Alternatives to surgery in children with mild OSA

David Gozal a,*, Mahmoud Ismail b, Pablo E. Brockmann c,d

a Department of Child Health and Child Health Research Institute, and MU Women and Children’s Hospital, University of Missouri School of Medicine, Columbia, MO, USA
b Department of Neurology and Sleep Medicine, University of Missouri School of Medicine, Columbia, MO, USA
c Department of Pediatric Cardiology and Pulmonology, Division of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile
d Pediatric Sleep Center, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

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Abstract    Precision medicine requires coordinated and integrated evidence-based combinatorial approaches so that diagnosis and treatment can be tailored to the individual patient. In this context, the treatment approach to mild obstructive sleep apnea (OSA) is fraught with substantial debate as to what is mild OSA, and as to what constitutes appropriate treatment. As such, it is necessary to first establish a proposed consensus of what criteria need to be employed to reach the diagnosis of mild OSA, and then examine the circumstances under which treatment is indicated, and if so, whether and when anti-inflammatory therapy (AIT), rapid maxillary expansion (RME), and/or myofunctional therapy (MFT) may be indicated.

KEYWORDS
Obstructive sleep apnea; Children; Antiinflammatory; Myofunctional therapy; Rapid maxillary expansion; Adenotonsillectomy

* Corresponding author. Department of Child Health, 400 N Keene Street, Ste 010, Columbia, MO 65201, USA.
E-mail address: gozald@health.missouri.edu (D. Gozal).
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What constitutes mild obstructive sleep apnea (OSA)?

In the last decade, both the parents of our patients and, of course, medical practitioners have come to expect that a personalized and precise approach to their child’s sleep problems is needed. We have further identified that such precision requires much better definition of the spectrum of disease with accurate decision trees that enable reliable categorization in “severity cells” that carry specifically tailored and optimized interventions. For example, emerging data in adults have recently shown that sleep duration, sleep quality, sleep continuity, and sleep regularity are all fundamentally important determinants of end-organ morbidities associated with sleep disorders. In otherwise healthy children, the presence of irregular sleep schedules has also been associated with obesity risk, and as a corollary with cardiovascular and metabolic risk.

In the context of OSA, clinical history and physical examination, the pillars of medical practice for centuries are notoriously inaccurate in predicting who among symptomatic patients actually suffers from OSA when compared to an overnight sleep study (PSG) as the diagnostic tool. Consequently, symptom-based assessments are poor discriminators of those children who despite typical symptoms of OSA will display evidence of a “normal” PSG based on current consensus criteria. Not so long ago, many of our clinical colleagues endorsed an approach that stipulated that every child who is symptomatic, e.g., habitually snores during sleep, should undergo adenotonsillectomy (AT), without requiring any diagnostic test such as a PSG. Since then, professional associations such as the American Academy of Pediatrics, American Academy of Sleep Medicine, American Academy of Otolaryngology-Head and Neck Surgery Foundation, European Respiratory Society, have further suggested that in the presence of characteristic OSA symptoms and some supportive physical findings, implementation of simplified testing procedures could replace the gold standard PSG in the form of home-based multichannel respiratory recordings or even single channel overnight oximetry. We have been among the latter, particularly based on the concern of limited access to PSG testing for children along with excessive financial costs. Development of such validated scalable diagnostic tools that can be automated would substantially reduce financial burden as well as time consuming labor involved in scoring and interpretation of polysomnograms. Such approaches if adopted more universally, would result not only in expedited evaluation of many children who currently are required to wait for long periods of time before being diagnosed, but would also facilitate access to pediatric sleep laboratories for those children in whom the diagnosis is uncertain, or the clinical presentation is more complex and requires more sophisticated diagnostic approaches.

For the sake of an example, please consider the scenario in which a 3-year-old otherwise healthy girl is referred to the sleep clinic by her primary care physician because of seasonal allergic rhinitis, occasional sinus infections and otitis media, habitual snoring, frequent nightmares and occasional night terrors, difficulty to wake up in the morning, and falling asleep in the car or in daycare while also displaying inattentive and disruptive behaviors in class. Let’s now assume multiple options: (a) PSG shows an obstructive apnea-hypopnea index (AHI) of 8 events/hour of sleep, in which case AT is clearly the unanimous consensus for treatment; (b) PSG shows an AHI > 2 but <5 events/hour or (c) PSG shows an AHI <1 events/hour. Indeed, if the apnea-hypopnea index (AHI) of this child is less than 1/hour TST, we will tell the parents that the PSG is normal, and this will be the end of the consultation, while if option (b) is the one, some may recommend AT, while others will recommend non-surgical treatment approaches. However, option (c) reflects a consultation prompted by the underlying symptoms, and even though the sleep study is normal does not necessarily mean that this child is fine and does not suffer from sleep disordered breathing.

What cut-off values of PSG-derived measures (i.e. AHI, ODI events/hour, respiratory arousal index, end-tidal CO2) should we then subscribe to as a reliable method demarcating normal from pathological? How would the use of statistical classifiers be helpful in this setting? For example, would 2, 3, or even 5 standard deviations beyond the mean of the sleep measure of interest that was obtained by evaluating a representative cohort of healthy community children spanning the whole pediatric age range be the accurate way of determining whether the individual patient’s result is pathological and requires treatment? Or more importantly, how do we measure the degree of “pathological” or even more critically provide an accurate prediction of the risk of morbidity? And if such measures were available, how would such classifiers affect the clinical decision tree? How many symptomatic children would be designated as “normal”, and of these how many would be really true (test specificity) or false negatives?

So, as we consider the topic of this review, we need to clarify first how we reach that decision to treat or not to treat. The now well-established poor correlation between phenotype and OSA severity based on PSG measures generates a high level of uncertainty in everything we decide to recommend, and as such the reader is alerted already here of this uncertainty and may seek to establish his/her own approach and conclusions.

A large body of work in the last 4 decades has somewhat conclusively established that two of the major consequences of upper airway obstructive events during sleep, namely repeated arousals (i.e. sleep fragmentation) and intermittent hypoxia are possible determinants of a complex cascade of pathophysiological processes that ultimately increase the risk of adverse neurocognitive, behavioral and cardiovascular consequences in children. Considering the importance of such systems in overall wellness and one’s future social and financial success, and health-related longevity, treatment of OSA should be viewed as rather urgent in children, particularly when daytime symptoms such as hyperactivity, inattention, somnolence, or poor school performance are detected by either parents or school teachers. AT has emerged as the most common treatment for OSA, yet is not only painful but also has the potential of complications, such as bleeding, post-surgical apnea, and oxyhemoglobin desaturations, as well as adverse intra-operative anesthetic events. Furthermore, after adenotonsillectomy, 20%-50% of the operated children may still have some degree of residual OSA, as dictated by the PSG.
criteria used to define residual OSA.40,41 Thus, the search for a test or group of tests that can accurately and reliably measure the morbidity of sleep-disordered breathing in a given child is ongoing.

Non-surgical anti-inflammatory therapy for "mild OSA"

Considering that inflammation as well as increased collapsibility are consistently present in adenotonsillar tissues and upper airway tissues in children with OSA,42–44 treatment with either systemic or topical anti-inflammatory agents may reverse these processes and resolve the underlying OSA. Indeed, several studies have emerged in the last 15 years supporting nonsurgical anti-inflammatory treatment approaches in children with OSA.

Mechanisms of action for anti-inflammatory agents

We need to consider that the location and cellular composition of the upper airway is in contiguity with the lower airways, and that substantial commonalities exist between these two artificially divided compartments. Similar to bronchial asthma or allergic rhinitis, anti-inflammatory medications such as nasal corticosteroids and leukotriene receptor antagonists reduce or block the activation or migration of innate inflammatory cells and corresponding molecular cascades into the airway, and mitigate the magnitude of the inflammatory processes in the airway. As is readily apparent, the local inflammation in the upper airway is the end-result of a complex interaction of networks involving production of a multitude of cytokines, chemotactic mediators, and adhesion molecules and upstream signaling pathways.45 Accordingly, application of anti-inflammatory agents aims to reduce the lifespan of inflammatory cells, including eosinophils, neutrophils, T and B-cell lymphocytes, and mast cells. Corticosteroids are particularly effective at such tasks via their binding to corticosteroid receptor antagonists and their translocation to the nucleus where they operate via transcriptional, epigenetic, and post-translational regulatory processes. We should also point out, that the expression of cysteinyl-leukotriene receptors is markedly enhanced in the tonsillar and adenoid tissues of children with OSA, and are predominantly located in T-cell lymphocytes (both CD4+ helper T cells and even more so in CD8+ cytotoxic T cell lymphocytes). In vitro studies from our laboratory using mixed cell cultures of either adenoids or tonsils showed that addition of leukotriene D4 to the media resulted in increased cellular proliferation and release of pro-inflammatory cytokines.46,47 When such cultures were treated with leukotriene receptor antagonists or with corticosteroids, dose-dependent reductions in proliferation and cytokine release occurred.46–49

Intranasal corticosteroids

The initial study aiming to examine the potential use of systemic corticosteroids in OSA in children was conducted over a period of 5 days and resulted in no significant changes in the severity of OSA.50 In 2001, the same group led by Brouillette conducted the first randomized, triple-blind controlled trial investigating the use of nasal fluticasone over a period of 6 weeks in children with OSA who were waiting for AT. Significant reduction of the AHI occurred in the fluticasone group (from 10.7/h to 5.8/h), while the AHI modestly increased from 11.0/h to 13.1/h in the placebo-treated group.51

In an ulterior randomized double blind crossover study involving a larger cohort, intranasal budesonide for 6 weeks in PSG diagnosed children with mild OSA (defined as AHI < 5 events/hour sleep) resulted in significant reductions in AHI and lateral X-rays of the upper airway showed that the size of the adenoids had also declined. Importantly, no evidence of rebound adenoid growth or AHI surges occurred within the first 8 weeks after discontinuation of the treatment.52 Criscuoli et al53 reported that significant clinical improvement was detectable after 2 weeks of nasal corticosteroid therapy in a cohort of 53 children. However, even though the improvements were long-lasting among responders, only 45% actually showed improved nasal obstruction and respiratory patterns during sleep. A large number of studies have been published on intranasal corticosteroids, but the majority did not assess the children using PSG (Table 1) such that the current evidence, albeit favorable to the use of these compounds for periods between 2 and 12 weeks, is still limited.54

Montelukast

After the initial study by Goldbart et al55 in 2005, which showed improvements in AHI in children with mild OSA in an open label trial, two double-blind, placebo-controlled studies have been conducted and revealed that oral montelukast therapy for a period of 12–16 weeks improves nocturnal symptoms, reduces the size of adenotonsillar tissues, and significantly reduces PSG-derived measures in the context of mild OSA.56,57 However, the emergence of side effects related to montelukast, particularly in the neuropsychiatric realm, raises a red flag that should prompt caution when making the decision to use this compound over an extended period of time.58–61

Comparison of treatment efficacy: nasal corticosteroids versus montelukast

Studies comparing head-to-head intranasal corticosteroids and oral montelukast revealed rather similar improvements in children with OSA.52,63 Based on these results, both therapies seem to be of comparable efficacy.

Combination nasal corticosteroids and montelukast

The rationale for using both montelukast and nasal corticosteroids as a combined therapy emerged after the individual success of each medication for reducing OSA severity. It also provides the option to achieve an initial suppression of the inflammatory processes described above, and then, continued treatment with montelukast over a longer period should induce a long-term sustained effect. In a large retrospective study that included 752 children with mild OSA, Kheirandish-Gozal et al64 indicated that approximately
| Study                          | Design          | Patients number (age) | PSG       | Treatment | Dose                        | Duration | Control  |
|-------------------------------|-----------------|-----------------------|-----------|-----------|-----------------------------|----------|----------|
| Corticosteroids               |                 |                       |           |           |                             |          |          |
| Brouillette 2001              | RCT             | 25 (1–10 y)           | AHI > 1/h | Fluticasone | 50 μg c/12 h, 1 week; 50 μg/24 h, 5 weeks | 6 weeks  | Placebo  |
| Yilmaz 2003                   | RCT             | 28 (12–18 y)          | No PSG    | Mometasone | 200 μg                      | 6 weeks  | –        |
| Criscuoli 2003                | RCT             | 53 (3.8 ± 1.3 y)      | No PSG    | Beclomethasone | 400 μg                    | 2 weeks, 24 weeks | –       |
| Cengel 2006                   | RCT             | 122 (3–15 y)          | No PSG    | Mometasone | 100 μg                      | 6 weeks  | –        |
| Berlucchi 2007                | RCT             | 60 (3–7 y)            | No PSG    | Mometasone | 100 μg                      | 40 weeks | –        |
| Kheirandish-Gozal 2008        | RCT, crossover  | 62 (6–12 y)           | Mild OSA  | Budesonide | 32 μg × nostril             | 6 weeks, washout, 6 weeks | Placebo |
| Barghawa 2014                 | RCT             | 100 (2–12 y)          | No PSG    | Mometasone | 200 μg                      | 8 weeks  | –        |
| Barghawa 2014                 | RCT             | 60 (2–12 y)           | No PSG    | Mometasone | 200 μg                      | 8 weeks  | –        |
| Hassanzadel 2013              | RCT             | 40 (4–12 y)           | No PSG    | Mometasone | 400 μg                      | 4 weeks  | –        |
| Rehman 2013                   | RCT             | 112 (3–8 y)           | No PSG    | Mometasone | NR                         | 8 weeks  | –        |
| Montelukast                   |                 |                       |           |           |                             |          |          |
| Goldbart 2005                 | RCT             | 24 (2–10 y)           | AHI 1–8/h | Montelukast | 4/5 mg                     | 12 weeks | Placebo  |
| Kheirandish-Gozal 2016        | RCT             | 64 (2–14 y)           | PSG-Mild OSA (AHI < 7/h) | Montelukast | 4/5/10 mg                  | 16 weeks | Placebo  |
| Montelukast and corticosteroids|                 |                       |           | Montelukast and corticosteroids | variable |          |          |
| Kheirandish-Gozal 2014        | Retrospective   | 752 (2–14 y)          | PSG-Mild OSA (AHI < 5/h) | Montelukast and corticosteroids | Montelukast Both None | 12 weeks | –        |
| Tuhaniouglu 2017              | RCT             | 120 (4–10 y)          |           | Mometasone | 100 μg                      | 12 weeks | Corticosteroids |

RCT: randomized controlled trial; OSA: obstructive sleep apnea; PSG: polysomnography.
80% of the children has virtual resolution of their mild OSA after 1-year or longer follow-up (AHI dropped from 4.5 ± 2.0 to 1.4 ± 0.09 events/h, p < 0.001). Interestingly, in a recent systematic review on the efficacy of these anti-inflammatory approaches for pediatric OSA, oral montelukast alone (n = 166 patients) led to an average reduction on 56% in the AHl (6.2 ± 3.1 events/h vs 2.7 ± 2.7 events/h), while the combination of the two approaches in 502 children resulted in remarkably similar results to those reported by Kheirandish-Gozal et al (4.7 ± 2.1 events/h pre-treatment to 1.4 ± 1.0 events/h post-treatment, with a mean difference of −4.2 events/h; p < 0.001).

Orofacial myofunctional exercise

Orofacial myofunctional exercises are designed to achieve improved function and balance of the orofacial muscles, particularly revolving around swallowing, breathing, speaking, and chewing. The sustained rehabilitation efforts usually consist of isometric and isotonic exercises involving all the oropharyngeal cavity, and aim to promote proprioception, range of motion, coordination, and strength of the orofacial structures.66

The intention to reduce the use of adenotonsillectomy (AT) as the immediate approach to pediatric OSA has led to initial exploration of myofunctional therapy as a non-surgical approach in selected children. The first issue that needs to be emphasized is that a great level of commitment, cooperation and adherence by the child and the family is required. Poor adherence signifies failure of the intervention, and adherence to MT cannot yet be tracked at this stage, such that more objective methods of delineating adherence will need to be developed in parallel with novel intervention strategies. In a study of 54 children (mean age 7.1 ± 2.5 years, 29 males) with OSA, MT led to improvements in mean oxygen saturation and in the oxygen desaturation index 3% (5.9 ± 2.3 vs 3.6 ± 1.8, p = 0.001) only in the children assigned to the treatment group compared to the no intervention group.67 Other open studies in which mouth breathing and altered tongue position at rest and during sleep are identified in children with OSA and are more often associated with dento-skeletal malocclusions, have led to implementation of MT. In most of these studies, improvement in tongue function within 2 months of oropharyngeal exercises was accompanied by better oximetry parameters during sleep among those children who followed the recommendations of oropharyngeal exercises, with an aim to eliminate mouth breathing and recover nasal breathing.68-70

In a recent study, the short-term therapeutic effect of passive myofunctional therapy using an oral appliance that advances the mandible during sleep was evaluated in children with OSA.71 Patients were instructed to wear their appliances and use their tongue to roll the bead inside the appliance (i.e. passive myofunctional therapy) during sleep every night. Improvements in AHl were noted after 6 months. In a similar study, we implemented an intraoral appliance that provided not only mandibular advancement but also imposed tongue repositioning passive exercises in 24 children with OSA and compared to 16 children who were left untreated over a period of 6 months (corresponding to the wait time before undergoing AT).72 Significant improvements in sleep related symptoms and improvements in the pharyngeal minimum cross-section area and volume occurred only among those who received the appliance.

Rapid maxillary expansion

Enlarging the intraoral and upper airway space will minimize airflow resistance and foster upper airway patency. Therefore, many different approaches have been developed aiming to achieve rapid maxillary expansion (RME). RME usually involves the placement of a fixed appliance with an expansion screw anchored to opposing teeth. This screw serves to expand the appliance gradually and to open the mid-palatal suture. Such expansion will therefore gradually increase the transverse diameter of the hard palate over the course of several months. It remains unclear whether RME alone is sufficient for treatment of mild OSA if significant adenotonsillar hypertrophy is present. In addition, only small uncontrolled studies with a relatively short follow-up period are currently available.73,74 Overall, it would appear that RME may have a role in carefully selected young patients, more specifically in those suffering from obvious malocclusion (high, narrow palate associated with deep bite, retractive bite or crossbite) and OSA.75,76 Further studies are clearly needed to evaluate more critically how to proceed with the optimal selection of patients with mild OSA who may benefit from RME, to define the optimal ages for RME intervention, and to establish the anticipated criteria for success.

The "do nothing" option

In the initial multicenter trial assessing the outcomes of AT for pediatric OSA (CHAT study),77,78 the control group was assigned to watchful waiting for 7 months. Among these children, the majority of which had mild OSA, a significant proportion exhibited normalization of their respiratory disturbances during sleep.79 Similar findings have been recently reported by another group of investigators.80

Conclusions

Nasal corticosteroids and oral montelukast have now been incorporated into the armamentarium of the treatment of mild OSA and have emerged as the preferred options when AT is not the preponderant and definitive equipoise selection. However, identifying those children who are more likely to benefit from such non-surgical treatments, and deciding what PSG criteria or other criteria are needed to reach such decision in an evidence-based manner, remain issues of contention. Since obesity and older age are apparent risk factors associated with increased failure rate of medical treatment, should we opt for alternative approaches in such cases? The duration of treatment is also not standardized and will undoubtedly require more evidence. In summary, there is no doubt that the symptomatic child referred for evaluation of snoring merits a well-structured and evidence-based treatment plan that is based on both the pathophysiological determinants of the
upper airway collapsibility and of treatments that optimize the risk benefit ratios of such selection. Much remains to be done, but hopefully we are on the correct trajectory to achieve such goals.

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Declaration of competing interest

None.

References

1. Zuraikat FM, Makarem N, Redline S, Aggarwal B, Jelic S, St-Onge MP. Sleep regularity and cardiometabolic health: is variability in sleep patterns a risk factor for excess adiposity and glycemic dysregulation. Curr Diab Rep. 2020;20:38.
2. Huang T, Mariani S, Redline S. Sleep irregularity and risk of cardiovascular events: the multi-ethnic study of atherosclerosis. J Am Coll Cardiol. 2020;75:991–999.
3. Lunsford-Avery JR, Damke K, Engelhard MM, Kollins SH, Mittal VA. Sleep/Wake regularity associated with default mode network structure among healthy adolescents and young adults. Sci Rep. 2020;10:509.
4. Fischer D, McHill AW, Sano A, et al. Irregular sleep and event schedules are associated with poorer self-reported well-being in US college students. Sleep. 2020;43(6):zs3200.
5. Spruyt K, Molfese DL, Gozal D. Sleep duration, sleep regularity, body weight, and metabolic homeostasis in school-aged children. Pediatrics. 2011;127:e345–e352.
6. Wu CR, Tu YK, Chuang LP, et al. Diagnostic meta-analysis of the Pediatric Sleep Questionnaire, OSA-18, and pulse oximetry in detecting pediatric obstructive sleep apnea syndrome. Sleep Med Rev. 2020;54:101355.
7. Corbelli R, Michelet M, Barazzone-Arigoffo C. Respiratory polygraphy data of children investigated for sleep-disordered breathing with different congenital or respiratory diseases. Data Brief. 2020;31:105859.
8. Ehsan Z, He S, Huang G, Hossain MM, Simakajornboon N. Can overnight portable pulse oximetry be used to stratify obstructive sleep apnea risk in infants? A correlation analysis. Pediatr Pulmonol. 2020;55:2082–2088.
9. Trucco F, Rosenthal M, Bush A, Tan HL. The McGill score as a screening test for obstructive sleep disordered breathing in children with co-morbidities. Sleep Med. 2020;68:173–176.
10. Michelet M, Blanchon S, Guinand S, et al. Successful home respiratory polygraphy to investigate sleep-disordered breathing in children. Sleep Med. 2020;68:146–152.
11. Liu CC, Chaput KH, Kirk V, Yunker W. Overnight oximetry in children undergoing adenotonsillectomy: a single center experience. J Otalaryngol Head Neck Surg. 2019;48:69.
12. Garde A, Hoppenbrouwer X, Dekhordi P, et al. Pediatric pulse oximetry-based OSA screening at different thresholds of the apnea-hypopnea index with an expression of uncertainty for inconclusive classifications. Sleep Med. 2019;60:45–52.
13. Jonas C, Thavagnanam S, Blecher G, Thambipillay G, Teng AY. Comparison of nocturnal pulse oximetry with polysomnography in children with sleep disordered breathing. Sleep Breath. 2020;24:703–707.
14. Scalzitti N, Hansen S, Maturo S, Lospinoso J, O’Connor P. Comparison of home sleep apnea testing versus laboratory polysomnography for the diagnosis of obstructive sleep apnea in children. Int J Pediatr Otorhinolaryngol. 2017;100:44–51.
15. Homero R, Kheirandish-Gozal L, Gutiérrez-Tobal GC, et al. Nocturnal oximetry-based evaluation of habitually snoring children. Am J Respir Crit Care Med. 2017;196:1591–1598.
16. Álvarez D, Alonso-Álvarez ML, Gutiérrez-Tobal GC, et al. Automated screening of children with obstructive sleep apnea using nocturnal oximetry: an alternative to respiratory polygraphy in unattended settings. J Clin Sleep Med. 2017;13:693–702.
17. Pavone M, Ullmann N, Verrillo E, De Vincentis G, Sitzia E, Cutrer A. At-home pulse oximetry in children undergoing adenotonsillectomy for obstructive sleep apnea. Eur J Pediatr. 2017;176:493–499.
18. Brockman PE, Perez JL, Maya A. Feasibility of unattended home polysomnography in children with sleep-disordered breathing. Int J Pediatr Otorhinolaryngol. 2013;77:1960–1964.
19. Kaditis A, Kheirandish-Gozal L, Gozal D. Algorithm for the diagnosis and treatment of pediatric OSA: a proposal of two pediatric sleep centers. Sleep Med. 2012;13:217–227.
20. Mason DG, Iyer K, Terrill PI, Wilson SJ, Suresh S. Pediatric obstructive sleep apnea assessment using pulse oximetry and dual RIP bands. Annu Int Conf IEEE Eng Med Biol Soc. 2010;2010:6154–6157.
21. Nixon GM, Kermack AS, Davis GM, Manoukian JJ, Brown KA, Brouillette RT. Planning adenotonsillectomy in children with obstructive sleep apnea: the role of overnight oximetry. Pediatrics. 2004;113:e19–e25.
22. Kirk VG, Bohn SG, Flemons WW, Remmers JE. Comparison of home oximetry monitoring with laboratory polysomnography in children. Chest. 2003;124:1702–1708.
23. Brouillette RT, Marielli A, Leimanis A, Waters KA, Luciano R, Ducharme FM. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. Pediatrics. 2000;105:405–412.
24. Vaquerizo-Vilar F, Alvarez D, Kheirandish-Gozal L, et al. Convolutional neural networks to detect pediatric apnea-hypopnea events from oximetry. Annu Int Conf IEEE Eng Med Biol Soc. 2019;2019:3555–3558.
25. Barroso-Garcia V, Gutiérrez-Tobal GC, Kheirandish-Gozal L, et al. Usefulness of spectral analysis of respiratory rate variability to help in pediatric sleep apnea-hypopnea syndrome diagnosis. Annu Int Conf IEEE Eng Med Biol Soc. 2019;2019:4580–4583.
26. Xu Z, Gutiérrez-Tobal GC, Wu Y, et al. Cloud algorithm-driven oximetry-based diagnosis of obstructive sleep apnea in symptomatic habitually snoring children. Eur Respir J. 2019;53(2):1801788.
27. Vaquerizo-Vilar F, Álvarez D, Kheirandish-Gozal L, et al. Wavelet analysis of oximetry recordings to assist in the automated detection of moderate-to-severe pediatric sleep apnea-hypopnea syndrome. PLoS One. 2018;13, e0208502.
28. Vaquerizo-Vilar F, Álvarez D, Kheirandish-Gozal L, et al. Improving the diagnostic ability of oximetry recordings in pediatric sleep apnea-hypopnea syndrome by means of multi-class adaboost. Annu Int Conf IEEE Eng Med Biol Soc. 2018;2018:167–170.
29. Gutiérrez-Tobal GC, Kheirandish-Gozal L, Vaquerizo-Vilar F, et al. Bispectral analysis to enhance oximetry as a simplified alternative for pediatric sleep apnea diagnosis. Annu Int Conf IEEE Eng Med Biol Soc. 2018;2018:175–178.
30. Vaquerizo-Vilar F, Álvarez D, Kheirandish-Gozal L, et al. Detrended fluctuation analysis of the oximetry signal to assist
in paediatric sleep apnoea-hypopnoea syndrome diagnosis. *Physiol Meas.* 2018;39:114006.

31. Crespo A, Álvarez D, Kheirandish-Gozal L, et al. Assessment of oximetry-based statistical classifiers as simplified screening tools in the management of childhood obstructive sleep apnea. *Sleep Breath.* 2018;22:1063–1073.

32. Vaquerizo-Villar F, Álvarez D, Kheirandish-Gozal L, et al. Utility of bispectrum in the screening of pediatric sleep apnea-hypopnea syndrome using oximetry recordings. *Comput Methods Programs Biomed.* 2018;156:141–149.

33. Brockmann PE, Alonso-Álvarez ML, Gozal D. Diagnosing Sleep apnea-hypopnea syndrome in children: past, present, and future. *Arch Bronconeumol.* 2018;54:303–305.

34. Álvarez D, Kheirandish-Gozal L, Gutierrez-Tobal GC, et al. Automated analysis of nocturnal oximetry as screening tool for childhood obstructive sleep apnea-hypopnea syndrome. *Annu Int Conf IEEE Eng Med Biol Soc.* 2015;2015:2800–2803.

35. Capdevila OS, Kheirandish-Gozal L, Dayyat E, Gozal D. Pediatriic obstructive sleep apnea: complications, management, and long-term outcomes. *Proc Am Thorac Soc.* 2008;5:274–282.

36. Gozal D, Brockmann PE, Alonso-Álvarez ML. Morbidity of pediatric obstructive sleep apnea in children: myth, reality, or hidden iceberg. *Arch Bronconeumol.* 2018;54:253–254.

37. Gozal D, Kheirandish-Gozal L. The multiple challenges of obstructive sleep apnea in children: morbidity and treatment. *Curr Opin Pediatr.* 2008;20:654–658.

38. Smith DL, Gozal D, Hunter SJ, Kheirandish-Gozal L. Frequency of snoring, rather than apnea-hypopnea index, predicts both cognitive and behavioral problems in young children. *Sleep Med.* 2017;34:170–178.

39. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2012;130:e714–e755.

40. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am J Respir Crit Care Med.* 2010;182:676–683.

41. Tan HL, Kheirandish-Gozal L, Gozal D. Obstructive sleep apnea in children: update on the recognition, treatment and management of persistent disease. *Expert Rev Respir Med.* 2016;10:431–439.

42. Gozal D, Kheirandish L. Oxidant stress and inflammation in the snoring child: confluent pathways to upper airway pathogenesis and end-organ morbidity. *Sleep Med Rev.* 2006;10:83–96.

43. Goldbart AD, Krishna J, Li RC, Serpero LD, Gozal D. Inflammatory mediators in exhaled breath condensate of children with obstructive sleep apnea syndrome. *Chest.* 2006;130:143–148.

44. Gozal D, Burnside MM. Increased upper airway collapsibility in children with obstructive sleep apnea during wakefulness. *Am J Respir Crit Care Med.* 2004;169:163–167.

45. Khalyfa A, Gharib SA, Kim J, et al. Transcriptive analysis identifies phosphatases as novel targets for adenotonsillar hypertrophy of pediatric obstructive sleep apnea. *Am J Respir Crit Care Med.* 2010;181:1114–1120.

46. Kim J, Bhattacharjee R, Dayyat E, et al. Increased cellular proliferation and inflammatory cytokines in tonsils derived from children with obstructive sleep apnea. *Pediatr Res.* 2009;66:423–428.

47. Dayyat E, Serpero LD, Kheirandish-Gozal L, et al. Leukotriene pathways and in vitro adenotonsillar cell proliferation in children with obstructive sleep apnea. *Chest.* 2009;135:1142–1149.

48. Kheirandish-Gozal L, Kim J, Goldbart AD, Gozal D. Novel pharmacological approaches for treatment of obstructive sleep apnea in children. *Expert Opin Investig Drugs.* 2013;22:71–85.

49. Kheirandish-Gozal L, Serpero LD, Dayyat E, et al. Corticosteroids suppress in vitro tonsillar proliferation in children with obstructive sleep apnea. *Eur Respir J.* 2009;33:1077–1084.

50. Al-Ghamdi SA, Manoukian JJ, Morielli A, Oudjhane K, Ducharme FM, Brouillette RT. Do systemic corticosteroids effectively treat obstructive sleep apnea secondary to adenotonsillar hypertrophy. *Laryngoscope.* 1997;107:1382–1387.

51. Brouillette RT, Manoukian JJ, Ducharme FM, et al. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. *J Pediatr.* 2001;138:838–844.

52. Kheirandish-Gozal L, Gozal D. Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome. *Pediatrics.* 2008;122:e149–e155.

53. Criscuoli G, Amora SD’, et al. Frequency of surgery among children who have adenotonsillar hypertrophy and improve after treatment with nasal beclomethasone. *Pediatrics.* 2003;111:e236–e238.

54. Khalya S, Hoffmann DU, Mitra S, Urszutz MS. Anti-inflammatory medications for obstructive sleep apnoea in children. *Cochrane Database Syst Rev.* 2020;1:CD007074.

55. Goldbart AD, Goldman JL, Veling MC, Gozal D. Leukotriene modifier therapy for mild sleep-disordered breathing in children. *Am J Respir Crit Care Med.* 2005;172:364–370.

56. Goldbart AD, Greenberg-Dotan S, Tal A. Montelukast for children with obstructive sleep apnea: a double-blind, placebo-controlled study. *Pediatrics.* 2012;130:e575–e580.

57. Kheirandish-Gozal L, Bandla HP, Gozal D. Montelukast for children with obstructive sleep apnea: results of a double-blind, randomized, placebo-controlled trial. *Ann Am Thorac Soc.* 2016;13:1736–1741.

58. Kovesi T. Neuropsychiatric side effects of montelukast. *J Pediatr.* 2019;212:248.

59. Glocker-Lauf SD, Finkelstein Y, Zhu J, Feldman LY, To T. Montelukast and neuropsychiatric events in children with asthma: a nested case-control study. *J Pediatr.* 2019;209;176–182.e4.

60. Calapai G, Casciaro M, Miroddi M, Calapai F, Navarra M, Gangemi S. Montelukast-induced adverse drug reactions: a review of case reports in the literature. *Pharmacology.* 2014;94:60–70.

61. Ernst P, Ernst G. Neuropsychiatric adverse effects of montelukast in children. *Eur Respir J.* 2017;50:1701020.

62. Yang DZ, Liang J, Zhang F, Yao HB, Shu Y. Clinical effect of montelukast sodium combined with inhaled corticosteroids in children with obstructive sleep apnea: a systematic review and meta-analysis. *Chest.* 2006;130:602.

63. Bluher AE, Brawley CC, Cunningham TD, Baldassari CM. Impact of montelukast and fluticasone on quality of life in mild pediatric sleep apnea. *Int J Pediatr Otolarlaryngol.* 2019;125:66–70.

64. Kheirandish-Gozal L, Bhattacharjee R, Bandla H, Gozal D. Antinflammatory therapy outcomes for mild OSA in children. *Chest.* 2014;146:88–95.

65. Liming BJ, Ryan M, Mack D, Ahmad I, Camacho M. Montelukast and nasal corticosteroids to treat pediatric obstructive sleep apnea: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg.* 2019;160:594–602.

66. de Felico CM, Folha GA, Ferreira CL, Medeiros AP. Expanded protocol of orofacial myofunctional evaluation with scores: validity and reliability. *Int J Pediatr Otolarlaryngol.* 2010;74:1230–1239.

67. Villa MP, Evangelisti M, Martella S, Barreto M, Del Pozzo M. Can myofunctional therapy increase tongue tone and reduce symptoms in children with sleep-disordered breathing. *Sleep Breath.* 2017;21:1025–1032.

68. de Felico CM, da Silva Dias FV, Folha GA, et al. Orofacial motor functions in pediatric obstructive sleep apnea and implications
for myofunctional therapy. *Int J Pediatr Otorhinolaryngol.* 2016;90:5–11.

69. Cheng SY, Kwong S, Pang WM, Wan LY. Effects of an oral-pharyngeal motor training programme on children with obstructive sleep apnea syndrome in Hong Kong: a Retrospective Pilot Study. *Hong Kong J Occup Ther.* 2017;30:1–5.

70. Van Dyck C, Dekeyser A, Vantricht E, et al. The effect of orofacial myofunctional treatment in children with anterior open bite and tongue dysfunction: a pilot study. *Eur J Orthod.* 2016;38:227–234.

71. Chuang LC, Lian YC, Hervy-Auboiron M, Guilleminault C, Huang YS. Passive myofunctional therapy applied on children with obstructive sleep apnea: a 6-month follow-up. *J Formos Med Assoc.* 2017;116:536–541.

72. Ribeiro Nunes Jr W, Gozial D, di Francesco RC. Cephalometric and pharyngometric evaluation in snoring children with sleep-disordered breathing and adenotonsillar hypertrophy under an orthodontic or orthopedic treatment. *J Child Sci.* 2019;9:e68–e74.

73. Junior MAJ, Crespo AN, Pauna HF. Rapid maxillary expansion in pediatric patients with obstructive sleep apnea: current and future perspectives. *Sleep Med.* 2018;51:7–8.

74. Camacho M, Chang ET, Song SA, et al. Rapid maxillary expansion for pediatric obstructive sleep apnea: a systematic review and meta-analysis. *Laryngoscope.* 2017;127:1712–1719.

75. Villa MP, Rizzoli A, Miano S, Malagola C. Efficacy of rapid maxillary expansion in children with obstructive sleep apnea syndrome: 36 months of follow-up. *Sleep Breath.* 2011;15:179–184.

76. Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion in children with obstructive sleep apnea syndrome. *Sleep.* 2004;27:761–766.

77. Marcus CL, Moore RH, Rosen CL, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med.* 2013;368:2366–2376.

78. Redline S, Amin R, Beebe D, et al. The Childhood Adenotonsillectomy Trial (CHAT): rationale, design, and challenges of a randomized controlled trial evaluating a standard surgical procedure in a pediatric population. *Sleep.* 2011;34:1509–1517.

79. Chervin RD, Ellenberg SS, Hou X, et al. Prognosis for spontaneous resolution of OSA in children. *Chest.* 2015;148:1204–1213.

80. Fehrm J, Nerfeldt P, Browaldh N, Friberg D. Effectiveness of adenotonsillectomy vs watchful waiting in young children with mild to moderate obstructive sleep apnea: a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg.* 2020;146:647–654.