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REVIEW ARTICLE

Recommendations for long-term home oxygen therapy in children and adolescents☆

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KEYWORDS
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Abstract

Objective: To advise pediatricians, neonatologists, pulmonologists, pediatric pulmonologists, and other professionals in the area on the main indications and characteristics of long-term home oxygen therapy in children and adolescents.

Data source: A literature search was carried out in the MEDLINE/PubMed database (1990 to 2011). Additionally, references from selected studies were included. As consistent scientific evidence does not exist for many aspects, some of the recommendations were based on clinical experience.

Data synthesis: Long-term home oxygen therapy has been a growing practice in pediatric patients and is indicated in bronchopulmonary dysplasia, cystic fibrosis, bronchiolitis obliterans, interstitial lung diseases, and pulmonary hypertension, among others. The benefits are: decrease in hospitalizations, optimization of physical growth and neurological development, improvement of exercise tolerance and quality of sleep, and prevention of pulmonary hypertension/*cor pulmonale*. The levels of oxygen saturation indicative for oxygen therapy differ from those established for adults with chronic

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obstructive pulmonary disease, and vary according to age and disease. Pulse oximetry is used to evaluate oxygen saturation; arterial blood gas is unnecessary. There are three available sources of oxygen: gas cylinders, liquid oxygen, and oxygen concentrators. The flows used are usually smaller, as are the number of hours/day needed when compared to the use in adults. Some diseases show improvement and oxygen therapy discontinuation is possible.
Conclusions: Long-term home oxygen therapy is increasingly common in pediatrics and has many indications. There are relevant particularities when compared to its use in adults, regarding indications, directions for use, and monitoring.

PALAVRAS-CHAVE
Oxigenoterapia domiciliar;
Crianças;
Oxigênio

Recomendações para oxigenoterapia domiciliar prolongada em crianças e adolescentes

Resumo
Objetivo: Orientar pediatras, neonatologistas, pneumologistas, pneumologistas pediátricos e outros profissionais envolvidos na área sobre as principais indicações e as particularidades da oxigenoterapia domiciliar prolongada em crianças e adolescentes.
Fontes dos dados: Pesquisa bibliográfica na base de dados MEDLINE/PubMed (1990 a 2011). Adicionalmente, referências de estudos selecionados foram incluídas. Como para muitos dos aspectos não existem evidências científicas consistentes, algumas recomendações citadas foram feitas com base em experiência clínica.
Síntese dos dados: Oxigenoterapia domiciliar prolongada tem sido uma prática crescente nos pacientes pediátricos e se encontra indicada em casos de displasia broncopulmonar, fibrose cística, bronquiolite obliterante, pneumopatias intersticiais, hipertensão pulmonar, etc. Ressaltam-se como benefícios: redução de internações, otimização do crescimento físico e do desenvolvimento neurológico, melhora da tolerância ao exercício e da qualidade do sono e prevenção da hipertensão pulmonar/*Cor pulmonale*. Os níveis de saturação de oxigênio indicativos para a oxigenoterapia diferem dos estabelecidos para adultos com doença pulmonar obstrutiva crônica e variam de acordo com a doença e faixa etária. Para a avaliação da saturação de oxigênio, utiliza-se a oximetria de pulso, sendo a gasometria arterial dispensável. Há três fontes de oxigênio disponíveis: cilindros gasosos, oxigênio líquido e concentradores de oxigênio. Os fluxos utilizados costumam ser menores, assim como o número de horas/dia necessários, quando comparados ao uso em adultos. Em algumas doenças há melhora, e a suspensão do oxigênio é possível.
Conclusões: Oxigenoterapia domiciliar prolongada é uma terapêutica cada vez mais comum em pediatria e suas indicações são numerosas. Há particularidades relevantes quando comparada aos adultos em relação às indicações, modo de uso e monitorização.

Introduction

Long-term home oxygen therapy (LTHOT) has become an increasingly common practice, and many patients benefit from its use. It has several clinical and physiological benefits, as well as greater comfort for patients and significant cost reduction when compared to hospitalizations.

Currently, in the United States, 1,000,000 patients receive home oxygen therapy, which is equivalent to 241 patients per 100,000 inhabitants; its annual cost exceeds US$ 2,000,000,000.[1]

The number of children who need LTHOT is increasing worldwide, including in Brazil.[2-4] To illustrate how this form of treatment is being incorporated into pediatric practice, bronchopulmonary dysplasia (BPD) and cystic fibrosis (CF) can be mentioned. The great advances in neonatology have increased the survival of very premature patients, and despite new neonatal approaches, BPD still has significant importance, and many of these patients are discharged on oxygen treatment. In the case of CF, the evolution of treatment associated with improved nutrition has increased the survival of these patients, but some require LTHOT in advanced stages of the disease, or while waiting for a lung transplant.

The use of LTHOT in pediatric patients has several special characteristics and important differences when compared to the use in adults. The present guidelines aim to standardize the use of LTHOT in pediatric patients for several clinical situations associated with chronic hypoxemia in patients who do not require assisted ventilation. As many aspects do not have consistent scientific evidence, some of the recommendations were based on clinical experience.

Effects of chronic hypoxemia

The main effects of chronic hypoxemia occur in the cardiovascular system, which responds with pulmonary vasoconstriction in unventilated localized areas, in order to maintain the ventilation/perfusion ratio. This mechanism, however, has a deleterious effect when there is diffuse alveolar hypoxia, as a generalized pulmonary vasoconstriction leads to pulmonary hypertension. This overload to the right ventricle results in *cor pulmonale*, with decreased myocardial contractility and cardiac output and subsequent right heart failure. Polycythemia can occur in this situation, leading to a worsening of pulmonary hypertension.

Chronic hypoxemia also leads to systemic involvement, such as deficit in the weight-height gain and retardation in the neurological and psychomotor development, as well a decrease in the quality of sleep.

Effects of oxygen therapy

Two classic studies in adult patients with chronic obstructive pulmonary disease (COPD) in the early 1980s formed the scientific basis for LTHOT. The "Nocturnal Oxygen Therapy Trial", an American study conducted in 1980, compared a group receiving oxygen (O_2) for 24 hours/day with another receiving O_2 for 12 hours at night: mortality rate in the first group was 11.9%/year and in the second, 20.6%/year.[5] In the following year, a British study compared a group that received O_2 for 15 hours/day with a control group that received no O_2: mortality rate in the first was 12%/year and in the control group, 29%/year.[6] Since then, LTHOT has been accepted by the scientific community and recommended for diseases that cause chronic hypoxemia.

The physiological and clinical beneficial effects of LTHOT were confirmed in several other studies.[7-9]

Physiological effects

- Increase in PaO_2, improving the transport and release of O_2 to tissues
- Hematocrit normalization
- Decrease in the pulmonary artery pressure, preventing the progression of pulmonary hypertension
- Increase in the right ventricle performance
- Prevention of *cor pulmonale* or its progression

Clinical effects

- Improvement of cognitive function
- Improvement of sleep efficiency
- Increased exercise tolerance
- Decreased number of hospitalizations
- Improvement in quality of life
- Increased survival

It should also be noted that the LTHOT is preferable to maintaining the child in the hospital, due to lower risk of infection, minimized psychological impact of prolonged hospitalization, improved quality of life, and decreased costs of treatment.[10-14]

Characteristics of long-term home oxygen therapy in children

Children present very specific characteristics regarding the indication, discontinuation, and maintenance of oxygen therapy; thus, the recommendations for adults do not apply to them. The main differences of LTHOT in children when compared to adults are:[10-14]

- Physical growth and neurological development must be considered.
- The evolution of some diseases that cause hypoxemia in children is generally good; many children require LTHOT only for a limited period of time.
- Most clinical conditions in children are characteristic to this age group, although older children and adolescents may have indications similar to those in adults.
- The indication and monitoring of oxygen use are performed by pulse oximetry and not by blood gas analysis.
- Specific equipment is necessary to allow for low oxygen flow.
- Many children need oxygen only at night, thus requiring fewer than the 15 hours recommended for LTHOT in adults.
- All children require adult supervision.
- Oxygen therapy should be provided at schools for school-age children.

Sources of oxygen

There are three possible sources for oxygen therapy at home: cylinders, oxygen concentrators, and oxygen in the liquid form (Figure 1), each with advantages and disadvantages.[15,16]

Pressurized gas cylinders

The cylinder stores the pressurized gas, thus providing 100% O_2. It presents as a major limitation the need to be changed frequently, as the largest available cylinder provides continuous O_2, with a 2 L/min flow, for only 75.5 hours. Portable cylinders can provide continuous O_2, with a flow of 2 L/min, for 5 hours.

Liquid oxygen

Liquid O_2 is stored in adequate devices (cryogenic tanks) and maintained at a temperature of –196°C. Each liter of liquid O_2 produces 863 liters of O_2 in gas form, which is then supplied as 100% O_2. The tanks have the capacity to hold 25 to 40 liters of liquid O_2. Thus, a tank with the capacity of 40 liters provides 33,600 liters of gaseous O_2, supplied continuously at a flow rate of 2 L/min for 11 days. Portable containers are available with autonomy of up to 8 hours, and are the best option to allow ambulation.

Figure 1 Sources of oxygen (gas cylinder, oxygen concentrator, and liquid oxygen).

There are now electronic devices that release the gas only during inspiration, substantially reducing the losses that occur with continuous flow, decreasing the need for refills. However, they are not recommended for small children due to lack of system activation by the child's spontaneous breathing.[17] The main disadvantage of liquid oxygen is its high cost.

Table 1 Percentage of oxygen released by the concentrator.

Used flow	Percentage of oxygen
≤ 2 L/min	≥ 95%
3 a 5 L/min	≥ 90%
> 5 L/min	< 90%

Concentrators

Concentrators filter the air by removing nitrogen and increasing O_2 concentration. The percentage of O_2 provided will depend on the used flow, as described in Table 1.

It has the advantages of being the easiest source to handle, occupying less space, and not requiring refills. Recently, portable concentrator models have been developed, aimed at facilitating patient ambulation.

Its main disadvantage is requiring electricity, which is an additional cost to the treatment. However, the cost can be up to 55% lower than that of cylinders.[4]

Table 2 summarizes the advantages and disadvantages of each O_2 source.

General considerations on the equipment

For children, the preference is for the use of concentrators, while maintaining a large volume cylinder in case of power failure. Concentrators provide flow of 1 to 4 L/min, and there are low-flow concentrators that provide flow from 0.1 to 1 L/min. Currently, there are concentrators that run on batteries in case of power failure.

When the required flow is less than 0.3 L/min. and the estimated duration of the LTHOT is less than 3 months, cylinders are the best option. It is important to recall that a flow < 0.25 L/min is not possible with liquid oxygen. For patients that require oxygen 24 hours/day, it is always necessary to have a portable way to supply it (small cylinders, liquid oxygen, or portable concentrator).

It is worth mentioning that LTHOT in Brazil has been regulated differently by diverse state and/or municipal health secretariats, which should provide this service to patients who have an indication for its use.

Oxygen administration forms

Oxygen should be provided preferably by nasal cannula; the use of oxygen masks may be exceptionally considered. The nasal cannula should be changed every one to two months, and the masks, every six to 12 months. In children with tracheostomy, oxygen should be administered through an appropriate mask for tracheostomy.[13]

Humidification must be considered when oxygen is supplied in flows greater than 1 L/min, and it is always indicated for patients with CF.[13]

Principles of pulse oximetry

Pulse oximetry, not arterial blood gas, is used in children as a parameter to indicate LTHOT. It is important to know the basics of this method, as well as the oxygen saturation levels by pulse oximetry (SpO_2) levels considered normal in children.

Pulse oximetry uses the principle of spectrophotometry, whereby each substance absorbs light in a specific way. The most commonly used pulse oximeters emit red (660 nm) and infrared (940 nm) light on one side of the sensor, and on the other side, capture the unabsorbed fraction of emitted light for each wavelength. Only the light that corresponds to the pulsatile mass, i.e., arterial blood, is analyzed. The

Table 2 Sources of oxygen.

Type	Advantages	Disadvantages
Pressurized gas cylinder	Widely available Does not require electricity	High cost Heavy and large Risk of falling and causing accidents Needs frequent refills Hinders ambulation
Liquid oxygen	Allows ambulation Does not require electricity	High cost Risk of burns during recharging Needs refills Available only in major cities
Concentrators	Widely available Unlimited volume of gas Low cost Easy handling Smaller size	Needs electricity Does not provide 100% oxygen

oxyhemoglobin absorbs infrared light preferentially, and reduced hemoglobin, the red light. Based on this difference, and comparing with reference values found in the population, the device calculates the SpO_2 levels.[18,19]

Dysfunctional hemoglobins, such as carboxyhemoglobin and methemoglobin, may distort the results, as they absorb light at wavelengths that overlap those absorbed by oxyhemoglobin and reduced hemoglobin. In recent years, a pulse co-oximeter (fractional oximetry) that emits a greater number of wavelengths has been developed, and has the advantage of differentiating these hemoglobins. The SpO_2 measured by co-oximetry usually shows a difference of approximately 2% less when compared to traditional oximetry. In situations where there is increased dyshemoglobins, the co-oximeter is the noninvasive method of choice for a more precise assessment.[20] Fetal hemoglobin does not interfere with saturation measurements performed with the pulse oximeter, making this assessment reliable in neonates.[18]

Regarding the accuracy of pulse oximeters for saturation levels above 70%, SpO_2 differs by less than 3% from SaO_2 (arterial O_2 saturation).

Factors that can alter SpO_2:[19]

- SaO_2 < 70%.
- Ambient light: intense sunlight or fluorescent light can decrease the values.
- Movement artifact.
- Sensor malposition: can increase or decrease the values.
- Pigments: very dark skin or dark nail polish can underestimate saturation values; high levels of bilirubin (> 20 mg/dL) can overestimate SpO_2.
- Intravascular dyes such as methylene blue.
- Hypoperfusion: shock, hypovolemia, and hypothermia.
- Peripheral vasoconstriction triggered by cold.
- Venous congestion: can originate venous pulses, which mislead the equipment. Venous pressure can increase with the use of cuffs, tourniquets, etc.
- Anemia: extreme cases can produce false results.
- Edema: due to light dispersion in edematous tissue.

The most often used site to measure oximetry is the tip of the finger. In children, the toe can be used, or even the foot in small infants. There are different sizes and types of sensors, and it is important that it fits the site where it will be used. The plethysmographic pulse wave is an important resource for the assessment of adequate sensor adaptation.[18,19]

Normal values of pulse oximetry

Healthy children younger than 1 year

Three longitudinal studies have investigated SpO_2 in children younger than 12 months. The study by Hunt et al.[21] found a median SpO_2 of 98% during sleep, considering only periods with regular breathing. SpO_2 did not vary with age (2 to 25 weeks old). The median number of desaturation episodes was four (one to 71), they were associated with apnea or periodic breathing, and decreased with age. A more recent study by the same group found no difference in basal SpO_2 between preterm and term infants. The desaturation episodes were more common in preterm infants up to 43 weeks of postconceptional age, when values were equal to those of full-term newborns.[22] The study by Masters et al.[23] identified a slight increase in basal saturation and a decrease in the time and number of desaturation episodes up to 6 months of age.

Cross-sectional studies, performed during sleep in the first two months of life and restricted to periods of regular breathing, found mean SpO_2 from 97.6% to 100%, even when preterm infants (without lung disease) were included.[24-27] The mean percentage of time with saturation < 90% in healthy term infants ranged from 0% to 2%,[21,23,28] and in premature infants it was 2.5%.[29]

Based on several studies, it can be concluded that the mean basal SpO_2 in healthy infants during the first year of life is approximately 97% to 98%.[13] It is noted, however, that a small percentage of normal children can present lower SpO_2 values, especially if the periods of irregular and

periodic breathing, which are frequent in young infants, are included.

Healthy children older than one year

A study carried out in children between 2 and 18 years found a median basal SpO_2 of 99.5% (5th percentile: 96.6%). The desaturation episodes had a frequency of 0.6/hour.[30] In elementary schoolchildren, another study showed a median SpO_2 of 97.9% (95 to 100). The median number of desaturation episodes > 4% was 0.8/hour.[31] Based on these studies, it can be concluded that the median basal SpO_2 in healthy children older than 1 year is approximately 98% (5th percentile: from 96% to 97%).[13]

Main indications for long-term home oxygen therapy in children and adolescents

Bronchopulmonary dysplasia

The term BPD, or chronic lung disease in preterm infants, no longer refers to a unique clinical entity which is clinically/anatomically and physiopathologically defined. The disease as originally described by Northway in 1967, a severe chronic lung disease that affected preterm infants with hyaline membrane syndrome undergoing prolonged and aggressive mechanical ventilation, practically no longer occurs.[32]

Medical knowledge of the major determinants of this clinical picture and improvement in neonatal care have changed the course of the disease.[33] Currently, the survival of extremely preterm infants, with lung immaturity at higher grades that also develop into chronic lung disease, has become a reality. In this "new" BPD, a lower degree of airway injury can be observed, but with altered alveolar architecture, dysmorphic pulmonary microvasculature, and varying degrees of interstitial involvement.[34] Therefore, currently, BPD is the diagnosis of premature newborns who, with 36 or more weeks of corrected gestational age (CGA), and at least 28 days of postnatal age, still need oxygen.[35,36] Many of them will be dependent on oxygen for months or years, thus making BPD the most frequent indication for LTHOT in children.[10]

Several aspects must be considered for oxygen supplementation in preterm infants:

- It is estimated that a fetus maintains normal intrauterine growth with an arterial saturation of 70%.[17]
- Normal basal SpO_2 for healthy newborns (term and premature > 33 weeks of CGA) presents mean values of 97% to 99%.[14,27,37]
- Continuing moderate hypoxia is associated with the development of pulmonary hypertension, increased airway resistance, growth deficit, increased risk of sudden death, and possible neurodevelopmental problems.[13,14]
- High arterial oxygen concentrations can lead to tissue damage in the retina, brain, and lungs in premature infants in animal and human studies.[13,17]
- It is yet to be determined which parameters related to the use of O_2 are the most significant in the genesis of diseases associated with its use in premature infants: degree of immaturity, oxygen fraction in inspired air, blood concentration of O_2, SpO_2 instability, or time of use.

Two important studies guide the references related to the use of long-term oxygen therapy in BPD:

- A study known as STOP-ROP (Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity) evaluated the development of prematurity retinopathy in 649 neonates (mean of 35 weeks post-menstrual age) who, for at least two weeks, were monitored for maintenance of SpO_2 between 89% and 94%, or between 96-99%. It was observed, at 3 months of CGA, that the group receiving higher SpO_2 presented a greater incidence of adverse events of pulmonary origin, and a greater percentage of children remained dependent on oxygen and diuretics.[38]
- The BOOST (Benefit of Oxygen Saturation Targeting) study followed 358 preterm infants who still required supplemental oxygen at 32 weeks of post-menstrual age. They were divided into two groups according to SpO_2 maintenance target (91% to 94% or 95% to 98%), and were evaluated at 12 months of CGA. There were no differences regarding growth or neuropsychomotor development between the two groups; however, the group with higher supplementation needed oxygen for a longer period of time and a higher percentage of children remained dependent on O_2 at 36 weeks of CGA. The largest number of deaths from pulmonary causes was observed in the group with high saturation target (although not statistically significant).[39]

Since then, lower SpO_2 target levels in the treatment of BPD have been recommended. However, it must be emphasized that the higher incidence of lung diseases in the group with high target saturations observed in the STOP-ROP study can be associated with a direct toxic effect of oxygen, as a greater fraction of O_2 in inspired air was used in some of these patients. This can be controlled in LTHOT situations, with O_2 flow limitation dispensed via the nasal cannula. It should be noted, too, that the population evaluated in the BOOST study was much younger than the children with BPD eligible for LTHOT.[37]

Further studies are needed to confirm these findings, as well as assessments of long-term effects of mild hypoxemia and of prolonged artificial maintenance of normal levels of SpO_2.

LTHOT is indicated for patients with clinically stable BPD who remain dependent on O_2 (saturation in ambient air ≤ 92%) and who do not present hypercarbia. There is no consensus on what should be the desired saturation of LTHOT in BPD. It is recommended to maintain SpO_2 ≥ 93% without frequent fluctuations (during sleep or feeding); high flows of O_2 and hyperoxia should be avoided (SpO_2 ≥ 99%). One exception is when the child already has associated pulmonary hypertension, in which case the saturation should be maintained > 95%.

In addition to the already mentioned physiological and clinical benefits of LTHOT, the following should be emphasized in BPD: reduced airway resistance, reduced intermittent desaturations, reduced risk of sudden death, and better physical growth and neurological development.[8,10,13,14,40-43]

The long-term prognosis of these patients is usually good, and the time of supplemental oxygen use should be evaluated individually, ranging from a few days to months or years.[14,44,45] Comorbidities must always be reassessed (malnutrition, heart disease, pulmonary hypertension, infection) if the oxygen requirement increases or is extended for too long.

Cystic fibrosis

There is insufficient evidence to establish the ideal time to indicate LTHOT in patients with CF, as its benefits are not well established: some studies show improvement in attendance and performance at school and work and in exercise duration, but no changes in hospitalization, disease progression, and mortality. It has been estimated that approximately 1% to 2% of children with CF receive LTHOT.[10,13,46-49]

Episodes of hypoxia in CF patients may occur during sleep, exercise, air travel, and infectious exacerbations, and are not limited to severe patients. Hypoxia during sleep and exercise may occur in stable patients who do not have hypoxia during the day.[50,51] The deleterious effects of hypoxia in patients with CF are numerous: pulmonary hypertension, worsening of pulmonary infection and inflammation, reduced exercise capacity and muscle strength, and worsening of quality of sleep and quality of life.

As the indications for LTHOT in CF are not well established, the same criteria used to indicate oxygen therapy in COPD is suggested, especially in older CF patients, i.e.: PaO_2 ≤ 55 mmHg or SpO_2 ≤ 88% or PaO_2 between 56-59 mmHg or SpO_2 = 89% associated with signs suggestive of *cor pulmonale* or presence of congestive heart failure or polycythemia (HT > 56%).[16] In infants and preschoolers with CF, supplemental oxygen is recommended according to the criteria used for BPD, that is, when the SpO_2 is < 93%. This earlier-onset oxygen supplementation aims primarily to optimize weight and height development and to prevent pulmonary hypertension. The desired SpO_2 with oxygen therapy in older patients with more severe disease must be equal to or slightly greater than 90%, avoiding excessive increases of saturation due to the risk of hypercapnia.[10,13,49]

Regarding the presence of hypoxia during sleep in CF, some authors have demonstrated that when resting SpO_2 is < 93%-94%, there is a great risk of desaturation occurring during sleep.[52] Another study in Brazil, evaluating 40 CF patients with and without significant pulmonary involvement, showed that forced expiratory volume in one second (FEV_1) < 64% is a good predictor of desaturation during sleep, with good sensitivity and specificity.[51] These data suggest that when FEV_1 is around 60% and/or SpO_2 levels during wakefulness are < 94%, nocturnal hypoxia may be occurring. In this situation, whenever possible, an oximetry measurement should be performed during sleep or even a polysomnography, to document the presence and degree of nocturnal hypoxemia; if supplemental oxygen is indicated, this information can guide the titration of O_2 at night. The use of oxygen therapy during sleep may facilitate sleep onset; however, there is no evidence of improvement in the quality of sleep.[49]

During exercise, desaturation is considered when there is a decrease of 4% or more in basal SpO_2; in this situation, oxygen supplementation during exercise and/or pulmonary rehabilitation should be considered, and may lead to improvement in exercise duration and performance.[53]

There is still much controversy about the real benefits of oxygen therapy on the morbimortality of CF patients, which is often seen as having only a palliative effect. Therefore, the ideal time for LTHOT indication should be thoroughly evaluated considering the psychological impact of this prescription, as it indicates disease worsening to the patient. It should be reserved mainly for patients who, in addition to meeting the laboratory criteria, also show symptom relief with its use.

Non-cystic fibrosis bronchiectasis

LTHOT indication for patients with bronchiectasis due to other causes follows the same criteria of those for CF.[13,14]

Bronchiolitis obliterans

Bronchiolitis obliterans, usually secondary to viral infections, is a cause of severe COPD in infants. It is often accompanied by hypoxemia and need for LTHOT during varying periods. There are no established oxygen saturation levels for the start of LTHOT in these patients. The use of the same criteria used in children with BPD (SpO_2 < 93%) is suggested, as it predominantly affects infants.[13,54,55]

Interstitial lung diseases

Interstitial lung diseases represent a rare and diverse group of lung diseases in children, where gas exchange is often compromised by the presence of hypoxemia. Therefore, many of these patients require LTHOT for varying periods, associated with drug therapy.[13,56-58]

Idiopathic pulmonary hypertension

The advent, in recent years, of several new specific pulmonary vasodilator agents has changed the management of idiopathic pulmonary hypertension (IPH), and there has been an improvement in survival of these patients.[59,60] There are no data confirming the benefits of continuous oxygen therapy for patients with IPH.[59-61] However, some patients with normal oxygen saturation at rest may have desaturations during sleep due to hypoventilation and also due to decreased lung volumes, with increased shunt fraction; in this situation, nocturnal oxygen therapy can help prevent desaturations through the pulmonary vasodilation. Other situations in which desaturations can occur are during exercise and during episodes of upper airway infection, in which oxygen use may also be necessary. In view of these considerations, the availability of oxygen at home must be evaluated individually in these patients,

and LTHOT should be considered when there is evidence of symptom relief or reversal of desaturation during exercise and/or sleep.[13,14]

Pulmonary hypertension secondary to lung disease

Pulmonary hypertension secondary to lung disease results from chronic alveolar hypoxia and considerably worsens the prognosis of the underlying disease. Chronic hypoxia leads to pulmonary vasoconstriction and endothelial dysfunction. Moreover, the pulmonary circulation is more reactive to hypoxia in children than in adults.[62] In these cases, oxygen is the most potent pulmonary vasodilator, and LTHOT can slow down and even reverse the alterations in the pulmonary vascular bed induced by hypoxia, and may contribute to improvement of survival.[13,63]

Congenital heart diseases

Home oxygen therapy is not indicated in cyanotic heart diseases. Cyanosis is a consequence of the decrease in pulmonary blood flow or of ineffective flow, such as parallel circulation or mixing of venous and arterial blood. Therefore, oxygen has little effect in increasing the SaO_2, and only polycythemia can be reduced.[13]

Pulmonary hypertension secondary to congenital heart diseases

PH secondary to congenital heart disease (Eisenmenger's syndrome) is refractory to oxygen, and there is controversy as to whether its use can improve patient survival.[64,65] In the final stages of PH, oxygen can provide symptomatic relief in children with severe right congestive heart failure and resting hypoxemia.[13] Children with congenital heart disease awaiting surgery (without Eisenmenger's syndrome) and increased pulmonary artery pressure responsive to oxygen can benefit from home oxygen therapy, as well as children recovering from the surgery.[14]

Intrapulmonary right-left shunt

Intrapulmonary shunt, usually due to arteriovenous malformations, is a cause of hypoxia. As alveolar oxygen levels are not affected, the impact on the pulmonary vasculature is lower than in other lung diseases. However, the impact of the low SaO_2 on other systems is unknown. In some cases, LTHOT can improve neurological development, diurnal activities, and other symptoms, despite the slight increase in saturation levels.[13]

Obstructive sleep apnea syndrome

The first line of treatment for obstructive sleep apnea syndrome (OSAS) in children consists of surgical removal of tonsils and adenoids.[66] In cases of postoperative residual OSAS, when surgery is impossible or when other factors are responsible for the clinical picture, continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) is indicated.[67] LTHOT indication is restricted to severe cases, usually associated with hypoventilation, in which, despite the use of NIV, hypoxemia persists. Another indication for LTHOT occurs in extreme cases, when none of the above can be used. Oxygen can then minimize oxyhemoglobin desaturation, but will not significantly affect the frequency or duration of obstructive events. In these cases, CO_2 levels should be monitored.[68,69]

Chronic hypoventilation

Chronic hypoventilation may have central or peripheral origin, due to alterations in chest wall structure or respiratory muscle weakness (neuromuscular diseases).[70,71] The treatment of choice is NIV via face mask or tracheostomy. Oxygen therapy can be used in milder and non-progressive cases, in cases when NIV use is impossible, and in cases in which, despite NIV, patients persist with hypoxemia due to inadequate ventilation or the presence of associated lung disease. When LTHOT is used alone, CO_2 levels must be monitored.[13]

Chronic encephalopathies

It is not uncommon for children with chronic encephalopathy to develop chronic hypoxemia and the need for LTHOT. This usually stems from multiple factors: recurrent pneumonia usually related to aspiration processes secondary to gastroesophageal reflux and/or dysphagia, ineffective cough, and pulmonary restriction due to scoliosis or other chest deformity.[13]

Sickle-cell anemia

The main objectives of LTHOT in patients with sickle cell anemia (SCA) are to prevent stroke episodes, recurrent painful crises, and secondary pulmonary hypertension.

When assessing levels of SaO_2 as a criterion for recommending LTHOT, it must be considered that its measurement is subject to several sources of error. If a blood gas analyzer calculates SaO_2 from the PaO_2 measurement using a standard curve of hemoglobin A dissociation, SaO_2 may be overestimated, as in SCA the curve may shift to the right.[72,73] If the device measures SaO_2 directly through co-oximetry, there will be no discrepancy. Pulse oximetry is also subject to error, both for superestimation or underestimation of the SpO_2 levels. In oximetry with two wavelengths, there may be an increased value due to the higher percentage of carboxyhemoglobin and methemoglobin in these patients.[74,75] Conversely, SpO_2 may be underestimated due to the geometry of the red cell, which can disperse light differently due to anemia, dark skin color, and inadequate perfusion of the extremities.[76]

Risk factors suggested for acute painful crisis include sickle cell type, severity of anemia, fetal hemoglobin con-

centration, and hypoxemia. Several authors defend that hypoxemia is not the most important factor, emphasizing that the level of hemoglobin S favors deoxygenation and polymerization, even with adequate levels of PaO_2.[72,77] Other studies, however, showed that the mean low nocturnal saturation was associated with increased risk of painful crisis and stroke episodes.[78,79]

Considering these data, it is suggested that SpO_2 should be measured during wakefulness and sleep, and when < 93%, PaO_2 should be measured through arterial blood. If PaO_2 is < 70 mmHg, LTHOT can be considered. Other clinical data, such as hemoglobin level, the percentage of hemoglobin S and fetal hemoglobin, the frequency of vaso-occlusive crisis, and the neurological and pulmonary involvement should be assessed simultaneously.

Palliative care

In adults with terminal cancer, it is controversial whether oxygen therapy alleviates the sensation of dyspnea. In children, there are no data on the management of terminal dyspnea, but in some cases there may be benefits with oxygen, as chronic hypoxia can cause irritability, headache, and restlessness. When indicated, the use of nasal cannula should be preferred, so as not to cover the child's face with a mask. The management of these cases should be individualized and if, together with the patient and family, symptom relief is observed, LTHOT should be used.[13,14]

Long-term home oxygen therapy *versus* noninvasive ventilation

It is important to differentiate patients with chronic hypoxemia from those in which NIV is the most appropriate treatment. The diseases that lead to alveolar hypoventilation, such as central nervous system disorders, neuromuscular disorders, diseases of the chest wall, and obesity hypoventilation syndrome are indications for NIV with two levels of pressure.[70] CPAP is mainly indicated for OSAS, although its use in CF has resulted in improved SpO_2 during sleep.[80] In parenchymal lung diseases, such as CF and bronchiolitis obliterans, NIV has been used sporadically in the advanced stages, in exacerbations, and when LTHOT leads to hypercapnia.[80,81]

Prerequisites for the indication of long-term home oxygen therapy

Before indicating LTHOT, some points should be considered, particularly in cases of BPD:[10,13]

- The need for oxygen must be stable, and saturation should stay at 93% or higher, without the frequent occurrence of desaturation episodes. The saturation should not fall below 90% for more than 5% of the time.
- Babies should be able to withstand short periods in ambient air, without the risk of rapid deterioration, in case of disconnection of the nasal cannula.
- There should be no other medical condition that impairs LTHOT, and the child should be stable and presenting satisfactory growth. There must not have been episodes of apnea for a period of two weeks.
- An echocardiogram is recommended in order to assess the presence of PH.
- The immunization schedule must be up to date.
- Parents/caregivers must want and be comfortable with returning the child home on oxygen therapy; they must be trained on LTHOT use and should be able to identify problems related to oxygen administration.
- The home environment should be satisfactory, and should be evaluated before hospital discharge.

General guidelines for long-term home oxygen therapy in children

- No smoking inside the house, and parents/caregivers must be warned against the danger of oxygen in contact with fire, such as candles, stove burners, and cigarettes.
- Older children should be instructed on how to use their oxygen equipment.
- Parents must be educated regarding the transportation of oxygen during travel. During air travel, the airline must be informed in advance.
- Parents must know with whom to communicate or where to go in case of emergencies, and must be able to identify empty cylinders, displaced cannulas, and blocked valves.

Long-term home oxygen therapy prescription

The titration of the oxygen flow should be performed at a time of clinical stability and at rest. Whenever possible, it should also be performed at feeding time in infants, during exercise in older children, and during sleep when there is suspicion of nocturnal desaturation.

SpO_2 in ambient air should be measured and recorded for at least six hours in hospitalized children. For outpatients, a measurement of at least 15 minutes is recommended. The titration is then started with low flows of oxygen (0.1 to 1 L/min) and after, if necessary, the flow can be increased by half liters until the desired saturation is attained, which will be the flow recommended for home use. The maximum tolerated flow through a nasal cannula is generally 4-5 L/min. It is common for infants with BPD to require very low O_2 flow (< 0.5 L/min.). In adults with COPD, the empirical addition of 1 L/min in the evening to the basal O_2 flow when oximetry during sleep cannot be performed is recommended.[16] This recommendation can be adopted for older children and adolescents.

LTHOT prescription must be made by the general or pediatric pulmonologist, and it must include the recommended oxygen source, mode of administration (nasal cannula, face mask, or tracheostomy), flow of O_2, and the period of use (day and/or night and/or during exercise).

The follow-up of patients on LTHOT should be carried out as follows: the first return consultation must be approxi-

mately within one month, and subsequent evaluations should be performed every two months in children with BPD and every four to six months in other clinical situations. In these reevaluations, it is necessary to verify the use of home oxygen therapy and to reevaluate SpO_2 in ambient air and with oxygen, maintaining or modifying the prescription of LTHOT.

It should be noted that there is no formal indication for continuous pulse oximetry monitoring in the home environment.[13]

Long-term home oxygen therapy weaning

Weaning patients from LTHOT is more relevant for patients with BPD, where there is usually a progressive improvement in the lung disease. There are few other clinical conditions in which it may be possible to remove the oxygen; it is sometimes possible in cases of interstitial pulmonary diseases and bronchiolitis obliterans.

Once the oxygen requirement reaches 0.1 L/min, weaning should be considered; the same saturation target used when LTHOT was instituted should be used for discontinuation (usually when the SpO_2 in ambient air is stable and above 93%). Children who needed oxygen 24h/day may at first use it only during sleep and meals. In some cases, total weaning can be accomplished all at once. The equipment used for LTHOT must remain in the residence for at least three months after the withdrawal or discontinuation. After oxygen therapy discontinuation, oximetry control must be carried out on two occasions approximately one month apart, and if it remains adequate, the oxygen equipment may safely be removed from the residence.[13,14]

Long-term home oxygen therapy failures

LTHOT failure is defined as the persistence/worsening of hypoxemia and dyspnea, exercise intolerance, decompensated *cor pulmonale*, and high hematocrit maintenance. The causes may be: lack of a suitable LTHOT program, which includes portable equipment; non-adherence to LTHOT due to insufficient information and/or for esthetic/social reasons, especially in adolescents; worsening/progression of the underlying disease or interruption of drug treatment; associated diseases.[16]

Conclusions

The use of LTHOT is increasingly common in children and adolescents; its indications are numerous and its use will tend to increase in the coming years, especially in BPD and CF. It has very relevant particularities when compared to adult LTHOT. Although there have been few studies on LTHOT in pediatric patients, there is already enough evidence to ensure its proper indication. Further studies are needed to assess the best time to indicate LTHOT in different clinical situations and its role in the quality of life and survival of these patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Doherty DE, Petty TL, Bailey W, Carlin B, Cassaburi R, Christopher K, et al. Recommendations of the 6th long-term oxygen therapy consensus conference. Respir Care. 2006;51: 519-25.
2. Mocelin HT, Fischer GB, Ranzi LC, Rosa RD, Philomena MR. Home oxygen therapy in children: seven years experience. J Pneumol. 2001;27:148-52.
3. Primhak RA, Hicks B, Shaw NJ, Donaldson GC, Balfour-Lynn IM. Use of home oxygen for children in England and Wales. Arch Dis Child. 2011;96:389-92.
4. Munhoz AS, Adde FV, Nakaie CM, Doria Filho U, Silva Filho LV, Rodrigues JC. Long-term home oxygen therapy in children and adolescents: analysis of clinical use and costs of a home care program. J Pediatr (Rio J). 2011;87:13-8.
5. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93:391-8.
6. Long term domiciliary oxygen therapy in chronic hypoxic corpulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1:681-6.
7. Guyatt GH, McKim DA, Austin P, Bryan R, Norgren J, Weaver B, et al. Appropriateness of domiciliary oxygen delivery. Chest. 2000;118:1303-8.
8. Kotecha S, Allen J. Oxygen therapy for infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed. 2002;87:F11-4.
9. Simonds AK. Home ventilation. Eur Respir J Suppl. 2003;47: 38s-46s.
10. Balfour-Lynn IM, Primhak RA, Shaw BN. Home oxygen for children: who, how and when? Thorax. 2005;60:76-81.
11. MacLean JE, Fitzgerald DA. A rational approach to home oxygen use in infants and children. Paediatr Respir Rev. 2006;7: 215-22.
12. Thoracic Society of Australia and New Zealand, Fitzgerald DA, Massie RJ, Nixon GM, Jaffe A, Wilson A, et al. Infants with chronic neonatal lung disease: recommendations for the use of home oxygen therapy. Med J Aust. 2008;189:578-82.
13. Balfour-Lynn IM, Field DJ, Gringras P, Hicks B, Jardine E, Jones RC, et al. BTS guidelines for home oxygen in children. Thorax. 2009;64:ii1-26.
14. Balfour-Lynn IM. Domiciliary oxygen for children. Pediatr Clin North Am. 2009;56:275-96.
15. Harrison G, Shaw B. Prescribing home oxygen. Arch Dis Child Fetal Neonatal Ed. 2007;92:F241-3.
16. Viegas CA, Adde FV, Paschoal IA, Godoy I, Machado MC. I Consenso Brasileiro de Oxigenoterapia Domiciliar Prolongada/ SBPT. J Pneumol. 2000;26:341-50.
17. Tin W, Gupta S. Optimum oxygen therapy in preterm babies. Arch Dis Child Fetal Neonatal Ed. 2007;92:F143-7.
18. McMorrow RC, Mythen MG. Pulse oximetry. Curr Opin Crit Care. 2006;12:269-71.
19. Sinex JE. Pulse oximetry: principles and limitations. Am J Emerg Med. 1999;17:59-67.
20. Barker SJ, Badal JJ. The measurement of dyshemoglobins and total hemoglobin by pulse oximetry. Curr Opin Anaesthesiol. 2008;21:805-10.
21. Hunt CE, Corwin MJ, Lister G, Weese-Mayer DE, Neuman MR, Tinsley L, et al. Longitudinal assessment of hemoglobin oxygen saturation in healthy infants during the first 6 months of age.

Collaborative Home Infant Monitoring Evaluation (CHIME) Study Group. J Pediatr. 1999;135:580-6.
22. Hunt CE, Corwin MJ, Weese-Mayer DE, Ward SL, Ramanathan R, Lister G, et al. Longitudinal assessment of hemoglobin oxygen saturation in preterm and term infants in the first six months of life. J Pediatr. 2011;159:377-83.
23. Masters IB, Goes AM, Healy L, O'Neil M, Stephens D, Harris MA. Age-related changes in oxygen saturation over the first year of life: a longitudinal study. J Paediatr Child Health. 1994;30: 423-8.
24. Stebbens VA, Poets CF, Alexander JR, Arrowsmith WA, Southall DP. Oxygen saturation and breathing patterns in infancy. 1: Full term infants in the second month of life. Arch Dis Child. 1991;66:569-73.
25. Poets CF, Stebbens VA, Alexander JR, Arrowsmith WA, Salfield SA, Southall DP. Oxygen saturation and breathing patterns in infancy. 2: Preterm infants at discharge from special care. Arch Dis Child. 1991;66:574-8.
26. Richard D, Poets CF, Neale S, Stebbens VA, Alexander JR, Southall DP. Arterial oxygen saturation in preterm neonates without respiratory failure. J Pediatr. 1993;123:963-8.
27. Poets CF, Stebbens VA, Lang JA, O'Brien LM, Boon AW, Southall DP. Arterial oxygen saturation in healthy term neonates. Eur J Pediatr. 1996;155:219-23.
28. Meyts I, Reempts PV, Boeck KD. Monitoring of haemoglobin oxygen saturation in healthy infants using a new generation pulse oximeter which takes motion artifacts into account. Eur J Pediatr. 2002;161:653-5.
29. Ng A, Subhedar N, Primhak RA, Shaw NJ. Arterial oxygen saturation profiles in healthy preterm infants. Arch Dis Child Fetal Neonatal Ed. 1998;79:F64-6.
30. Poets CF, Stebbens VA, Samuels MP, Southall DP. Oxygen saturation and breathing patterns in children. Pediatrics. 1993;92:686-90.
31. Urschitz MS, Wolff J, Von Einem V, Urschitz-Duprat PM, Schlaud M, Poets CF. Reference values for nocturnal home pulse oximetry during sleep in primary school children. Chest. 2003; 123:96-101.
32. Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr. 2011;23:167-72.
33. Chess PR, D'Angio CT, Pryhuber GS, Maniscalco WM. Pathogenesis of bronchopulmonary dysplasia. Semin Perinatol. 2006;30: 171-8.
34. Coalson JJ. Pathology of bronchopulmonary dysplasia. Semin Perinatol. 2006;30:179-84.
35. Monte LF, Silva Filho LV, Miyoshi MH, Rozov T. Displasia broncopulmonar. J Pediatr (Rio J). 2005;81:99-110.
36. Bancalari E, Claure N. Definitions and diagnostic criteria for bronchopulmonary dysplasia. Semin Perinatol. 2006;30: 164-70.
37. Ellsbury DL, Acarregui MJ, McGuinness GA, Eastman DL, Klein JM. Controversy surrounding the use of home oxygen for premature infants with bronchopulmonary dysplasia. J Perinatol. 2004;24:36-40.
38. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics. 2000;105:295-310.
39. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med. 2003;349:959-67.
40. Higgins RD, Bancalari E, Willinger M, Raju TN. Executive summary of the workshop on oxygen in neonatal therapies: controversies and opportunities for research. Pediatrics. 2007;119:790-6.
41. Groothuis JR, Rosenberg AA. Home oxygen promotes weight gain in infants with bronchopulmonary dysplasia. Am J Dis Child. 1987;141:992-5.
42. Garcia EA, Mezzacappa MA, Pessoto MA. Home oxygen therapy program for infants after neonatal unit discharge: report of a ten-year experience. Rev Paul Pediatr. 2010;28:276-82.
43. Moon NM, Mohay HA, Gray PH. Developmental patterns from 1 to 4 years of extremely preterm infants who required home oxygen therapy. Early Hum Dev. 2007;83:209-16.
44. Greenough A, Alexander J, Burgess S, Bytham J, Chetcuti PA, Hagan J, et al. Preschool healthcare utilization related to home oxygen status. Arch Dis Child Fetal Neonatal Ed. 2006;91:F337-41.
45. Bhandari A, Panitch HB. Pulmonary outcomes in broncho-pulmonary dysplasia. Semin Perinatol. 2006;30:219-26.
46. Zinman R, Corey M, Coates AL, Canny GJ, Connolly J, Levison H, et al. Nocturnal home oxygen in the treatment of hypoxemic cystic fibrosis patients. J Pediatr. 1989;114:368-77.
47. Urquhart DS, Montgomery H, Jaffé A. Assessment of hypoxia in children with cystic fibrosis. Arch Dis Child. 2005;90:1138-43.
48. Douglass H, Potter H, Jarad N. Current practice in prescription, assessment and use of oxygen therapy in cystic fibrosis: a national UK survey. J Cystic Fibrosis. 2008;7:S77.
49. Elphick HE, Mallory G. Oxygen therapy for cystic fibrosis. Cochrane Database Syst Rev. 2009;(1):CD003884.
50. Frangolias DD, Wilcox PG. Predictability of oxygen desaturation during sleep in patients with cystic fibrosis: clinical, spirometric, and exercise parameters. Chest. 2001;119:434-41.
51. de Castro-Silva C, de Bruin VM, Cavalcante AG, Bittencourt LR, de Bruin PF. Nocturnal hypoxia and sleep disturbances in cystic fibrosis. Pediatr Pulmonol. 2009;44:1143-50.
52. Milross MA, Piper AJ, Norman M, Willson GN, Grunstein RR, Sullivan CE, et al. Predicting sleep-disordered breathing in patients with cystic fibrosis. Chest. 2001;120:1239-45.
53. Narang I, Pike S, Rosenthal M, Balfour-Lynn IM, Bush A. Three-minute step test to assess exercise capacity in children with cystic fibrosis with mild lung disease. Pediatr Pulmonol. 2003; 35:108-13.
54. Fischer GB, Sarria EE, Mattiello R, Mocelin HT, Castro-Rodriguez JA. Post infectious bronchiolitis obliterans in children. Paediatr Respir Rev. 2010;11:233-9.
55. Champs NS, Lasmar LM, Camargos PA, Marguet C, Fischer GB, Mocelin HT. Post-infectious bronchiolitis obliterans in children. J Pediatr (Rio J). 2011;87:187-98.
56. Paiva MA, Amaral SM. Chronic interstitial lung diseases in children. J Bras Pneumol. 2009;35:792-803.
57. Clement A, Nathan N, Epaud R, Fauroux B, Corvol H. Interstitial lung diseases in children. Orphanet J Rare Dis. 2010;5:22.
58. Das S, Langston C, Fan LL. Interstitial lung disease in children. Curr Opin Pediatr. 2011;23:325-31.
59. Berger S, Konduri GG. Pulmonary hypertension in children: the twenty-first century. Pediatr Clin North Am. 2006;53:961-87.
60. Schulze-Neick I, Beghetti M. Issues related to the management and therapy of paediatric pulmonary hypertension. Eur Respir Rev. 2010;19:331-9.
61. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009;30:2493-537.
62. Fishman AP. Hypoxia on the pulmonary circulation. How and where it acts. Circ Res. 1976;38:221-31.
63. Fuso L, Baldi F, Di Perna A. Therapeutic strategies in pulmonary hypertension. Front Pharmacol. 2011;2:21.
64. Bowyer JJ, Busst CM, Denison DM, Shinebourne EA. Effect of long term oxygen treatment at home in children with pulmonary vascular disease. Br Heart J. 1986;55:385-90.

65. Sandoval J, Aguirre JS, Pulido T, Martinez-Guerra ML, Santos E, Alvarado P, et al. Nocturnal oxygen therapy in patients with the Eisenmenger syndrome. Am J Respir Crit Care Med. 2001; 164:1682-7.
66. Darrow DH. Surgery for pediatric sleep apnea. Otolaryngol Clin North Am. 2007;40:855-75.
67. Kirk VG, O'Donnell AR. Continuous positive airway pressure for children: a discussion on how to maximize compliance. Sleep Med Rev. 2006;10:119-27.
68. Marcus CL, Carroll JL, Bamford O, Pyzik P, Loughlin GM. Supplemental oxygen during sleep in children with sleep-disordered breathing. Am J Respir Crit Care Med. 1995;152:1297-301.
69. Aljadeff G, Gozal D, Bailey-Wahl SL, Burrell B, Keens TG, Ward SL. Effects of overnight supplemental oxygen in obstructive sleep apnea in children. Am J Respir Crit Care Med. 1996;153: 51-5.
70. Robert D, Argaud L. Clinical review: long-term noninvasive ventilation. Crit Care. 2007;11:210.
71. Benditt JO. Initiating noninvasive management of respiratory insufficiency in neuromuscular disease. Pediatrics. 2009;123: S236-8.
72. Seakins M, Gibbs WN, Milner PF, Bertles JF. Erythrocyte Hb-S concentration. An important factor in the low oxygen affinity of blood in sickle cell anemia. J Clin Invest. 1973;52:422-32.
73. Moreira GA. Respiratory repercussions of sickle cell anemia. J Bras Pneumol. 2007;33:18-20.
74. Ortiz FO, Aldrich TK, Nagel RL, Benjamin LJ. Accuracy of pulse oximetry in sickle cell disease. Am J Respir Crit Care Med. 1999;159:447-51.
75. Blaisdell CJ, Goodman S, Clark K, Casella JF, Loughlin GM. Pulse oximetry is a poor predictor of hypoxemia in stable children with sickle cell disease. Arch Pediatr Adolesc Med. 2000;154: 900-3.
76. Pianosi P, Charge TD, Esseltine DW, Coates AL. Pulse oximetry in sickle cell disease. Arch Dis Child. 1993;68:735-8.
77. Uong EC, Boyd JH, DeBaun MR. Daytime pulse oximeter measurements do not predict incidence of pain and acute chest syndrome episodes in sickle cell anemia. J Pediatr. 2006;149: 707-9.
78. Hargrave DR, Wade A, Evans JP, Hewes DK, Kirkham FJ. Nocturnal oxygen saturation and painful sickle cell crises in children. Blood. 2003;101:846-8.
79. Kirkham FJ, Hewes DK, Prengler M, Wade A, Lane R, Evans JP. Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. Lancet. 2001;357:1656-9.
80. Milross MA, Piper AJ, Dobbin CJ, Bye PT, Grunstein RR. Sleep disordered breathing in cystic fibrosis. Sleep Med Rev. 2004; 8:295-308.
81. Fauroux B, Burgel PR, Boelle PY, Cracowski C, Murris-Espin M, Nove-Josserand R, et al. Practice of noninvasive ventilation for cystic fibrosis: a nationwide survey in France. Respir Care. 2008; 53:1482-9.