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2022 Brazilian Thoracic Association recommendations for long-term home oxygen therapy

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ABSTRACT

Some chronic respiratory diseases can cause hypoxemia and, in such cases, long-term home oxygen therapy (LTOT) is indicated as a treatment option primarily to improve patient quality of life and life expectancy. Home oxygen has been used for more than 70 years, and support for LTOT is based on two studies from the 1980s that demonstrated that oxygen use improves survival in patients with COPD. There is evidence that LTOT has other beneficial effects such as improved cognitive function, improved exercise capacity, and reduced hospitalizations. LTOT is indicated in other respiratory diseases that cause hypoxemia, on the basis of the same criteria as those used for COPD. There has been an increase in the use of LTOT, probably because of increased life expectancy and a higher prevalence of chronic respiratory diseases, as well as greater availability of LTOT in the health care system. The first Brazilian Thoracic Association consensus statement on LTOT was published in 2000. Twenty-two years later, we present this updated version. This document is a nonsystematic review of the literature, conducted by pulmonologists who evaluated scientific evidence and international guidelines on LTOT in the various diseases that cause hypoxemia and in specific situations (i.e., exercise, sleep, and air travel). These recommendations, produced with a view to clinical practice, contain several charts with information on indications for LTOT, oxygen sources, accessories, strategies for improved efficiency and effectiveness, and recommendations for the safe use of LTOT, as well as a LTOT prescribing model.

Keywords: Oxygen; Hypoxia; Oxygen inhalation therapy; Delivery of health care.

INTRODUCTION

Chronic respiratory diseases can cause resting or exercise-induced hypoxemia, being among the main causes of decreased quality of life and life expectancy. Because especially of their infectious complications and their related hospitalizations, chronic respiratory diseases result in high costs for public and supplementary health care, as well as for patients and their families. For those who develop hypoxemia, the prescribing of long-term home oxygen therapy (LTOT) may provide benefits, such as a decrease in perceived dyspnea, improved exertional tolerance, and increased life expectancy.

Home oxygen has been used empirically for more than 70 years, and support for LTOT is based on two landmark studies from the 1980s, one by the Nocturnal Oxygen Therapy Trial Group[1] and one by the Medical Research Council Working Party.[2] Both studies demonstrated that oxygen use improves survival in COPD patients.

Improved survival with LTOT has been demonstrated in patients with stable COPD and severe, chronic hypoxemia.[3-6] In recent decades, accumulated evidence has shown that LTOT has other beneficial effects, such as reduced depression, improved cognitive function, improved quality of life, improved exercise capacity, and reduced hospitalizations.[7-16] In addition, LTOT can stabilize or even reverse

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pulmonary hypertension (PH) and decrease both cardiac arrhythmias and myocardial ischemia in patients with COPD.[17,18] However, the use of LTOT in other respiratory diseases that cause severe hypoxemia is based on extrapolation of COPD-related data, largely supported by knowledge of respiratory physiology and cellular respiration, which are identical regardless of the disease causing the hypoxemia, as well as its systemic effects.

The first Brazilian Thoracic Association consensus statement on LTOT was published in 2000 and remains a reference for many oxygen therapy protocols in Brazil.[19] In the last 22 years, there has been a large increase in the use of LTOT, partly because of increased life expectancy and an increasing number of patients diagnosed with chronic lung diseases, notably COPD and interstitial lung diseases (ILDs), as well as the fact that the availability of LTOT in the health care system has increased. In addition, in the last 2 years, a proportion of COVID-19 survivors needed to use oxygen during a transition period or became chronic oxygen users.

In Brazil, the protocols for provision of LTOT for free are municipal and state protocols, and this is one of the reasons why we do not have reliable national data on the total number of LTOT users. In the USA, more than 1.5 million patients were receiving LTOT in 2018.[20]

In Brazil, access to LTOT is guaranteed by the Brazilian Unified Health Care System's Organic Laws (Federal Laws no. 8080/90 and no. 8142/90) that regulate the conditions for health promotion, protection, and recovery and for guaranteeing this right to every citizen.

We brought together 16 pulmonologists with expertise in oxygen therapy, who conducted a nonsystematic review of the literature and international guidelines for scientific evidence on LTOT in the various diseases that cause hypoxemia and on oxygen use in specific situations (i.e., sleep, exercise, and air travel). With a view to clinical practice, we created several charts to facilitate patient management, with information on main indications for LTOT; different sources of oxygen supply and necessary accessories; strategies for increased adherence, efficiency, and effectiveness; cost reduction; and recommendations for the safe use of LTOT; as well as a LTOT prescribing model (Charts 1-10 and Figure 1). In these recommendations, we chose to use the term LTOT, although we understand that the meaning intended here is broader, that is, it is oxygen supplementation for outpatients, for use during any activity, inside or outside their home.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF HYPOXEMIA

Oxygen is essential in oxidative phosphorylation, promoting ATP synthesis for energy production. Arterial oxygen content is dependent on the partial pressure of inspired oxygen, which, in turn, is dependent on atmospheric pressure, ventilation, the actual gas exchange, and hemoglobin concentration and affinity for oxygen.[21]

Only a small fraction (less than 2%) of arterial oxygen content is dissolved in plasma and is free from hemoglobin. At sea level, an SpO_2 of 96-98% corresponds to approximately 20 mL of oxygen for every 100 mL of blood.[22] The delivery of oxygen to the tissues, in turn, is dependent on arterial oxygen content and cardiac output. The lower the oxygen concentration, the greater the hemoglobin-oxygen affinity, and, consequently, the more decreased the delivery of oxygen to the tissues. An increase in body temperature, acidosis from any cause, or an increase in 2,3-diphosphoglycerate produces a shift in the hemoglobin dissociation curve to the right, decreasing hemoglobin-oxygen affinity and increasing the delivery of oxygen to the tissues.[23]

Hypoxemia can be assessed by calculating the alveolar-arterial oxygen tension difference ($P[A\text{-}a]O_2$) or by calculating the oxygenation index (PaO_2/FiO_2). In hypoxemic patients with $P(A\text{-}a)O_2$ within the normal range, the likely pathophysiological mechanism is the presence of hypoventilation. In those with increased $P(A\text{-}a)O_2$ and persistent hypoxemia despite oxygen supplementation or with increased FiO_2, the presence of cardiac or intrapulmonary shunt is suggested. In those who respond to supplemental oxygen, ventilation-perfusion (V/Q) mismatch or altered diffusion should be considered.[24]

Acute or chronic hypoxemia induces various physiological responses aimed at maintaining adequate delivery of oxygen to the tissues. When PaO_2 is below 60 mmHg, there is an increased ventilatory stimulus, increasing PaO_2 and reducing $PaCO_2$. The vascular beds irrigating the hypoxic tissue dilate, inducing compensatory tachycardia to increase cardiac output and improve oxygen delivery. The pulmonary vasculature contracts to improve the V/Q ratio in the affected areas. If hypoxemia does not resolve, renal activation will occur to increase erythropoietin production and stimulate erythrocytosis, increasing oxygen transport and delivery capacity. These initial benefits may have harmful long-term effects, since long-term vasoconstriction, erythrocytosis, and increased cardiac output can cause PH and right ventricular failure, decreasing survival. In addition, the energy cost of increased ventilation and increased oxygen demand may contribute to malnutrition in COPD patients.[21-24]

DEFINITION OF HYPOXEMIA

At sea level, barometric pressure is 760 mmHg (or 1 atm), FiO_2 is 0.21 (or, as per clinical practice, 21%, a term that is used in scientific papers and will be used in this document), and PaO_2 is 80-100 mmHg in healthy individuals. Therefore, PaO_2 is dependent on altitude, although it should also be adjusted for age (with aging, there is a progressive reduction in PaO_2). Hypoxemia is defined as a PaO_2 below the lower limit

Chart 1. Indications for home oxygen therapy.[a]

Treatment modality and parameters to recommend its use
Assumptions Strong evidence based on studies of COPD and on use of supplemental oxygen for more than 15 h/day Oxygen therapy increases survival and improves pulmonary hemodynamics, quality of life, sleep quality, and cognition. It does not reduce the frequency of exacerbations. Use of supplemental oxygen for 24 h has an additional effect on survival in comparison with use of supplemental oxygen for 12-15 h. Oxygen therapy is available free of charge under the auspices of the Brazilian SUS municipal and state programs. The indication for use of oxygen therapy should be evaluated when patients are in a stable phase of their disease and receiving optimal treatment, with an SpO_2 of ≤ 92%. The indication for use of oxygen therapy should be confirmed by arterial blood gas analysis performed with the patient at rest in a sitting position and breathing room air. Correction of hypoxemia (SpO_2 ≥ 90-92%) should be confirmed, and increases in $PaCO_2$ should be monitored. Indications A PaO_2 of ≤ 55 mmHg (7.3 kPa) or an SpO_2 of ≤ 88% A PaO_2 of 56-59 mmHg (7.4-8.0 kPa) or an SpO_2 of ≤ 89% associated with PH, edema caused by heart failure, or hematocrit > 55%
Ambulatory oxygen therapy (during exercise and physical activity) An SpO_2 of ≤ 88% during physical activity and improved exercise tolerance with the use of oxygen Ambulatory oxygen therapy contributes to increasing the number of hours of daily oxygen therapy use. Although ambulatory oxygen therapy improves exercise capacity, there are conflicting results regarding improved quality of life. Ambulatory oxygen therapy can improve training duration and intensity during rehabilitation.
Nocturnal oxygen therapy An SpO_2 of ≤ 90% on ≥ 30% of the recording and evidence of PH or erythrocytosis (improvement in SpO_2 should be confirmed) One study[155] showed no benefit in patients who did not meet criteria for long-term home oxygen therapy (low power and adherence).
Oxygen therapy during air travel (see Chart 9) Indications: an SpO_2 of < 92% or an SpO_2 of 92-95% and ≤ 84% on a 6MWT or HAST
Palliative oxygen therapy Palliative oxygen therapy is generally not indicated for patients with advanced disease and dyspnea without hypoxemia. Oxygen is less effective than opioids in relieving dyspnea.

[a]Based on Hardinge et al.,[6] Jacobs et al.,[20] González-Moro et al.,[25] Lacasse et al.,[155] and the Global Initiative for Chronic Obstructive Lung Disease.[156] SUS: *Sistema Único de Saúde* (Unified Health Care System); PH: pulmonary hypertension; 6MWT: six-minute walk test; and HAST: hypoxia altitude simulation test.

of normal; however, this does not necessarily mean that oxygen supplementation will be required.

Classically, the prescribing of LTOT in patients with chronic respiratory diseases other than COPD relies on extrapolation of data from COPD studies. Pulse oximetry is used to screen patients for resting hypoxemia; when SpO_2 is ≤ 92%, a request for arterial blood gas analysis on room air is indicated; in addition, the presence or absence of hypercapnia should be evaluated. :The indications for LTOT are as follows: severe hypoxemia with a PaO_2 ≤ 55 mmHg or an SaO_2 ≤ 88% or a PaO_2 ≤ 59 mmHg or an SaO_2 ≤ 89% in the presence of edema, *cor pulmonale* (PH), or polycythemia (hematocrit > 55%).[6,20,25] The daily duration of LTOT should be at least 15 h/day, including the sleep period, and the oxygen flow rate should be high enough to raise PaO_2 above 60 mmHg or raise SpO_2 above 90%.[6,20,25]

≥Exercise-induced hypoxemia is defined as a reduction ≥ 4 points in exertional SpO_2, even if baseline SpO_2 is within the normal range. LTOT in patients with exercise-induced hypoxemia remains controversial in the literature, it being advisable to consider the magnitude of the decrease in perceived dyspnea after oxygen supplementation or to consider its use in pulmonary rehabilitation.

The mechanisms of action of supplemental oxygen are beyond the correction of hypoxemia and the improvement of oxygen delivery to the cells. In healthy individuals exposed to hypoxic conditions, the accumulation of hypoxia-inducible factors in the cell nucleus upregulates several genes responsible for the physiological responses to hypoxia, including remodeling of the pulmonary vasculature, culminating in PH and increased erythropoiesis.[26,27] Limited evidence from animal models suggests that some of the therapeutic effects of LTOT are mediated by inhibition of hypoxia-inducible factors.[28]

LTOT IN PATIENTS WITH COPD

Although observational studies have suggested benefits of using supplemental oxygen in COPD, two randomized clinical trials (RCTs) were critical in establishing the basis for the use of LTOT.[1,2] The study by the Medical Research Council Working Party[2] followed 87 COPD patients for 5 years who had

Chart 2. Sources of high-pressure oxygen.[a]

Sources	Advantages	Disadvantages
	Stationary cylinders - 20-50 L in general (30-75 kg)	
	• Are available nationwide • Are available free of charge in the Brazilian SUS • Can store O_2 for days • Require no power supply • Can deliver high O_2 flow rates	• Are heavy and difficult to transport • Require support for transportation • Pose a risk of falls and explosions • Have low autonomy: a 50-L cylinder delivering an O_2 flow rate of 1 L/min 24 h/day would last an average of 125 h (a refill every 5 days) • Are expensive because multiple monthly refills are required • Keep patients bound to their homes
	Portable cylinders - 3-5 L in general	
	• Facilitate use outside the home (outpatient use) • Weigh 3.5-5.5 kg	• Low autonomy depending on pressure and size: a 3-L cylinder delivering an O_2 flow rate of 1 L/min would last 4.5 h • Depending on size, weight, and degree of dyspnea, a wheeled cart might be needed in order to help patients move around.
		

Notes:
• 1 bar = 0.988 atm; 1 kgf/cm^2 = 0.97 atm; and 1 atm = 760 mmHg. In practice, 1 atm = 1 bar = 1 kgf/cm^2
• A 50-L cylinder at 200-bar pressure expands to 10,000 L (10 m^3) in the atmosphere
• Duration in minutes = (N of liters in the cylinder × pressure on the manometer)/N of L/min of O_2
• A cylinder delivering 10,000 L in the atmosphere at a flow rate of 2 L/min: autonomy of 5,000 min or 83.3 h (3.4 days)
• A portable cylinder delivering up to 270 L in the atmosphere (3 L × 90 bar) at a flow rate of 1 L/min: autonomy of 270 min or 4.5 h
• A total of 90 L of O_2 are consumed when nebulized O_2 is delivered at a flow rate of 6 L/min for 15 min.

[a]Based on Hardinge et al.,[6] Jacobs et al.,[20] González-Moro et al.,[25] O'Driscoll et al.,[124] Hardavella et al.,[157] and the Chest Foundation.[158] SUS: *Sistema Único de Saúde* (Unified Health Care System); and atm: standard atmospheres.

severe hypoxemia, hypercapnia, and *cor pulmonale*. Patients were randomized into two groups: placebo (no supplemental oxygen) and intervention (LTOT for at least 15 h/day). At the end of follow-up, mortality was 45.2% in the oxygen group and 66.7% in the control group.[2] The study by the Nocturnal Oxygen Therapy Trial Group[1] randomized 203 hypoxemic COPD patients into two groups: continuous supplemental oxygen and 12-h nocturnal supplemental oxygen. The follow-up period was 12 months, and mortality was higher in the nocturnal oxygen group (hazard ratio = 1.94; p = 0.01).

Studies that have demonstrated increased survival with LTOT involved patients with severe hypoxemia (PaO_2 ≤ 55 mmHg or SaO_2 ≤ 88%). In contrast, the use of LTOT in COPD patients with moderate hypoxemia showed no survival benefit.[29-31] Other studies of individuals with COPD also demonstrate that LTOT has other benefits in severely hypoxemic COPD patients, such as improvement in quality of life, exercise capacity, and cognitive function, as well as a reduction in pulmonary vascular resistance, right atrial pressure, cardiovascular morbidity, and hospitalizations.[13,15-18,32-34]

As previously mentioned, the mechanisms of action of supplemental oxygen are beyond the correction of hypoxemia and the improvement of oxygen delivery to the cells. In healthy individuals exposed to hypoxic conditions, the accumulation of hypoxia-inducible factors in the cell nucleus upregulates several genes responsible for the physiological responses to hypoxia, including remodeling of the pulmonary vasculature, leading to PH and increased erythropoiesis.[26,27] Limited evidence from animal models suggests that some of the therapeutic effects of LTOT are mediated by inhibition of hypoxia-inducible factors.[28]

LTOT is indicated for COPD patients with persistent severe hypoxemia who are clinically stable and have been on optimal drug therapy for at least one month. Those who are clinically unstable, for example, after a recent exacerbation, should receive temporary oxygen supplementation until clinical reassessment 1-3 months after decompensation, since approximately 50% will not require LTOT at follow-up.[35,36] It is recommended that all patients assess the need to increase the oxygen flow rate during exercise and sleep. Excessive oxygen flows should be avoided in order to minimize the side effects of oxygen, especially a worsening of hypercapnia in patients with carbon dioxide retention, with an increase in the risk of sensorial depression and, in extreme cases, of coma due to carbon dioxide narcosis,[37] and it is suggested that SpO_2 be maintained at 90-92%.

Chart 3. Sources of liquid oxygen (stored at −183°C; 1 L of liquid oxygen = 860 L of gaseous oxygen).[a]

Sources	Advantages	Disadvantages
	Stationary aluminum cylinders/tanks for home use (volume, 20-40 L; weight, 40-65 kg)	
	• Require no power supply • Are noise-free • Tanks equipped with wheels make it easier to move around the house • Refill portable cylinders • Have good autonomy, with refills every 8-20 days depending on the volume of the tank and on the O_2 flow rate • Deliver O_2 flow rates of up to 7 L/min	• Size and weight make them difficult to transport • Make it difficult for patients to move around the house • Pose a risk of frostbite, especially when refilling portable cylinders • Available only in major cities • Are relatively expensive, albeit less so than gaseous O_2 cylinders
	Small, portable aluminum cylinders (volume, 0.5-1.2 L; weight, 2.5-3.9 kg)	
	• Are small and light • Make it easier for patients to go outside their homes and move around • Have autonomy to deliver an O_2 flow rate of 1 L/min (range, 5-14 h) • Can be transported by patients • Can be refilled by stationary cylinders/tanks for home use	• Have low autonomy when delivering O_2 flow rates ≥ 3 L/min • Are not available in the Brazilian SUS • Are expensive

[a]Based on Hardinge et al.,[6] the Brazilian Thoracic Association,[19] González-Moro et al.,[25] O'Driscoll et al.,[124] Hardavella et al.,[157] and the Chest Foundation.[158] SUS: *Sistema Único de Saúde* (Unified Health Care System).

Pulse oximetry is used to screen patients for hypoxemia; when SpO_2 is ≤ 92%, arterial blood gas analysis is indicated. Arterial blood gas analysis is necessary for prescribing LTOT and is also useful for detecting hypercapnia. As previously mentioned, the indications for LTOT include a PaO_2 ≤ 55 mmHg or an SaO_2 ≤ 88% or a PaO_2 ≤ 59 mmHg or an SaO_2 ≤ 89% in the presence of edema, PH, *cor pulmonale*, or polycythemia (hematocrit > 55%).[6,20,25]

Hypoxemic patients with suspected obstructive sleep apnea (OSA) syndrome or alveolar hypoventilation should be referred for polysomnography. It should be emphasized that in such cases correction of hypoxemia may be achieved with noninvasive ventilation alone, even without supplemental oxygen.[38]

Smokers should be referred to smoking cessation programs and instructed not to smoke while using oxygen, not because oxygen is flammable, but because it accelerates combustion and increases the risk of fires and explosions.[39] In addition, smoking increases blood levels of carbon monoxide, which has a high affinity for hemoglobin and reduces oxygen transport.[6,25,27]

Adherence to treatment is essential for achieving the expected benefits of LTOT. Adherence can range from 45% to 70% and can be improved by identifying barriers, facilitators, and prescriber attitudes.[40] Many patients use oxygen for less than 15 h/day, use oxygen flows lower than those prescribed by their doctors, or both, because they lack guidance about their illness and about the role of oxygen in the treatment, have little improvement in their symptoms, or are afraid of becoming dependent on LTOT.[6,20,25,41,42] High-quality support from the health care team improves patient adherence to the correct use of oxygen (Chart 6). The decision to prescribe LTOT should be carefully considered, as should the decision to discontinue it. Oba et al.[43] observed that only 35% of patients were reassessed correctly and that the rate of appropriate reassessment was significantly higher among pulmonologists than among general practitioners (65% vs. 17%).

LTOT IN PATIENTS WITH CHRONIC LUNG DISEASES OTHER THAN COPD

Cystic fibrosis

In patients with cystic fibrosis (CF), chronic airway infection causes lung damage that results in chronic

Chart 4. Oxygen concentrators (oxygen from room air).[a]

Concentrators	Advantages	Disadvantages
	Stationary concentrators for continued home use	
	• Are medium-sized and are equipped with wheels that make it easier for patients to move around the house • There are dozens of brands available at different price ranges. • Newer models are virtually noise-free • Newer models can deliver O_2 flow rates of up to 10 L/min • An hour meter[b] makes it easier to assess treatment adherence	• Are expensive (5,000-15,000 Brazilian *reais*) • High power consumption (Patients should ask for a discount on electricity bills.) • Older models are larger and noisier. • Most deliver an O_2 flow rate of ≤ 5 L/min
	Portable concentrators	
  	• Are small • Relatively light (weighing 3-5 kg) • Make it easier for patients to go outside their homes and move around • Are approved for in-flight use by most airlines • Pulse flow: reduced O_2 consumption and increased autonomy	• Battery life ranges from 3 h to 12 h. • Continuous O_2 flow rates of ≤ 2 L/min in most cases • Are expensive (10,000-20,000 Brazilian *reais*): a longer battery life translates to a higher cost, as does a lower weight. Portable concentrators equipped with pulse flow modes (i.e., O_2 delivered at inhalation) are also more expensive.

[a]Based on Hardinge et al.,[6] the Brazilian Thoracic Association,[19] González-Moro et al.,[25] O'Driscoll et al.,[124] Hardavella et al.,[157] the Chest Foundation,[158] the American Association for Respiratory Care,[159] and Tanni et al.[160]
[b]The hour meter shows how long the concentrator has been used.

hypoxemia, with respiratory failure being the leading cause of death.[44,45] The proportion of CF patients receiving oxygen is unknown, and the impact of LTOT on the survival and quality of life of these patients remains unclear.[45] A review[45] of 11 studies on oxygen use in patients with CF, only one of which assessed its long-term benefit, concluded that LTOT had no discernible effect on mortality, hospitalization, or disease progression when compared with no oxygen therapy, although it reduced absenteeism from school and work.

There is little evidence for prescribing LTOT in patients with advanced CF, although in the short term some improvement in PaO_2 during sleep and exercise has been demonstrated.[46] The Cystic Fibrosis Foundation guidelines[47] suggest that patients with advanced CF be annually evaluated for exertional hypoxemia, nocturnal hypoxemia, hypercapnia, and PH, as well as recommending oxygen use in patients with an SpO_2 ≤ 88% during sleep or during exercise. The British Thoracic Society guidelines[6] recommend that the indications for LTOT in CF be the same as those in COPD.

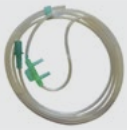
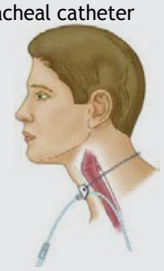
ILDs

COPD and ILDs are the main indications for LTOT.[48] Recent large RCTs of idiopathic pulmonary fibrosis concluded that 21-28% of study participants received supplemental oxygen therapy.[49,50] However, those rates did not differentiate between resting hypoxemia and exertional hypoxemia. A retrospective study of 400 patients conducted in Australia in specialist ILD clinics reported a prevalence of resting hypoxemia of 3.5%.[51]

Definitions of exertional hypoxemia vary widely, but regardless, exertional hypoxemia is common in ILD patients, being more severe in ILD than in COPD when compared with the severity of lung function impairment. In addition, exertional hypoxemia is a marker of poor prognosis for these patients.[52-55] Nocturnal hypoxemia affects approximately 27% of patients, and the association with sleep-disordered breathing may increase this prevalence.[56]

The benefit of LTOT in ILD patients is uncertain. A systematic review[57] found no consistent effects on exertional dyspnea, although exercise capacity

Chart 5. Devices and accessories for long-term home oxygen therapy.[a]

Options	Advantages	Disadvantages
Nasal cannulas • A low O_2 flow rate at a large volume of air • Every 1 L/min adds 3-4% of O_2 to the inhaled air. • For an O_2 flow rate of 1-6 L/min, an FiO_2 of 24-50% 	• Are light • Silicone cannulas are more comfortable than plastic cannulas. • Are more convenient for patients • Do not interfere with speech • Facilitate oral feeding	• O_2 concentration varies depending on the disease and breathing pattern • Variations in FiO_2 depending on the O_2 flow rate (e.g., for an O_2 flow rate of 2 L/min, FiO_2 is 24-35%) • An O_2 flow rate > 4 L/min can cause discomfort. • Can irritate the nostrils • Severe nasal obstruction can interfere with the flow of O_2.
(Simple) face masks • Translucent plastic • Small volume • Fastened by elastic bands 	• Do not irritate or hurt the nostrils • For an O_2 flow rate of 5-10 L/min, an FiO_2 of 35-55%	• Cover the nose and mouth • Interfere with oral communication • Need to be removed before oral feeding • Can cause discomfort and suffocation (claustrophobia)
Other options • Venturi masks  • Nonrebreather masks  • Transtracheal catheter 	• Indicated for situations requiring precise O_2 concentrations (high concentrations in patients with severe hypoxemia and low concentrations in CO_2 retainers) • Increased cost because of the need for higher O_2 flow rates • O_2 flow rates vary depending on the manufacturer; in general, 4-15 L/min for an O_2 concentration of 24-60%. • Widely used in patients with acute respiratory failure requiring high O_2 flow rates • An O_2 flow rate of 10-15 L/min - an FiO_2 of 80-95% (an O_2 flow rate of < 10 L/min can cause the reservoir to collapse) • Improves patient cosmesis and reduces O_2 consumption • Transtracheal insertion carries a small risk of complications. • Can have adverse effects if it remains in the airway for a prolonged period of time • Should not be used in hypersecretory patients	

[a]Based on Hardinge et al.,[6] Jacobs et al.,[20] González-Moro et al.,[25] O'Driscoll et al.,[124] Hardavella et al.,[157] the Chest Foundation,[158] and Schwartz et al.[161] Note: at O_2 flow rates of ≤ 5 L/min, the use of a hose of ≤ 30 m does not affect O_2 flow rates or FiO_2.(Aguiar et al.).[162]

improved. Studies on the use of LTOT in ILD patients have a high risk of bias, and it is therefore not possible to estimate the impact of LTOT on survival.[57] Current clinical guidelines have consistently recommended LTOT for ILD patients on the basis of the same criteria as those used for COPD patients.[4,6,58-62]

PH

Precapillary PH is a hemodynamic diagnosis that includes pulmonary arterial hypertension (PAH, group I), PH due to respiratory diseases (group III), and chronic thromboembolic PH (group IV), and can cause hypoxemia.[63] Several pathophysiological mechanisms, such as decreased cardiac output in patients with PH, V/Q mismatch, right-to-left shunt, and decreased oxygen diffusion capacity, are involved in hypoxemia, which may be increased by pulmonary vasoconstriction.[64-66]

A study conducted by Ulrich et al.[64] demonstrated that the use of supplemental oxygen in patients with PAH or chronic thromboembolic PH resulted in benefit

Chart 6. Strategies to improve the efficacy of long-term home oxygen therapy.

- Educate patients on their disease and the role of O_2
  - Emphasize the importance of adhering to pharmacological treatments and using O_2 correctly (at least 15 h/day, including the sleep period)
  - Explain that the outcome of LTOT is an increase in quality of life and life expectancy
  - Advise patients on symptoms of CO_2 retention
  - Advise patients on how to operate the devices
  - Advise patients on how to avoid or reduce the risks of using O_2 (see details in Chart 7)
- Correctly fill out the health department protocols
- Provide patients using a concentrator with a report for exemption from or a discount on electricity bills
- In conjunction with patients and on the basis of current recommendations, personal preferences, availability, and costs, decide on the following:
  - O_2 source: a gaseous O_2 cylinder, a liquid O_2 cylinder, or an O_2 concentrator
  - O_2 delivery interface: a cannula, a catheter, or a mask
  - Need for humidification (strong evidence is lacking)
    - Absence of indication for use of low O_2 flow rates (of < 5 L/min)
    - Use of heat and moisture exchangers (at 32-36°C) in patients requiring high O_2 flow rates and in tracheostomized patients
    - Use of a (non-heated) humidifier bottle (there is no evidence of its benefits, and it increases the risk of infections)
- By means of consultations, home visits, home-made photographs/videos, emails, apps, or social media, monitor and advise on the following:
  - Treatment adherence, by means of direct or indirect evaluation, as follows:
    Talk to patients and their families.
    - Check power consumption (in the case of patients using stationary O_2 concentrators).
    - Check the duration of and time elapsed between refills of stationary cylinders.
    - Read the hour meter (in the case of patients using O_2 concentrators).
    - Check for reduced hematocrit and treatment response.
  - Proper handling and hygiene of O_2 sources and accessories
    - Accessories: wash with soap and water; clean with a water/vinegar solution (10:1) and, subsequently, rinse with hot water; and allow to air dry
    - Change cannulas and masks regularly
    - Clean the concentrator filters in accordance with the manufacturer instructions
  - Select the appropriate O_2 flow rate for target SpO_2
    - Attention to decalibration and variations in flows across flow meters
- Periodically check whether or not patients should continue to receive O_2 therapy, especially in the following cases:
  - In patients with improved clinical control of the disease
  - In those for whom O_2 therapy has been indicated following hospital charge: reevaluate the need for O_2 therapy one month later

[a]Based on Hardinge et al.,[6] Jacobs et al.,[20] González-Moro et al.,[25] O'Driscoll et al.,[124] the Chest Foundation,[158] and the American Association for Respiratory Care.[159] LTOT: long-term home oxygen therapy.

in exercise capacity and quality of life. In addition, there was improvement in nocturnal SpO_2 and in sleep disturbances in those with exercise-induced hypoxemia and sleep disorders (sleep apneas and nocturnal hypoxemia). Although the duration of oxygen supplementation was short (up to 5 weeks), it is unknown whether the positive effects of oxygen supplementation during exercise translate to long-term benefits.[67,68] An observational study of PAH concluded that the risk of death was significantly higher among patients with severe DL_{CO} reduction (< 40% of predicted) who did not use supplemental oxygen than among those who did. However, the latter group had more PAH-specific medication use, which constitutes a selection bias.[69]

The use of LTOT in adult patients with Eisenmenger syndrome remains controversial, and there are limited data in the literature. A prospective controlled study[70] showed no impact of nocturnal oxygen use on exercise capacity, disease natural history, or survival in the 2-year follow-up period. Therefore, the use of LTOT is optional in these patients, and its prescription should be individualized.[70]

Recommendations in guidelines on the use of supplemental oxygen in PH are controversial, probably because of the absence of long-term studies.[74] Despite limited evidence, it is suggested that LTOT be prescribed for PH patients with a PaO_2 < 60 mmHg, considering symptomatic benefit and correction of exertional desaturation.[6,25]

Chart 7. Recommendations for the safe use of oxygen.[a]

- Irritation of mucous membranes and drying of secretions
  - Use humidifiers and/or saline nasal gel
- Fires and burns
  - Do not smoke or allow anyone to smoke in the home during O_2 use.
  - Keep away from sources of fire or flame, such as stoves, cigarettes, and candles.
  - Do not use emollients (because of the risk of combustion).
  - Dry hands well after using an alcohol-based hand rub.
- Leaks and explosions
  - Choose companies that follow best practices for the transport and handling of cylinders and, in particular, cylinder valves.
  - Maintenance should be performed by trained professionals only.
  - Allow easy access to and storage of cylinders in the home.
  - Keep cylinders in an upright position in well-ventilated spaces, away from the sunlight and other sources of heat (> 5 meters).
  - Close valves when O_2 is not being used.
  - Avoid hitting, tilting, and dropping the cylinders.
  - Always keep cylinders in the same place unless there is an important reason to move them.
  - Strictly follow the guidelines for handling cylinders, especially when refilling portable liquid O_2 cylinders, because of the risk of frostbite (caused by liquid O_2 at −183°C).
- CO_2 retention
  - Reduce O_2 flow rates in patients presenting with or at risk of CO_2 retention.
    - Maintain an SpO_2 of 90-92%.
    - If necessary, monitor $PaCO_2$ and pH.
- Pulmonary toxicity
  - Avoid high O_2 flow rates, especially at an FiO_2 > 50%.

[a]Based on Hardinge et al.,[6] Jacobs et al.,[20] González-Moro et al.,[25] O'Driscoll et al.,[124] the Chest Foundation,[158] and the American Association for Respiratory Care.[159]

LTOT IN PATIENTS WITH ADVANCED, CHRONIC DISEASES AND IN PALLIATIVE CARE

Promoting early interventions that not only alleviate the symptoms caused by disease progression, but also reduce emergency department visits and hospitalizations and ensure end-of-life care is essential in palliative care planning. Ideally, this requires the participation of a multidisciplinary team consisting of physicians, physiotherapists, nurses, psychologists, and social workers, with appropriate knowledge and training; however, an attending physician with a clear understanding of the patient's condition is capable of managing the disease progression, prioritizing symptom control.[72]

The use of oxygen therapy in palliative care requires the assessment of the causes that can be reversed and of objective criteria such as SpO_2, an overall assessment of the patient's needs, and an individualized treatment plan. This plan should be jointly developed by the health care team, the patient, and his or her caregivers.[73]

LTOT can relieve dyspnea if this is associated with hypoxemia, bearing in mind that dyspnea is a subjective sensation and is often independent of hypoxemia.[4] Symptom control in patients with advanced, chronic diseases is a widely discussed therapeutic resource. Current studies and recommendations demonstrate limited usefulness of oxygen therapy in some situations.[74] In practice, it is observed that the benefits of oxygen therapy are overestimated, whereas its possible risks and limitations are underestimated. An observational study including 114 patients who were near death revealed no benefit from oxygen use, with no difference between administration of oxygen and of medical air for symptom relief when PaO_2 > 55 mmHg.[75] The eventual improvement would be due to air flowing on the face, with trigeminal nerve stimulation and a reduction in dyspnea; therefore, there is no benefit from oxygen therapy in this context. The British Thoracic Society guidelines,[6] for example, recommend that oxygen use be limited to those patients with an SpO_2 < 90% on room air and that there is no role for routine SpO_2 monitoring as long as the patient is comfortable in the last days of life.[76]

The side effects of oxygen therapy include acute hypercapnia with central effects and lung injury due to oxidative stress that generally occurs at high oxygen flows.[77] The use of the oxygen therapy equipment can also lead to activity restriction, dryness of the mucous membranes, and discomfort caused by nasal cannulas

Chart 8. Protocols for the use of long-term home oxygen therapy: key points.

- Assumptions
  - LTOT is provided free of charge by municipal/state health departments via the Brazilian SUS by filling out protocols.
  - Patients and their families should be advised on the disease and the benefits of O_2 therapy, as well as on risk-reducing precautions (see Chart 7).
- Protocol for approval of LTOT

Full patient/legal guardian identification

  - Name, sex, date of birth, level of education, occupation, home address, and telephone number(s)
  - Indication for O_2 therapy, underlying disease, comorbidities, and a list of all medications used

Essential documentation

  - Arterial blood gas analysis
  - A report on the underlying disease, including a description of all relevant test results
  - Copies of the patient's (and legal guardian's) RG (ID card), CPF (individual registration number), and SUS card
  - Tests: X-ray and complete blood count
  - Proof of residence
  - A prescription for O_2 therapy
  - Source of O_2 (gaseous O_2 cylinder or O_2 concentrator via the SUS)
  - Number of L/min (at rest, during exercise, and during sleep)
  - Nasal cannula (roughly equivalent to): $FiO_2 = 21\% + (4 \times O_2$ flow rate)
  - Increase the O_2 flow rate by 0.5-1 L/min during exercise and sleep
  - O_2 delivered by catheter or mask (describe the type of O_2 delivery interface)
  - Therapeutic range for SaO_2 or SpO_2 when an oximeter is available
  - Minimum number of hours of daily use, always including the sleep period
- Periodic evaluations
  - Evaluate treatment adherence.
  - Evaluate clinical improvement and check SpO_2 with and without the use of O_2.
  - Provide clarification and correct errors in use of O_2.

Based on municipal and state protocols. LTOT: long-term home oxygen therapy; SUS: *Sistema Único de Saúde* (Unified Health System); RG: *Registro Geral*; and CPF: *Cadastro de Pessoa Física*.

or face masks.[78] The limitations caused by the use of oxygen therapy should be carefully evaluated by a multidisciplinary health care team, since some of them can have a great impact on the quality of end of life in individuals with advanced disease.[74]

The management of dyspnea in patients with advanced, chronic disease is based on the objective assessment of dyspnea, application of energy conservation techniques, optimization of treatment of the underlying disease and its complications, oxygen therapy when hypoxemia is present, cardiopulmonary rehabilitation, and use of noninvasive ventilation.[78] The use of oral opioids, notably morphine and dihydrocodeine, in doses not exceeding 30 mg/day of morphine or equivalent, has been considered beneficial in the palliation of dyspnea, with no increased risk of respiratory depression, despite adverse effects such as drowsiness, nausea, vomiting, and constipation.[79,80]

LTOT IN POST-COVID-19 PATIENTS

SARS-CoV-2 has infected and caused the death of millions of people worldwide, having a major impact on the health care system in several countries, including the lack of oxygen supply. During the pandemic, some concepts related to oxygen use, such as silent hypoxemia[81-83] and high-flow oxygen therapy,[84,85] were widely cited and discussed. Silent hypoxemia occurred most frequently in the elderly and in people with diabetes; in such patients, the hyperventilatory response to hypoxemia may be dampened. A direct action of the virus in the respiratory center, reducing the response to hyperventilation, is a hypothesis that has yet to be confirmed. A shift of the oxyhemoglobin dissociation curve to the left in infected patients could explain the fact that some patients possess greater tolerance to hypoxemia than others.[81-83]

Many patients with post-COVID-19 syndrome who developed sequelae after hospital discharge required LTOT. One study found that 13.2% of the patients who were discharged from the hospital required LTOT, and that that need decreased progressively as patients clinically recovered.[86] In another study, the risk factors associated with the need for LTOT after hospital discharge of patients with moderate to severe COVID-19 were as follows: being male; being ≥ 50 years of age; and having ≥ 3 comorbidities, especially previous lung disease.[87]

Chart 9. Oxygen therapy during air travel.[a,b]

- Assumptions
  - At sea level: BP = 760 mmHg, FiO_2 = 21%, and PaO_2 = 96-98 mmHg
  - On large aircraft flying at altitudes of up to 45,000 feet (13,716 m)
  - If aircraft cabins were not pressurized, BP and PaO_2 would be very low.
  - When pressurized, aircraft cabin conditions are equivalent to an altitude of 8,000 feet (2,438 m), where BP = 565 mmHg, FiO_2 = 15.1%, and PaO_2 = 53-75 mmHg or SpO_2 = 89-94%.
  - Aircraft cabin air is cooler and drier; many hours spent sitting immobile can cause leg edema and increase the risk of VTE.
  - Sleep and exertion can worsen hypoxemia and dyspnea.
- Absolute respiratory contraindications to air travel
  - Untreated active tuberculosis, pneumothorax < 60 days before, thoracic surgery < 15 days before, and hemoptysis
  - Need for an O_2 flow rate > 4 L/min
- Recommendations for oxygen use during air travel
  - SpO_2 < 92%
  - SpO_2 = 92-95% and ≤ 84% on a 6MWT or HAST
- Recommendations
  - Send a medical report including the ICD code(s) and the MEDIF in advance to the airlines.
  - The MEDIF must be filled in by the patient and his/her physician, being valid for 30 days.
  - Consult the list of portable O_2 concentrator brands approved for in-flight use.
  - Batteries must be enough to power a concentrator for 150% of the duration of the flight.
  - Passengers who have special needs (including auditory, visual, and ambulatory needs) and who travel frequently can fill out an FREMEC at an IATA member airline (the FREMEC is valid for one year).
  - Patients should pack their prescriptions and both their regular and exacerbation medications in their carry-on baggage.
  - Patients should request an aisle seat near a lavatory in order to reduce the need for moving around and improve humidity.
  - Patients should remain well hydrated during the flight and avoid the use of sedatives and alcoholic beverages.
  - Given that airports do not provide O_2, the airline should be informed in advance about the need for O_2 use outside the aircraft.
  - Patients must travel with a companion (see rules regarding seat discount).

BP: barometric pressure; VTE: venous thromboembolism; 6MWT: six-minute walk test; HAST: hypoxia altitude simulation test; ICD: International Classification of Diseases; MEDIF: Medical Information Form; FREMEC: Frequent Traveller's Medical Card; and IATA: International Air Transport Association. [a]Based on Ahmedzai et al.,[146] Sponholz Araújo,[151] Stoller J,[152] and the Brazilian National Civil Aviation Agency.[154] [b]See specific guidelines: Decree no. 4.794/SPO, issued on April 15, 2021 by the Brazilian National Civil Aviation Agency, and airline recommendations.

National and international guidelines on LTOT do not have specific guidelines for hospital discharge after SARS-CoV-2 infection. A task force of the European Respiratory Society/American Thoracic Society (ATS)[88] recommends that hospitalized patients with COVID-19 be evaluated for the need for oxygen supplementation at rest and during exercise, since progressive improvement in gas exchange is expected; however, some patients will require oxygen after hospital discharge. Another possibility is the presence of desaturation only during exercise, and therefore the need or absence of need for oxygen supplementation should be assessed.[88] The detection of decreased SpO_2 justifies the investigation of previously unknown pulmonary and cardiovascular comorbidities. Early reassessment after hospital discharge is recommended because the need for LTOT may be short-lived.[88]

LTOT IN PEDIATRIC PATIENTS

The initiation, continuation, and discontinuation of oxygen therapy in children have relevant particularities. Therefore, recommendations for adults do not apply to children. The main differences between LTOT in children and adults are as follows[89-93]:

- Physical growth and neurological development should be considered.
- The course of some diseases that cause hypoxemia in children is usually favorable; therefore, many children require LTOT only for a limited period of time.
- Most clinical conditions are peculiar to this age group, although the indications for LTOT in older children and adolescents may be similar to those in adults.
- The prescribing and monitoring of oxygen use are based on pulse oximetry rather than on arterial blood gas analysis.

Chart 10. Long-term home oxygen therapy. International guideline recommendations.[a]

Guidelines	Notes
LTOT (O_2 > 15 h/day) for COPD accompanied by a PaO_2 of ≤ 55 mmHg	
2015 BTS - Improves survival and pulmonary hemodynamics	RC - A
2020 ATS - or an SpO_2 of ≤ 88% (oximeter)	strong RC/mod QE
2020 SEPAR - Improves survival and quality of life	con RC/high QE
LTOT (O_2 > 15 h/day) for COPD accompanied by a PaO_2 = 56-59 mmHg	
2015 BTS - In case of peripheral edema, polycythemia (Ht ≥ 55%), or PH	RC - A
2020 ATS - SpO_2 = 89% + edema, Ht ≥ 55%, or cor pulmonale	strong RC/mod QE
2020 SEPAR - In case of RVF, PH, or polycythemia	con RC/mod QE
O_2 during exercise for COPD accompanied by an SpO_2 of ≤ 88% during physical activity	
2015 BTS - Do not recommend short-term O_2 therapy before or during exercise	RC - A
2020 ATS - In case of increased hypoxemia on exertion (a PaO_2 of ≤ 55 mmHg or = 56-59 mmHg + edema, Ht ≥ 55%, or cor pulmonale	cd RC/mod QE
2020 SEPAR - Can improve quality of life Can be useful during rehabilitation programs	weak RC/low QE weak RC/mod QE
O_2 during sleep in patients with COPD	
2015 BTS - Not recommended if criteria for LTOT are not met	RC - A
2020 ATS - Not evaluated	--
2020 SEPAR - If SpO_2 < 90%/≥ 30% of the total sleep time + RVF or polycythemia	con RC/high QE
O_2 for chronic diseases similar to COPD	
2015 BTS - CF, ILD, and advanced HF if PaO_2 ≤ 55 mmHg or ≤ 59 mmHg + edema, PH, or polycythemia	RC - D
2020 ATS - ILD accompanied by a PaO_2 of ≤ 55 mmHg (or an SpO_2 of ≤ 88%) or a PaO_2 = 56-59 mmHg (or an SpO_2 of ≤ 89%) + edema, Ht ≥ 55%, or cor pulmonale	strong RC/very low QE
2020 SEPAR - no comments on it	--
O_2 for palliative care	
2015 BTS - Not recommended for patients without hypoxemia or with mild hypoxemia	RC - A
2020 ATS - Not evaluated	--
2020 SEPAR - Not recommended for patients without hypoxemia[37]	--
Other issues	
2020 ATS - LTOT should not be prescribed for COPD patients with moderate hypoxemia (SpO_2 = 89-93%).	cd RC/low QE

LTOT: long-term home oxygen therapy; BTS: British Thoracic Society; ATS: American Thoracic Society; SEPAR: *Sociedad Española de Neumologia y Cirurgia Torácica*; Ht: hematocrit; PH: pulmonary hypertension; RVF: right ventricular failure; CF: cystic fibrosis; ILD: interstitial lung disease; HF: heart failure; RC: recommendation; QE: quality of evidence; con: consistent; mod: moderate; cd: conditional; D: based on consensus opinion. [a]2015 BTS: Hardinge et al.[6]; 2020 ATS: Jacobs et al.[20]; and 2020 SEPAR: González-Moro et al.[25]

- Specific equipment is required to allow for low oxygen flows.
- Many children require oxygen therapy overnight only, requiring fewer hours than those normally prescribed in adult LTOT.
- Periods such as physical activity (which includes bathing), sleep, and even feedings can lead to drops in saturation; therefore, provision of higher oxygen flow rates on these occasions should be individualized.
- All children require supervision from an adult.
- Provision of oxygen may be necessary at school for school-age children.

Conditions that most often lead to the need for LTOT in pediatric patients include bronchopulmonary dysplasia (BPD), CF, bronchiolitis obliterans, ILDs, and sickle cell disease. Because BPD is exclusive to pediatric patients and because LTOT has some peculiarities in pediatric CF patients, we chose to address these two conditions in more detail.

BPD

The most current definition of BPD is a diagnosis based on persistent radiographic changes of the lung parenchyma in preterm infants born at ≤ 32 weeks of gestational age or at 36 weeks of corrected gestational age who require ventilatory support for three or more days to maintain arterial saturation at 90-95%.[94,95]

BPD is the most common indication for LTOT in children and occurs in approximately 40% of very low birth weight newborns (< 1,000 grams).[93,96-98] Its incidence has not decreased over the years, precisely because of important advances in neonatal care, which has increasingly allowed the survival of extremely preterm infants.[94-97]

The benefits of LTOT include improvement in physical growth, neurological development, and sleep pattern, as well as a reduction in airway resistance, pulmonary artery pressure, risk of sudden death, and nocturnal awakenings. In addition, keeping the child at home

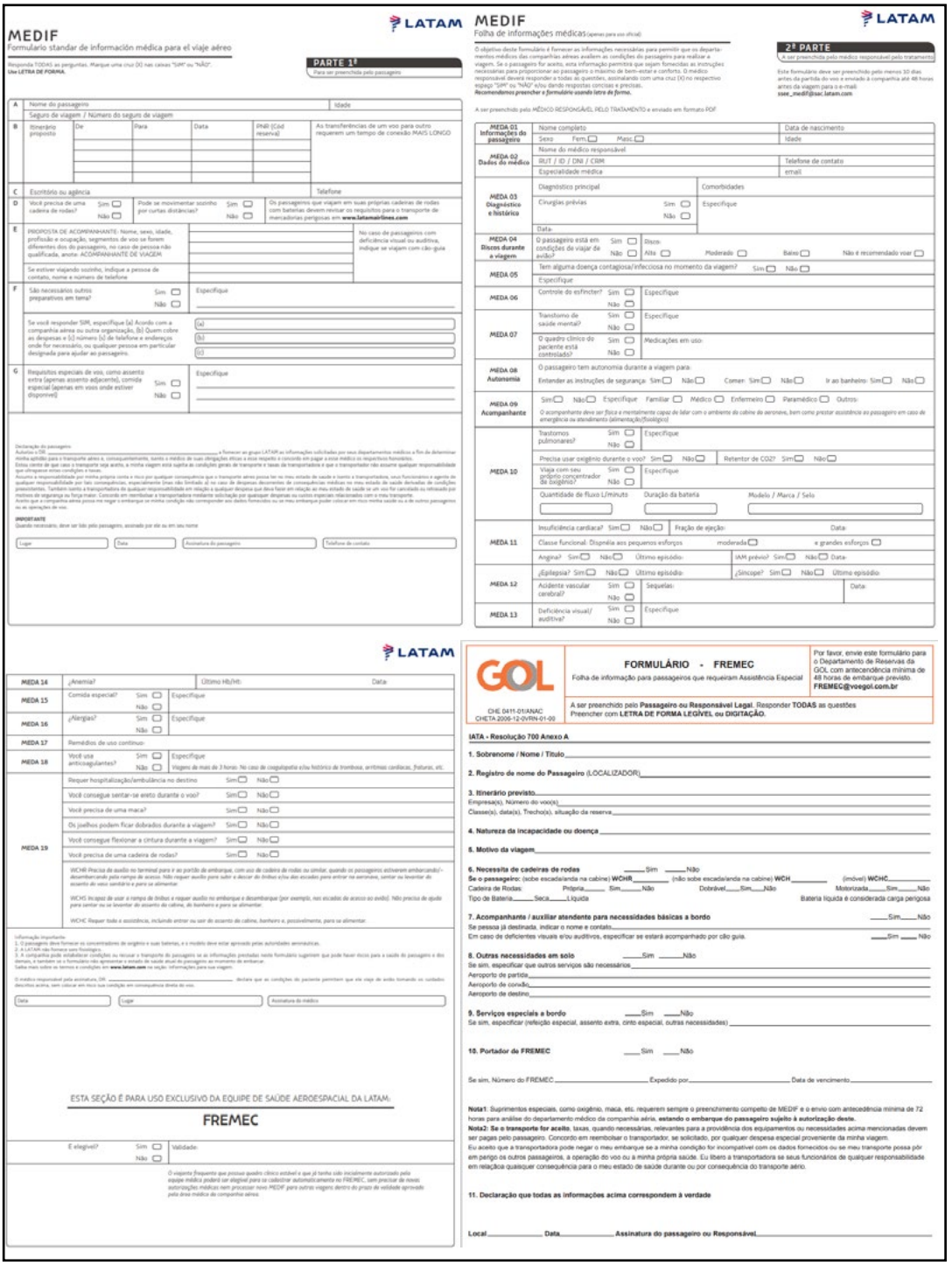


Figure 1. Examples of medical certificates requested by airlines to prove that the passenger is fit to fly: the Medical Information Form (MEDIF) and the Frequent Traveller's Medical Card (FREMEC).

with the family allows a better emotional bond and reduces the risk of nosocomial infections.[89,93]

LTOT is indicated for the patient who is clinically stable, remains oxygen dependent (SpO_2 ≤ 92% on room air), and does not have hypercapnia. Two important studies[99,100] demonstrated that maintaining SpO_2 at > 95% was related to a worse outcome, with the need to continue LTOT for a longer period. Since then, maintaining SpO_2 at > 95% has been avoided.[99,100] In contrast, another study[101] compared an SpO_2 target of 85-89% with that of 91-95% for children born before 28 weeks of gestation and demonstrated

that an SpO_2 target of < 90% was associated with an increased risk of death before discharge, resulting in the early discontinuation of the study.[101] Current recommendations are that SpO_2 should be between 90% and 95%, without frequent fluctuations during sleep or feedings.[102,103]

LTOT should be considered for patients with BPD who were born at ≥ 36 weeks of corrected gestational age, are clinically stable, and experience a weight gain of 20 grams per day.

The initial oxygen flow rate is 1-2 L/min, maintaining SpO_2 between 92% and 95%. A decrease in oxygen flow may be considered after 4 weeks if the patient is stable and continue experiencing adequate weight gain. The oxygen flow rate should be reduced by 0.25-0.1 L/min, initially while the child is awake, as long as SpO_2 remains at ≥ 92%.[97]

CF

The prescribing of LTOT in CF patients should be individualized, and, in general, children and adolescents should receive it via a nasal cannula, with pertinent adaptations, as in the case of patients with a tracheostomy.[104] Oxygen therapy will reduce dyspnea and delay the onset of *cor pulmonale*. School children and adolescents with a PaO_2 ≤ 55 mmHg or an SpO_2 ≤ 88% should receive oxygen at the lowest flow rate possible to maintain SpO_2 at > 90%.[90,104] Recent publications by the ATS recommend considering the prescription of LTOT for pediatric CF patients who maintain saturation at 90-93% but have exertional dyspnea.[89,90] The prescription of LTOT for infants and preschool children is indicated to maintain SpO_2 at ≥ 93%, in a manner similar to that in patients with BPD.[92]

Weaning from LTOT in pediatric patients

Weaning from LTOT may occur with lung growth and maturation, and possible improvement of the lung disease. The physician should clinically evaluate the patient and make sure, on the basis of SpO_2 measurements, that weaning is feasible.[89,90] Weaning will be adjusted weekly by gradually reducing oxygen flow or by discontinuing LTOT for increasingly longer periods of the day, maintaining weekly to monthly medical visits to ensure safe weaning.[89] Infants receiving flows of up to 0.1 L/min, preschool children receiving flows of 0.1 to 0.25 L/min, and older children receiving flows of 0.25 to 0.5 L/min may be able to discontinue LTOT. After oxygen is discontinued, it is strongly suggested that nocturnal oximetry with an appropriate pediatric device be performed.[89,90] The LTOT equipment must remain in the patient's home for as long as necessary to ensure his or her safety[89]; the national recommendation suggests a period of at least 3 months after LTOT discontinuation.[92] Then, monitoring by oximetry should be performed on two occasions one month apart, and, if oximetry values remain adequate, the LTOT equipment can be removed from the patient's home.[92]

LTOT IN PATIENTS WITH SLEEP-DISORDERED BREATHING

Sleep-disordered breathing is characterized by repetitive sleep-related respiratory events, causing intermittent hypoxemia and sleep fragmentation, and includes OSA, central sleep apnea (CSA), and sleep-related hypoventilation; OSA is the most prevalent form of sleep-disordered breathing.[105]

The intensity and frequency of intermittent hypoxemia during recurrent episodes of apnea/hypopnea during sleep commonly lead to cardiovascular, metabolic, and neurocognitive consequences, impacting morbidity and mortality.[106]

Positive airway pressure (PAP) is the standard therapy for maintaining upper airway patency and correcting intermittent hypoxemia.[105,107] However, although PAP is an extremely effective treatment, PAP adherence is limited.[105,107,108]

OSA

A systematic review and meta-analysis of RCTs showed the superiority of CPAP over nocturnal oxygen use in reducing the apnea-hypopnea index (AHI) in individuals with OSA.[109] However, previous studies have documented an increase in the duration of obstructive respiratory events during nocturnal oxygen use.[38,110] In a recent meta-analysis, supplemental oxygen therapy, when compared with CPAP, was less efficient in reducing the AHI, the duration of SpO_2 < 90%, and systemic blood pressure, as well as in improving sleep quality.[111] Oxygen can be used in conjunction with PAP therapy when SpO_2 remains at ≤ 88% for at least 5 min despite adequate titration and complete control of obstructive events (initiate oxygen at 1 L/min and titrate to maintain SpO_2 at 88-94%).[112]

CSA

Previous studies have reported the beneficial effect of oxygen supplementation on CSA associated with Cheyne-Stokes respiration in individuals with congestive heart failure (CHF).[113,114] Two meta-analyses compared the effect of CPAP, adaptive servo-ventilation (ASV), and oxygen supplementation on the AHI and on left ventricular ejection fraction (LVEF) in CHF patients with CSA associated with Cheyne-Stokes respiration.[115,116] The first meta-analysis,[115] which included 919 patients, showed that ASV was most likely to reduce the AHI, followed by oxygen supplementation and CPAP. In the second meta-analysis,[116] which included 951 patients, CPAP and ASV, in contrast to nocturnal oxygen, were found to be equally efficient in improving LVEF. Although ASV can improve the AHI and LVEF, one study observed increased mortality in CHF patients with CSA and an LVEF ≤ 45%.[117] Nocturnal oxygen therapy may not eliminate obstructive events that often coexist with central events in patients with CHF.[118] In patients with CSA, nocturnal oxygen effectively reduces the AHI secondary to CSA and improves SpO_2, and may serve as an alternative to PAP therapy.[108,119]

However, long-term studies assessing the impact of LTOT on CSA are lacking.

COPD-OSA overlap syndrome

The COPD-OSA overlap syndrome causes more severe nocturnal hypoxemia than either COPD or OSA alone, leading to a poor prognosis.[120,121] Nocturnal oxygen therapy may be indicated in COPD patients when nocturnal hypoxemia persists despite appropriate treatment.[38,108,110] However, because oxygen suppresses the hypoxic respiratory drive, it may contribute to prolonging apnea duration, leading to hypercapnia and acidosis in patients with OSA, especially those with COPD-OSA overlap syndrome or hypoventilation.[38,108,110] Current treatment of patients with COPD-OSA overlap syndrome includes regular CPAP therapy, noting that CPAP is indicated in severe or moderate OSA when there are associated symptoms or significant nocturnal hypoxemia. There is no indication for CPAP in mild OSA.[120]

In observational studies, patients with COPD-OSA overlap syndrome who were treated with CPAP had survival rates comparable to those of patients with COPD alone, whereas those with this overlap syndrome who were not treated with CPAP had higher mortality.[121]

Obesity hypoventilation syndrome

The obesity hypoventilation syndrome (OHS) comprises the triad of obesity, gas exchange abnormalities (hypercapnia), and absence of alternative explanations for hypoventilation. The most recent publications by the ATS and the European Respiratory Society recommend that CPAP, rather that BiPAP, be used as first-line treatment for outpatients with OHS and severe OSA, an association that is present in more than 70% of patients with OHS.[122,123] However, noninvasive ventilation is preferred in a minority of the patients with OHS who do not have OSA or have milder forms of OSA (approximately < 30%). Oxygen therapy alone in OHS should be avoided because of its detrimental effect on ventilation and the risk of it precipitating hypercapnic respiratory failure.[123]

OXYGEN THERAPY DURING EXERCISE AND PULMONARY REHABILITATION

Tissue oxygenation depends on factors including the transfer of oxygen from the atmosphere to the lungs; adequate oxygen delivery to peripheral tissues through hemoglobin transport and adequate blood flow; oxygen delivery to the mitochondria for aerobic ATP synthesis; and muscle oxygen utilization.[124]

The main effects that oxygen therapy during exercise has on COPD and ILD are as follows: a central effect, preventing reduced cerebral oxygenation; a ventilatory effect, with decreased respiratory drive resulting from reduced carotid chemoreceptor stimulation and reduced dynamic hyperinflation; a cardiovascular effect, achieved through pulmonary vasodilation, increased cardiac output, and decreased pulmonary artery pressure; and a muscle effect, with reduced muscle dysfunction, reduced lactic acid production, and reduced activity of muscle metaboreceptors, reducing respiratory drive.[125-127] Modulation of these mechanisms can improve symptoms such as dyspnea and fatigue, as well as improving quality of life and exercise capacity, particularly during rehabilitation. However, controversy remains in the literature regarding oxygen therapy, especially for normoxemic patients with or without exercise-induced hypoxemia.

COPD

Exercise-induced hypoxemia is common in patients with COPD, being found in almost half of patients referred for pulmonary rehabilitation (PR). In general, these patients do not tolerate high-intensity exercise, and a reduction in training intensity is required in many cases; this, however, could limit the efficacy of PR.[128] In a study evaluating acute oxygen therapy, 124 patients with moderate to severe COPD were divided into three groups: normoxemic patients, patients with resting hypoxemia, and patients with exercise-induced hypoxemia; they underwent a six-minute walk test (6MWT) while receiving oxygen or compressed air.[129] The two groups of patients with hypoxemia benefited from oxygen therapy delivered by nasal cannula (NC), with increased exercise capacity, although the difference was not clinically significant (> 30 m).[129] In a study comparing the effects of oxygen and compressed air delivered during exercise training in normoxemic patients without exercise-induced hypoxemia (n = 29), oxygen therapy resulted in increased training intensity and exercise capacity (cycle ergometer endurance: 14.5 min vs. 10.5 min; $p < 0.05$) during a PR program.[130] It is of note that oxygen responders present with higher oxygen desaturation[131] and lower exercise capacity[132] at baseline or a > 10% increase in the distance covered at baseline.[132]

In a multicenter study involving 111 patients with moderate to severe COPD and exercise-induced hypoxemia (an SpO_2 of < 90% during the 6MWT), oxygen therapy did not result in an increase in exercise capacity or quality of life when compared with supplemental compressed air. It is of note that both groups benefitted from exercise training, with significant increases in exercise capacity and quality of life.[133] However, the question remains whether the proposed level of training intensity was actually achieved.[134] In another study, patients with severe to very severe COPD and resting hypoxemia (n = 50) received oxygen therapy (constant oxygen flow rates vs. automated oxygen titration).[135] Automated oxygen titration resulted in improvements in oxygenation, walking endurance time, SpO_2, PaO_2, and dyspnea, with no impact on $PaCO_2$. In comparison with nonresponders, those who responded to automated oxygen titration tended to have lower lactate values, less leg fatigue at the end of the endurance test, and less dyspnea.[135] In a study comparing oxygen therapy delivered via a Venturi mask and high-flow nasal cannula (HFNC)

oxygen therapy during exercise training, both groups of patients benefitted from the exercise training program, with significant improvements in exercise capacity, symptoms, and quality of life.[136]

In a recent systematic review and meta-analysis of 7 studies evaluating oxygen therapy and PR, it was shown that oxygen therapy delivered during PR did not improve exercise capacity, dyspnea scores, or quality of life, although the level of evidence was weak, primarily because of the heterogeneous interventions across studies.[137]

Despite the conflicting results across studies, international guidelines state that patients receiving LTOT should receive oxygen therapy during exercise training and increase the flow as the demand for oxygen increases during exercise.[6,20,25] In some cases, there might be a need for a formal assessment demonstrating improvement in exercise tolerance with the addition of acute oxygen therapy.[6,20,25]

ILD

Patients with ILD have reduced exercise tolerance (as assessed by the 6MWT), maximal oxygen uptake, and endurance time. Reduced exercise capacity is associated with poor survival. In a study comparing acute oxygen therapy and supplemental compressed air in patients with mild to moderate ILD (n = 72) and exercise-induced hypoxemia, oxygen was found to increase endurance time, reduce desaturation, and reduce the number of symptoms.[138] Respondents were those who achieved a lower nadir SpO_2 on the 6MWT performed when receiving compressed air at baseline[138]; a similar result was found when an FiO_2 = 50% was compared with supplemental compressed air.[139]

It is known that patients with ILD can have significant desaturation (e.g., an SpO_2 of < 80% on exertion), and it is not always possible to maintain an SpO_2 > 90% with the use of oxygen therapy delivered by NC. In a study comparing oxygen therapy delivered by a conventional NC and oxygen therapy delivered by a pendant NC with an incorporated reservoir (Oxymizer; Drive DeVilbiss Healthcare, Port Washington, NY, USA) in patients receiving ambulatory oxygen therapy (n = 21), there was improvement in exercise tolerance, but no impact on dyspnea.[140] Although oxygenation improved, the improvement was not sustained during exercise, even with the use of the Oxymizer.[140] In a study of patients with severe ILD (n = 25) tested on room air, receiving oxygen therapy via NC at 4 L/min, or receiving HFNC oxygen therapy with an FiO_2 of 50% at 30-50 L/min (heated to 34°C and humidified), those who received HFNC oxygen therapy showed higher endurance time than did those in the other two groups, with HFNC oxygen therapy being associated with delayed oxygen desaturation kinetics, impaired chronotropic response, reduced perception of dyspnea, and reduced ratings of perceived leg fatigue.[141] In comparison with an FiO_2 of 21%, hyperoxia (an FiO_2 of 30-60%) resulted in increased endurance time, decreased ventilation, reduced perception of dyspnea,[142] and significantly improved muscle oxygenation as assessed by fatigability, with reduced leg discomfort during exercise.[127]

Although oxygen therapy has been found to increase exercise capacity, a systematic review showed that oxygen therapy has no impact on dyspnea during exercise in patients with ILD.[57] Because patients with ILD require high oxygen flow rates in many cases, it is important to select the most appropriate oxygen delivery interface (an NC or a simple face mask, for example), and when a higher oxygen concentration is required, other devices should be evaluated, including nonrebreather masks and HFNC, the latter being selected and used in accordance with institutional protocols.

PH

The benefits and safety of PR in patients with PH have been reported, particularly in the last 15 years. In the guidelines for PR in patients with PH,[143] based on published protocols, oxygen was delivered as needed, and desaturation was considered an adverse event in 16 (2.4%) of the 674 patients included in the study. In an evaluation of 519 patients included in different studies, exercise training was generally based on ~60% of the maximum HR (which should not exceed 120 bpm) and an SpO_2 > 85-90%. An oxygen desaturation of < 85-90% or an HR > 120 bpm were used as criteria to adjust training intensity, resulting in early exercise termination or a reduction in training intensity.[144,145]

OXYGEN DURING AIR TRAVEL

Commercial aircraft flights can reach altitudes of up to 45,000 feet (13,716 m), resulting in major reductions in barometric pressure and PaO_2.[146] Aircraft cabins are pressurized to an altitude of 8,000 feet (2,438 m), and, at this altitude, FiO_2 inside the aircraft is 15.1%; in a healthy individual, depending on his/her age and minute ventilation, PaO_2 and SaO_2 decrease to 60-75 mmHg and 89-94%, respectively.[146-148]

In situations of hypobaric hypoxia, an adequate PaO_2 is maintained through an increase in minute ventilation, HR, and cardiac output, as well as pulmonary vasoconstriction with redistribution of blood flow to apical regions, affecting V/Q. Although most individuals tolerate these changes well, some can experience dyspnea, sleepiness, cognitive changes, fainting, and chest pain.

Patients with chronic lung disease, especially those on LTOT or with borderline SpO_2 levels, as well as patients with other diseases that are accompanied by hypoxemia, will experience worsening hypoxemia and can present with clinical manifestations during flights.[147-150] Therefore, patients at risk of hypoxemia during air travel should be evaluated for the need for oxygen therapy. The use of LTOT, the presence of comorbidities, and reports of respiratory symptoms

such as dyspnea, cough, and chest pain during previous flights should be investigated. Patients should only travel when they are in a stable phase of their disease.[148] In addition, during flights, passengers remain immobile for long periods of time and are exposed to low temperatures and dry air, all of which are factors that increase the risk of exacerbations and other complications, such as venous thromboembolism, thus reinforcing the importance of maintaining an adequate SpO_2 during air travel.[151]

Patients with an SpO_2 > 95% on room air can fly without supplemental oxygen; however, those with an SpO_2 of ≤ 92% should receive supplemental oxygen during air travel. Patients with an SpO_2 between 92% and 95% should undergo a 6MWT or a hypoxia altitude simulation test, the latter being rarely available in Brazil. Patients in whom SpO_2 remains ≤ 84% during either of the aforementioned tests will also require supplemental oxygen during air travel.[149,150] A hypoxia altitude simulation test simulates an aircraft cabin with decreased barometric pressure and FiO_2. Ideally, the test should be performed in a hypobaric chamber; however, hypobaric chambers are scarcely available, and test results are unreliable when the test is performed in a normobaric chamber.[149,150]

Patients who require an oxygen flow rate > 4 L/min in order to correct hypoxemia should be discouraged from flying, and, if they do fly, they should use aeromedical transport.[151] It is of note that these recommendations are primarily based on studies of patients with COPD and are extrapolated to other respiratory diseases.[152,153]

After performing an evaluation, the attending physician must fill out a Medical Information Form, which is provided by airlines and which, in addition to including other relevant information, states that the patient is fit to fly provided that he/she receives the required oxygen flow rate. The form should be filled out at least 72 h before the flight so that there is enough time to submit it to the airline. Patients should plan their trips in advance because time for approval varies across companies.[151-153]

On the aircraft, oxygen therapy can be delivered via oxygen supplied by the airline (an oxygen cylinder or concentrator) or via the patient's own portable oxygen concentrator, provided that it has been approved for in-flight use. While staying at airports, patients must use their own portable oxygen concentrators. The Brazilian *Agência Nacional de Aviação Civil* (National Civil Aviation Agency) has recently published supplementary guidelines on the use of portable oxygen concentrators on commercial aircraft.[154] The most important points are as follows: only brands approved for in-flight use are allowed; neither concentrators nor batteries can be checked at the airline counter; and batteries must be enough to power a concentrator for at least 150% of the duration of the flight. Unfortunately, commercial airlines do not have homogeneous rules regarding how the aforementioned form should be or the supply of oxygen. Attending physicians must seek information on company policies and procedures in order to provide appropriate patient guidance (Chart 9 and Figure 1).

PRECAUTIONS WHEN PRESCRIBING LTOT

Some precautions should be taken when prescribing LTOT. Patients should receive continuing education and training in oxygen device use, safety, and self-management. Physicians prescribing LTOT should be prepared to do the following: a) determine the objective of and need for LTOT by means of arterial blood gas analysis; b) fill out reports correctly and adhere to municipal or state protocols; c) select a qualified supplier of durable medical equipment; d) titrate oxygen on different occasions (e.g., at rest, during activities of daily living, during sleep, on exertion/during exercise, during trips, and during exacerbations) in order to determine the oxygen flow rate required to maintain an SpO_2 > 90%; e) test the flowmeter, because the oxygen flow rate being displayed might be different from that which is actually being supplied; f) prescribe the most appropriate oxygen flow rate for each specific situation, the minimum duration of use, a variety of sources of oxygen supply, and necessary accessories; g) reassess periodically the need for LTOT for prescription renewal/change; and h) educate patients and their families on the correct use of LTOT, focusing on the importance of treatment adherence. The recommendations are summarized in Charts 1-7 (on practical aspects of prescribing oxygen) and Chart 8 (on the protocol for prescribing oxygen), as well as in Chart 9 and Figure 1 (on air travel).

FINAL CONSIDERATIONS

The use of LTOT became widespread beginning in the 1980s. Despite the scarcity of studies and the number of unanswered questions, the benefits of LTOT were quickly disseminated, and several pulmonology societies around the world began to recommend the use of LTOT. The recommendations herein reflect an integration of current and previously established evidence—with LTOT being prescribed for patients with severe resting hypoxemia in order to improve survival and quality of life—supported by studies of patients with COPD. Existing evidence suggests that LTOT should not be prescribed for COPD patients with moderate resting hypoxemia. Oxygen prescription for ILD patients with severe resting hypoxemia is strongly recommended. Evidence is still lacking on the role of LTOT in other lung diseases, such as PH, and on the use of LTOT during sleep and during physical activity. Future studies should evaluate the safety of the shared decision between patients and their physicians regarding LTOT and the best approach to discontinuing LTOT in patients without severe resting hypoxemia.

It should be noted that LTOT programs have high costs and that it is important to prescribe LTOT

correctly so that patients can really benefit from it, achieving the expected results in the medical, social, work, and family realms.[6,19,20,25] We analyzed in detail the recommendations in the three most recent international guidelines on LTOT,[6,20,25] and they are summarized in Chart 10. Although we agree with the recommendations, we emphasize the need for further studies, particularly those focusing on chronic diseases other than COPD.

AUTHOR CONTRIBUTIONS

All authors participated in all stages of the study (including the planning of the study and the writing, reviewing, and revising of the manuscript) and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93(3):391-398. https://doi.org/10.7326/0003-4819-93-3-391
2. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1(8222):681-686. https://doi.org/10.1016/S0140-6736(81)91970-X
3. Timms RM, Khaja FU, Williams GW. Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. Ann Intern Med. 1985;102(1):29-36. https://doi.org/10.7326/0003-4819-102-1-29
4. McDonald CF, Whyte K, Jenkins S, Serginson J, Frith P. Clinical Practice Guideline on Adult Domiciliary Oxygen Therapy: Executive summary from the Thoracic Society of Australia and New Zealand. Respirology. 2016;21(1):76-78. https://doi.org/10.1111/resp.12678
5. Lacasse Y, Bernard S, Maltais F. Eligibility for home oxygen programs and funding across Canada. Can Respir J. 2015;22(6):324-330. https://doi.org/10.1155/2015/280604
6. Hardinge M, Suntharalingam J, Wilkinson T; British Thoracic Society. Guideline update: The British Thoracic Society Guidelines on home oxygen use in adults. Thorax. 2015;70(6):589-591. https://doi.org/10.1136/thoraxjnl-2015-206918
7. Ferguson GT, Cherniack RM. Management of chronic obstructive pulmonary disease. N Engl J Med. 1993;328(14):1017-1022. https://doi.org/10.1056/NEJM199304083281408
8. 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(5):519-525.
9. Croxton TL, Bailey WC. Long-term oxygen treatment in chronic obstructive pulmonary disease: recommendations for future research: an NHLBI workshop report. Am J Respir Crit Care Med. 2006;174(4):373-378. https://doi.org/10.1164/rccm.200507-1161WS
10. Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. 2011;155(3):179-191. https://doi.org/10.7326/0003-4819-155-3-201108020-00008
11. Petty TL, Bliss PL. Ambulatory oxygen therapy, exercise, and survival with advanced chronic obstructive pulmonary disease (the Nocturnal Oxygen Therapy Trial revisited). Respir Care. 2000;45(2):204-213.
12. Crockett AJ, Cranston JM, Moss JR, Alpers JH. A review of long-term oxygen therapy for chronic obstructive pulmonary disease. Respir Med. 2001;95(6):437-443. https://doi.org/10.1053/rmed.2001.1064
13. Eaton T, Lewis C, Young P, Kennedy Y, Garrett JE, Kolbe J. Long-term oxygen therapy improves health-related quality of life. Respir Med. 2004;98(4):285-293. https://doi.org/10.1016/j.rmed.2003.10.008
14. Wedzicha JA. Effects of long-term oxygen therapy on neuropsychiatric function and quality of life. Respir Care. 2000;45(1):119-126.
15. Ringbaek TJ, Viskum K, Lange P. Does long-term oxygen therapy reduce hospitalisation in hypoxaemic chronic obstructive pulmonary disease?. Eur Respir J. 2002;20(1):38-42. https://doi.org/10.1183/09031936.02.00284202
16. Morrison DA, Stovall JR. Increased exercise capacity in hypoxemic patients after long-term oxygen therapy. Chest. 1992;102(2):542-550. https://doi.org/10.1378/chest.102.2.542
17. Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Pelletier A. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1985;131(4):493-498. https://doi.org/10.1164/arrd.1985.131.4.493
18. Zieliński J, Tobiasz M, Hawrylkiewicz I, Sliwiński P, Pałasiewicz G. Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. Chest. 1998;113(1):65-70. https://doi.org/10.1378/chest.113.1.65
19. Sociedade Brasileira de Pneumologia e Tisiologia. Oxigenioterapia domiciliar prolongada (ODP). J Pneumol. 2000;26(6):341-350. https://doi.org/10.1590/S0102-35862000000600011
20. Jacobs SS, Krishnan JA, Lederer DJ, Ghazipura M, Hossain T, Tan AM, et al. Home Oxygen Therapy for Adults with Chronic Lung Disease. An Official American Thoracic Society Clinical Practice Guideline [published correction appears in Am J Respir Crit Care Med. 2021 Apr 15;203(8):1045-1046]. Am J Respir Crit Care Med. 2020;202(10):e121-e141. https://doi.org/10.1164/rccm.202009-3608ST
21. Collins JA, Rudenski A, Gibson J, Howard L, O'Driscoll R. Relating oxygen partial pressure, saturation and content: the haemoglobin-oxygen dissociation curve. Breathe (Sheff). 2015 Sep;11(3):194-201. https://doi.org/10.1183/20734735.001415
22. Carvalho CRR. Fisiopatologia Respiratória. São Paulo: Atheneu; 2005.
23. Wagner PD. The physiological basis of pulmonary gas exchange: implications for clinical interpretation of arterial blood gases. Eur Respir J. 2015 Jan;45(1):227-43. https://doi.org/10.1183/09031936.00039214
24. Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. Eur Respir J. 2014 Oct;44(4):1023-41. https://doi.org/10.1183/09031936.00037014
25. González-Moro JMR, Quiroga LB, Navarrete BA, Michavila IA, Lobato SD. Oxigenoterapia continua domiciliaria [Article in Spanish]. Open Respir Arch. 2020;2(2):33-45. https://doi.org/10.1016/j.opresp.2020.03.004
26. Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell. 2012 Feb 3;148(3):399-408. https://doi.org/10.1016/j.cell.2012.01.021
27. West JB. Physiological Effects of Chronic Hypoxia. N Engl J Med. 2017;376(20):1965-1971. https://doi.org/10.1056/NEJMra1612008
28. Wan J, Lata C, Santilli A, Green D, Roy S, Santilli S. Supplemental oxygen reverses hypoxia-induced smooth muscle cell proliferation by modulating HIF-alpha and VEGF levels in a rabbit arteriovenous fistula model. Ann Vasc Surg. 2014;28(3):725-736. https://doi.org/10.1016/j.avsg.2013.10.007
29. Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Enrhart M, Schott R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J. 1999;14(5):1002-1008. https://doi.org/10.1183/09031936.99.14510029
30. Górecka D, Gorzelak K, Sliwiński P, Tobiasz M, Zieliński J. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax. 1997;52(8):674-679. https://doi.org/10.1136/thx.52.8.674
31. Long-Term Oxygen Treatment Trial Research Group, Albert RK, Au DH, Blackford AL, Casaburi R, Cooper JA Jr, et al. A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation. N Engl J Med. 2016;375(17):1617-1627. https://doi.org/10.1056/NEJMoa1604344
32. Haidl P, Clement C, Wiese C, Dellweg D, Köhler D. Long-term oxygen therapy stops the natural decline of endurance in COPD patients with reversible hypercapnia. Respiration. 2004;71(4):342-347. https://doi.

org/10.1159/000079637

33. Heaton RK, Grant I, McSweeny AJ, Adams KM, Petty TL. Psychologic effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med. 1983;143(10):1941-1947. https://doi.org/10.1001/archinte.1983.00350100121023
34. Clini E, Vitacca M, Foglio K, Simoni P, Ambrosino N. Long-term home care programmes may reduce hospital admissions in COPD with chronic hypercapnia. Eur Respir J. 1996;9(8):1605-1610. https://doi.org/10.1183/09031936.96.09081605
35. Guyatt GH, Nonoyama M, Lacchetti C, Goeree R, McKim D, Hells-Ansdell D, et al. A randomized trial of strategies for assessing eligibility for long-term domiciliary oxygen therapy. Am J Respir Crit Care Med. 2005;172(5):573-580. https://doi.org/10.1164/rccm.200412-1692OC
36. Timms RM, Kvale PA, Anthonisen NR, Boylen CT, Cugell DW, Petty TL, et al. Selection of patients with chronic obstructive pulmonary disease for long-term oxygen therapy. JAMA. 1981;245(24):2514-2515. https://doi.org/10.1001/jama.1981.03310490032020
37. Abdo WF, Heunks LM. Oxygen-induced hypercapnia in COPD: myths and facts. Crit Care. 2012;16(5):323. https://doi.org/10.1186/cc11475
38. Alford NJ, Fletcher EC, Nickeson D. Acute oxygen in patients with sleep apnea and COPD. Chest. 1986;89(1):30-38. https://doi.org/10.1378/chest.89.1.30
39. Carlos WG, Baker MS, McPherson KA, Bosslet GT, Sood R, Torke AM. Smoking-Related Home Oxygen Burn Injuries: Continued Cause for Alarm. Respiration. 2016;91(2):151-155. https://doi.org/10.1159/000443798
40. Avdeev SN, Aisanov ZR, Chuchalin AG. Compliance as a critical issue in long-term oxygen therapy. Monaldi Arch Chest Dis. 1999;54(1):61-66.
41. Cullen DL, Stiffler D. Long-term oxygen therapy: review from the patients' perspective. Chron Respir Dis. 2009;6(3):141-147. https://doi.org/10.1177/1479972309103046
42. Jacobs SS, Lindell KO, Collins EG, Garvey CM, Hernandez C, McLaughlin S et al. Patient Perceptions of the Adequacy of Supplemental Oxygen Therapy. Results of the American Thoracic Society Nursing Assembly Oxygen Working Group Survey. Ann Am Thorac Soc. 2018;15(1):24-32. https://doi.org/10.1513/AnnalsATS.201703-209OC
43. Oba Y, Salzman GA, Willsie SK. Reevaluation of continuous oxygen therapy after initial prescription in patients with chronic obstructive pulmonary disease. Respir Care. 2000;45(4):401-406.
44. Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519-2531. https://doi.org/10.1016/S0140-6736(16)00576-6
45. Elphick HE, Mallory G. Oxygen therapy for cystic fibrosis. Cochrane Database Syst Rev. 2013;2013(7):CD003884. https://doi.org/10.1002/14651858.CD003884.pub4
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(3):368-377. https://doi.org/10.1016/S0022-3476(89)80553-0
47. Kapnadak SG, Dimango E, Hadjiliadis D, Hempstead SE, Tallarico E, Pilewski JM, et al. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. J Cyst Fibros. 2020;19(3):344-354. https://doi.org/10.1016/j.jcf.2020.02.015
48. Khor YH, Renzoni EA, Visca D, McDonald CF, Goh NSL. Oxygen therapy in COPD and interstitial lung disease: navigating the knowns and unknowns. ERJ Open Res. 2019;5(3):00118-2019. https://doi.org/10.1183/23120541.00118-2019
49. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760-1769. https://doi.org/10.1016/S0140-6736(11)60405-4
50. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in N Engl J Med. 2014 Sep 18;371(12):1172]. N Engl J Med. 2014;370(22):2083-2092. https://doi.org/10.1056/NEJMoa1402582
51. Khor YH, Goh NS, Glaspole I, Holland AE, McDonald CF. Exertional Desaturation and Prescription of Ambulatory Oxygen Therapy in Interstitial Lung Disease. Respir Care. 2019;64(3):299-306. https://doi.org/10.4187/respcare.06334
52. Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2003;168(9):1084-1090. https://doi.org/10.1164/rccm.200302-219OC
53. Lettieri CJ, Nathan SD, Browning RF, Barnett SD, Ahmad S, Shorr AF. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Respir Med. 2006;100(10):1734-1741. https://doi.org/10.1016/j.rmed.2006.02.004
54. Du Plessis JP, Fernandes S, Jamal R, Camp P, Johannson K, Schaeffer M, et al. Exertional hypoxemia is more severe in fibrotic interstitial lung disease than in COPD. Respirology. 2018;23(4):392-398. https://doi.org/10.1111/resp.13226
55. Vainshelboim B, Kramer MR, Izhakian S, Lima RM, Oliveira J. Physical Activity and Exertional Desaturation Are Associated with Mortality in Idiopathic Pulmonary Fibrosis. J Clin Med. 2016;5(8):73. https://doi.org/10.3390/jcm5080073
56. Troy LK, Young IH, Lau EMT, Wong KKH, Yee BJ, Torzillo PJ, et al. Nocturnal hypoxaemia is associated with adverse outcomes in interstitial lung disease. Respirology. 2019;24(10):996-1004. https://doi.org/10.1111/resp.13549
57. Bell EC, Cox NS, Goh N, Glaspole I, Westall GP, Watson A, et al. Oxygen therapy for interstitial lung disease: a systematic review. Eur Respir Rev. 2017;26(143):160080. https://doi.org/10.1183/16000617.0080-2016
58. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society [published correction appears in Thorax. 2008 Nov;63(11):1029. multiple author names added]. Thorax. 2008;63 Suppl 5:v1-v58. https://doi.org/10.1136/thx.2008.101691
59. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824. https://doi.org/10.1164/rccm.2009-040GL
60. Cottin V, Crestani B, Valeyre D, Wallaert B, Cadranel J, Dalphin JC, et al. Diagnosis and management of idiopathic pulmonary fibrosis: French practical guidelines. Eur Respir Rev. 2014;23(132):193-214. https://doi.org/10.1183/09059180.00001814
61. Funke-Chambour M, Azzola A, Adler D, Barazzone-Argiroffo C, Benden C, Boehler A, et al. Idiopathic Pulmonary Fibrosis in Switzerland: Diagnosis and Treatment. Respiration. 2017;93(5):363-378. https://doi.org/10.1159/000464332
62. Magnet FS, Schwarz SB, Callegari J, Criée CP, Storre JH, Windisch W. Long-Term Oxygen Therapy: Comparison of the German and British Guidelines. Respiration. 2017;93(4):253-263. https://doi.org/10.1159/000455879
63. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913. https://doi.org/10.1183/13993003.01913-2018
64. Ulrich S, Saxer S, Hasler ED, Schwarz EI, Schneider SR, Furian M, et al. Effect of domiciliary oxygen therapy on exercise capacity and quality of life in patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension: a randomised, placebo-controlled trial. Eur Respir J. 2019;54(2):1900276. https://doi.org/10.1183/13993003.002762019
65. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 2010;122(2):164-172. https://doi.org/10.1161/CIRCULATIONAHA.109.898122
66. Trip P, Nossent EJ, de Man FS, van den Berk IA, Boonstra A, Groepenhoff H, et al. Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. Eur Respir J. 2013;42(6):1575-1585. https://doi.org/10.1183/09031936.00184412
67. Ulrich S, Hasler ED, Saxer S, Furian M, Müller-Mottet S, Keusch S, et al. Effect of breathing oxygen-enriched air on exercise performance in patients with precapillary pulmonary hypertension: randomized, sham-controlled cross-over trial. Eur Heart J. 2017;38(15):1159-1168. https://doi.org/10.1093/eurheartj/ehx099
68. Ulrich S, Keusch S, Hildenbrand FF, Lo Cascio C, Huber LC, Tanner FC, et al. Effect of nocturnal oxygen and acetazolamide on exercise

performance in patients with pre-capillary pulmonary hypertension and sleep-disturbed breathing: randomized, double-blind, cross-over trial. Eur Heart J. 2015;36(10):615-623. https://doi.org/10.1093/eurheartj/eht540

69. Farber HW, Badesch DB, Benza RL, Elliott CG, Frantz RP, McGoon MD, Selej M, et al. Use of supplemental oxygen in patients with pulmonary arterial hypertension in REVEAL. J Heart Lung Transplant. 2018;37(8):948-955. https://doi.org/10.1016/j.healun.2018.03.010
70. 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(9):1682-1687. https://doi.org/10.1164/ajrccm.164.9.2106076
71. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT) [published correction appears in Eur Respir J. 2015 Dec;46(6):1855-6]. Eur Respir J. 2015;46(4):903-975. https://doi.org/10.1183/13993003.01032-2015
72. Oliveira EP, Medeiros Junior P. Palliative care in pulmonary medicine. J Bras Pneumol. 2020;46(3):e20190280. https://doi.org/10.36416/1806-3756/e20190280
73. Martins M, Campôa E, Ferreira M, Reis-Pina P. Autonomy and dyspnea in palliative care: A case report. Pulmonology. 2020;26(2):105-107. https://doi.org/10.1016/j.pulmoe.2019.05.005
74. Stanzani L, Reis-Pina P. Oxygen Therapy in Advanced Chronic Disease [Article in Portuguese]. Med Interna. 2020;27(2):186-187. doi: 10.24950/CE/74/20/2/2020 https://doi.org/10.24950/CE/74/20/2/2020
75. Campbell ML, Yarandi H, Dove-Medows E. Oxygen is nonbeneficial for most patients who are near death. J Pain Symptom Manage. 2013;45(3):517-523. https://doi.org/10.1016/j.jpainsymman.2012.02.012
76. Ambrosino N, Fracchia C. Strategies to relieve dyspnoea in patients with advanced chronic respiratory diseases. A narrative review. Pulmonology. 2019;25(5):289-298. https://doi.org/10.1016/j.pulmoe.2019.04.002
77. Gillon S, Clifton IJ. Breathlessness in palliative care: a practical guide. Br J Hosp Med (Lond). 2019;80(2):72-77. https://doi.org/10.12968/hmed.2019.80.2.72
78. Pan CX, Palathra BC, Leo-To WF. Management of Respiratory Symptoms in Those with Serious Illness. Med Clin North Am. 2020;104(3):455-470. https://doi.org/10.1016/j.mcna.2019.12.004
79. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMGA, Datla S, Dirksen CD, Johnson MJ, et al. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. Eur Respir J. 2017;50(5):1701153. https://doi.org/10.1183/13993003.01153-2017
80. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. BMJ. 2014;348:g445. https://doi.org/10.1136/bmj.g445
81. Tobin MJ, Laghi F, Jubran A. Why COVID-19 Silent Hypoxemia Is Baffling to Physicians. Am J Respir Crit Care Med. 2020;202(3):356-360. https://doi.org/10.1164/rccm.202006-2157CP
82. Busana M, Gasperetti A, Giosa L, Forleo GB, Schiavone M, Mitacchione G, et al. Prevalence and outcome of silent hypoxemia in COVID-19. Minerva Anestesiol. 2021;87(3):325-333. https://doi.org/10.23736/S0375-9393.21.15245-9
83. Fisher HK. Hypoxemia in COVID-19 patients: An hypothesis. Med Hypotheses. 2020;143:110022. https://doi.org/10.1016/j.mehy.2020.110022
84. Crimi C, Pierucci P, Renda T, Pisani L, Carlucci A. High-Flow Nasal Cannula and COVID-19: A Clinical Review. Respir Care. 2022;67(2):227-240. https://doi.org/10.4187/respcare.09056
85. Ospina-Tascón GA, Calderón-Tapia LE, García AF, Zarama V, Gómez-Álvarez F, Álvarez-Saa T, et al. Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: A Randomized Clinical Trial [published correction appears in JAMA. 2022 Mar 15;327(11):1093]. JAMA. 2021;326(21):2161-2171. https://doi.org/10.1001/jama.2021.20714
86. Loerinc LB, Scheel AM, Evans ST, Shabto JM, O'Keefe GA, O'Keefe JB. Discharge characteristics and care transitions of hospitalized patients with COVID-19. Healthc (Amst). 2021;9(1):100512. https://doi.org/10.1016/j.hjdsi.2020.100512
87. Ray A, Chaudhry R, Ray S, Mitra S, Pradhan S, Sunder A, et al. Prolonged Oxygen Therapy Post COVID-19 Infection: Factors Leading to the Risk of Poor Outcome. Cureus. 2021;13(2):e13357. https://doi.org/10.7759/cureus.13357
88. Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: Interim Guidance on Rehabilitation in the Hospital and Post-Hospital Phase from a European Respiratory Society and American Thoracic Society-coordinated International Task Force. Eur Respir J. 2020;56(6):2002197. https://doi.org/10.1183/13993003.02197-2020
89. Hayes D Jr, Wilson KC, Krivchenia K, Hawkins SMM, Balfour-Lynn IM, Gozal D, et al. Home Oxygen Therapy for Children. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2019;199(3):e5-e23. https://doi.org/10.1164/rccm.201812-2276ST
90. Krivchenia K, Hawkins SM, Iyer NP, Hayes D Jr, Deterding RR, Ruminjo J, et al. Clinical Practice Guideline Summary for Clinicians: Home Oxygen Therapy for Children. Ann Am Thorac Soc. 2019;16(7):781-785. https://doi.org/10.1513/AnnalsATS.201902-136CME
91. Rahimi S. New guidelines for home oxygen therapy in children. Lancet Respir Med. 2019;7(4):301-302. https://doi.org/10.1016/S2213-2600(19)30076-1
92. Adde FV, Alvarez AE, Barbisan BN, Guimarães BR. Recommendations for long-term home oxygen therapy in children and adolescents. J Pediatr (Rio J). 2013;89(1):6-17. https://doi.org/10.1016/j.jped.2013.02.003
93. 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 Suppl 2:ii1-ii26. https://doi.org/10.1136/thx.2009.116020
94. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. Am J Respir Crit Care Med. 2019;200(6):751-759. https://doi.org/10.1164/rccm.201812-2348OC
95. Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, et al. Bronchopulmonary Dysplasia: Executive Summary of a Workshop. J Pediatr. 2018;197:300-308. https://doi.org/10.1016/j.jpeds.2018.01.043
96. Hennelly M, Greenberg RG, Aleem S. An Update on the Prevention and Management of Bronchopulmonary Dysplasia. Pediatric Health Med Ther. 2021;12:405-419. https://doi.org/10.2147/PHMT.S287693
97. Gilfillan M, Bhandari A, Bhandari V. Diagnosis and management of bronchopulmonary dysplasia. BMJ. 2021;375:n1974. https://doi.org/10.1136/bmj.n1974
98. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA. 2015;314(10):1039-1051. https://doi.org/10.1001/jama.2015.10244
99. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics. 2000;105(2):295-310. https://doi.org/10.1542/peds.105.2.295
100. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med. 2003;349(10):959-967. https://doi.org/10.1056/NEJMoa023080
101. BOOST II United Kingdom Collaborative Group; BOOST II Australia Collaborative Group; BOOST II New Zealand Collaborative Group, Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al. Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013;368(22):2094-2104. https://doi.org/10.1056/NEJMoa1302298
102. Cummings JJ, Polin RA; COMMITTEE ON FETUS AND NEWBORN. Oxygen Targeting in Extremely Low Birth Weight Infants [published correction appears in Pediatrics. 2016 Dec;138(6):]. Pediatrics. 2016;138(2):e20161576. https://doi.org/10.1542/peds.2016-1576
103. Duijts L, van Meel ER, Moschino L, Baraldi E, Barnhoorn M, Bramer WM, et al. European Respiratory Society guideline on long-term management of children with bronchopulmonary dysplasia. Eur Respir J. 2020;55(1):1900788. https://doi.org/10.1183/13993003.00788-2019
104. Athanazio RA, Silva Filho LVRF, Vergara AA, Ribeiro AF, Riedi CA, Procianoy EDFA, et al. Brazilian guidelines for the diagnosis and treatment of cystic fibrosis. J Bras Pneumol. 2017;43(3):219-245.

https://doi.org/10.1590/s1806-37562017000000065

105. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017;13(3):479-504. https://doi.org/10.5664/jcsm.6506
106. Beaudin AE, Waltz X, Hanly PJ, Poulin MJ. Impact of obstructive sleep apnoea and intermittent hypoxia on cardiovascular and cerebrovascular regulation. Exp Physiol. 2017;102(7):743-763. https://doi.org/10.1113/EP086051
107. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2019;15(2):335-343. https://doi.org/10.5664/jcsm.7640
108. Zeineddine S, Rowley JA, Chowdhuri S. Oxygen Therapy in Sleep-Disordered Breathing. Chest. 2021;160(2):701-717. https://doi.org/10.1016/j.chest.2021.02.017
109. Mehta V, Vasu TS, Phillips B, Chung F. Obstructive sleep apnea and oxygen therapy: a systematic review of the literature and meta-analysis. J Clin Sleep Med. 2013;9(3):271-279. https://doi.org/10.5664/jcsm.2500
110. Gold AR, Schwartz AR, Bleecker ER, Smith PL. The effect of chronic nocturnal oxygen administration upon sleep apnea. Am Rev Respir Dis. 1986;134(5):925-929. https://doi.org/10.1164/arrd.1986.134.5.925
111. Sun X, Luo J, Wang Y. Comparing the effects of supplemental oxygen therapy and continuous positive airway pressure on patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. Sleep Breath. 2021;25(4):2231-2240. https://doi.org/10.1007/s11325-020-02245-4
112. Kushida CA, Chediak A, Berry RB, Brown LK, Gozal D, Iber C, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med. 2008;4(2):157-171. https://doi.org/10.5664/jcsm.27133
113. Javaheri S, Ahmed M, Parker TJ, Brown CR. Effects of nasal O2 on sleep-related disordered breathing in ambulatory patients with stable heart failure. Sleep. 1999;22(8):1101-1106. https://doi.org/10.1093/sleep/22.8.1101
114. Staniforth AD, Kinnear WJ, Starling R, Hetmanski DJ, Cowley AJ. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne-Stokes respiration. Eur Heart J. 1998;19(6):922-928. https://doi.org/10.1053/euhj.1997.0861
115. Chen C, Wen T, Liao W. Nocturnal supports for patients with central sleep apnea and heart failure: a systemic review and network meta-analysis of randomized controlled trials. Ann Transl Med. 2019;7(14):337. https://doi.org/10.21037/atm.2019.06.72
116. Schwarz EI, Scherff F, Haile SR, Steier J, Kohler M. Effect of Treatment of Central Sleep Apnea/Cheyne-Stokes Respiration on Left Ventricular Ejection Fraction in Heart Failure: A Network Meta-Analysis. J Clin Sleep Med. 2019;15(12):1817-1825. https://doi.org/10.5664/jcsm.8092
117. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med. 2015;373(12):1095-1105. https://doi.org/10.1056/NEJMoa1506459
118. Gold AR, Bleecker ER, Smith PL. A shift from central and mixed sleep apnea to obstructive sleep apnea resulting from low-flow oxygen. Am Rev Respir Dis. 1985;132(2):220-223.
119. Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J. 2017;49(1):1600959. https://doi.org/10.1183/13993003.00959-2016
120. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med. 2010;182(3):325-331. https://doi.org/10.1164/rccm.200912-1869OC
121. Machado MC, Vollmer WM, Togeiro SM, Bilderback AL, Oliveira MV, Leitão FS, et al. CPAP and survival in moderate-to-severe obstructive sleep apnoea syndrome and hypoxaemic COPD. Eur Respir J. 2010;35(1):132-137. https://doi.org/10.1183/09031936.00192008
122. Mokhlesi B, Masa JF, Brozek JL, Gurubhagavatula I, Murphy PB, Piper AJ, et al. Evaluation and Management of Obesity Hypoventilation Syndrome. An Official American Thoracic Society Clinical Practice Guideline [published correction appears in Am J Respir Crit Care Med. 2019 Nov 15;200(10):1326]. Am J Respir Crit Care Med. 2019;200(3):e6-e24. https://doi.org/10.1164/rccm.201905-1071ST
123. Masa JF, Pépin JL, Borel JC, Mokhlesi B, Murphy PB, Sánchez-Quiroga MÁ. Obesity hypoventilation syndrome. Eur Respir Rev. 2019;28(151):180097. https://doi.org/10.1183/16000617.0097-2018
124. O'Driscoll BR, Howard LS, Earis J, Mak V; British Thoracic Society Emergency Oxygen Guideline Group; BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax. 2017;72(Suppl 1):ii1-ii90. https://doi.org/10.1136/thoraxjnl-2016-209729
125. Dilektasli AG, Porszasz J, Stringer WW, Casaburi R. Physiologic Effects of Oxygen Supplementation During Exercise in Chronic Obstructive Pulmonary Disease. Clin Chest Med. 2019;40(2):385-395. https://doi.org/10.1016/j.ccm.2019.02.004
126. Dipla K, Boutou AK, Markopoulou A, Pitsiou G, Papadopoulos S, Chatzikosti A, et al. Exertional Desaturation in Idiopathic Pulmonary Fibrosis: The Role of Oxygen Supplementation in Modifying Cerebral-Skeletal Muscle Oxygenation and Systemic Hemodynamics. Respiration. 2021;100(6):463-475. https://doi.org/10.1159/000514320
127. Marillier M, Bernard AC, Verges S, Moran-Mendoza O, O'Donnell DE, Neder JA. Oxygen supplementation during exercise improves leg muscle fatigue in chronic fibrotic interstitial lung disease. Thorax. 2021;76(7):672-680. https://doi.org/10.1136/thoraxjnl-2020-215135
128. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation [published correction appears in Am J Respir Crit Care Med. 2014 Jun 15;189(12):1570]. Am J Respir Crit Care Med. 2013;188(8):e13-e64. https://doi.org/10.1164/rccm.201309-1634ST
129. Jarosch I, Gloeckl R, Damm E, Schwedhelm AL, Buhrow D, Jerrentrup A, et al. Short-term Effects of Supplemental Oxygen on 6-Min Walk Test Outcomes in Patients With COPD: A Randomized, Placebo-Controlled, Single-blind, Crossover Trial. Chest. 2017;151(4):795-803. https://doi.org/10.1016/j.chest.2016.11.044
130. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. Am J Respir Crit Care Med. 2003;168(9):1034-1042. https://doi.org/10.1164/rccm.200212-1525OC
131. Neunhäuserer D, Steidle-Kloc E, Weiss G, Kaiser B, Niederseer D, Hartl S, et al. Supplemental Oxygen During High-Intensity Exercise Training in Nonhypoxemic Chronic Obstructive Pulmonary Disease. Am J Med. 2016;129(11):1185-1193.
132. Dyer F, Callaghan J, Cheema K, Bott J. Ambulatory oxygen improves the effectiveness of pulmonary rehabilitation in selected patients with chronic obstructive pulmonary disease. Chron Respir Dis. 2012;9(2):83-91. https://doi.org/10.1177/1479972312438702
133. Alison JA, McKeough ZJ, Leung RWM, Holland AE, Hill K, Morris NR, et al. Oxygen compared to air during exercise training in COPD with exercise-induced desaturation. Eur Respir J. 2019;53(5):1802429. https://doi.org/10.1183/13993003.02429-2018
134. Langer D, Gosselink R. Why does oxygen supplementation during exercise training in COPD patients with exercise-induced desaturation not consistently improve exercise capacity?. Eur Respir J. 2019;54(5):1901586. https://doi.org/10.1183/13993003.01586-2019
135. Schneeberger T, Jarosch I, Leitl D, Gloeckl R, Hitzl W, Dennis CJ, et al. Automatic oxygen titration versus constant oxygen flow rates during walking in COPD: a randomised controlled, double-blind, crossover trial [published online ahead of print, 2021 Oct 16]. Thorax. 2021;thoraxjnl-2020-216509. https://doi.org/10.1136/thoraxjnl-2020-216509
136. Vitacca M, Paneroni M, Zampogna E, Visca D, Carlucci A, Cirio S, et al. High-Flow Oxygen Therapy During Exercise Training in Patients With Chronic Obstructive Pulmonary Disease and Chronic Hypoxemia: A Multicenter Randomized Controlled Trial. Phys Ther. 2020;100(8):1249-1259. https://doi.org/10.1093/ptj/pzaa076
137. Liu Y, Gong F. Determination of whether supplemental oxygen therapy is beneficial during exercise training in patients with COPD: A systematic review and meta-analysis. Exp Ther Med. 2019;18(5):4081-4089. https://doi.org/10.3892/etm.2019.8026
138. Arizono S, Furukawa T, Taniguchi H, Sakamoto K, Kimura T, Kataoka K, et al. Supplemental oxygen improves exercise capacity in IPF patients with exertional desaturation. Respirology. 2020;25(11):1152-1159. https://doi.org/10.1111/resp.13829
139. Dowman LM, McDonald CF, Bozinovski S, Vlahos R, Gillies R,

Pouniotis D, et al. Greater endurance capacity and improved dyspnoea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxaemia. Respirology. 2017;22(5):957-964. https://doi.org/10.1111/resp.13002

140. Nishiyama O, Miyajima H, Fukai Y, Yamazaki R, Satoh R, Yamagata T, et al. Effect of ambulatory oxygen on exertional dyspnea in IPF patients without resting hypoxemia. Respir Med. 2013;107(8):1241-1246. https://doi.org/10.1016/j.rmed.2013.05.015
141. Edvardsen A, Jarosch I, Grongstad A, Wiegand L, Gloeckl R, Kenn K, et al. A randomized cross-over trial on the direct effects of oxygen supplementation therapy using different devices on cycle endurance in hypoxemic patients with Interstitial Lung Disease. PLoS One. 2018;13(12):e0209069. https://doi.org/10.1371/journal.pone.0209069
142. Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, et al. Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. Eur Respir J. 2017;49(5):1602494. https://doi.org/10.1183/13993003.02494-2016
143. Grünig E, Eichstaedt C, Barberà J-A, Benjamin N, Blanco I, Bossone E, et al. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. Eur Respir J. 2019;53(2):1800332. https://doi.org/10.1183/13993003.00332-2018
144. Marra AM, Egenlauf B, Bossone E, Eichstaedt C, Grünig E, Ehlken N. Principles of rehabilitation and reactivation: pulmonary hypertension. Respiration. 2015;89(4):265-273. https://doi.org/10.1159/000371855
145. Grünig E, Lichtblau M, Ehlken N, Ghofrani HA, Reichenberger F, Staehler G, et al. Safety and efficacy of exercise training in various forms of pulmonary hypertension. Eur Respir J. 2012;40(1):84-92. https://doi.org/10.1183/09031936.00123711
146. Ahmedzai S, Balfour-Lynn IM, Bewick T, Buchdahl R, Coker RK, Cummin AR, et al. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. Thorax. 2011;66 Suppl 1:i1-i30. https://doi.org/10.1136/thoraxjnl-2011-200295
147. Bellinghausen AL, Mandel J. Assessing Patients for Air Travel. Chest. 2021;159(5):1961-1967. https://doi.org/10.1016/j.chest.2020.11.002
148. Ergan B, Akgun M, Pacilli AMG, Nava S. Should I stay or should I go? COPD and air travel. Eur Respir Rev. 2018;27(148):180030. https://doi.org/10.1183/16000617.0030-2018
149. Gong H Jr, Tashkin DP, Lee EY, Simmons MS. Hypoxia-altitude simulation test. Evaluation of patients with chronic airway obstruction. Am Rev Respir Dis. 1984;130(6):980-986.
150. Dillard TA, Moores LK, Bilello KL, Phillips YY. The preflight evaluation. A comparison of the hypoxia inhalation test with hypobaric exposure. Chest. 1995;107(2):352-357. https://doi.org/10.1378/chest.107.2.352
151. Sponholz Araújo J. Viagens aéreas em portadores de doença pulmonar avançada. In: Augusto V. Manual de Assistência Domiciliar em Doença Pulmonar Avançada. São Paulo: Grupo Editorial Nacional; 2013. p. 246-265.
152. Stoller J. Evaluation of patient for supplemental oxygen during air travel. Barnes PJ, Diffenbach P, editors. UpToDate. Waltham, MA: UpToDate Inc. [cited 2022 Mar 10]. Available from: https://www.uptodate.com/contents/evaluation-of-patients-for-supplemental-oxygen-during-air-travel
153. Orritt R, Powell P, Saraiva I. Why is medical oxygen a challenge for people travelling by air?. Breathe (Sheff). 2019;15(3):182-189. https://doi.org/10.1183/20734735.0202-2019
154. Agência Nacional de Aviação Civil (ANAC) [homepage on the Internet]. Brasília: ANAC; [updated 2021 Apr 15; cited 2022 Mar 1]. Instrução suplementar IS no. 119-007. Revisão A. Concentradores portáteis de oxigênio. Available from: https://www.anac.gov.br/assuntos/legislacao/legislacao-1/iac-e-is/is/is-119-007
155. Lacasse Y, Sériès F, Corbeil F, Baltzan M, Paradis B, Simão P, et al. Randomized Trial of Nocturnal Oxygen in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2020;383(12):1129-1138. https://doi.org/10.1056/NEJMoa2013219
156. Global Initiative for Chronic Obstructive Lung Disease [homepage on the Internet]. Bethesda: GOLD [cited 2022 Mar 1]. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2022 report. Available from: https://goldcopd.org
157. Hardavella G, Karampinis I, Frille A, Sreter K, Rousalova I. Oxygen devices and delivery systems. Breathe (Sheff). 2019;15(3):e108-e116. https://doi.org/10.1183/20734735.0204-2019
158. Chest Foundation [homepage on the Internet]. Glenview (IL): the Foundation; [updated 2021 Nov 19; cited 2022 Mar 1]. Oxygen therapy (Last updated 19/11/2021). Available from: https://foundation.chestnet.org/lung-health-a-z/oxygen-therapy/
159. American Association for Respiratory Care [homepage on the Internet]. Irving (TX): the Association; [cited 2022 Mar 1]. A guide to portable concentrators. Available from: https://www.aarc.org/education/online-courses/a-guide-to-portable-oxygen-concentrators/
160. Tanni SE, Vale SA, Lopes PS, Guiotoko MM, Godoy I, Godoy I. Influence of the oxygen delivery system on the quality of life of patients with chronic hypoxemia. J Bras Pneumol 2007;33(2):161-167. https://doi.org/10.1590/S1806-37132007000200010
161. Schwartz MD Christopher KL, Schwartz EK. Transtracheal oxygen therapy. Stoller JK, Colt HG, Diffenbach P, editors. UpToDate. Waltham, MA: UpToDate Inc. [cited 2022 Mar 10]. Available from: UpTodate 2021. Available from: https://www.uptodate.com/contents/transtracheal-oxygen-therapy/print
162. Aguiar C, Davdson J, Carvalho A, Iamonti V, Cortopassi F, Nascimento O, et al. Tubing length for long-term oxygen therapy. Respir Care. 2015;60(2):179-182 https://doi.org/10.4187/respcare.03454