

ONLINE SUPPLEMENT

**HOME OXYGEN THERAPY FOR CHILDREN:
AN OFFICIAL AMERICAN THORACIC SOCIETY GUIDELINE**

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METHODS

Panel Composition: The project was proposed by the co-chairs through the ATS Pediatrics Assembly and approved by the ATS Board of Directors. Potential panelists were identified by the co-chairs based on their expertise in pediatric diseases known to be complicated by chronic hypoxemia. All potential panelists disclosed their conflicts of interest to the ATS. No panelist was determined to have conflicts of interest that warranted recusal from participation in certain recommendations or disqualification from the guideline panel. The final guideline panel consisted of 20 members: 2 co-chairs, 16 physician experts, 1 nurse, 1 patient representative, and 3 methodologists.

Questions: The guideline panel drafted key clinical questions in a PICO (Population, Intervention, Comparator, and Outcome) format at a face-to-face meeting in Washington, D.C. in May 2017. The final questions were approved by the full guideline panel. Outcomes that might be affected by each of the interventions were identified by an electronic survey and then numerically rated (from 1 to 9) according to their importance by a second electronic survey. The evidence was assessed only for outcomes whose average rating fell into the “important” (median rating 4-6) or “critical” (median rating 7-9) categories.

Literature search: The published literature was searched in Medline, Cochrane Central Database of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews. The sensitive search strategy consisted of controlled vocabulary terms (such as Medical Subject Headings) and keyword terms that describe children and home supplemental oxygen (Table E1). Filters were used to narrow the search results to studies that enrolled human subjects, were published in the English language, and were published within the past ten years. The initial search was conducted in June 2017 and a targeted update was performed immediately prior to submission for peer review. For each study that was

selected, the bibliography was searched for additional relevant studies and a “cited by” search using the PubMed search engine was performed. For each clinical practice guideline or systematic review that was identified, the bibliography was searched for additional relevant studies. Finally, the guideline panel submitted additional studies for consideration. Study selection was performed in duplicate.

Evidence synthesis: The methodology team reviewed all publications retrieved from the literature searches for relevance, initially screening based on title and/or abstract and then reviewing the full text of potentially relevant publications. Data from selected studies were extracted into structured data tables. Data extraction was performed in duplicate. When data from individual studies were amenable to pooling, a random effects model was used to pool results across studies using the Cochrane Collaboration Review Manager, version 5.3. Relative risk (RR) was used to report the results for dichotomous outcomes and the mean difference (MD) was used to report the results for continuous outcomes, each with an accompanying 95% confidence interval (CI).

The Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to assess certainty in the estimated effects (i.e., the quality of evidence) for each intervention on each outcome of interest. The certainty was categorized into one of four levels: high, moderate, low, or very low. The full guideline panel was presented the evidence summary by the methodology team and then provided input and feedback.

Recommendations: The guideline panel met by webinar in November 2017 to discuss the evidence summaries and formulate recommendations. No relevant studies were identified for several questions, so the panel decided to make recommendations based upon normative values and their collective clinical experience. Following a repeat systematic search of the literature and evidence synthesis focused upon summarizing normative values, a second webinar was convened in January 2018 to

complete the evidence discussion and formulation of recommendations. The panelists made decisions about whether to recommend for or against an intervention based on: the balance of desirable consequences (benefits) and undesirable consequences (burdens, adverse effects, and costs), quality of evidence, cost and cost-effectiveness, feasibility, and acceptability to patients (i.e., patient values and preferences). Using the GRADE approach, each recommendation was rated as either “strong” or “conditional”. The meanings of “strong” and “conditional” recommendations are described in Table 1 of the guideline. All recommendations were formulated and graded by discussion and consensus; voting was never required.

Manuscript preparation: The initial draft of the manuscript was written by the co-chairs and methodology team with major contributions from taskforce members for certain sections. All members of the guideline panel reviewed the manuscript; comments were addressed by the co-chairs and the revised manuscript was redistributed to the full panel for further review. Revision and full panel review occurred multiple times. Once the manuscript was approved by the full panel, it was submitted for external peer review.

Peer review: External peer review was organized and overseen by the ATS Assistant Documents Editor. Comments from the reviewers were collated into a single decision letter and sent to the co-chairs. The manuscript was subsequently revised by the panel according to feedback received from the peer reviewers. Following several cycles of review and revisions, the manuscript was deemed satisfactory and sent to the ATS Board of Directors for further review and final approval

TABLE E1: PICO QUESTIONS

1. Should children with [see below] and chronic hypoxemia receive home oxygen therapy?
 - a. P= cystic fibrosis + chronic hypoxemia, I= home oxygen therapy, C= no home oxygen therapy
 - b. P= bronchopulmonary dysplasia + chronic hypoxemia, I= home oxygen therapy, C= no home oxygen therapy
 - c. P= sleep disordered breathing + chronic nocturnal hypoxemia, I= home oxygen therapy, C= no home oxygen therapy
 - d. P= sickle cell disease + chronic hypoxemia, I= home oxygen therapy, C= no home oxygen therapy
 - e. P= pulmonary hypertension without congenital heart disease + chronic hypoxemia, I= home oxygen therapy, C= no home oxygen therapy
 - f. P= pulmonary hypertension with congenital heart disease + chronic hypoxemia, I= home oxygen therapy, C= no home oxygen therapy
 - g. P= diffuse lung disease + chronic hypoxemia, I= home oxygen therapy, C= no home oxygen therapy

TABLE E2: SEARCH STRATEGY AND RESULTS

1	child [MH]	1,708,794
2	child*	2,387,711
3	pediatric*	628,293
4	infant [MH]	1,031,442
5	infant*	1,152,129
6	newborn*	689,106
7	neonat*	278,868
8	premature	162,732
9	“low birth weight”	35,820
10	“very low birth weight”	10,402
11	LBW	3,081
12	VLBW	36,457
13	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12	3,202,702
14	Oxygen inhalational therapy [MH]	169
15	“supplemental oxygen”	3,119
16	“oxygen therapy”	9,048
17	“long-term oxygen”	1,044
18	“ambulatory oxygen”	100
19	“domiciliary oxygen”	229
20	14 OR 15 OR 16 OR 17 OR 18 OR 19	12,120
21	Human [MH]	16,426,957
22	English [LA]	22,691,771
23	21 AND 22	12,978,594
24	13 AND 20 AND 23	2,353
25	Filter 24: Publication date during past 10 years	952

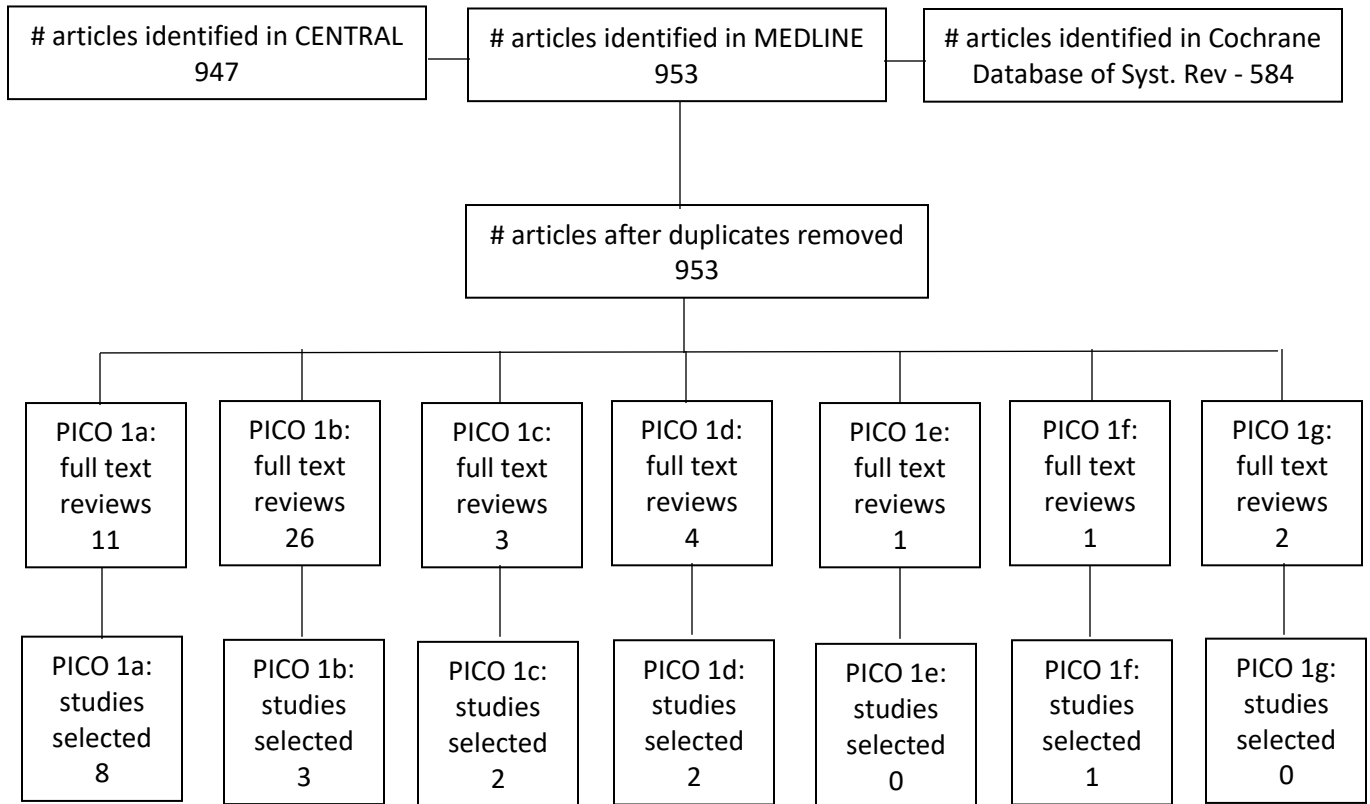
Strategy was adapted for the Cochrane Controlled Clinical Trials (CENTRAL) and Cochrane Database of Systematic Reviews databases.

TABLE E3: STUDY SELECTION CRITERIA

For all PICO questions, will seek studies that enrolled the population specified in the question, compared home oxygen therapy to no home oxygen therapy, and measured one or more of the pre-specified outcomes. In light of the expectation of little direct evidence, will cast a wide net and consider indirect evidence. Will proceed as follows:

1. Will seek randomized trials that compared supplemental oxygen versus no supplemental oxygen in children and measured clinical outcomes. If some are found, then stop. If none are found, then . . .
2. Will seek controlled observational studies (i.e., prospective or retrospective cohort studies, case-control studies) that compared supplemental oxygen versus no supplemental oxygen in children and measured clinical outcomes. If some are found, then stop. If none are found, then . . .
3. Will seek uncontrolled studies (i.e., case series or case reports) that reported clinical outcomes among children receiving supplemental oxygen. If some are found, then stop. If none are found, then . . .
4. Will rely upon the guideline panel's clinical experience to formulate recommendations.

FIGURE E1: FLOW OF INFORMATION DIAGRAM



EVIDENCE PROFILES

TABLE E4: Cystic Fibrosis

Bibliography

1. Zinman R, Corey M, Coates AL, Canny GJ, Connolly J, Levison H, Beaudry PH. Nocturnal home oxygen in the treatment of hypoxemic cystic fibrosis patients. *J Pediatr*. 1989 Mar;114(3):368-77.
2. Spier S, Rivlin J, Hughes D, Levison H. The effect of oxygen on sleep, blood gases, and ventilation in cystic fibrosis. *Am Rev Respir Dis*. 1984 May;129(5):712-8.
3. Falk B, Nini A, Zigel L, Yahav Y, Aviram M, Rivlin J, et al. Effect of low altitude at the Dead Sea on exercise capacity and cardiopulmonary response to exercise in cystic fibrosis patients with moderate to severe lung disease. *Pediatric Pulmonology* 2006;41(3):234-41.
4. Gozal D. Nocturnal ventilatory support in patients with cystic fibrosis: comparison with oxygen. *European Respiratory Journal* 1997;10(9):1999-2003.
5. Marcus CL, Bader D, Stabile MW, Wang C-I, Osher AB, Keens TG. Supplementation oxygen and exercise performance in patients with cystic fibrosis with severe pulmonary disease. *Chest* 1992;101(1):52-7.
6. McKone EF, Barry SC, FitzGerald MX, Gallagher CG. The role of oxygen during submaximal exercise in patients with cystic fibrosis. *European Respiratory Journal* 2002;20(1):134-42.
7. Milross MA, Piper AJ, Norman M, Becker HF, Willson GN, Grunstein RR, et al. Low-flow oxygen and bilevel ventilatory support: effects on ventilation during sleep in cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2001;163(1):129-34.
8. Nixon PA, Orenstein DM, Curtis SE, Ross EA. Oxygen supplementation during exercise in cystic fibrosis. *American Review of Respiratory Disease* 1990;142(4):807-11.

Quality assessment							# Patients	Effect ⁶	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other				
Mortality										
1 ¹	RCT	serious ²	none	serious ³	serious ⁴	none	28	29% versus 29% RR 1.0 (95% CI 0.31 to 3.22)	⊕○○○ VERY LOW	CRITICAL
Exercise capacity (minutes)										

2 ⁵	RCT	serious ²	none	serious ³	serious ⁴	none	36	MD +1.04 minutes (95% CI +0.21 to +1.88 minutes)	⊕000 VERY LOW	CRITICAL
Growth at 6 months (measured as % ideal body weight)										
1 ¹	RCT	serious ²	none	serious ³	serious ⁴	none	28	MD -2% (95% CI -5.11% to +1.11%)	⊕000 VERY LOW	CRITICAL
Growth at 12 months (measured as % ideal body weight)										
1 ¹	RCT	serious ²	none	serious ³	serious ⁴	none	28	MD -1% (95% CI -5.70% to +3.70%)	⊕000 VERY LOW	CRITICAL
Pulmonary hypertension / cor pulmonale (measured as proportion of patients with abnormal RV function at rest)										
1 ¹	RCT	serious ²	none	serious ³	serious ⁴	none	28	58% versus 50% RR 1.17 (95% CI 0.56 to 2.45)	⊕000 VERY LOW	CRITICAL
Sleep-disordered breathing (measured as arousals per hour)										
1 ⁶	RCT	serious ²	none	serious ⁷	serious ⁴	none	28	MD -2.1 arousals/hour (95% CI -4.57 to +0.37 arousals/hour)	⊕000 VERY LOW	CRITICAL
Lung function (measured as post-exercise oxygen saturation)										
3 ⁸	RCT	serious ²	none	serious ³	serious ⁴	none	66	MD +7.02% (95% CI +2.23% to +11.81%)	⊕000 VERY LOW	IMPORTANT
Lung function (measured as peak-exercise oxygen saturation)										
3 ⁸	RCT	serious ²	none	serious ³	serious ⁴	none	66	MD +7.19% (95% CI -2.51% to +16.89%)	⊕000 VERY LOW	IMPORTANT

Lung function (measured as peak-exercise oxygen desaturation)										
1 ⁹	RCT	serious ²	none	serious ³	serious ⁴	none	22	-5% versus -12% MD +7% (95% CI +2.48% to +11.52%)	⊕○○○ VERY LOW	IMPORTANT
School attendance at 6 months										
1 ¹	RCT	serious ²	none	serious ³	serious ⁴	none	28	71% versus 21% RR 3.3 (95% CI 1.16 to 9.59)	⊕○○○ VERY LOW	IMPORTANT
School attendance at 12 months										
1 ¹	RCT	serious ²	none	serious ³	serious ⁴	none	28	91% versus 20% RR 4.55 (95% CI 1.30 to 15.9)	⊕○○○ VERY LOW	IMPORTANT

- 1- Zinman, et al.
- 2- Most trials were unblinded.
- 3- PICO question is about home oxygen therapy, but study administered short-term oxygen.
- 4- Trial(s) was(were) small with few events.
- 5- Falk, et al. and Marcus, et al.
- 6- Gozal, et al.
- 7- PICO question is about home oxygen therapy, but study administered nocturnal oxygen.
- 8- Falk, et al., McKone, et al., and Nixon, et al.
- 9- Marcus, et al.

TABLE E5: Bronchopulmonary Dysplasia

Bibliography

1. Moyer-Mileur LJ, Nielson DW, Pfeffer KD, Witte MK, Chapman DL. Eliminating sleep-associated hypoxemia improves growth in infants with bronchopulmonary dysplasia. *Pediatrics*. 1996 Oct;98(4 Pt 1):779-83.
2. Benatar A, Clarke J, Silverman M. Pulmonary hypertension in infants with chronic lung disease: non-invasive evaluation and short term effect of oxygen treatment. *Arch Dis Child Fetal Neonatal Ed*. 1995 Jan;72(1):F14-9.
3. Mourani PM, Ivy DD, Gao D, Abman SH. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2004; 170:1006-1013.
4. Harris MA, Sullivan CE. Sleep pattern and supplementary oxygen requirements in infants with chronic neonatal lung disease. *Lancet*. 1995 Apr 1;345(8953):831-2.

Quality assessment							# Patients	Effect ⁶	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other				
Weight gain (g/kg/day)										
1 ¹	Observational study	none	none	none	serious ²	none	14	15.9 g/kg/day versus 3.7 g/kg/day MD +12.2 g/kg/day (95% CI +7.22 to +17.18 g/kg/day)	⊕000 VERY LOW	CRITICAL
Development of pulmonary hypertension (measured as the mean pulmonary artery pressure in mmHg)										
2 ³	RCT	none	none	serious ⁴	serious ²	none	39	MD -10.03 mmHg (95% CI -16.41 to -3.64 mmHg)	⊕000 VERY LOW	CRITICAL
Severity of sleep-disordered breathing (measured as REM arousals)										
1 ⁵	RCT	none	none	serious ⁶	serious ²	none	7	Decreased; values not reported	⊕000 VERY LOW	CRITICAL
Sleep duration										

1 ⁵	RCT	none	none	serious ⁶	serious ²	none	7	Increased; values not reported	⊕○○○ VERY LOW	IMPORTANT
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- 1- Moyer-Mileur, et al.
- 2- The study(ies) was(were) small with few events.
- 3- Benatar, et al. and Mourani, et al.
- 4- PICO question is about home oxygen therapy, but study administered short-term oxygen.
- 5- Harris, et al.
- 6- PICO question is about home oxygen therapy, but study administered nocturnal oxygen.

TABLE E6: Sleep-disordered breathing

Bibliography

1. Marcus CL, Carroll JL, Bamford O, et al. oxygen during sleep in children with sleep-disordered breathing. Am J Respir Crit Care Med 1995; 152:1297–301.
2. Aljadeff G, Gozal D, Bailey-Wahl SL, et al. Effects of Overnight Oxygen in OSA in Children. Am J Respir Crit Care Med 1996; 153:51-5.

Quality assessment							# Patients	Effect ⁶	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other				
Severity of sleep-disordered breathing (measured as the apnea index)										
2 ¹	RCT + non-randomized trial	serious ²	none	serious ³	serious ⁴	none	39	MD -3 events/hour (95% CI -12.92 to +6.68 events/hour)	⊕000 VERY LOW	CRITICAL
Severity of sleep-disordered breathing (measured as the hypopnea index)										
1 ⁵	Non-randomized trial	serious ²	none	serious ³	serious ⁴	none	16	MD -3.8 events/hour (95% CI -19.32 to +11.72 events/hour)	⊕000 VERY LOW	CRITICAL
Severity of sleep-disordered breathing (measured as the mean SpO2)										
1 ⁵	Non-randomized trial	serious ²	none	serious ³	serious ⁴	none	16	MD +8.2% (95% CI +5.58 to +10.82%)	⊕000 VERY LOW	CRITICAL
Severity of sleep-disordered breathing (measured as the nadir SpO2)										
1 ⁵	Non-randomized trial	serious ²	none	serious ³	serious ⁴	none	16	MD +20.7% (95% CI +11.29 to +30.11%)	⊕000 VERY LOW	IMPORTANT
Severity of sleep-disordered breathing (measured as the mean SpO2 during REM sleep)										

1 ⁶	RCT	serious ²	none	serious ³	serious ⁴	none	23	MD +4% (95% CI -0.16 to +8.16%)	⊕○○○ VERY LOW	IMPORTANT
Severity of sleep-disordered breathing (measured as the mean SpO2 during NREM sleep)										
1 ⁶	RCT	serious ²	none	serious ³	serious ⁴	none	23	MD +3% (95% CI -0.39 to +6.39%)	⊕○○○ VERY LOW	IMPORTANT
Severity of sleep-disordered breathing (measured as the nadir SpO2 during REM sleep)										
1 ⁶	RCT	serious ²	none	serious ³	serious ⁴	none	23	MD +9% (95% CI +1.57 to +16.43%)	⊕○○○ VERY LOW	IMPORTANT
Severity of sleep-disordered breathing (measured as the nadir SpO2 during NREM sleep)										
1 ⁶	RCT	serious ²	none	serious ³	serious ⁴	none	23	MD +4% (95% CI -0.47 to +8.47%)	⊕○○○ VERY LOW	IMPORTANT

1- Marcus, et al. and Aljadeff, et al.

2- Unblinded and patients were not consecutive.

3- PICO question is about home oxygen therapy, but study administered short-term oxygen (x 1 night only).

4- The study(ies) was(were) small with few events.

5- Aljadeff, et al.

6- Marcus, et al.