Review

Treatment of obstructive sleep apnea in children

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Practice Points

- Over the last decade, the incidence of pediatric adenotonsillectomy (AT) has almost doubled due to the increased recognition of the morbidities associated with obstructive sleep apnea (OSA); AT remains the leading treatment for OSA in children.

- AT significantly improves the severity of OSA in children with adenotonsillar hypertrophy, but there are still significant numbers of children with residual OSA post-AT, especially in obese children.

- AT in children with OSA results in significant improvements in sleep quality, quality of life, psychological health and important risk factors for cardiovascular disease such as elevated blood pressure, increased blood pressure variability, dampened blood pressure and heart rate control, and a reduction in inflammatory markers.

- Continuous positive airway pressure is an efficacious treatment for some children with OSA, commonly those who are obese, have craniofacial abnormalities or neuromuscular disorders. Optimizing adherence in the early period of treatment has long-term benefits on levels of use, which in turn impacts on the extent of improvements in other aspects of functioning.

- There is evidence supporting the use of nasal corticosteroid spray and leukotriene modifiers in children, especially those with mild OSA and those with persistent disease after AT.

- The treatment of children with OSA using rapid maxillary expansion or mandibular advancement splints requires careful clinical assessment, including that of the dentition, and a multidisciplinary approach is likely to lead to the best outcomes.

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SUMMARY   Obstructive sleep apnea (OSA) is a common condition in children and is characterized by repeated episodes of hypoxia, hypercapnia and/or sleep disruption. In children, OSA is usually due to adenotonsillar hypertrophy and the most common treatment is adenotonsillectomy (AT). AT is a highly effective treatment in most cases, but a significant subset of children have residual OSA following AT, especially children who are obese. This review discusses the treatment options for children with OSA, including AT, continuous positive airway pressure therapy, topical corticosteroids, leukotriene receptor antagonists, and dental/orthodontic treatments. AT is the first-line therapy for most children and is likely to remain so, but continuing research into alternatives to surgery is important into the future.

The term 'sleep-disordered breathing' describes abnormal patterns of breathing that are present during sleep, encompassing obstructive sleep apnea (OSA), disorders of respiratory drive and respiratory insufficiency during sleep related to comorbid conditions, such as neuromuscular disease. OSA is a common condition in children of all ages, from infants to adolescents. It is usually associated with relative enlargement of the tonsils and adenoids, but can also be due to functional and anatomic abnormalities of the upper airway, such as craniofacial dysostosis. In this review, we will focus exclusively on the treatment of snoring and OSA in otherwise healthy children, with the exception of discussing the treatment of OSA in children with obesity. Of note, there are no randomized controlled trials to date that have compared treatment with watchful waiting, so the studies in this review are observational studies looking at data before and after intervention and not comparing intervention with nonintervention.

Estimates of children who habitually snore (i.e., snore more than 3 nights/week) range from 1.5 to 35%, depending upon the methodology used and the age range studied [1,2]. Between 1.2 and 5.7% of children have OSA [3]. The cardinal symptom of OSA is habitual snoring, which may occur in isolation, without disturbances of sleep or gas exchange, this is usually termed primary snoring. OSA is defined by repeated episodes of upper airway obstruction during sleep associated with desaturation and/or arousal from sleep. The adverse cardiovascular outcomes [4] and neurocognitive and neurobehavioral impairments [5] that have been associated with OSA are thought to be mediated, at least in part, by the repeated arousals from sleep and hypoxic episodes that are characteristic of OSA. However, many studies have now shown measurable cognitive deficits [6], behavioral problems [7] and cardiovascular

changes, such as elevated blood pressure [8,9], even in children with primary snoring.

Pathophysiology of OSA in children

Obstructive events during sleep, where the upper airway either partially or totally collapses, occurs through a complex interaction between sleep state, the mechanics of pressure and flow within the airway, and respiratory drive [10]. The most common etiology of OSA in children is enlarged adenoids and tonsils; the prevalence of the condition peaks in the preschool years when the lymphoid tissue is largest in relation to the bony structure of the upper airway [11,12]. MRI studies have demonstrated reduced upper airway volume and larger tonsils, adenoids and soft palates in children with OSA than age-matched children who do not have OSA [13]. It has been suggested that the site of maximal upper airway obstruction is the retropalatal region where the lower pole of the adenoids and the upper pole of the tonsils overlap [14].

Cephalometric assessments have been carried out to assess the bony structures of the face and airway in children with OSA. These have consistently found relative retrognathia, a large posterior facial height, a narrow nasopharyngeal airway, an anterior tongue base position and a long soft palate to be associated with an increased incidence of OSA [15,16]. It is not known if the cephalometric changes seen are primary, contributing to the cause of obstruction, or secondary, arising because of airway obstruction for another reason, such as chronic nasal obstruction. The latter suggestion is supported by one study that showed improvements of cephalometric changes in children with OSA treated with adenotonsillectomy (AT) [17].

An additional comorbidity that has developed over the last decade in a growing number

of children with OSA is that of obesity. It has been reported that childhood obesity increases the risk of developing OSA to the extent that for every 1 kg/m² increment in BMI above the mean BMI for age and gender, there is a 12% increased risk of developing OSA [10]. Obesity promotes both narrowing of the upper airway due to fatty infiltration of upper airway structures and increased pharyngeal collapsibility due to subcutaneous fat deposits in the region of the anterior neck cervical region [18]. In addition, the extra fat in the abdominal wall and cavity and in the thoracic wall acts to reduce the resting lung volume, resulting in a loss of caudal traction on the upper airway and an increase in pharyngeal collapsibility [19].

Diagnosis of sleep-disordered breathing in children

The clinical evaluation of children with suspected OSA involves taking a thorough history relating to the child's sleep patterns and parental observations of breathing during sleep. Studies have consistently found, however, that symptom scores are not reliable in detecting OSA in snoring children [20,21]. They do, however, have a high negative predictive value – a child who does not snore or have noisy breathing during sleep, or have witnessed apnea or increased breathing effort during sleep is very unlikely to have OSA [22]. The extent to which the disorder is impacting on the functioning of the child in domains such as daytime performance and quality of life may also be assessed clinically. Physical examination should include both factors associated with a risk of OSA such as tonsil size, nasal inflammation and retrognathia, and potential consequences of OSA, such as poor growth and hypertension **(Box 1)** [23].

Formal confirmation of the diagnosis requires objective assessment of sleep and breathing, with the gold standard for diagnosis being attended overnight polysomnography. Polysomnography measures multiple physiologic parameters to determine sleep quality and respiratory function. This test is not easily available in many parts of the world, as well as being expensive and relatively invasive for children and parents. Less complicated types of testing such as overnight oximetry, actigraphy, video recordings, daytime nap polysomnography and ambulatory polysomnography performed in the child's home are attractive due to their ease of use and lower cost, but they have consistently been shown to have poor sensitivity and a low negative predictive value for OSA and, thus, are not helpful for ruling out the diagnosis [3]. Treatment for obstructive symptoms is very often undertaken without formal testing – it has been estimated that only 10% of these children undergoing AT for upper airway obstruction were referred for preoperative polysomnography [24]; this may be even lower in some settings [25,26]. The need for polysomnography before and after AT has been debated by otolaryngology surgeons and sleep and respiratory physicians. Against the need for preoperative polysomnography are studies reporting that children with primary snoring or mild OSA benefit from surgery, and so determining the severity of OSA is not necessary in determining treatment [27]. That polysomnography should be performed prior to AT, is supported by studies that show not all children undergoing AT for suspected OSA do in fact have OSA on objective testing, thereby potentially subjecting these children to unnecessary surgery, which may have no clinical benefit [25]. An added benefit to preoperative polysomnography is to identify children at increased risk of operative complications and persistence of OSA following AT [25,26].

Whether preoperative polysomnography is performed or not, careful evaluation of the extent to which symptoms respond to treatment is necessary. A recent meta-analysis reported that, although significant improvements in the apnea–hypopnea index (AHI) were observed following AT, the cure rate for OSA by AT (defined as a post-AT AHI <1 event/h) was only 59.8% [28]. Children with comorbid conditions, including obesity, with more severe OSA at baseline, have an increased risk of having persistent OSA following AT [29,30]. One study showed that less than 5% of all children who have AT have a postoperative polysomnography [24], therefore, many cases of persistent OSA after AT are likely to be missed. The recently revised clinical practice guidelines for the management of childhood OSA syndrome from the American Academy of Pediatrics recommend that clinicians reassess all patients with OSA for persisting signs and symptoms 6–8 weeks after AT to determine whether further evaluation and treatment are indicated [3].

As well as these tests, evaluation of adenoidal size using a lateral neck x-ray or endoscopic

Box 1. Common signs and symptoms of sleep-disordered breathing.
Night-time symptoms
▪ Habitual snoring
▪ Witnessed apneas and labored breathing
▪ Gasping/choking/snorting
▪ Mouth breathing
▪ Sleeping with hyperextension of neck
▪ Restlessness/frequent awakenings/sweating
▪ Enuresis
Daytime symptoms
▪ Poor behavior
▪ Inattention at school or preschool
▪ Poor performance at school
▪ Hyperactivity
▪ Excessive sleepiness
▪ Morning headaches
▪ Noisy and/or mouth breathing
Physical examination findings relevant to obstructive sleep apnea
▪ Adenotonsillar hypertrophy
▪ Micrognathia/retrognathia
▪ Nasal inflammation and obstruction
▪ Failure to thrive/obesity
▪ Hypertension
▪ High-arched palate
Data taken from [3,31,37,125].

examination may be helpful in planning treatment. Other types of radiographic evaluation such as cephalometric studies, CT imaging and MRI scanning are usually reserved for research settings, but may also be useful for assessment in children with complex comorbidities in whom treatment decisions are not straightforward [31].

Natural history of OSA

There are limited data on the natural history of snoring and OSA in children and, thus, this aspect remains to be fully elucidated. A study of only 13 children (age range at initial study was 11 months to 12.3 years) diagnosed with primary snoring performed re-evaluation 3 years later [32]. As only the youngest of the group (aged 11 months) developed OSA in the time between the studies, the authors concluded that children with primary snoring are unlikely to develop OSA and therefore, it was safe to defer treatment in these children. A later cross-sectional, population-based cohort study of primary school children (mean age: 9.6 years) categorized children into habitual snorers (frequently or always) or nonsnorers (never or occasionally) by questionnaire [33]. The habitual snorers were

followed-up a year later and 48.8% (n = 39) were still habitual snorers. Those with persistent snoring differed from those who no longer snored regularly by lower maternal education, higher household smoking, louder snoring and lower likelihood of previous ear, nose and throat surgery. Li *et al.* investigated the natural history and progression of 45 children (aged 6–13 years) with mild OSA (AHI: 1–5 events/h) over a 2-year timeframe and reported that 29% had worsened OSA [34]. Multivariate linear regression associated worsening OSA with younger age of the child at baseline, male gender, presence of enlarged tonsils at baseline, increased waist circumference at follow-up and persistently large tonsils at follow-up. The mean obstructive AHI (OAHI) of the children who did not progress to worsened OSA over the 2 years decreased slightly from 2.2 events/h (range: 1.4–2.8) at baseline to 1.7 events/h (range: 0.7–2.4) at follow-up, indicating that there was also not a significant improvement in the severity of their OSA. Further studies that involve much larger cohorts and extended time frames are needed before definitive conclusions can be made regarding the progression of disease severity in children with snoring and OSA.

Treatment of OSA in children

Treatment options for pediatric OSA fall into four main categories: AT, anti-inflammatory agents, continuous positive airway pressure (CPAP) and dental/orthodontic treatments **(Figure 1)**. The choice of treatment will depend on the severity of the disorder, the presence of comorbid conditions, and the physical examination and history findings.

Adenotonsillectomy

AT is the most common treatment for pediatric OSA, particularly for moderate-to-severe cases when there is adenotonsillar hypertrophy and no contraindication to surgery [3]. Various different techniques for removing tonsil and adenoid tissue are available, but an indepth discussion on the different surgical techniques of AT and their impact on postoperative complications is beyond the scope of this review.

An epidemiological study in the USA that investigated the 35-year trends in tonsillectomy and AT reported that the incidence of pediatric AT for the indication of upper airway obstruction increased from 12% of all patients receiving

AT in 1970 to 77% in 2005 [35]. Not only have overall numbers increased, but the indication for surgery has markedly shifted from recurrent infection to upper airway obstruction. Similar results were found in a later study, also performed in the USA, which determined that from 1996–2006, the incidence of pediatric AT almost doubled due to the increased recognition of the morbidities associated with OSA [36]. The American Academy of Otolaryngology – Head and Neck Surgery published a clinical practice guideline for tonsillectomy in children in 2011 [37]. With regard to children with OSA and tonsillar hypertrophy, the guideline recommends that clinicians ask the caregivers about comorbid conditions that might improve after tonsillectomy, including growth retardation, poor school performance, enuresis and behavioral problems. When the child has had an abnormal polysomnographic study and tonsillar hypertrophy is also identified, the guidelines recommend counseling caregivers about tonsillectomy as a means to improve health, but also counseling that OSA may still persist following surgery and require further management.

Removing only the adenoids has been associated with an increased risk of persistence of OSA when compared with AT [38]. Repeat adenoidectomy is sometimes required for persistent or recurrent symptoms, with the likelihood of repeat adenoidectomy being 2.5-times higher in children under 5 years of age at the time of the first surgery and also higher in those whose first surgery was adenoidectomy alone [39].

■ Perioperative complications of AT
AT for OSA in childhood is associated with an increased risk of postoperative complications, particularly respiratory compromise [40–43]. Recognized risk factors for respiratory compromise include age <3 years, weight <third percentile for age, craniofacial anomalies, severe OSA, cardiac disease, prematurity and hypotonia [42–46]. Complications occurring in the first 24–48 h after surgery range from desaturation requiring supplemental oxygen to emergency reintubation. The effect of age on the prevalence of postoperative respiratory complications was investigated in over 2000 children who had AT for OSA [47]. Overall, 6.4% of children developed a postoperative respiratory complication, while children younger than 3 years of age had a nearly twofold increased risk of respiratory

complications compared with those children who were between 3 and 5 years old (9.8 vs 4.9%). Similar studies also illustrated that the most important predictors of postoperative respiratory morbidity were young age, obesity and the initial severity of the OSA [43,45,48]. A recent large review in the UK of 1735 children (61.4% diagnosed with OSA) who underwent AT between 2003 and 2010 showed a significantly higher chance of pediatric intensive care admission in children with comorbidities such as Down syndrome, cardiac disease, obesity, cerebral palsy, craniofacial abnormalities, mucopolysaccharidoses and hemoglobinopathy, compared with children with no comorbidities [49].

The underlying pathophysiology of postoperative respiratory compromise is several fold. Despite the removal of the obstructing lymphoid tissue, upper airway obstruction may persist in the immediate postoperative period, which has been shown to be the major cause of the high incidence of oxygen desaturation observed in these children [50]. These findings led to the
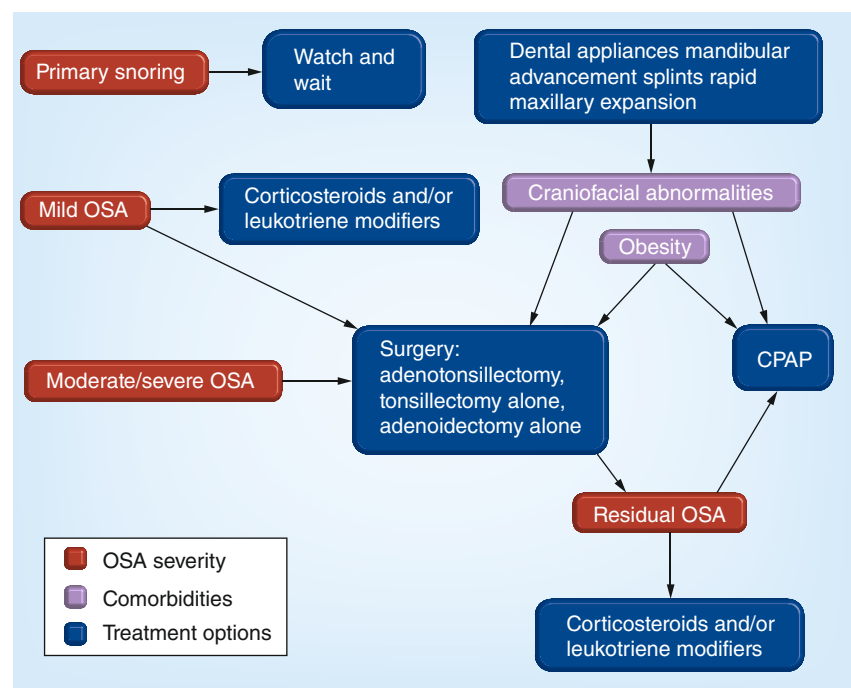

Figure 1. The treatment of snoring and obstructive sleep apnea in children depends on the severity of the condition and the presence of comorbidities. The most common treatment pathways are shown, but different pathways and options may be applicable in individual cases. When comorbidities are present, treatment of OSA is an integral part of the overall management of the child's condition.
CPAP: Continuous positive airway pressure; OSA: Obstructive sleep apnea.

recommendation for continuous pulse oximetry and overnight observation postoperatively for at least the first night following surgery in children with severe OSA [50]. In addition, children with OSA are also more susceptible to developing depressed ventilation and apnea in response to opiate analgesia [51].

The risk of post-AT hemorrhage may actually be lower in children undergoing AT for OSA rather than recurrent infection. This is postulated to be either because OSA is associated with an upregulation of prothrombotic factors, or because recurrent tonsil infections increase the risk of hemorrhage [52].

■ **Efficacy of AT for children with OSA**
Over the last decade, there has been a raft of studies evaluating the efficacy of AT as a treatment for pediatric OSA. These studies have investigated both improvements in polysomnography measures of OSA severity and sleep quality [53–61], associated morbidities such as autonomic dysfunction [60,62–67], behavior and psychological functioning [58,68,69], metabolic markers [67,70], markers of inflammation [67,71] and endothelial function [72]. There is currently a large, multicenter randomized controlled trial underway in the USA – CHAT. This study has been designed to assess neuropsychological and health outcomes in children with mild-to-moderate OSA randomized to receive early AT compared with watchful waiting with supportive care over a 7-month period [73]. The results of this study are not yet available, but it aims to be the definitive study that will document the effectiveness of AT, the standard treatment modality for pediatric OSA. It will provide critical evidence that OSA directly contributes to the adverse outcomes that are known to be associated with it. Of note, however, is the milder severity of disease in the children included and the short duration of follow-up.

■ **Polysomnography measures of OSA severity & sleep quality following AT**
Early reports investigating the effect of AT as an intervention for OSA suggested relatively high cure rates (85–95%) [74,75]. However, a systematic review and meta-analysis of the pediatric literature (mean age: 6.5 years) with OSA who underwent AT between 1995 and 2008 found that, while there were significant improvements in OSA severity as defined by the AHI after AT, complete resolution of OSA did not always occur. In this study, 'cure' of OSA was defined as an AHI <1 event/h of sleep (only 66.3% of patients achieved this) [28]. The authors point out, however, that the included studies showed significant heterogeneity, quoting a cure rate in uncomplicated patients (e.g., excluding those with morbid obesity) of 73.8%.

Additionally, studies with a range of follow-up periods were included and the timing of follow-up polysomnography after AT is likely to affect the likelihood of cure.

Similar results were reported in an abstract from a multicenter collaborative retrospective review of pre- and post-AT polysomnography studies of 578 children (mean age: 6.9 years) with OSA [61]. Only 27.2% of children had a complete resolution of OSA (AHI <1 event/h), although AT resulted in a significant reduction in AHI overall. However, data in the body of the paper support an actual cure rate of 50.5%, as pointed out in a subsequent letter to the editor [76]. In fact, if upper airway resistance syndrome is considered sufficient to constitute a 'cure' (and the definition of this problem in children is not well defined), the cure rate reported rises to 82%, and if obese children are excluded, the cure rate is 85% or even higher for milder disease. An additional problem acknowledged by the authors of the study was its retrospective nature, with children only recalled for a sleep study after AT was included. This raises the possibility that children with persistent symptoms are more likely to be included, lowering the cure rate demonstrated. Age (>7 years) and higher BMI Z-score were the two major factors that contributed to post-AT AHI, asthma and the severity of pre-AT OSA were moderate predictors of post-AT AHI in nonobese children. Of note in this analysis was the very large range in the timeframe of the post-AT polysomnography (40–720 days).

A significant improvement in OSA in children following AT has been demonstrated in studies using both subjective and objective criteria. Studies have demonstrated that there is a significant improvement in sleep behavior and quality of life following AT in children with OSA. AHI [58,59] and OSA-18 scores were reduced [58], concurrent with improved OSA severity. In children who had complete resolution of their OSA (AHI <1 event/h) following AT, sleep architecture was also normalized [57]. The multicenter

retrospective review by Bhattacharjee and colleagues also reported that post-AT polysomnography studies demonstrated significant improvements in the major indices of sleep architecture, with significantly fewer night-time awakenings and improved sleep efficiency [61]. A recent retrospective analysis of pre- and post-AT polysomnography studies (mean: 98 days post-AT) of 37 children (age range: 3–13 years) with diagnosed OSA also reported significant reductions in the AHI and arousal index post-AT; however, there was no change in the conventional measures of sleep architecture, such as the time spent in each sleep stage and sleep efficiency [53]. In addition to polysomnography, this study included a novel ECG-based cardiopulmonary coupling analysis, where high frequency coupling is used as a marker of stable sleep and low frequency coupling as a marker of unstable or fragmented sleep. AT resulted in an increase in stable sleep and a decrease in unstable sleep findings that were not detected by conventional polysomnography.

A meta-analysis of four studies that reported polysomnography results before and after AT (mean 4.8 months post-AT) from 110 obese children (mean age: 8.4 years) with OSA showed that, although AT in obese children resulted in a reduction in AHI and an improvement in oxygen saturation nadir, it was less likely to result in a complete cure, with 49% having a post-AT AHI of <5 events/h, 25% having a post-AT AHI <2 events/h and only 12% having a post-AT AHI <1 event/h [29]. By contrast, a single study of 22 obese Greek children (mean age: 5.8 years) with OSA, reported no difference in the efficacy of AT (post-AT polysomnography 1–14 months after surgery) when compared with 48 nonobese, age-matched children with OSA [77].

Alternative surgical options may be appropriate for children who have persistent OSA after AT, including supraglottoplasty for occult laryngomalacia and removal of the lingual tonsillar tissue, if present. However, even following these adjunct procedures, there are still a significant number of children who have persistent OSA, particularly if obesity is present [30,78,79].

In summary, these studies confirm results from earlier research that overwhelmingly concur that AT significantly improves the severity of OSA in children with tonsillar hypertrophy, but that there are still significant numbers of children with residual OSA post-AT, especially obese children [54–56].

■ Cardiovascular function following AT

Several studies have investigated the effect of AT on indicators of cardiovascular and autonomic function [80]. However, most of the studies carried out to date are limited, as they have been based on variable and short-term follow-up periods, and many have not objectively measured OSA severity using the gold standard – polysomnography [81]. Studies using 24-h ambulatory blood pressure monitoring in 44 children with OSA pre- and post-AT showed that 44% of the children had resolution of their OSA and this was concomitant with a significant decrease in the diastolic blood pressure [65]. Furthermore, eight children who had nocturnal hypertension pre-AT had a significant reduction in their systolic and diastolic blood pressure and six of these children became normotensive following AT. However, it is important to note that eight children who were normotensive pre-AT became hypertensive post-AT. These eight children, plus the two children who were hypertensive pre-AT and remained hypertensive post-AT, were more likely to have residual OSA (AHI >1 event/h) following surgery. In another study, morning office blood pressure was measured in 58 children (mean age: 6.2 years) with OSA and 17 control children (mean age: 6.5 years) undergoing AT for recurrent tonsillitis and/or otitis media [67]. Post-AT (2–14 months following surgery), children who had a complete resolution of their OSA (AHI <1 event/h) had reduced diastolic blood pressure. By contrast, children with residual OSA (AHI >1 event/h) and control children, had increased systolic blood pressure post-AT, which the authors speculated was due to the increase in age and somatic growth between the pre-and post-AT studies, despite the fact that blood pressure was reported as an index to account for age, gender and height.

Pulse rate variability and tachycardia have been reported to be reduced post-AT in concert with reduced or resolved symptoms of OSA [62]. Similarly, both heart rate and the low frequency/high frequency ratio of heart rate variability, which indicates cardiac sympathovagal balance, has been shown to decrease post-AT [64], suggesting decreased sympathetic activity post-AT associated with improved OSA.

Further investigating the effect of AT on autonomic function, a study by Crisalli *et al.* analyzed baroreflex sensitivity (the reflex that is responsible for the short-term control of

blood pressure) and blood pressure variability in 194 children (mean age: 9.6 years; 133 children with OSA and 61 healthy controls) [63]. The children with OSA underwent AT and had polysomnography prior to surgery and repeated at 6 weeks and 6 months following surgery. The control children also had polysomnography at study entry and again 6 months later. Following AT, the children with OSA had increased baroreflex sensitivity and decreased blood pressure variability during both wakefulness and sleep, and decreased blood pressure during sleep and heart rate during wakefulness. These results are suggestive of a return to autonomic function following AT that became similar to that of the control children. In addition, the normal increase in baroreflex sensitivity observed as the night progresses, which is lost in children with OSA, was restored after AT in the children with severe OSA. The change in the AHI and arousal index was predictive of improved baroreflex sensitivity, however, AT did not completely normalize baroreflex sensitivity within 6 months of surgery.

In a study of the effects of AT on cardiac function in children with OSA and controls using echocardiography with a tissue Doppler imaging facility, children with OSA were identified as having diastolic dysfunction pre-AT, which was improved at 6 months post-AT compared with controls [66].

In summary, the studies discussed above suggest that the cardiovascular dysfunction associated with OSA in children is improved following AT concomitant with improvements in OSA severity, even if OSA is not entirely resolved.

▪ Behavior & neurocognition following AT

In a review of 25 studies investigating behavioral and neurocognitive outcomes following AT in children with OSA, all studies reported improvement in one or more of the outcome measures such as quality of life, behavioral problems including hyperactivity and aggression, and neurocognitive skills including memory, attention and school performance [69]. The time between pre- and post-AT testing ranged from 2 months to 3 years, age ranges for the studies were not provided. The authors commented that many of the studies reviewed showed limited correlations between behavioral, cognitive or quality of life measurements and polysomnography parameters at either baseline or post-AT,

which suggests that current methods may not be adequate to accurately assess sleep disruption and/or the relationship between severity of OSA and neuropsychological outcomes is nonlinear.

▪ Inflammation & endothelial cell function following AT

A relatively new area of research related to OSA in children has been the investigation of markers of inflammation and vascular reactivity. There has been a large body of literature that has investigated markers of systemic inflammation [82–87] and local upper airway inflammation [88–91]. Two studies have demonstrated that children with OSA showed significantly reduced levels of CRP, a proinflammatory protein, following AT [71,92]. Endothelin 1, a potent vasoconstrictor stimulated by hypoxia, has also been shown to be significantly reduced post-AT. Endothelial function has also been studied pre- and post-AT using measurements of CD40 ligand (sCD40L), asymmetric dimethylarginine and nitrotyrosine levels [72] in 26 children (mean age: 6.9 years) with OSA and eight age-, gender-, ethnicity- and BMI-matched controls. Post-AT measurements were taken 4–6 months after surgery. This study illustrated that the postocclusive hyperemia that was blunted in children with OSA was reversed following surgery, indicating a return to normal endothelial cell function. AT did not change the levels of asymmetric dimethylarginine, however, increased levels of sCD40L indicated improved endothelial function following AT.

In summary, although numerous studies to date have indicated that AT does not always completely resolve OSA in children, studies do demonstrate that AT results in significant improvements in the severity of the disorder, concomitant with improved sleep quality, quality of life, psychological health and the important risk factors for cardiovascular disease such as elevated blood pressure, increased blood pressure variability, dampened blood pressure and heart rate control, and a reduction in inflammatory markers. Research needs to continue to determine what the threshold for treatment of OSA should be in terms of benefit in these domains.

CPAP treatment

CPAP treatment is based on the premise that a column of air pressure acts as a splint to the upper airway, preventing collapse. It is delivered

noninvasively using a mask applied to the nose and/or mouth and is used as a treatment in children when AT or other therapies have not resulted in sufficient clinical improvement, or in cases when surgery is not indicated. Children who are obese, or those with craniofacial abnormalities or neuromuscular disorders are the most common candidates for CPAP treatment [93,94]. CPAP was first used in adults with OSA in 1981 [95] and in children a few years later [96]. CPAP pressure needs to be individualized, usually by manual adjustment during a polysomnographic study until airway obstruction is resolved. Recommendations for conducting CPAP titrations have been published by the positive airway pressure titration taskforce of the American Academy of Sleep Medicine [97]. CPAP therapy has been shown to be an efficacious treatment for OSA in children with resolution of obstructive events and better sleep quality [93,96,98–100]. Since its inception as a treatment for pediatric OSA, industry research and development has resulted in an increasing range of CPAP masks appropriate for pediatric use.

Adherence to CPAP use has been the focus of several pediatric studies [94,101,102]. In all studies, there is a wide range of nightly hours of use, with most reporting an average of approximately 5 h per night [94,101,102]. Given that children sleep for substantially longer times than this, this amount of time is less than optimal and likely to impact on the clinical benefit of the therapy. Patterns of CPAP use are established very early in children, as in adults, with usage hours in the first week predicting longer-term usage over the subsequent 3 months [94]. A positive attitude of parents towards therapy is an important predictor of successful treatment [102]. Commitment to use was demonstrated in a study when a minimum of 1 h use per night on six or more nights per week from the beginning of therapy predicted the children who would go on to be adherent in the longer term, compared with those who at the beginning of treatment used the mask for less than 1 h per night or used it less consistently during the first week [94]. CPAP adherence is also associated with family and demographic factors, with baseline severity of OSA not usually being found to have a significant impact [94,103]. Education and behavior modification programs have been demonstrated to improve adherence [102,104,105].

Few studies have examined the benefit of CPAP on daytime functioning in children. A recent study of 52 children with a mean usage of approximately 3 h per night showed improvements in attention deficits, daytime sleepiness, behavior, and caregiver- and child-reported quality of life [93]. The relationship between adherence to CPAP and outcomes in children is complex to tease out, with the falling sleep requirements as children get older likely to influence the hours of CPAP use that might result in improvements in functioning. In adults, CPAP adherence is related to perceived benefits [106], but this is likely to be very different in children, particularly in very young children and also in those with neurodevelopmental disability. However, early data showing improvements with even low amounts of CPAP usage are encouraging.

Serious side effects associated with CPAP are rare; side effects are mainly local such as eye irritation and nasal symptoms such as dryness, epistaxis, rhinorrhoea and congestion. Nasal symptoms are usually alleviated by the use of heated humidification, raising the moisture content of inspired air and reducing dryness. Facial side effects such as skin injury, including transient and prolonged erythema and skin necrosis, can also occur in children on CPAP therapy [107]. Concerns have been raised about midface hypoplasia as a possible consequence of prolonged CPAP use via nasal mask [108].

In summary, CPAP is an efficacious treatment for some children with OSA, commonly those who are obese, or with craniofacial abnormalities or neuromuscular disorders. Optimizing adherence in the early period of treatment has long-term benefits on levels of use, which are in turn likely to impact on the extent of improvements in other aspects of functioning; however, to date, this has received little research attention.

Corticosteroids & leukotriene modifiers

The pathophysiologic mechanisms by which OSA mediates end-organ damage have been postulated to be oxidative stress via increased generation and propagation of reactive oxygen species, the initiation and amplification of inflammatory processes. Obesity, genetic susceptibility and environmental modulators act to modify an individual's phenotypic expression in relation to end-organ morbidity [84,109]. Studies in children with OSA have investigated the association of OSA

with both systemic inflammation and localized inflammation of the upper airway tissue.

Systemic inflammation has been associated with OSA by studies that have identified upregulation of plasma CRP [85,87], increased neutrophils in the sputum [86], increased urinary levels of cysteinyl leukotrienes [83] and increased levels of leukotrienes and prostaglandins in exhaled breath condensate [82] in children with OSA. Markers of local upper airway inflammation have also been identified in children with OSA: increased proinflammatory cytokines TNF-α, IL-6, IL-1α and increased T cells and decreased B cells in tonsillar tissue [91], increased leukotriene receptor expression in tonsillar tissue [88], increased cysteinyl leukotriene receptor expression in T cells from tonsillar tissue [90] and upregulation of glucocorticoid receptors in adenotonsillar tissue [89]. Thus far, two types of medications, which offer a therapeutic alternative to AT, have been studied in children, corticosteroids and leukotriene modifiers.

Corticosteroids have been shown to reduce tonsillar proliferation *in vitro*, in tissue samples collected from children with OSA during AT [110]. Administration of systemic corticosteroids has been shown to lead to a reduction in the size of lymphoid tissues due to anti-inflammatory and lympholytic effects; however, a short course of systemic prednisone was found not to have a significant effect on adenoidal size or the severity of OSA [111]. Furthermore, adverse effects preclude the long-term use of this therapy for OSA in children. Topical corticosteroids have a higher benefit-to-risk ratio than systemic steroids and may be used for long periods, thus providing a promising alternative for treatment of OSA without the risks of high-dose oral steroids [11]. Over the last decade, a number of studies have evaluated the use of topical nasal glucocorticoid treatment for OSA, demonstrating efficacy in reducing the severity of OSA symptoms and also in reducing the size of the adenoids [11,112–114]. Intranasal corticosteroids are effective in relieving nasal obstruction in allergic rhinitis; allergic sensitization is more prevalent among children who snore than among those who do not snore. Intranasal corticosteroids have also been demonstrated to reduce adenoidal size, independent of the individual's atopic status [11]. A study of 62 children with polysomnographically diagnosed mild OSA were recruited onto a double-blind,

randomized, crossover trial of intranasal budesonide and polysomnographic assessment and radiographs for assessment of adenoid size were performed [112]. A 6-week treatment with intranasal budesonide effectively reduced the severity of mild OSA and the degree of the underlying adenoidal hypertrophy. This effect persisted for at least 8 weeks after cessation of therapy [112]. A recent study determined the effect of intranasal corticosteroid therapy on Tregs and other inflammatory cytokines in adenoid tissues in children with OSA [113]. The children were treated with fluticasone furoate nasal spray for 2 weeks prior to AT. Adenoid cells isolated from fluticasone-treated patients released significantly less IL-6 compared with nontreated adenoid tissue. However, there were no significant differences in the number of CD4/FOXP3⁻, CD25/FOXP3⁻ or TGF-β-positive cells.

Similar studies have evaluated the efficacy of leukotriene receptor agonists such as montelukast. Oral therapy with montelukast was demonstrated to reduce adenoid size, apnea index and respiratory-related sleep disturbances in children with mild OSA [115,116]. In a recent double-blind, placebo-controlled study, 46 children (mean age: 4.8 years) diagnosed with OSA were treated with either daily oral montelukast or a placebo for 12 weeks [117]. The children who received montelukast showed a significant reduction in the obstructive apnea index, the symptoms exhibited by the children as determined by questionnaire, and the size of the adenoids determined by lateral neck radiography. One study has investigated the effect of a combined therapy of an intranasal steroid plus an oral leukotriene modifier in children with residual OSA following AT [118]. Intranasal budesonide and oral montelukast were administered for 12 weeks to 22 children (mean age: 6.3 years) who had a residual AHI >1 event/h and <5 events/h, 10–14 weeks after AT. A further 14 children who met the same criteria were enrolled as controls, but did not receive the medication. Following 12 weeks of treatment, there were significant improvements in AHI, in SpO$_2$ nadir and in the arousal index in the treatment group that was not found in the placebo group.

Thus, there is evidence supporting the use of nasal corticosteroid spray and leukotriene modifiers in children, especially in those with mild OSA and with persistent disease after AT.

Dental/orthodontic treatments for OSA

A common phenotype in children with OSA is a narrow upper airway with maxillary constriction, a high arched palate and/or retrognathia and increased posterior facial height. Mandibular advancement splints (MAS) are indicated in adults with mild-to-moderate OSA as an alternative to CPAP [119] and are a particularly attractive option in children with retrognathia. To date, there is only one study investigating MAS in children [120]. Of the 19 children randomized to the treatment arm of that study, 74% tolerated the treatment well, while 26% of the treatment group did not complete the treatment period due to refusal to wear the device or being unable to tolerate it. A total of 31% of the control group were also lost to follow-up, therefore follow-up results were only available for 14 children who wore the device and nine controls. Significant improvement was seen in the AHI, daytime symptoms (oral breathing, nasal stuffiness) and night-time symptoms (habitual snoring and restless sleep) [120]. A subsequent Cochrane review identified that study as the only evidence regarding the use of MAS in children concluded that there was no strong evidence of the effectiveness of MAS in children. However, it acknowledged that oral appliances may be considered as an auxiliary in the treatment of children who have craniofacial anomalies, which are risk factors for apnea and that the best treatment is decided when a multiprofessional team (including a dentist) is consulted [121]. There have been no studies of the long-term effects of the use of MAS on the growing facial skeleton and unerupted teeth.

Another increasingly popular dental/orthodontic treatment used to enlarge the upper airway is rapid maxillary expansion (RME). RME improves nasal breathing by expanding the maxilla in the transverse plane, thereby lowering the palate and enlarging the nasal airway. It can be achieved by orthodontic or surgical methods, with the most common method involving an expansion device containing a screw that is anchored to the upper molars. Expansion is achieved by winding the screw over a period of days; the device is then anchored for a maintenance period, usually 1 year in duration. Several studies have demonstrated improvements in OSA using RME [122–124]. Children with enlarged tonsils (occupying more than 50% of the pharyngeal diameter) may be less likely to respond to RME [123]; children with a retrusive bite more likely [124]. In summary, for this treatment, as for MAS, careful clinical assessment, including of the dentition and involvement of a multidisciplinary team, are more likely to lead to the best treatment outcomes.

Conclusion

Over the last decade, there has been significant research into outcomes of different treatment for OSA in children. AT is the most common treatment, but has recently been demonstrated to not be as effective as previously thought, especially in obese children. A number of other treatments have received research attention in recent years, with anti-inflammatory therapies (nasal corticosteroids and leukotriene receptor antagonists) showing particular utility in cases of mild OSA. CPAP therapy is becoming more common in children, owing mainly to the rising prevalence of obesity. Dental and orthodontic treatments have become promising alternatives for some children. AT is likely to remain the first-line therapy for most children with OSA, but continuing research into alternative therapies is important for the future.

Future perspective

As the availability of attended overnight polysomnography is very limited worldwide, improved tools are needed to identify children at risk of OSA who would benefit from treatment. While AT leads to improvement in OSA in most children, the cure may not be complete, especially in obese children. The threshold for severity of disease warranting treatment is not known and further research is needed to inform clinicians on the criteria for the selection of patients for surgery and other therapies, including the optimal age at which treatment should be offered. In the case of CPAP therapy, the relative contributions made by maternal education, socioeconomic status and different cultural beliefs on uptake and adherence also needs to be teased out so that programs can be developed to optimize adherence. Further research is also needed to assess the outcomes of CPAP therapy on areas such as cognitive function, behavior and cardiovascular outcomes. More evidence is needed to substantiate the efficacy and safety of dental/orthodontic therapy for OSA in children during the period when their facial bones and dentition are still growing and developing.

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