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Consensus Statement on Chronic and Subacute High Altitude Diseases

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ABSTRACT

Léon-Velarde, Fabiola, Marco Maggiorini, John T. Reeves, Almaz Aldashev, Ingrid Asmus, Luciano Bernardi, Ri-Li Ge, Peter Hackett, Toshio Kobayashi, Lorna G. Moore, Dante Penaloza, Jean-Paul Richalet, Robert Roach, Tianyi Wu, Enrique Vargas, Gustavo Zubieta-Castillo, and Gustavo Zubieta-Calleja. Consensus on high altitude diseases. *High Alt Med Biol* 6:147–157, 2005.—This is an international consensus statement of an ad hoc committee formed by the International Society for Mountain Medicine (ISMM) at the VI World Congress on Mountain Medicine and High Altitude Physiology (Xining, China; 2004) and represents the committee's interpretation of the current knowledge with regard to the most common chronic and subacute high altitude diseases. It has been developed by medical and scientific authorities from the committee experienced in the recognition and prevention of high altitude diseases and is based mainly on published, peer-reviewed articles. It is intended to include all legitimate criteria for choosing to use a specific method or procedure to diagnose or manage high altitude diseases. However, the ISMM recognizes that specific patient care decisions depend on the different geographic circumstances involved in the development of each chronic high altitude disease. These guidelines are established to inform the medical services on site who are directed to solve high altitude health problems about the definition, diagnosis, treatment, and prevention of the most common

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chronic high altitude diseases. The health problems associated with life at high altitude are well documented, but health policies and procedures often do not reflect current state-of-the-art knowledge. Most of the cases of high altitude diseases are preventable if on-site personnel identify the condition and implement appropriate care.

Key Words: hypoventilation; chronic mountain sickness; polycythemia; pulmonary hypertension; right-heart failure; hypoxia; Andes; Himalayas

CONSENSUS STATEMENT ON CHRONIC AND SUBACUTE HIGH ALTITUDE DISEASES

Xining, August 2004

Ad Hoc Committee on Chronic and Subacute High Altitude Diseases
Co-Chairs: Fabiola León-Velarde (Perú) and Marco Maggiorini (Switzerland), Secretary: John T. Reeves (USA)
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INTRODUCTION

The partial pressure of oxygen in inspired air falls with increasing terrestrial elevation above sea level. As a consequence of the hypobaric hypoxic environments, human residents at high altitudes develop numerous physiologic responses, including, in particular, increases in hemoglobin concentration [Hb] and pulmonary artery pressure (Antezana et al., 1982; Hurtado, 1964; Monge-M and Monge-C, 1966; Penaloza et al., 1963). In severely hypoxic residents, large increases in Hb and/or pulmonary artery pressure may be associated with potentially fatal illnesses (Hurtado, 1942; Monge-M et al., 1928; Penaloza and Sime, 1971; Penaloza et al., 1971; Winslow and Monge-C, 1987; Wu et al., 1998a). However, a uniform description of these illnesses has been lacking, with the result that nomenclatures and diagnostic criteria have varied over time and in different high altitude regions of the world. Also contributing to a confusing medical picture is that the altitude-related illnesses are often of insidious onset and have multiple manifestations, which may vary among individuals. In economically depressed and rural areas, health policies, diagnostic procedures, and treatment regimens often do not reflect state-of-the-art knowledge. A consensus, which develops a consistent nomenclature and diagnostic criteria, could quickly improve public health in many high altitude areas. Furthermore, research into the epidemiology, pathophysiology, etiology, and therapy of the illnesses would be facilitated. At the 1998 Matsumoto, Japan (1998a; 1998b) meeting of the International Society of Mountain Medicine, an International Working Group was convened to develop a consensus statement for chronic mountain sickness (CMS), originally described by Carlos Monge-M (Monge-M et al., 1928) and characterized by excessive Hb. Over the next 6 years the Working Group developed the present Consensus Statement for altitude residents (2001; 2003; León-Velarde and Reeves, 1999), which encompasses not only CMS, but also considered the frequently associated disorder, high altitude pulmonary hypertension (HAPH).

The Working Group focused on CMS and HAPH because they are frequent and potentially fatal, chronic, hypoxia-related illnesses in high altitude populations. CMS and HAPH also represent separate manifestations of chronic hy-

poxia, that is, stimulation of erythropoiesis and stimulation of pulmonary hypertension, respectively. In many CMS patients, both manifestations are present simultaneously (Penaloza and Sime, 1971; Penaloza et al., 1971). However, occasionally CMS patients may have little or no elevation of pulmonary artery pressure or resistance beyond the normal increase at high altitude (Antezana et al., 1998; Vargas et al., 2003). Alternatively, particularly in children and young adults, life-threatening HAPH may occur with little or no increase in Hb (Anand and Wu, 2004; Lin and Wu, 1974; Sui et al., 1988). Therefore, the current Consensus Statement proposes two separate pathophysiologies in these altitude-related illnesses, with the recognition that in a given patient they may or may not coexist.

In addition, when dealing with the definition, diagnosis, treatment, and prevention of these sicknesses, the altitude of residence of the patients must be taken into account, because the prevalence and intensity of these diseases increase with the altitude of residence.

Establishing better definitions of high altitude-related illnesses is important for the millions of people who live above 2500 m worldwide. In South America, three of the four main Andean countries (Bolivia, Colombia, Ecuador, and Perú) have their capitals (La Paz, Bogotá, and Quito) at high altitude. In South America, some 35 million people live above 2500 m. In Asia, the countries of Afghanistan, Bhutan, China, India, Kyrgyzstan, and Nepal have 2% to 45% of their populations living above 2500 m. In China alone, there are four high plateaus (Qinghai–Tibet, Inner Mongolia, Yun-Gui, and the Yellow Land Plateau) with a total population of nearly 80 million people. In North America, Mexico and the western United States have relatively smaller, but increasing, high altitude populations (Niermeyer et al., 2001). It is estimated that up to 5% to 10% of high altitude inhabitants may develop CMS or HAPH.

The present guidelines have been developed to identify and manage altitude-related diseases. Currently, the most effective treatment for advanced high altitude illnesses is relocation of the patient to a lower elevation, but this is seldom feasible due to the socioeconomic problems involved. Clearer disease definitions will promote more effective and international cooperative research aiming to prevent migration of patients under difficult conditions, thus helping stabilize high altitude populations. Also, implementation of these guidelines should promote early disease detection. With education of patients and their health providers, as well as with proper medical management, life-threatening altitude illnesses can be prevented and the quality of life improved. Although further research will result in evolution of these guidelines, the present Consensus Statements aims to better define high altitude disease by unifying information currently available.

CHRONIC MOUNTAIN SICKNESS (CMS) OR MONGE'S DISEASE

Historical terms

High altitude excessive polycythemia or erythrocytosis, excessive erythrocytosis, high altitude pathologic erythrocytosis.

Definition of the disease

A clinical syndrome that occurs to natives or long-life residents above 2500 m. It is characterized by excessive erythrocytosis (females Hb $\geq$ 19 g/dL; males Hb $\geq$ 21 g/dL), severe hypoxemia, and in some cases moderate or severe pulmonary hypertension, which may evolve to cor pulmonale, leading to congestive heart failure. The clinical picture of CMS gradually disappears after descending to low altitude and reappears after returning to high altitude.

Exclusion criteria

The consensus group considers that:

i. A diagnosis of CMS should be made in persons without chronic pulmonary diseases (pulmonary emphysema, chronic bronchitis, bronchiectasis, cystic fibrosis, lung cancer, etc.) or other underlying chronic medical conditions that worsen the hypoxemia. In these cases, with increased risk of developing excessive erythrocytosis secondary to hypoxemia, a diagnosis of secondary CMS

is pertinent. Normal respiratory function should be confirmed by lung function tests.

ii. Persons living below an altitude of 2500 m are excluded from the diagnosis of CMS.

Diagnosis of the disease

Clinical symptoms. Headache, dizziness, breathlessness and/or palpitations, sleep disturbance, fatigue, localized cyanosis, burning in the palms of the hands and soles of the feet and dilatation of the veins, muscle and joint pain, loss of appetite, lack of mental concentration, and alterations of memory.

Clinical signs. Excessive erythrocytosis (females Hb $\geq$ 19 g/dL; males Hb $\geq$ 21 g/dL), severe hypoxemia, pulmonary hypertension (as defined in the high altitude pulmonary hypertension section, not mandatory), and heart failure (not mandatory).

Risk factors

Previous history of CMS, history of lack of respiratory sensitivity to hypoxia and hypoventilation, sleep apnea and all hypopneas, overweight, postmenopausal state.

(Arias-Stella et al., 1973; Arregui et al., 1994; Ergueta et al., 1971; Ge, 1989; Ge and Helun, 2001; Ge et al., 1998; Hurtado, 1942; Kryger and Grover, 1983; Kryger et al., 1978c; León-Velarde and Arregui, 1994; León-Velarde et al., 1993; León-Velarde et al., 1994; León-Velarde et al., 1997; León-Velarde et al., 2001; León-Velarde et al., 2003; Monge-C et al., 1992; Monge-C et al., 2001; Monge-M et al., 1928; Moore et al., 1998; Pei et al., 1989; Penaloza, 2003; Penaloza and Sime, 1971; Penaloza et al., 1971; Sime et al., 1975; Vargas et al., 2003; Wu, 2001; Wu et al., 1992; Zubieta-Castillo et al., 1998).

The Qinghai CMS score

The Qinghai score has been designed to assess CMS severity and to compare CMS cases within and among different countries in the world. It is based on the following symptoms and the Hb at the altitude of residence:

Breathlessness and/or palpitations
- 0 No breathlessness/palpitations
- 1 Mild breathlessness/palpitations
- 2 Moderate breathlessness/palpitations
- 3 Severe breathlessness/palpitations

Sleep disturbance
- 0 Slept as well as usual
- 1 Did not sleep as well as usual
- 2 Woke many times, poor night's sleep
- 3 Could not sleep at all

Cyanosis
- 0 No cyanosis
- 1 Mild cyanosis
- 2 Moderate cyanosis
- 3 Severe cyanosis

Dilatation of veins
- 0 No dilatation of veins
- 1 Mild dilatation of veins
- 2 Moderate dilatation of veins
- 3 Severe dilatation of veins

Paresthesia
- 0 No paresthesia
- 1 Mild paresthesia
- 2 Moderate paresthesia
- 3 Severe paresthesia

Headache
- 0 No headache
- 1 Mild headache symptoms
- 2 Moderate headache
- 3 Severe headache, incapacitating

Tinnitus
- 0 No tinnitus
- 1 Mild tinnitus
- 2 Moderate tinnitus
- 3 Severe tinnitus

Hb

Males: $>$ 18g $<$ 21g/dL; score = 0
$\geq$ 21 g/dL; score = 3
(León-Velarde et al., 1993; Monge-C et al., 1992)

Females: $>$ 16 g/dL $<$ 19 g/dL; score = 0
$\geq$ 19 g/dL; score = 3
(León-Velarde et al., 1997; León-Velarde et al., 2001)

According to the sum of points given for each symptom and the Hb, CMS is defined as follows (Wu et al., 1997; Wu et al., 1998a):

Absent	Score = 0 − 5
Mild	Score = 6 − 10
Moderate	Score = 11 − 14
Severe	Score $>$ 15

HIGH ALTITUDE PULMONARY HYPERTENSION (HAPH)

Historical terms

Chronic mountain sickness of the vascular type, high altitude heart disease (HAHD), hypoxic cor pulmonale, infant subacute mountain sickness, pediatric high altitude heart disease, and adult subacute mountain sickness.

Definition of the disease

A clinical syndrome that occurs to children and adults resident above 2500 m. It is characterized by a mean pulmonary artery pressure >30 mmHg or a systolic pulmonary artery pressure >50 mmHg measured at the altitude of residence, right ventricular hypertrophy, heart failure, moderate hypoxemia and the absence of excessive erythrocytosis (females Hb < 19 g/dL; males Hb < 21 g/dL).

Exclusion criteria

The consensus group considers that the following disorders should be ruled out

i. Other causes of pulmonary hypertension, including persistent pulmonary hypertension of the newborn.

ii. Chronic obstructive pulmonary diseases such as chronic bronchitis, chronic obstructive emphysema, and chronic cor pulmonale.
iii. Interstitial lung disease, including pneumoconiosis.
iv. Other cardiovascular diseases complicated with pulmonary hypertension, such as coronary heart disease, valvular heart disease, dilative and hypertensive cardiomyopathy, and congenital heart diseases.

Diagnosis of the disease

Mean pulmonary artery pressure >30 mmHg or a systolic pulmonary artery pressure >50 mmHg measured at the altitude of residence.

For screening, pulmonary artery pressure is assessed using echocardiography. Systolic pulmonary pressure is calculated adding estimated right atrial pressure to the pressure gradient between the right ventricle and the right atrium (ΔP-RV/RA) assessed using the modified Bernoulli equation ($\Delta P\text{-}RV/RA = 4V^2$), where V is the peak velocity of the regurgitant jet across the tricuspid valve. For confirmation of the diagnosis, as well as to exclude pulmonary hypertension due to heart diseases, invasive measurement of the pulmonary artery pressure should be considered.

Clinical symptoms and signs. Dyspnea, cough, cyanosis, sleep disturbance, irritability, and clinical signs of right heart failure.

Chest x-ray. Increased cardiac size, enlargement of the right atrium and ventricle, prominence of central and peripheral pulmonary arteries.

Electrocardiogram. Right axis deviation of QRS, clockwise rotation of the ventricles, evidence of marked right ventricular hypertrophy.

Echocardiography. Signs of right ventricular hypertrophy and/or failure.

Note: In infants living or traveling to high altitude, a high mean pulmonary artery pressure value could be considered when >50 mmHg or a high systolic pulmonary artery pressure when >65 mmHg, measured at the altitude of residence up to 6 months of age. As a reference, pulmonary artery pressures (PAP) obtained by cardiac catheterization in healthy children born and living at high altitudes (4300 to 4500 m) in the Peruvian Andes (Sime et al., 1963) are given:

Children 1 to 5 years: systolic, diastolic, and mean PAP: 58, 32, 45 mmHg
Children 6 to 14 years: systolic, diastolic, and mean PAP: 41, 18, 28 mmHg

Risk factors

History of high altitude pulmonary hypertension, history of persistent excessive pulmonary vasoconstriction in response to hypoxia, hypoxemia during sleep.

HAPH, chronic onset (Aldashev et al., 2002; Ge and Helun, 2001; Ge et al., 2003; Maggior-

ini and León-Velarde, 2003; Moore et al., 1998; Penaloza and Sime, 1971; Penaloza et al., 1971; Sarybaev and Mirrakhimov, 1998; Wu et al., 1992; Wu et al., 1998b; Wu et al., 1998c). **HAPH, acute onset** (Anand et al., 1990; Anand and Wu, 2004; Chen et al., 1982; Li and Ji, 1989). **HAPH, in children** (Blount, 1963; Khoury and Hawes, 1963; Li et al., 1966; Lin and Wu, 1974; Ma et al., 2004; Niermeyer et al., 1995; Penaloza et al., 1964; Penaloza and Gamboa, 1986; Pollard et al., 2001; Sime et al., 1963; Sui et al., 1988; Wu and Liu, 1955; Wu et al., 1998d; Wu and Miao, 2002; Wu et al., 2003).

TREATMENT OF HIGH ALTITUDE DISEASES

Chronic mountain sickness or Monge's disease

The ideal treatment is migration to low altitude. As the cause of chronic high altitude diseases is hypoxia, sea-level euoxia reverts all the physiological variables affected by the diseases, but with different time courses.

Phlebotomy is an alternative to reduce hematocrit (Monge-M et al., 1928; Winslow et al., 1985; Winslow and Monge-C, 1987). Phlebotomy can be done alone (Sedano et al., 1988a) or by isovolemic hemodilution (volume replacement) (Manier et al., 1988; Sedano and Zaravia, 1988; Winslow et al., 1985), the latter being a better choice due to the long-lasting improvement of symptoms.

Oxygen supplementation and respiratory training (slow breathing technique) improves blood oxygenation and reduces blood erythropoietin (Bernardi et al., 2003).

Medroxyprogesterone (20 to 60 mg/day for 10 weeks) increases ventilation and normalizes Pa_{O_2} and PA_{O_2} with a parallel drop in hematocrit and subsequent reduction of symptoms (Kryger et al., 1978a; Kryger et al., 1978b; Kryger and Grover, 1983).

Acetazolamide (250 mg/day for 3 weeks) increases ventilation during sleep and increases O_2 saturation, with a parallel drop in erythropoietin and hematocrit and subsequent reduction of symptoms (Richalet et al., 2004a).

Some Tibetan herbs, such as *Rhodiola,* may help sleep at high altitude (Xi et al., 2000).

High altitude pulmonary hypertension (HAPH)

The ideal treatment is migration to low altitude, but alternative proposals still to be proven should be directed to the reduction of pulmonary hypertension.

Calcium-channel blockers as nifedipin (Aldashev et al., 2005; Antezana et al., 1998; Zhao et al., 2001) (20 to 30 mg/12 h), NO inhalation (40 pp for 15 min), NO 15 pp plus O_2 50% (Anand et al., 1998; Duplain et al., 2000; Wilkins et al., 2002), as well as prostaglandin (Das, 1980) and phosphodiesterase inhibitors (Ghofrani et al., 2004; Richalet et al., 2004; Wilkins et al., 2002), have been demonstrated to decrease hypoxemia, pulmonary hypertension, and the alveolar–arterial gradient.

Note: There is an urgent need for randomized controlled trials using calcium-channel blockers, endothelin receptor antagonists, prostaglandins, or phosphodiesterase-5 inhibitors.

Management of CMS and HAPH. The studies are classified by the level of evidence to assist readers in evaluating the strength of the data associated with particular treatments. However, it should be noted that no long-term controlled trials have been made and that not all human studies are classified. Thus, more research and clinical trials are required before recommendations can be made regarding drug treatment of CMS.

Only those reporting a therapeutic endpoint(s), such as a decrease of Hb and/or HAPH, or measured improvement in sign and symptoms, and/or physiological variables affected by the diseases, are considered. Anecdotal reports are not classified because important clinical details are often missing and the evidence from them is generally considered weak.

EXTRINSIC FACTORS CONTRIBUTING TO THE ONSET OF HIGH ALTITUDE DISEASES

Altitudes above 2500 m, delay in recognition of early warning signs, no health plan to identify and treat excessive polycythemia, lack of ed-

TABLE 1. REPORTS OF TREATMENT IN CHRONIC MOUNTAIN SICKNESS (CMS) AND HIGH ALTITUDE PULMONARY HYPERTENSION (HAPH) CASES WITH DIFFERENT LEVELS OF EVIDENCE

Location	*Altitude*	N *of cases*	*Disease*	*TX*	*Target*	*Outcome*	*Level of evidence*	*Ref.*
China	3008–4888	13	CMS	Isovolemic hemodilution	Decrease Hct	Improved signs and symptoms	NR controlled single group	Wu, 1979
USA	3100	5	CMS	Medroxy-progesterone	Improve oxygenation, decrease Hct	Decreased Hct	P–D double-blind crossover trial	Kryger et al., 1978b
China	3300	129	CMS	*Rhodiola*, a Tibetan herb	Decrease erythrocyte deformability and lipid peroxidation	Improved signs and symptoms	P–D double-blind controlled R-trial	Xi et al., 2000
Bolivia	3600	31	CMS and HAPH	Nifedipine	Decrease HAPH (D.E.)	Decrease >20% in Ppa in 2/3 of the subjects	NR case-control series	Antezana et al., 1998
Bolivia	3600	40	CMS	Almitrine	Increase ventilation, decrease Hct	Increased Pa_{O_2}, decreased Pa_{CO_2}	P–D double-blind controlled R-trial	Villena et al., 1985
Bolivia	3600	8	CMS	Isovolemic hemodilution	Increase C.O. and ventilation, decrease Hct, decrease HAPH (H.C.)	Decreased VE/Q m, improved Pa_{O_2}	NR controlled single group	Manier et al., 1988
China	3658	60	CMS	Medroxy-progesterone	Improve oxygenation, decrease Hct	Improved signs and symptoms	NR controlled single group	Zhou et al., 1983
Perú	3700	155	CMS	Bloodletting	Decrease Hct	Improved signs and symptoms	NR controlled single group	Sedano et al., 1988b
Perú	3700	36	CMS	Isovolemic hemodilution	Decrease Hct	Improved signs and symptoms	NR controlled single group	Sedano and Zaravia, 1988
Perú	4430	1	CMS	Isovolemic hemodilution	Decrease Hct	Improved oxygen transport	NR prepost series	Winslow et al., 1985
Perú	4430	10	CMS	O_2 supplementation and breathing technique	Improve oxygenation, decrease Hct	Improved signs and symptoms	NR case-control series	Bernardi et al., 2003
Perú	4430	10	CMS	Acetazolamide	Increase ventilation, decrease Hct	Increased Sa_{O_2}, decreased Hct	P–D double-blind controlled R-trial	Richalet et al., 2004

C.O., cardiac output; D.E., Doppler echocardiography; H.C., heart catheterization; NR, nonrandomized; P–D, placebo–drug; Ppa, systolic pulmonary arterial pressure; R-trial, randomized clinical trial; Sa_{O_2}, oxygen saturation; TX, treatment; VE/Q m, ventilation–perfusion mismatching.

ucation and awareness of high altitude illnesses, possibility of increased genetic susceptibility.

CONSIDERATIONS FOR RISK REDUCTION

Encourage proper education regarding chronic high altitude illnesses, ensure that in high altitude hospitals clinical examination includes specific questions regarding high altitude diseases, provide medical services on site directed to solve high altitude health problems.

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