Home Oxygen Therapy for Children

An Official American Thoracic Society Clinical Practice Guideline

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Background: Home oxygen therapy is often required in children with chronic respiratory conditions. This document provides an evidence-based clinical practice guideline on the implementation, monitoring, and discontinuation of home oxygen therapy for the pediatric population.

Methods: A multidisciplinary panel identified pertinent questions regarding home oxygen therapy in children, conducted systematic reviews of the relevant literature, and applied the Grading of Recommendations, Assessment, Development, and Evaluation approach to rate the quality of evidence and strength of clinical recommendations.

Results: After considering the panel's confidence in the estimated effects, the balance of desirable (benefits) and undesirable (harms and burdens) consequences of treatment, patient values and preferences, cost, and feasibility, recommendations were developed for or against home oxygen therapy specific to pediatric lung and pulmonary vascular diseases.

Conclusions: Although home oxygen therapy is commonly required in the care of children, there is a striking lack of empirical evidence regarding implementation, monitoring, and discontinuation of supplemental oxygen therapy. The panel formulated and provided the rationale for clinical recommendations for home oxygen therapy based on scant empirical evidence, expert opinion, and clinical experience to aid clinicians in the management of these complex pediatric patients and identified important areas for future research.

Keywords: children; home; hypoxemia; oxygen

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Cystic Fibrosis

- **For patients with cystic fibrosis complicated by severe chronic hypoxemia, we recommend that home oxygen therapy be prescribed** *(strong recommendation, very low-quality evidence).*
- **For patients with cystic fibrosis who have both mild chronic hypoxemia and dyspnea on exertion, we suggest that home oxygen therapy be prescribed** *(conditional recommendation, very low-quality evidence).*

Bronchopulmonary Dysplasia

- **For patients with bronchopulmonary dysplasia complicated by chronic hypoxemia, we recommend that home oxygen therapy be prescribed** *(strong recommendation, very low-quality evidence).*

Sleep-disordered Breathing

- **For patients with sleep-disordered breathing complicated by severe nocturnal hypoxemia who cannot tolerate positive airway pressure therapy or are awaiting surgical treatment of sleep-disordered breathing, we suggest that home oxygen therapy be prescribed** *(conditional recommendation, very low-quality evidence).*

Sickle Cell Disease

- **For patients with sickle cell disease complicated by severe chronic hypoxemia, we suggest that home oxygen therapy be prescribed** *(conditional recommendation, very low-quality evidence).*

Pulmonary Hypertension without Congenital Heart Disease

- **For patients with pulmonary hypertension without congenital heart disease complicated by chronic hypoxemia, we recommend that home oxygen therapy be prescribed** *(strong recommendation, very low-quality evidence).*

Pulmonary Hypertension with Congenital Heart Disease

- **For patients with pulmonary hypertension with congenital heart disease complicated by chronic hypoxemia, supplemental oxygen will impact hemodynamics and physiology; we recommend that home oxygen therapy NOT be initiated in these children, regardless of previous reparative or palliative congenital heart surgery, until there has been consultation with a pediatric pulmonologist or cardiologist who has expertise in the management of pulmonary hypertension in this clinical setting** *(strong recommendation, very low-quality evidence).*

Interstitial Lung Disease

- **For patients with interstitial lung disease complicated by severe chronic hypoxemia, we recommend that home oxygen therapy be prescribed** *(strong recommendation, very low-quality evidence).*
- **For patients with interstitial lung disease who have mild chronic hypoxemia and either dyspnea on exertion or desaturation during sleep or exertion, we suggest that home oxygen therapy be prescribed** *(conditional recommendation, very low-quality evidence).*

Implementation

- **The expert panel unanimously agreed that optimal implementation of the above recommendations consists of all of the following:**
  - Oxygen therapy to maintain an oxygen saturation as measured by pulse oximetry in an acceptable range

according to age and respiratory condition as outlined in this document
- Use of oxygen equipment that is of the appropriate size, developmental stage, and flow rate to function properly
- Oxygen therapy monitoring by pulse oximetry in the home

Introduction

Home oxygen therapy (HOT) is used to maintain health by addressing physiologic and metabolic requirements for children with chronic lung and pulmonary vascular diseases. Enabling a child to receive HOT also confers psychological advantages by allowing the child to remain within the family unit at home, reducing healthcare costs compared with hospitalization. Despite children having significantly different pulmonary physiology from adults and additional requirements for optimal lung growth and development, indications for funding HOT as determined by the Centers for Medicare and Medicaid Services (CMS) are the same for pediatric and adult patients. These include *1*) Pa_{O_2} less than 55 mm Hg (<7.33 kPa); *2*) oxygen saturation as measured by pulse oximetry (Sp_{O_2}) less than 88%; or *3*) Pa_{O_2} 55–59 mm Hg (7.33–7.87 kPa) or Sp_{O_2} 89% accompanied by cor pulmonale, a hematocrit greater than 55%, or a history of edema (1). The basis of these indications by CMS is predicated on seminal studies in adult patients with chronic obstructive pulmonary disease showing reductions in mortality with continuous oxygen therapy (2, 3). Despite the lack of pediatric patients in these historic studies performed over 35 years ago, CMS coverage determination for HOT is the same for pediatric patients of all ages compared with adult patients.

Recognizing the need for clinical guidance regarding HOT specifically for children, the American Thoracic Society (ATS) convened a task force of specialists in pediatric and neonatal medicine, respiratory therapy, nursing, and population health, together with parents, to conduct systematic reviews and use available evidence to inform recommendations for the use of HOT in chronic lung and pulmonary vascular diseases of childhood.

The target audience of this guideline is clinicians who manage children with diseases complicated by chronic hypoxemia. This group includes pediatric pulmonologists, pediatric cardiologists, neonatologists, general pediatricians and family practitioners, emergency medicine and primary care clinicians, other healthcare professionals, and policy makers. Clinicians, patients, third-party payers, stakeholders, or the courts should never view the recommendations contained in this guideline as dictates. Though evidence-based guidelines can summarize the best available evidence regarding the effects of an intervention in a given patient population, they cannot take into account all of the unique clinical circumstances that may arise when managing a patient, and as such their implementation is at the discretion of each treating clinician.

Methods

This clinical practice guideline was developed in accordance with policies and procedures of the ATS. *See* the online supplement for a detailed description of the methods. The meaning of strong and conditional recommendations is described in Table 1.

Definition of Hypoxemia

With an immense medical literature on hypoxemia, the panel focused this document on the treatment of sustained low Sp_{O_2} levels, or "chronic hypoxemia," and HOT for specific respiratory conditions of childhood. With unanimous agreement, the panel determined that a low Sp_{O_2} for a duration of 2 weeks was sufficient evidence for chronic hypoxemia in a child with one of these respiratory conditions if otherwise clinically stable, thus achieving a threshold where HOT should be considered. One caveat is that growth and development may result in clinical resolution of chronic hypoxemia in some pediatric patients.

To define hypoxemia, we conducted a systematic search for data about normal oxygenation in children that identified 1,711 articles, most of which were excluded by review of their title and abstract (*see* Table E1 in the online supplement). We selected 31 studies that measured oxygenation in healthy children to inform our decision making (4–33). Of note, the studies enrolled subjects with different age ranges. For analysis, we decided to categorize children as younger than 1 year old or 1 year old and older. *See* Table 2 for normative values of oxyhemoglobin saturations in healthy children during wakefulness and sleep that originated from work described in the paragraphs below. For the purpose of this document, the term "desaturation" will represent oxyhemoglobin desaturation.

Children Younger Than 1 Year Old

Children younger than 1 year old had a mean Sp_{O_2} of 97.8% (SD, ±1.4%) (27, 29, 32) and a median Sp_{O_2} of 98.7%, with a range from 97.9% to 99.8% (8, 9, 14, 15, 27, 29, 31, 32), during wakefulness. Desaturation events were common during the initial 48 hours of life. One study reported that 5% of the time was spent with a mean Sp_{O_2} less than 92.5% (±3.9%) and 10% of the time was spent with a mean Sp_{O_2}

Table 1. Meanings of the Strength of the Recommendations

A *Strong* Recommendation Conveys . . .	A *Conditional* Recommendation Conveys . . .
It is the right course of action for >95% of patients.	It is the right course of action for >50% of patients but may not be right for a sizable minority.
"Just do it. Don't waste your time thinking about it, just do it."	"Slow down, think about it, discuss it with the patient."
You would be willing to tell a colleague that he or she did the wrong thing if he or she did not follow the recommendation.	You would NOT be willing to tell a colleague that he or she did the wrong thing if he or she did not follow the recommendation because there is clinical equipoise.
The recommended course of action may make a good performance metric.	The recommended course of action would NOT make a good performance metric.

Table 2. Normative Values

	Wakefulness		Sleep		Desaturation Nadir	
	Mean (±SD)	Median (Range)	Mean (±SD)	Median (Range)	Mean (±SD)	Median (Range)
Children <1 yr old	97.8% (±1.4%)	98.7% (97.9–99.8%)	96.3% (±1.3%)	Not reported	86% (±1.5%)	85.5% (83–88%)
Children ⩾1 yr old	97.6% (±0.7%)	97.5% (97–98%)	97.8% (±0.7%)	Not reported	94.6% (±3.1%)	93% (91–94%)

less than 95.3% (±2.9%) (32); another reported that 3–4% of the time was spent with Sp_{O_2} of 90% or less (27). With respect to duration, studies estimated that 26% of neonates had desaturations to less than or equal to 80% for a median duration of 9.3 seconds (31), 92% had desaturations to less than or equal to 88% for more than 20 seconds (24), and 100% had desaturations to less than or equal to 88% for more than 10 seconds (27). Desaturation events diminished with age. At an age of 1 month, infants had desaturations to Sp_{O_2} less than or equal to 80% a median of 0.9 times per hour (range, 0 to 15.1) for a median duration of 1.2 seconds (range, 0.3 to 2.2 s) (15); at ages of 6 weeks, 3 months, and 6 months, infants had desaturations to a Sp_{O_2} less than or equal to 80% a median of 0.7, 0.4, and 0.5 times per hour (9); and at an age of 1.4 years (range, 1.1 to 1.9 yr), infants had desaturations of greater than or equal to 3% a median of 0.1 times per hour (range, 0 to 2.2) (14). During sleep, mean Sp_{O_2} decreased to 96.3% (±1.3%) (19) with episodes of desaturation that reached a nadir at a mean of 86% (±1.5%) (19) or a median of 85.5% with a range from 83% to 88% (8, 13). Infants 2 weeks, 3 months, and 6 months old spent 5% of sleep time with a median Sp_{O_2} less than 92% (73–99%), 96% (83–98%), and 95.5% (69–99%), respectively, and spent 10% of sleep time with a median Sp_{O_2} less than 96% (77–99%), 97% (86–100%), and 97% (75–99%), respectively (7).

Children Aged 1 Year Old and Older

Children aged 1 year old and older had a mean Sp_{O_2} of 97.6% (±0.7%) (16, 24, 32, 33) and a median Sp_{O_2} of 97.5%, with a range from 97% to 98% (14, 16, 18, 24), during wakefulness. During sleep, the mean Sp_{O_2} remained 97.8% (±0.7%) (33), with episodes of desaturation that reached a nadir at a mean of 94.6% (±3.1%) (16, 20, 22, 23, 25, 26, 33) and a median of 93%, with a range from 91% to 94% (16, 18, 20, 21, 23). Desaturation events were infrequent. Children had desaturations greater than or equal to 3% or greater than or equal to 4% a mean of 0.6 times per hour (±1.0) (16, 23, 26, 33) and a median of 0.4 times per hour (range, 0.1–0.8) (14, 16, 18, 23). The mean duration of desaturation events was 0.3 seconds (±0.1 s), and the median duration was 0 seconds (range, 0 to 5.8 s) (23), with less than 1% of sleep spent with a Sp_{O_2} less than 95% (16) and less than 0.03% of sleep spent with a Sp_{O_2} less than 90% (16, 33). Clusters of desaturation occurred with a mean frequency of 0.1 clusters per hour (±0.2) and a median frequency of 0 clusters per hour (range, 0–0.7) (23).

Oxygen saturation is lower among normal children of all age groups living at a high altitude. Children 1 year old and younger living at 2,560 and 3,200 m had median Sp_{O_2} of 92% and 87%, respectively, according to two studies (5, 6), whereas another study found that those living at altitudes of 1,371, 2,073, 2,393, 2,405, and 2,484 m had Sp_{O_2} ranges of 95–96.7%, 93.9–95.4%, 91.8–93.4%, 93.4–96.1%, and 93.7–96.2%, respectively (28). Children older than 1 year old residing at an altitude of roughly 1,600 m had a median Sp_{O_2} of 95.4% (range, 93.1–96.9%) and a median nadir Sp_{O_2} of 86% (range, 81–89%) (17), whereas those living at roughly 4,000 m had a mean Sp_{O_2} of 87.4% (SD not estimable) and a mean nadir Sp_{O_2} of 80% (SD, ±7.5%) (11, 18). Desaturation events were more frequent at high altitude than at sea level, but they were less common among older children. Children 1–6 years old living at 1,600 m had desaturations greater than or equal to 4% a median of 4.0 times per hour (17), whereas children older than 6 years old living at 4,000 m had desaturations greater than or equal to 4% a median of 1.6 times per hour (18). Owing to lack of studies, adjustments for targeted saturation levels in children at altitude cannot be adequately addressed in this guideline.

With these studies as background and a primary objective of identifying potentially harmful hypoxemia while ensuring that virtually no normal children are determined to have abnormal oxygenation, the panel defined hypoxemia at or near sea level as follows:

- In children younger than 1 year old, hypoxemia was defined as spending 5% of the recording time with Sp_{O_2} less than or equal to 90% or, if measurements are taken intermittently, obtaining three independent measurements of Sp_{O_2} less than or equal to 90%.
- In children aged 1 year old and older, hypoxemia was defined as spending 5% of the time with Sp_{O_2} less than or equal to 93% or, if measurements are taken intermittently, obtaining three independent measurements of Sp_{O_2} less than or equal to 93%.

Additional conclusions from the panel included the following:

- Pulse oximetry is sufficient for diagnosing hypoxemia in pediatric patients because arterial blood analysis for Pa_{O_2} is not practical for routine monitoring, owing to technical difficulty in children and the pain associated with the arterial stick.
- On very rare occasions, an arterial blood gas for Pa_{O_2} may be required to assess for hypoxemia in a child, specifically when pulse oximetry may not accurately measure Sp_{O_2}, including altered hemoglobin states (e.g., carboxyhemoglobin, methemoglobin) or in diseases affecting hemoglobin, such as sickle cell disease (SCD).
- Intermittent pulse oximetry appears suitable with the different thresholds reflecting greater variability of Sp_{O_2} among healthy children younger than 1 year old, particularly the youngest children, with this left at the discretion of the treating clinician according to the clinical scenario of the patient.
- In a child, three intermittent measurements, if abnormal, can diagnose hypoxemia, but normal intermittent measurements cannot exclude it; this can be

done only by continuous oximetric monitoring, which includes a period of sleep. More advanced evaluation with polysomnography may be needed on a case-by-case basis at the discretion of the treating clinician.
- Averaging time for pulse oximetry measurements should take into account the age of the child, the underlying respiratory condition, and the current clinical scenario.
- A duration of 2 weeks defines chronicity of hypoxemia in a child.
- Hypoxemia in a child should account for anticipated Sp_{O_2} measurement alterations according to altitude.

Consequences of Untreated Hypoxemia

The pathobiology of hypoxemia encompasses a large body of work in the medical literature, which we expect will continue to expand rapidly. Moreover, we envision future research will better delineate the effects of hypoxemia at the cellular and molecular levels (34, 35). We briefly review in this section the potential consequences of hypoxemia that pediatric patients may experience, with the caveat that expanding research in this area may influence these recommendations. Intermittent hypoxemia occurs more frequently in children with lung disease and has been associated with deleterious consequences on pulmonary circulation, neurodevelopment, cognition, sleep, and growth (36). Lower basal oxygen saturation in children is associated with more episodes of spontaneous desaturations (37), placing them at even further risk for complications of hypoxemia.

Pulmonary Circulation

Chronic alveolar hypoxia elicits pulmonary vasoconstriction leading to pulmonary hypertension (PH), particularly in children with respiratory disorders, such as sleep-disordered breathing (SDB), bronchopulmonary dysplasia (BPD), cystic fibrosis (CF), and SCD. Previous work in animal models, including neonatal models, defined oxygen levels that induce hypoxic pulmonary vasoconstriction (38–41). Compared with adults (42), children with SDB and intermittent hypoxemia are at increased risk for PH (43). Intermittent hypoxemia adversely affects alveolar and vascular development in infants with BPD (44, 45). Correction of the hypoxemia in neonates with BPD and PH using supplemental oxygen can ameliorate physiologic complications (45–48), with HOT resolving right ventricular hypertrophy when Sp_{O_2} is maintained above 94–95% (49). In CF, continuous hypoxemia during wakefulness and other physiologic factors is associated with the development of PH independent of lung function (50, 51). Nocturnal hypoxemia and SDB appear to be influential in the development of PH in SCD (52, 53). Hemolysis, hypercoagulability, ischemia-reperfusion injury, oxidative stress, inflammation, and genetic susceptibility are additional factors that impact the development of PH (54). Although the response to mild levels of alveolar hypoxia may have minimal effects in many children, others may have adverse effects at similar levels of inspired oxygen with regard to heightened pulmonary vascular reactivity or remodeling, as reflected in infants with BPD (46), young adults with a history of perinatal asphyxia (55), and others. Such susceptibility has been demonstrated in experimental studies of genetic rat strains (56) or endothelial nitric oxide synthase–deficient mice (57), in which even mild chronic alveolar hypoxia elicits striking PH. These findings suggest that genetic, epigenetic, and disease pathobiology can increase the risk for pulmonary vascular disease even at levels that would be considered mild in nonsusceptible individuals.

Neurodevelopment and Cognition

The adverse cognitive and behavioral outcomes of hypoxemia in children with obstructive sleep apnea (OSA) have been extensively investigated and published elsewhere. Those data highlight the effects of hypoxemia on brain development and subsequent functioning as major concerns in children. For example, a *post hoc* analysis of a large international trial including 1,019 premature infants surviving to a postmenstrual age of 36 weeks found that prolonged hypoxemic episodes of more than 1 minute were associated with increased risk of death or adverse neurodevelopmental outcome at 18 months (58). However, in a multicenter, double-blind, randomized, controlled trial of 358 infants born at less than 30 weeks of gestation who continued to receive supplemental oxygen at 32 weeks postmenstrual age, no significant developmental benefit was seen at 1 year when children with measured Sp_{O_2} of 91–94% were compared with those with Sp_{O_2} of 95–98% (59).

A previous systematic review of 55 studies investigating children with congenital heart disease (CHD), SDB, asthma, and chronic ventilatory impairment and infants with respiratory instability identified that chronic intermittent hypoxemia negatively influences development, behavior, and academic achievement (60). In 995 school-aged children in fourth to sixth grades who underwent overnight pulse oximetric studies, hypoxemia was associated with impaired performance in mathematics (61). In the assessment of hypoxemia and the effects on cognition, investigators often study populations at high altitudes. A recent study found that short- and long-term exposures to high altitude at 3,500 m negatively affected executive function, memory, and processing speed in children and adolescents (62). However, we found no studies that assessed the effect of treatment on clinical outcomes.

In children with CHD undergoing surgical repair, cerebral tissue oxygenation appears to be an important determinant of cognitive development (63). Newborns with unrepaired CHD may have decreased cerebral oxygen delivery owing to chronic hypoxemia, so brain growth and development can be adversely affected without surgical intervention (64). In children with CF and hypoxemia, nocturnal HOT improved school attendance and performance (65, 66). Early research in SCD showed that hypoxemia is associated with episodic memory issues (67).

Sleep

Older studies have identified that exposure to hypoxemia during sleep predisposes infants to increased periodic breathing, hypoventilation, and central apneas and places those individuals at increased risk for brief resolved unexplained events (BRUEs) (formerly apparent life-threatening events) (68, 69). Risk factors for more severe BRUEs in premature infants include central apnea longer than 30 seconds, Sp_{O_2} less than 80% for 10 seconds, bradycardia to less than 50–60 beats per minute for 10 seconds, and upper respiratory infection symptoms (70, 71).

In 91 premature infants with previous BRUEs, unsuspected Sp_{O_2} less than 95% events (range, 80–93%) had occurred in 25% of the cohort (72).

In a comparison of premature infants with and without BPD who were recently weaned from supplemental oxygen (<7 d), children with BPD had significantly lower Sp_{O_2} and experienced significantly more central apnea that resolved with supplemental oxygen use (73). In one study of infants with BPD, an Sp_{O_2} of 90% was associated with sleep fragmentation with less REM sleep that improved with supplemental oxygen administration (74), whereas another study showed no change in sleep architecture in infants with BPD whose Sp_{O_2} was greater than 93% (75).

Some patients with CF have SDB associated with bone and soft tissue structural alterations of the upper airway and chronic rhinosinusitis (76, 77). Earlier studies established sleep-related hypoventilation as the primary factor associated with nocturnal hypoxemia in CF (78–81). More recent research comparing children with CF with healthy control individuals who were matched for age and body mass index found that mean Sp_{O_2} and nadir Sp_{O_2} were significantly lower in the CF group (82, 83). Using polysomnography in pediatric and young adult patients with CF and normal healthy control subjects, FEV_1 less than 64% predicted sleep-related desaturation with good sensitivity and specificity (84).

In SCD, studies have established that clinical outcomes are worse in the setting of hypoxemia and SDB (85–89), with more severe reductions in Sp_{O_2} occurring in children who have both SCD and OSA (85, 90). However, reductions in Sp_{O_2} persisted in some children with SCD despite adenotonsillectomy (91, 92), suggesting that other factors may contribute to hypoxemia in SCD. Supporting this point, hemoglobin SS is associated with more severe nocturnal hypoxemia than is hemoglobin SC (91), and treatment of patients with SCD with hydroxyurea is associated with improvement in hypoxemia (93, 94).

Concerns exist for severe nocturnal hypoxemia in children with CHD because these patients can have continuous low Sp_{O_2} and potentially reduced cerebral blood flow. Infants and older children with CHD can present with SDB (95–98), whereas patients with acyanotic CHD are often obese, placing them at greater risk for OSA (99). Children with Eisenmenger syndrome can have significant nocturnal hypoxemia because of SDB, especially with higher hemoglobin concentrations (100). Reductions in Sp_{O_2} can occur during sleep in children with CHD, independent of whether they have PH, sleep disturbances, or significant arrhythmias (101). Surgical correction of congenital cardiac lesions can increase the risk for SDB in patients with CHD, so close monitoring is needed for this high-risk group (95, 102).

For children with interstitial lung disease (ILD), nocturnal hypoxemia is very common with sustained reductions of Sp_{O_2} during sleep and throughout REM sleep periods (103). Moreover, the ATS guideline for ILD in children reported hypoxemia as an important component of the diagnostic evaluation of pediatric patients with suspected ILD, and it recommends routine measurement of Sp_{O_2} by pulse oximetry in all aspects of life, including sleep and during feeding, for infants (104).

Growth

In infants with BPD, improved growth occurs when Sp_{O_2} during sleep is greater than 92% compared with Sp_{O_2} of 88–91% (105). A second study in premature infants with BPD found promotion of growth when Sp_{O_2} was maintained above 93% with supplemental oxygen (106). In both of these studies, a negative effect on growth was seen when supplemental oxygen was stopped (105, 106). However, the previously discussed trial in infants born at less than 30 weeks of gestation found no growth benefit associated with higher Sp_{O_2} (59).

Although nutritional support can improve pulmonary status in CF (107), it is not clear whether treatment of hypoxemia improves nutritional status. Hypoxemia in the CF population increases the risk for PH, reduced exercise ability, and loss of skeletal muscle strength, all of which are associated with poor nutritional status (108). When compared with healthy control individuals, the body mass index of patients with CF with moderate to severe lung disease did not correlate with exercise-induced hypoxemia. In another study, compared with healthy control subjects, the nutritional status of subjects with CF was not associated with hypoxemia or hypercapnia during exercise or sleep, whereas airflow obstruction was the single correlate to sleep-related hypoxemia and hypercapnia (109).

Relative to asymptomatic children with acyanotic CHD, children with cyanotic CHD have shorter stature and leaner body mass associated with adipose hypocellularity (110). In the setting of hypoxemia, early development of heart failure produces tissue changes that handicap growth (111). Among the CHD patient population, the risk for malnutrition and growth failure is greatest in those with cyanotic CHD and PH (112).

In children with neuroendocrine cell hyperplasia of infancy, a recent study evaluating growth trajectory and oxygen use found that some subjects had improvement in growth velocity with the initiation of supplemental oxygen (113). With growth and maturation, some children with chronic pulmonary disorders requiring HOT will have a limited duration of treatment (114).

Indications for HOT

Our systematic search of the literature identified 952 articles, most of which were excluded by review of their title and abstract (Table E2). Table 3 provides a summary of the final recommendations by the panel, with details of the evidence base outlined in the following sections for each pediatric respiratory condition.

Question 1: Should Children with Cystic Fibrosis Complicated by Chronic Hypoxemia Be Treated with HOT?

Evidence base. We identified no studies that directly compared home oxygen with no oxygen in children with CF complicated by chronic hypoxemia, possibly because of concerns about the safety of having such a control group. We therefore selected eight studies that indirectly addressed the question by comparing use of either short-term oxygen or nocturnal home oxygen with no oxygen in children with CF complicated by chronic hypoxemia (65, 80, 115–120). Seven trials were randomized crossover trials (80, 115–120), and the remaining trial was a randomized trial with parallel groups (65). All trials enrolled children or young adults with both CF (mean age, 22 to 27 yr)

Table 3. Summary of Recommendations for Home Oxygen Therapy in Children with Strength of the Recommendation and Level of Evidence

Pediatric Respiratory Condition	Recommendation	Strength of Recommendation and Level of Evidence
Cystic fibrosis	For patients with cystic fibrosis complicated by severe chronic hypoxemia, we recommend that home oxygen therapy be prescribed.	Strong recommendation, very low-quality evidence
	For patients with cystic fibrosis who have both mild chronic hypoxemia and dyspnea on exertion, we suggest that home oxygen therapy be prescribed.	Conditional recommendation, very low-quality evidence
Bronchopulmonary dysplasia	For patients with bronchopulmonary dysplasia complicated by chronic hypoxemia, we recommend that home oxygen therapy be prescribed.	Strong recommendation, very low-quality evidence
Sleep-disordered breathing	For patients with sleep-disordered breathing complicated by severe nocturnal hypoxemia who cannot tolerate positive airway pressure therapy or are awaiting surgical treatment of sleep-disordered breathing, we suggest that home oxygen therapy be prescribed.	Conditional recommendation, very low-quality evidence
Sickle cell disease	For patients with sickle cell disease complicated by severe chronic hypoxemia, we suggest that home oxygen therapy be prescribed.	Conditional recommendation, very low-quality evidence
Pulmonary hypertension without congenital heart disease	For patients with pulmonary hypertension without congenital heart disease complicated by chronic hypoxemia, we recommend that home oxygen therapy be prescribed.	Strong recommendation, very low-quality evidence
Pulmonary hypertension with congenital heart disease	For patients with pulmonary hypertension with congenital heart disease complicated by chronic hypoxemia, supplemental oxygen will impact hemodynamics and physiology; we recommend that home oxygen therapy NOT be initiated in these children, regardless of previous reparative or palliative congenital heart surgery, until there has been consultation with a pediatric pulmonologist or cardiologist who has expertise in the management of pulmonary hypertension in this clinical setting.	Strong recommendation, very low-quality evidence
Interstitial lung disease	For patients with interstitial lung disease complicated by severe chronic hypoxemia, we recommend that home oxygen therapy be prescribed.	Strong recommendation, very low-quality evidence
	For patients with interstitial lung disease who have mild chronic hypoxemia and either dyspnea on exertion or desaturation during sleep or exertion, we suggest that home oxygen therapy be prescribed.	Conditional recommendation, very low-quality evidence

and chronic hypoxemia (mean Sp_{O_2} in the mid-80% range; mean Pa_{O_2}, <65 mm Hg [<8.67 kPa]; or desaturations to <90%). Three trials compared an $F_{I_{O_2}}$ of 0.30–0.39 with an $F_{I_{O_2}}$ of 0.21 administered into the breathing circuit during an exercise test (116, 119, 120); three trials compared an $F_{I_{O_2}}$ of 0.30–0.31 with an $F_{I_{O_2}}$ of 0.21 administered by nasal cannula or through a continuous positive airway pressure device during a sleep study (80, 117, 118); one trial compared being in a naturally high-oxygen environment below sea level with being at sea level (115); and one trial compared nocturnal HOT titrated to an awake Pa_{O_2} greater than 70 mm Hg (>9.33 kPa) with a nocturnal $F_{I_{O_2}}$ of 0.21 administered by nasal cannula during sleep. All trials were small, ranging from 6 to 28 patients.

Meta-analyses revealed that short-term oxygen use increased exercise duration (mean difference [MD], +1.04 min; 95% confidence interval [CI], +0.21 to +1.88 min) and postexercise oxygen saturation (MD, +7%; 95% CI, +2.23% to +11.81%); there was also a trend toward a higher peak exercise oxygen saturation (MD, +7.19%; 95% CI, −2.51% to +16.89%). Single studies revealed that short-term oxygen

use mitigated oxygen desaturation during exercise (−5% vs. −12%; MD, +7%; 95% CI, +2.48% to +11.52%) (113), improved oxygen saturation during REM sleep (90% vs. 79%; MD, +11%; 95% CI, +4.38% to +17.62%) and non-REM (NREM) sleep (94% vs. 88%; MD, +6%; 95% CI, +1.36% to +10.64%) (118), reduced sleep latency (18 vs. 24 min; MD, −6 min; 95% CI, −0.25 to −11.75 min) (118), and improved school attendance at 6 months (71% vs. 21%; relative risk, 3.3; 95% CI, 1.16 to 9.59) and 12 months (91% vs. 20%; relative risk, 4.55; 95% CI, 1.30 to 15.9) (65). There were trends toward more REM sleep time (18% vs. 13%; MD, +6%; 95% CI, −0.93% to +12.93%) and a lower arousal index (6 vs. 8.1 arousals/h; MD, −2.1 arousals/h; 95% CI, −4.57 to +0.37 arousals/h). There were no differences in mortality (65), growth (65), total sleep time (118), respiratory function (65), or right ventricular function (65).

The panel had very low confidence that the estimated effects described above would be the same for HOT in patients with CF complicated by chronic hypoxemia, because the evidence from which the estimates were derived was indirect (i.e., the question was about HOT, but the estimates were from trials that used short-term oxygen or nocturnal HOT) and the trials were all small with few events.

Benefits. In patients with CF who have chronic hypoxemia, short-term oxygen use increased exercise duration, increased postexercise oxygen saturation, mitigated oxygen desaturation during exercise, improved oxygen saturation during REM and NREM sleep, and reduced sleep latency; there was also a trend toward increased peak exercise oxygen saturation, increased REM sleep time, and a decreased arousal index. Nocturnal HOT improved school attendance at 6 and 12 months.

Harms. No harms were reported in any of the trials.

Conclusions. Despite having very low confidence in the estimated effects, the panel was certain that the benefits of HOT exceed the harms, burdens, and cost in patients with CF with severe chronic hypoxemia (Sp_{O_2}, <90%). This was based on the large number of beneficial outcomes and absence of harmful outcomes, decades of clinical experience collectively managing thousands of such patients, and recognition that prolonged chronic hypoxemia contributes to serious health consequences such as PH and cor pulmonale. The panel also concluded that the benefits of HOT likely exceed the harms, burden, and cost in patients with CF who have mild hypoxemia (Sp_{O_2}, 90–93%) that is chronic, accompanied by sequelae of hypoxemia (e.g., dyspnea on exertion, PH, cor pulmonale), or that occurs in the context of an exacerbation requiring antibiotics.

What others are saying. Clinical practice guidelines of the British Thoracic Society (BTS) published in 2009 recommended HOT for hypoxemic children with CF as "a means to improve school attendance" and to "obtain symptomatic relief" (121). Those guidelines further recommended monitoring carbon dioxide concentrations when the oxygen therapy is initiated.

ATS recommendations.

- **For patients with CF complicated by severe chronic hypoxemia, we recommend that HOT be prescribed** *(strong recommendation, very low-quality evidence).* Severe chronic hypoxemia is defined as either *1*) greater than or equal to 5% of recording time spent with an Sp_{O_2} less than 90% if measurements are obtained by continuous recording or *2*) at least three separate findings of an Sp_{O_2} less than 90% if measurements are obtained intermittently.
- **For patients with CF who have both mild chronic hypoxemia and dyspnea on exertion, we suggest that HOT be prescribed** *(conditional recommendation, very low-quality evidence).* Mild chronic hypoxemia is defined as either *1*) greater than or equal to 5% of recording time spent with an Sp_{O_2} 90–93% if measurements are obtained by continuous recording or *2*) at least three separate findings of an Sp_{O_2} 90–93% if measurements are obtained intermittently.

Question 2: Should Children with Bronchopulmonary Dysplasia Complicated by Chronic Hypoxemia Be Treated with HOT?

Evidence base. We identified 11 observational studies that compared HOT with no oxygen therapy in children whose BPD was complicated by chronic hypoxemia. Ten of the studies were excluded because there was an unacceptable risk of bias owing to the patients receiving HOT being more severely ill than the patients in the no-oxygen group. The remaining study was selected for analysis (105).

The study enrolled 63 infants with BPD who were receiving HOT but had an Sp_{O_2} greater than or equal to 92% in room air. The infants were admitted for continuous pulse oximetry in room air during sleep and then categorized into three groups: those who *1*) maintained an Sp_{O_2} greater than or equal to 92%, *2*) had desaturations to 88–91% for more than 1 hour, or *3*) had desaturations to less than 88% for more than 1 hour. Those who maintained an Sp_{O_2} greater than or equal to 92% or had desaturations to 88–91% had their supplemental oxygen discontinued, whereas those who had desaturations to less than 88% had their supplemental oxygen continued. For the groups whose oxygen was discontinued, various growth parameters were measured before and after discontinuation of oxygen and compared. Because the issue being addressed concerns children with chronic hypoxemia, our analysis focused on the 14 infants who had desaturations to 88–91% during sleep. The study revealed that the rate of weight gain was greater while the infants were receiving supplemental oxygen than after discontinuation (15.9 g/kg/d vs. 3.7 g/kg/d; MD, 12.2 g/kg/d; 95% CI, 7.22 to 17.18 g/kg/d).

The panel supplemented this study with indirect evidence. Two studies enrolled patients with BPD who had ongoing high oxygen requirements: one compared hemodynamics measured by right heart catheterization during the inhalation of 80% oxygen for 10 minutes with those measured during the inhalation of room air for 10 minutes (45), and the other compared hemodynamics measured during the inhalation oxygen targeting a Pa_{O_2} greater than 120 mm Hg (>16 kPa) with those measured during the inhalation oxygen targeting a Pa_{O_2} of 55 to 120 mm Hg (7.33–16 kPa) (122). Meta-analysis found that oxygen administration was associated with lower mean pulmonary artery pressure (MD, −10.03 mm Hg [−1.34 kPa]; 95% CI, −16.41 to −3.64 mm Hg [−2.19 to −0.49 kPa]). Another study enrolled patients with BPD who required oxygen to keep their Sp_{O_2} above 90% and compared polysomnography results while subjects breathed either an extra 0.25 L/min of supplemental oxygen or their baseline amount of oxygen (74). The higher amount

of oxygen was associated with increased total sleep duration, increased REM sleep duration, and decreased REM arousals, although the values of each were not reported.

The panel had very low confidence that the estimated effects described above are the same for HOT in patients with BPD complicated by chronic hypoxemia. The direct evidence was derived from a single, small observational study. The indirect evidence derived estimates from small observational studies that used short-term oxygen or nocturnal HOT rather than HOT.

Benefits. In patients with BPD who have chronic hypoxemia, HOT increased the growth rate, short-term oxygen use decreased the mean pulmonary artery pressure, and nocturnal oxygen administration improved sleep duration and decreased arousals.

Harms. No harms were reported in any of the studies.

Conclusions. The panel emphasized that patients with chronic hypoxemia due to BPD generally reach a phase in their medical care when they face two alternatives: receive long-term oxygen in the hospital or at home. This occurs when other medical issues have stabilized but altered oxygenation levels are only slowly improving. The panel was certain, despite its very low confidence in the estimated effects, that the benefits of HOT exceed the harms, burdens, and cost. In addition to improved growth, lower pulmonary artery pressure, improved sleep duration, and fewer arousals from sleep, it enables the patient and family to be at home and diminishes the likelihood of harm by preventing the nosocomial and iatrogenic consequences of hospitalization. The strength of the panel's recommendation is strong because its primary intention is to prevent the harmful effects of prolonged hospitalization.

What others are saying. The BTS clinical practice guidelines recommended HOT for infants with chronic neonatal lung disease, including BPD, because BTS similarly concluded that HOT improves multiple clinical outcomes, is preferable to a prolonged hospital stay for quality of life and psychological impact, and enables earlier discharge from the hospital (121). In the more recent guidelines for pediatric PH published as a combined effort by the ATS with the American Heart Association (AHA), supplemental oxygen therapy was graded as reasonable to avoid episodic or sustained hypoxemia with a suggested goal of maintaining Sp_{O_2} between 92% and 95% in children with established BPD and PH (123).

ATS recommendation.

- **For patients with BPD complicated by chronic hypoxemia, we recommend that HOT be prescribed** *(strong recommendation, very low-quality evidence)*. Chronic hypoxemia is defined as either *1*) greater than or equal to 5% of recording time spent with an Sp_{O_2} less than or equal to 93% if measurements are obtained by continuous recording or *2*) at least three separate findings of an Sp_{O_2} less than or equal to 93% if measurements are obtained intermittently.

Question 3: Should Children with Sleep-disordered Breathing Complicated by Chronic Hypoxemia Be Treated with HOT?

Evidence base. We identified two studies that compared nocturnal oxygen with no oxygen therapy in children with SDB complicated by nocturnal hypoxemia (124, 125). One study was a randomized crossover trial that enrolled children (mean age, 5 yr) who had suspected OSA plus desaturation during sleep to less than 92% (124); the other study was an observational study that enrolled children (mean age, 4.3 yr) who had tonsillar hypertrophy and desaturations during sleep to less than 90% (125). Both studies compared the effects of supplemental oxygen with room air during sleep; one study provided oxygen at a rate of 1 L/min (124), and the other provided oxygen at a rate needed to keep the patient's Sp_{O_2} above 95% (125).

The apnea index was the only outcome measured by both studies; when pooled by meta-analysis, oxygen use during sleep was associated with no change in the apnea index (MD, −3 events/h; 95% CI, −12.92 to +6.68 events/h). In single studies, oxygen use during sleep was associated with a higher mean Sp_{O_2} (MD, +8.2%; 95% CI, +5.58% to +10.82%), nadir Sp_{O_2} (MD, +20.7%; 95% CI, +11.29% to +30.11%), and nadir Sp_{O_2} during REM sleep (MD, +9%; 95% CI, +1.57% to +16.43%). It was also associated with trends toward a higher mean Sp_{O_2} during REM sleep (MD, +4%; 95% CI, −0.16% to +8.16%), mean Sp_{O_2} during NREM sleep (MD, +3%; 95% CI, −0.39% to +6.39%), and nadir Sp_{O_2} during NREM sleep (MD, +4%; 95% CI, −0.47% to +8.47%). There was no difference in the hypopnea index (MD, −3.8 events/h; 95% CI, −19.32 to +11.72 events/h) or changes in overall end-tidal P_{CO_2} levels, although P_{CO_2} increased significantly in a few patients.

The panel's confidence in the accuracy of these estimated effects in the patient population of interest to them was very low. There was indirectness of the intervention because the question is about HOT provided chronically at night, but the studies used oxygen provided during a single night. There was also indirectness of outcomes because those assessed were all short-term physiologic measures rather than the long-term clinical outcomes that the panel would have preferred. In addition, the studies were small, and there was a risk of bias, because neither study reported enrolling consecutive patients and one study was not blinded.

Benefits. In patients with SDB with nocturnal desaturation, HOT during sleep increased both the mean and nadir Sp_{O_2} during sleep.

Harms. No harms were reported in any of the studies.

Conclusions. The panel concluded that the benefits of HOT likely exceed the harms, burdens, and cost for the majority of patients with severe nocturnal hypoxemia due to SDB who either cannot tolerate positive airway pressure therapy or are awaiting surgical treatment of their SDB. Although the studies above merely show that giving oxygen increases oxygenation, there is abundant evidence that improving nocturnal oxygenation by other means, such as positive airway pressure, mitigates adverse cardiopulmonary consequences of nocturnal hypoxemia in children. The panel had no reason to suspect that relief of nocturnal hypoxemia by oxygen or positive airway pressure will lead to different consequences.

What others are saying. The BTS clinical practice guidelines emphasized that positive airway pressure is the therapy of choice for children with OSA; however, for children in whom application of positive airway pressure is not possible, the BTS recommended HOT but urged monitoring of CO_2 levels during the initiation of oxygen therapy (121).

ATS recommendation.

- **For patients with SDB complicated by severe nocturnal hypoxemia who cannot tolerate positive airway pressure therapy or are awaiting surgical treatment of SDB, we suggest that HOT be prescribed** *(conditional recommendation, very low-quality evidence)*. Severe nocturnal hypoxemia is defined as greater than or equal to 5% of recording time spent with a Sp_{O_2} less than 90% during sleep.

Question 4: Should Children with Sickle Cell Disease Complicated by Chronic Hypoxemia Be Treated with HOT?

Evidence base. Many studies reported associations between hypoxemia and outcomes such as stroke and pain crises, but they were excluded because they did not compare use of oxygen with no oxygen therapy. We identified two observational studies that evaluated patients before, during, and after receiving supplemental oxygen (126, 127). Both studies enrolled patients with SCD, but neither reported the ages of the patients or the degree of chronic hypoxemia. One study of three patients administered oxygen at 5 L/min by nasal prongs (126), and the other study of four patients administered 70–100% oxygen continuously for 8 to 20 days (127).

Measures of oxygenation increased during oxygen therapy. In one study, the Pa_{O_2} ranged from 72 to 83 mm Hg (9.60 to 11.07 kPa) before receiving supplemental oxygen and from 146 to 175 mm Hg (19.47 to 23.33 kPa) while receiving oxygen (126). In the other study, which reported a single representative patient only, the Sp_{O_2} was 89% before the initiation of oxygen, 100% during administration, and 83% after discontinuation (127). In both studies, the number and percentage of sickle cells decreased during oxygen administration, although this was not accompanied by less hemolysis. The amount of sickle cells rebounded when the oxygen was discontinued, with six of seven patients rebounding to higher-than-baseline levels and the remaining patient rebounding to baseline levels (126, 127). One study was terminated early because two of three patients developed pain crises after discontinuation of the supplemental oxygen, although none of the four patients in the other study experienced a pain crisis (126).

The panel's confidence in the accuracy of these estimated effects in the patient population of interest to them was very low. There was indirectness of the intervention because the oxygen was provided at much higher levels than current norms. In addition, there was a risk of bias for multiple reasons: The studies were not blinded, did not report enrolling consecutive patients, and did not report all of the data that were collected.

Benefits. Oxygen therapy increased oxygenation and decreased the amount of sickle cells.

Harms. After discontinuation of continuous oxygen, the amount of sickle cells rebounded to higher-than-baseline levels, and some patients developed a pain crisis.

Conclusions. The panel acknowledged that the studies described above raise serious concerns about the potential for harm if oxygen is discontinued in patients with SCD. However, the panel had very low confidence in the findings owing to the studies' small size (only seven patients total) and publication age (cointerventions were different in 1944 and 1984). Moreover, the panel has collectively used oxygen in hundreds of patients with SCD for a variety of reasons without increases in sickle cell crises or acute chest syndrome upon discontinuation, and it was concerned about the untoward effects of allowing severe chronic hypoxemia to go unabated.

What others are saying. The BTS clinical practice guidelines recommended HOT for children with SCD and persistent nocturnal hypoxemia to reduce stroke and pain crises (121). Although the National Health Service guidelines on SCD and thalassemia do not specifically make recommendations related to supplemental oxygen use, the need for guidance in the delivery of oxygen therapy was suggested (128). In an evidence-based summary of the management of SCD, long-term oxygen therapy was not addressed, but maintenance of Sp_{O_2} above 95% was strongly recommended during acute chest syndrome, and exchange transfusion was recommended when the Sp_{O_2} dropped below 90% (129). In patients with SCD with concomitant PH, the pediatric PH guidelines suggested optimization of therapies with no specifics about oxygen therapy (123).

ATS recommendation.

- **For patients with SCD complicated by severe chronic hypoxemia, we suggest that HOT be prescribed** *(conditional recommendation, very low-quality evidence)*. Severe chronic hypoxemia is defined as either *1*) greater than or equal to 5% of recording time spent with an Sp_{O_2} less than 90% if measurements are obtained by continuous recording or *2*) at least three separate findings of an Sp_{O_2} less than 90% if measurements are obtained intermittently.

Question 5: Should Children with Pulmonary Hypertension without Congenital Heart Disease Be Treated with HOT?

Evidence base. We identified no studies that compared the effects of HOT with no oxygen therapy in children with PH complicated by chronic hypoxemia. The panel discussed whether to review indirect evidence from adults but judged adults with PH to be too indirect a population to inform recommendations in children. Instead, the panel decided to inform its recommendations with their collective nonsystematic clinical observations derived from caring for many such patients over several decades. Nonsystematic clinical observations give very low confidence in the estimated effects.

Conclusions. The panel emphasized that empirical evidence comparing HOT with no oxygen therapy will never be forthcoming, because withholding HOT in such patients is ethically questionable. The panel's collective clinical experience suggests that children with chronic hypoxemia due to PH are less dyspneic and more active when receiving HOT. Although harmful consequences of HOT are infrequent, there can be effects on quality of life. Most important, the panel was particularly certain about the potential of HOT to benefit patients by mitigating the undesirable consequences of chronic hypoxemia because it directly interrupts the vicious cycle of PH causing hypoxemia, which in turn worsens the PH.

What others are saying. The BTS clinical practice guidelines recommended HOT for children with idiopathic PH complicated by sleep-associated desaturations, for children with idiopathic PH who have severe hypoxemia, and for PH secondary to

pulmonary disease. They recommended against HOT for PH associated with cardiac effects, owing to lack of good evidence (121). In comparison, the combined ATS and AHA guidelines on pediatric PH reported that treatment of hypoxemia with oxygen therapy was reasonable in children with PH who had an Sp_{O_2} less than 92%, especially if associated with any concomitant lung disease (123).

ATS recommendation.

- **For patients with PH without CHD complicated by chronic hypoxemia, we recommend that HOT be prescribed** *(strong recommendation, very low-quality evidence)*. Chronic hypoxemia is defined as either *1*) greater than or equal to 5% of recording time spent with an Sp_{O_2} less than or equal to 93% if measurements are obtained by continuous recording or *2*) at least three separate findings of an Sp_{O_2} less than or equal to 93% if measurements are obtained intermittently.

Question 6: Should Children with Pulmonary Hypertension with Congenital Heart Disease Be Treated with HOT?

Evidence base. We identified no studies that compared the effects of HOT with no oxygen therapy exclusively in children with CHD. The only relevant study was a nonrandomized trial of supplemental oxygen for patients with PH in which 13 of the 15 patients had CHD (130). Nine patients were assigned to receive HOT for at least 12 hours per day, and six patients were assigned no HOT. The patients were followed for up to 5 years. Baseline values revealed a trend toward higher Sp_{O_2} in the HOT group (+5%; −4.43% to +14.43%), a trend toward lower pulmonary vascular resistance in the HOT group (−7 mm Hg/min/m^2/L; 95% CI, +3.67 to −17.67 mm Hg/min/m^2/L), and no difference in the pulmonary artery pressure. Mortality was lower among children who received HOT (0% vs. 83%; relative risk not estimable). Exercise capacity and symptoms were reportedly measured by questionnaire, but the results were not described. The study provided very low confidence in its estimated effects.

Benefits. HOT was associated with lower mortality and trends toward decreased pulmonary vascular resistance and increased pulmonary blood flow.

Harms. No harms were reported in the study.

Conclusions. The panel acknowledged that the evidence favored HOT but had very low confidence in the estimated effects, owing to the study design, potential bias, and imprecision. They also expressed concern that in some patients with unrepaired CHD and significant left-to-right shunt, increased pulmonary blood flow can be harmful rather than beneficial. Generally speaking, they strongly believed that the fine balance between the potential for either beneficial or harmful effects dictates that such patients be evaluated and treated by clinicians with experience in managing such complicated patients. In children with surgically repaired CHD, however, concerns of high pulmonary blood flow would not persist, and the effects of oxygen therapy to avoid hypoxemia, especially in the setting of PH, are likely greater than potential adverse effects.

What others are saying. The BTS clinical practice guidelines recommended against HOT for cyanotic CHD unless accompanied by other respiratory problems. They similarly recommended against HOT for acyanotic CHD (121). The combined ATS and AHA guidelines on pediatric PH did not address oxygen therapy in children with CHD and chronic hypoxemia (123).

ATS recommendation.

- **For patients with PH with CHD complicated by chronic hypoxemia, supplemental oxygen will impact hemodynamics and physiology; we recommend that HOT NOT be initiated in these children, regardless of previous reparative or palliative congenital heart surgery, until there has been consultation with a pediatric pulmonologist or cardiologist who has expertise in the management of PH in this clinical setting** *(strong recommendation, very low-quality evidence).*

Question 7: Should Children with Interstitial Lung Disease Complicated by Chronic Hypoxemia Be Treated with HOT?

Evidence base. We identified no studies that compared the effects of HOT with no oxygen therapy in children with ILD complicated by chronic hypoxemia. The panel discussed whether to review indirect evidence from adults but judged adults with ILD to be too indirect a population to inform recommendations in children. Instead, the panel decided to inform its recommendations with their collective nonsystematic clinical observations. Nonsystematic clinical observations give very low confidence in the estimated effects.

Conclusions. The panel again emphasized that empirical evidence comparing oxygen use with no oxygen therapy will never be forthcoming, because withholding HOT in such patients is ethically questionable. The panel was certain that the benefits of HOT exceed the harms, burdens, and cost in patients with ILD with severe chronic hypoxemia (Sp_{O_2}, <90%). This was based on the large number of beneficial outcomes that they have observed in their clinical practices and the absence of harmful outcomes, decades of clinical experience in managing many such patients, and recognition that prolonged chronic hypoxemia can contribute to serious health consequences such as PH and cor pulmonale. The panel also concluded that the benefits of HOT likely exceed the harms, burden, and cost in patients with ILD who have mild hypoxemia (Sp_{O_2} 90–93%) that is chronic, accompanied by sequelae of hypoxemia (e.g., dyspnea on exertion), or associated with desaturation during sleep or exertion.

What others are saying. The BTS clinical practice guidelines recommended HOT for children with ILD complicated by chronic hypoxemia who are otherwise ready for hospital discharge (121). Although specific recommendations for oxygen therapy were not addressed, the recent guideline on ILD in children recommended routine measurement of Sp_{O_2} for pediatric patients by pulse oximetry, with supplemental oxygen potentially indicated during the day, during the night, and with exercise for all children as well as during feeding for infants (104).

ATS recommendations.

- **For patients with ILD complicated by severe chronic hypoxemia, we recommend that HOT be prescribed** *(strong recommendation, very low-quality evidence)*. Severe chronic hypoxemia is defined as either *1*) greater than or equal to 5% of recording time spent with an Sp_{O_2} less than 90% if measurements are obtained by continuous recording or *2*) at least three separate findings of an Sp_{O_2} less than 90% if measurements are obtained intermittently.
- **For patients with ILD who have both mild chronic hypoxemia and either dyspnea on exertion or desaturation**

during sleep or exertion, we suggest that HOT be prescribed *(conditional recommendation, very low-quality evidence).* Mild chronic hypoxemia is defined as either *1*) greater than or equal to 5% of recording time spent with an Sp_{O_2} 90–93% if measurements are obtained by continuous recording or *2*) at least three separate findings of an Sp_{O_2} 90–93% if measurements are obtained intermittently.

Providing HOT

Evidence-based data that address the optimal modalities of home oxygen delivery and monitoring in the pediatric population are limited. Although an in-depth discussion of specific delivery and monitoring methods is beyond the scope of this guideline, panel members identified important considerations for equipment choice, including the patient's age, size, and developmental stage, as well as the required flow rate. Furthermore, equipment choices should remain under appropriate supervision.

Equipment

- All children require access to age-appropriate equipment and supplies that will meet their supplemental oxygen needs. These items should be reimbursed by insurers to ensure safe and effective delivery of oxygen in the home. The prescriber should recognize that there is currently significant geographic variability in access to and reimbursement for pediatric patient–specific equipment.
- Oxygen concentrators are one of the most commonly used delivery systems in the home and may be stationary or portable, whereas tanks may be more readily available according to local preferences. The stationary devices are large and require reliable sources of electricity. In areas where power outages are common, backup generators or alternative sources of oxygen are required. There are various types of concentrators available, with flows most commonly ranging from 1 to 5 L/min, providing up to $F_{I_{O_2}}$ 0.95 (131).
- Children require access to low-flow delivery systems. Low-flow meters should be used to deliver flows ranging from 0.1 to 1 L/min for infants and young children (121). Some equipment companies have low-flow concentrators available to provide oxygen at 0.1 L/min without the use of a flowmeter.
- Size-adequate oxygen cylinders can be used in infants and small children as the primary source of home oxygen if flow rates are low (<0.3 L/min) and if the duration of oxygen therapy is expected to be limited to a few months (121).
- Portability of equipment is an important concern for pediatric patients. Continuous flow portable concentrators are small and may be battery operated to allow for increased mobility. Adaptation for strollers and/or wheelchairs should be considered (132). Lightweight cylinders allow for easier mobility, though they do not last as long as standard cylinders outside the home. If using a stationary oxygen system (e.g., concentrator, tanks) at home, a portable system is necessary to allow for travel to school, medical visits, and so forth.
- Pulse oxygen delivery systems (also called "oxygen conserver devices") are used in adult patients to restrict oxygen administration to the period of inspiration, thereby avoiding the waste of oxygen delivery during exhalation and assuring a consistent dose of oxygen per breath, regardless of respiratory rate. Varying by device, this technology relies on pressure, volume, or time to trigger oxygen release (131). Because of higher respiratory rates and low inspiratory volumes in children, pulse oxygen delivery systems should not be used in infants or young children, although they can be considered for use in adolescents (121).
- Humidification of the oxygen circuit should be provided for flow rates above 1 L/min and can be achieved through cold bubble or heated humidification devices (121). A benefit to humidification of low-flow oxygen therapy (<1 L/min) has not been clearly established (133).
- The addition of humidification (or other modifications to the original circuit) may alter flow delivery. Appropriate equipment (such as a gas flowmeter device) should be available for families to monitor flow delivery.
- Home oxygen is typically delivered via nasal cannula in the pediatric population. The delivered $F_{I_{O_2}}$ is dependent on the flow through the prongs, the level of entrainment, and the child's tidal volume, with the delivered $F_{I_{O_2}}$ ranging from 0.22 to 0.95 at a maximum flow of 2 L/min (134, 135). Cannulae should be appropriately secured to the face to prevent skin breakdown and should be replaced as often as weekly if required. The prescribers should be proactive in delineating the appropriate oxygen delivery interface to minimize the risk of equipment-related complications, with special attention to maintaining skin integrity. Older patients or those not tolerating nasal cannulas with a higher oxygen flow rates may opt for the use of an appropriate oxygen mask, although more variability in $F_{I_{O_2}}$ based on mask positioning and patient tidal volume may be present (134).
- Increased storage efficiency and portability have made liquid oxygen an attractive option for the adult population (131). Liquid oxygen cannot currently be delivered using continuous flows less than 0.25 L/min (121) and may not be readily available. Storage of liquid oxygen is not efficient for those needing intermittent supplemental oxygen.
- The high-flow nasal cannula has the ability to deliver much higher flow rates at varying oxygen concentrations. Although not routinely used in the pediatric home setting, there are reports of successful cases using outpatient high-flow nasal cannulas for hypoxemia secondary to OSA (136) and tracheomalacia (137).

Monitoring

Arterial blood gas measurements are not routinely used to assess oxygenation in clinically stable children with chronic diseases, owing to pain and discomfort from arterial puncture. Pulse oximetry is the primary method of monitoring Sp_{O_2} in the pediatric population. The oximeter measures red and infrared light absorption of oxygenated and deoxygenated hemoglobin to estimate the Sp_{O_2} (138). Oximetric measurements have generally been shown to correlate at 2–3% above measured arterial saturation, with accuracy worsening when Sp_{O_2} measures below 90% (139). Some limitations to accurate Sp_{O_2} determinations with pulse oximeters include improper probe placement, movement artifact, nail color, ambient light, reduced distal extremity

perfusion, hypothermia, skin pigmentation, and dysfunctional hemoglobin (134, 140).

The use of in-home pulse oximetry for long-term monitoring of HOT in children is unanimously endorsed by the panel. Such monitoring can alert caregivers to interruptions in oxygen delivery that may suggest clinical deterioration or the need for clinical intervention such as airway suctioning, patient repositioning, and so forth (141–146). The panelists recognize the limitations of the literature on in-home pulse oximetry use in the care of children, so further research is recommended to identify best practice of this valuable medical equipment that has its own drawbacks. During times of illness, pulse oximetry can provide important information to the caregiver, potentially decreasing the need for visits to the emergency department (147). The presence of a pulse oximeter can also identify reduced Sp_{O_2} during periods of exertion or during infant feeding. However, concerns regarding home oximetry monitoring include the nuisance of frequent alarms, increased caregiver anxiety, and the potential for overreliance by caregivers on normal Sp_{O_2} versus overall clinical status (121). Because Sp_{O_2} is only one facet of a patient's clinical status, pediatric patients with increased work of breathing and potential hypoventilation need to be assessed by a clinician, regardless of Sp_{O_2}.

With the panel recommending the monitoring of children on HOT with pulse oximetry in the home, appropriate caregiver training is required for its use and application. Such training should include an understanding of when to apply the pulse oximeter and how to interpret the measurements obtained. It is of great importance that pediatric patient–specific sensors be prescribed by healthcare providers.

Home Safety

Assurance of safety and support of all children and adolescents on HOT should be a priority. Home caregiver education should address appropriate management of the equipment and skills to interpret and respond to abnormal Sp_{O_2} measurements while applying these data to the clinical status of the child. Education regarding the risks of smoking and open flames in the home, as well as the use of oil-based products or other fuels near the oxygen source, should be provided (121, 134, 140). The focus on the dangers of smoke exposure should include the flammability of compressed oxygen and the known harms that inhaled smoke imparts to growing infants and children. The panel recommends documentation of competency in the delivery of HOT to a child once all home caregivers have completed education. It is also imperative to ensure access to reliable electricity and a telephone in case of emergencies (121). Communication between the prescribing healthcare provider, durable medical equipment agency, and other key parties is important to provide appropriate care to these medically complex patients.

Follow-up

Regular follow-up with a healthcare provider is required for children on HOT, because repeated assessment of oxygen needs and changes in respiratory status should be performed. An outpatient continuous pulse oximetry study (nocturnal or daytime) can provide a more complete and objective assessment of Sp_{O_2} than what can be obtained by parental report and evaluation in a clinic setting. In addition to Sp_{O_2}, feeding patterns and growth, together with activity tolerance, should be assessed.

Any concern of hypoventilation should be investigated with capillary blood gas analysis or serum bicarbonate determination, which are widely available, or with end-tidal or transcutaneous CO_2 measurements, which are often immediately available in hospital settings but not readily available in an outpatient setting or in the home. Although each of these methods has its limitations (148), they all have the potential for more widespread use in the future. Depending on the clinical scenario, a more definitive evaluation with polysomnography may be necessary.

Discontinuation of HOT

Although some conditions may warrant indefinite HOT, improvements in respiratory function that occur with age, maturation, treatment, clinical course, and so forth can lead to an opportunity to wean (progressively decrease) or discontinue (stop altogether) HOT. Improvements in respiratory status amenable to weaning of oxygen therapy are most applicable to infants with chronic lung disease of prematurity, but a standardized approach may nonetheless be helpful in other populations. Criteria for the justification and initiation of HOT are outlined by CMS, but weaning or discontinuation is not. Although many healthcare providers reduce or wean supplemental oxygen in the outpatient setting gradually and with the guidance of nocturnal oxygen assessments (121, 149–152), there are no widely accepted, evidence-based guidelines, and few report using a standardized protocol (149). The panel unanimously agrees that a large, prospective trial comparing weaning strategies is needed. Nonetheless, we describe a consensus-based approach to identifying patient readiness for weaning and discontinuation of HOT, the process for doing so, and the monitoring necessary to determine its safety and tolerance. The use, weaning, or discontinuation of other therapies (e.g., diuretics in BPD) is outside the scope of this guideline, although providers are cautioned to avoid making multiple abrupt changes in treatment at one time.

Assessing Readiness

As previously mentioned, the measurement of arterial blood for Pa_{O_2} is not practical for routine outpatient monitoring of a child's respiratory status; therefore, pulse oximetry to monitor Sp_{O_2} is standard for the purposes of analyzing gas exchange. A child may be considered appropriate for weaning of HOT if the following criteria are met, which are based on this panel's consensus opinion and shaped by an earlier survey of pediatric pulmonologists (150):

- Reassuring medical examination by a qualified healthcare provider that takes into account the child's underlying medical condition(s), gestational age, condition-specific growth charts, home altitude, and so forth; ideally, the examination should meet these criteria:
  - Period of relatively stable health (no current or recent acute illness)
  - Age- and condition-appropriate growth, including positive trends in weight gain, linear growth, and head circumference
  - Meeting developmental milestones as expected for clinical condition, where factors that may influence development, such as prematurity, concurrent syndrome, perinatal neurodevelopmental insult, and so forth, must be considered
  - Acceptably low frequency and/or severity of illnesses requiring hospitalization

- Physical examination not suggestive of impaired respiratory function (breathing effort, respiratory rate, and so forth are as expected for clinical course)
- Reassuring objective measurement of oxygenation, in which the following should be considered:
  - Oxygen saturation measured at steady state (not "spot checked") by continuous pulse oximetry in room air meets patient-specific goal.
  - Unfortunately, wakeful pulse oximetry did not correlate with nocturnal oxygenation in a population of premature infants with BPD (121). Brief pulse oximetry during wakefulness alone may be appropriate for some patients, whereas others may require monitoring during feeding and/or while asleep with an overnight, in-home pulse oximetry study.
  - In general, the same oxygenation goals that prompted initiation of HOT should be used.
- Depending on the underlying process, consider an echocardiogram to demonstrate absence of or improvement in findings suggestive of PH or right heart strain (e.g., normal or improving estimation of right ventricular pressure, lack of ventricular septal flattening)

Weaning of HOT

Once readiness for weaning of HOT is determined, it is suggested either to decrease oxygen flow rate gradually or to withdraw its use during certain periods of the day. Some children may tolerate a reduction from around-the-clock home oxygen to nocturnal use only, whereas infants and other children with special circumstances may need to continue HOT with certain daytime activities (e.g., car rides, naps, during feeding).

When gradually decreasing the oxygen flow rate, it is practical to wean by halving because conventional home oxygen delivery devices easily allow for this (1 L/min to 0.5 L/min then 0.25 L/min, and so forth) before room air challenges. We suggest weaning the flow rate gradually over the course of weeks while frequently monitoring for adverse effects. This should include regular (weekly to monthly) visits with a qualified healthcare provider to assess the child as outlined above.

Successful Discontinuation of HOT

Once the child has tolerated weaning HOT to a sufficiently low flow rate, then discontinuation can be considered. Preterm neonates with BPD had more successful room air challenges and clinical stability at 6 months postdischarge if previously stable receiving less than or equal to 20 ml/kg/min of oxygen (153). By consensus, the panel recommended that room air challenges be considered for clinically stable children under 1 year of age receiving less than 0.1 L/min and children up to preschool age receiving 0.1–0.25 L/min. By extrapolation, a flow rate less than 0.25–0.5 L/min could be considered for school-age and older children. With HOT occurring in terms of flow rate, it is not pertinent to wean or discontinue oxygen use on the basis of F_{IO_2}.

Once a patient is considered ready for discontinuation of nighttime HOT altogether, then an in-home, room air, nocturnal pulse oximetry study should be performed using appropriate pediatric equipment and reference ranges as outlined in this document. Healthcare providers should encourage families to maintain accessibility to HOT for several months after discontinuation, particularly through the winter season, when viral illnesses are prevalent. This allows for ample opportunity to determine whether the withdrawal of HOT was well timed, in addition to how well respiratory illnesses are tolerated without supplemental oxygen.

As suggested when assessing for patient readiness to wean HOT, it is necessary to monitor responses to each change repeatedly. Given the chronicity of these respiratory conditions, changes should be made on a weeks to months basis, as opposed to more quickly, so that subtle deterioration is not missed and suboptimal therapy is promptly reversed. The factors to monitor reflect those assessed when considering patient readiness and include patient growth, development, cardiorespiratory status, and stability of health (e.g., handling of respiratory illnesses, travel to altitude).

HOT and its necessary equipment are often burdensome and costly. However, home caregivers and healthcare providers are reminded that the processes treated by HOT are chronic in nature, its use is low risk, and patience is often rewarded. Conversely, weaning HOT too soon or too abruptly can lead to patient and home caregiver stress.

Conclusions

Despite widespread use of HOT in children for various lung and pulmonary vascular diseases, there is a striking paucity of data regarding its implementation, efficacy, monitoring, and discontinuation. With limited evidence, the panel provides recommendations based on expert opinion and experiences associated with patient-important outcomes that will aid clinicians in the management of complex pediatric patients requiring HOT. Future research should address important areas including Sp_{O_2} levels associated with optimal growth and development and the identification of best practice for weaning and discontinuing HOT in children. ■

This official clinical practice guideline was prepared by an *ad hoc* subcommittee of the ATS Assembly on Pediatrics.

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