and El Alto, in Bolivia, between 3,100 m and 4,100 m, as well as Lhasa, in Tibet at 3,600 m, stand as living proof of the perfect human physiological adaptation to the highlands. The acute high altitude diseases AMS, HAPE and HACE upon arrival to high altitude can be successfully diagnosed and treated in high altitude cities with the adequate resources, and by understanding the management differences derived from the difficulties found in mountain climbing activities as compared to the arrival to a high altitude city. 100% recovery is possible having a prompt diagnosis and treatment. Treatment should be centered in treating all existing pathologies in the patient. Evacuation to sea level from high altitude cities is not recommended as it does not represent an emergency found as while performing an outdoor activity such as in mountain climbing where few resources are available. The interpretation of publications regarding the treatment of acute high altitude pathologies should always be evaluated based on the resources available at the site and context. Historically, most research was performed by sea-level scientists whose perspective and expertise should be contrasted to that of the highlander residents and practitioners.

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