REVIEW

Paediatrics: how to manage obstructive sleep apnoea syndrome

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Abstract
Obstructive sleep apnoea syndrome (OSAS) is defined as the intermittent reduction or cessation of airflow due to partial or complete obstruction of the upper airway during sleep. Paediatric OSAS has specific contributing factors, presenting symptoms and management strategies in various age groups. Untreated OSAS can lead to detrimental effects on neurocognitive development and cardiovascular and metabolic functions of a growing child. In the past decade, practice guidelines have been developed to guide the evaluation and management of OSAS. This article provides a narrative review on the current diagnostic and treatment options for paediatric OSAS. Alternative diagnostic tools other than the standard polysomnography are discussed. Adenotonsillectomy is considered the first-line therapy yet it is not suitable for treatment of all OSAS cases. Nocturnal non-invasive positive airway pressure ventilation is effective and could be the priority treatment for patients with complex comorbidities, residual OSAS post-adenotonsillectomy or obesity. However, intolerance and non-adherence are major challenges of positive airway pressure therapy especially in young children. There is increasing evidence for watchful waiting and other gentler alternative treatment options in mild OSAS. The role of anti-inflammatory drugs as the primary or adjunctive treatment is discussed. Other treatment options, including weight reduction, orthodontic procedures and myofunctional therapy, are indicated for selected patients. Nevertheless, the successful management of paediatric OSAS often requires a multidisciplinary team approach.

Keywords: adenotonsillectomy, anti-inflammatory drugs, children, obstructive sleep apnoea, obstructive sleep-disordered breathing, polysomnography, positive airway pressure.

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Introduction
Obstructive sleep apnoea syndrome (OSAS) is the severe end of obstructive sleep-disordered breathing (SDB) spectrum, which is defined as a syndrome of upper airway dysfunction during sleep, characterized by snoring and/or increased respiratory effort secondary to increased upper airway resistance and pharyngeal collapsibility.1 Obstruction of the airway occurs when airflow is partially reduced (hypopnoea) or almost completely ceased (apnoea) and is associated with abnormal gaseous exchange or arousals from sleep. Primary snoring and upper airway resistance syndrome, identified as respiratory effort-related arousals (RERA) in polysomnography (PSG) without gaseous exchange abnormalities, are considered milder forms of obstructive SDB.2 The condition affects all ages, from infants to the elderly, with a higher prevalence and more severe cases in the geriatric population.3–5 In 1975, Guilleminault et al. reported the first case series of eight children aged 5–14 years with OSAS diagnosed by nocturnal polygraphic monitoring similar to adults.6 With more research, it has since been recognized that children have specific features, with the consequence that the diagnostic criteria for adults are not applicable to children.7 In the second edition of International Classification of Sleep Disorders (ICSD-2), published by the American Academy of Sleep Medicine (AASM) in collaboration with other international sleep societies in 2005, paediatric OSAS was listed as one of the sleep-related breathing disorders (SRBDs) distinguished from that of adults.8 In 2012, the American Academy of Pediatrics published the first set of formal guidelines for the diagnostic criteria and management of childhood OSAS.8 The European Respiratory Society released two sets of guidelines with algorithms and more specific recommendations to guide the evaluation and management of obstructive SDB for...
children aged 2–18 years old and for infants under 2 years old in 2016 and 2017, respectively.1,2 Recently, members of the International Pediatric Otolaryngology Group formulated an expert-based consensus of recommendations for the diagnosis and management of paediatric OSAS focusing on the surgical perspective.10 Despite the availability of guidelines, a personalized diagnostic and treatment plan has to be devised according to patient factors and the availability of resources. This article provides a narrative updated review on the diagnostic tools and treatment options of paediatric OSAS. This review will mainly focus on the management of children aged 2–18 years as the risk factors and management approaches for young infants are diverse and differ from those for older children.2

Methods
A search of literature limited to English language was performed using the PubMed, Google Scholar and Cochrane Library databases in November 2020 with keywords “obstructive sleep apnoea” or “obstructive sleep disordered breathing” and “diagnosis”, “treatment” or “management” and “children” or “adolescent”. The search strategy included clinical trials, observational studies, meta-analyses, guidelines, reviews and cross-references of the relevant articles.

Specific features of paediatric OSAS
The prevalence of OSAS in children was reported to be 1–5%,9 with a peak at pre-school age corresponding to the time of adenotonsillar hypertrophy and a later peak during adolescence when obesity becomes more prevalent. Unlike in adults, there is a lack of male predominance. The pathogenesis of OSAS is multifactorial, with three core groups of contributing factors: (1) abnormal craniofacial anatomy; (2) increased tissue deposition/infiltration; and (3) increased airway collapsibility. The risk factors, clinical presentation, PSG findings, options and indications for treatment in children with OSAS differ from those in adults.11 Prematurity, craniofacial syndromes and neuromuscular diseases are the main factors in infants and young children, whereas adenotonsillar hypertrophy is a major factor at pre-school age and obesity becomes a major risk in older children and adolescents. The cardinal feature of daytime sleepiness in adults is uncommon in children. On the contrary, children present with hyperactivity, restless sleep and learning difficulties. Children are known to present with relatively fewer symptoms and hence require increased vigilance by physicians to achieve earlier diagnosis of the problem. In PSG, continuous snoring with hypopnoea is more commonly observed in children while alternating snoring with obstructive apnoeas are typical for adults.12,13 Surgical and non-surgical treatment options for paediatric OSAS differ from those of adults, with adenotonsillectomy (AT) being the most common procedure performed and special attention being required for anaesthesia management in paediatric patients.1,10,14,15

Diagnosis
Definition of OSAS
In the latest edition of the ICSD (ICSD-3), the following two criteria have to be fulfilled for a diagnosis of paediatric OSAS (<18 years of age): (1) a clinical criterion: signs and symptoms with at least one feature of snoring, laboured or obstructed breathing, daytime consequences of sleepiness, hyperactivity, behavioural or learning problems and (2) a PSG criterion: more than one obstructive event (obstructive apnoea, mixed apnoea or obstructive hypopnoea) per hour of sleep, i.e. obstructive Apnoea–Hypopnoea Index (AHI) of ≥1 event per hour of total sleep time or obstructive hypoventilation defined as hypercapnia (PaCO$_{2}$ ≥50 mmHg) in ≥25% of total sleep time associated with snoring, flattening of inspiratory pressure flow or paradoxical thoracoabdominal motion.16,17 The Respiratory Disturbance Index (RDI) includes RERA events in addition to obstructive apnoeas and hypopnoeas. The scoring of RERA is optional in children and cut-off values of RDI of more than 1.5, 2 or 3 had been used by some experts for a diagnosis of paediatric OSAS.18,19 Despite the considerable amount of literature available, there is no consensus on the cut-off AHI or RDI values that are most representative of different severity of OSAS for the paediatric age group. Most guidelines define severity as mild for an obstructive AHI value of 1 to <5 events per hour, moderate for an AHI value of 5 to <10 events per hour, and severe for an AHI value of 10 or more events per hour.1,10,20 For indication of treatment, most experts agree that moderate-to-severe OSAS (AHI ≥5 per hour) requires treatment and those with an AHI value of <1 per hour do not require intervention, yet the best practice for those with mild OSAS is still not known.1 In fact, the severity of symptoms and impact on patients, rather than the PSG numerical figures, are more important for clinical judgement and treatment decisions.

Polysomnography
The ICSD-3 requires a PSG criterion for the diagnosis of paediatric OSAS. Since 1968, the Rechtschaffen and Kales criteria have been adopted for the scoring of sleep staging and associated events in PSG. Marcus et al. published the normal values of PSG parameters for children and adolescents in 1992.21 In 2007, the AASM issued the first edition of the PSG scoring manual for adults and children to provide standards on rules, terminology and technical specifications.22 A separate chapter on scoring criteria for term infants less than 2 months was included in the updated version (version 2.2) in 2015.23 For adolescents aged 13–18 years, either paediatric or adult scoring criteria can be used. The recent updated version (version 2.6) was released in 2020.19 The AASM has provided standard practice parameters on respiratory indications for PSG in children, stating that PSG is indicated whenever clinical assessment suggests OSAS, before OSAS treatment with AT or nocturnal positive airway pressure.
(PAP), or if there are residual symptoms post-AT. Consensus statements from the International Pediatric Otolaryngology Group represented by otolaryngologists recommend that full-night video PSG or in-hospital attended polygraphy are performed before AT in children <2 years old, in those with craniofacial abnormalities (including Down’s syndrome) and in obese children, while it is not mandatory for otherwise healthy children.

Technician-attended, in-laboratory full PSG classified as type 1 sleep study remains the reference standard for the diagnosis of OSAS in children. Other abbreviated sleep studies are classified as type 2 unattended or home PSG, type 3 limited channel or cardiorespiratory sleep studies, and type 4 with one to two parameters usually including pulse oximetry (PO) monitoring. The home sleep apnoea test more commonly performed in adults may not be adequate for children, especially for those with comorbidities who are at risk of nocturnal hypventilation in whom CO₂ monitoring is required. While increasingly popular, commercially available sleep trackers and actigraphy have poor correlations with PSG parameters and are unreliable for the diagnosis of OSAS.

Performing PSG in children is technically demanding and costly and there could be practical difficulties due to limited facilities and trained personnel, leading to a long waiting time. The American Academy of Pediatrics and European Respiratory Society guidelines state that alternative diagnostic tests can be considered if PSG is not available.

**Alternative diagnostic tools**

Snoring is the most common presenting symptom of OSAS and most experts agreed that habitual snoring, defined as snoring ≥3 nights, warrants further evaluation. Alternative diagnostic tools, including sleep questionnaires, clinical scoring tools and overnight PO, have been used to identify at-risk children for earlier evaluation and intervention if standard PSG is not easily accessible, albeit with different predictive values when compared with a full PSG.

**Sleep questionnaires**

In a systematic review on 15 scoring systems based on sleep questionnaires developed for snoring, none performed well enough to be considered accurate diagnostic tests for paediatric OSAS. The widely used Paediatric Sleep Questionnaire (PSQ)-SRBD scale for children 2–18 years old has a sensitivity of 71–84% for studies included in a meta-analysis but a specificity as low as 13%. The Obstructive Sleep Apnea 18-item Quality of Life Questionnaire (OSA-18) is available for children aged 6 months to 12 years as a measure on impact of quality of life and has variable sensitivity and specificity in different studies for the diagnosis of paediatric OSAS. Despite the limitations of sleep questionnaires in diagnosis, PSQ-SRBD and OSA-18 are recommended by consensus statements as part of the clinical evaluation and could be useful for the monitoring of outcomes. Validated questionnaires developed in different languages are being used as diagnostic and epidemiological screening tools for children at risk of OSAS.

**Clinical charts/physical examination**

The Sleep Clinical Record/Score (SCS) is a more comprehensive assessment tool that includes scores on physical examination other than subjective symptoms and clinical history of cognitive and behavioural problems. Anthropometric parameters specific for OSAS are assessed such as facial phenotypes, tonsillar size, tongue position, dental malocclusion and obesity. SCS has been evaluated as a tool for the diagnosis of OSAS in symptomatic school-aged and pre-school children with a sensitivity of 96.5% and 74%, respectively. Among all the items in SCS, the presence of oral breathing, nasal obstruction, septum nose deviation, tonsillar hypertrophy at grade 3 or 4, Friedman palate position III–IV, and a narrow palate was found to be significantly higher in the OSAS group as compared with the primary snoring group. In practice, the assessment and documentation of these clinical features are needed whether or not the scores are computed for the prediction of diagnosis or for monitoring.

**Overnight PO**

Continuous monitoring with PO is available at low cost and can be performed without the need of hospitalization. Brouillette et al. first proposed the McGill oximetry scoring system (1–4) based on the number of desaturation clusters and of desaturations below thresholds of 90%, 85% and 80%. It is now widely adapted as a tool for the prediction of OSAS and of urgency for surgery in children with adenotonsillar hypertrophy. The Australasian Sleep Association has laid down technical and report standards for overnight oximetry in the evaluation of OSAS in children. McGill scores of 2–4 are interpreted as positive while a score of 1 is inconclusive and OSAS cannot be excluded. Kaditis et al. analysed 25 published studies with extra parameters of baseline SpO₂ and oxygen desaturation index, with the aim of providing more specific interpretation for different age groups when PSG is not available. In a meta-analysis of three sleep screening tools, namely PSQ-SRBD score, OSA-18 score and PO, PO yielded superior specificity in detecting mild, moderate and severe paediatric OSAS (86%, 75% and 83%, respectively). PO combined with sleep questionnaires or SCS may help to identify severe patients for early intervention and prioritize patients for evaluation in resource-limited settings.

**Evaluation of the upper airway**

On diagnosis of OSAS in otherwise healthy children with enlarged tonsils, further investigation is usually not necessary. Radiological imaging of upper airway and flexible nasoendoscopy (FNE) performed during wake and sleep are being used to assess the site and degree of airway obstruction. The adenoidal–nasopharyngeal ratio or tonsillar–pharyngeal...
There is increasing use of DISE for the initial evaluation of children with upper airway obstruction and suspected adenoid hypertrophy. FNE is well tolerated by most children and it has the advantage of direct visualization of adenoids without the risk of radiation as in radio-imaging. Static CT or MRI to delineate the anatomy of the upper airway are only indicated for complex cases with craniofacial abnormalities like mandibular hypoplasia and mucopolysaccharidoses.

In patients with complex conditions at risk of multilevel obstruction, severe OSAS without enlarged adenoids or tonsils, persistent OSAS after AT, dynamic visualization of upper airway during sleep by drug-induced sleep endoscopy (DISE) and cine MRI of the upper airway can help to identify the target level for surgical correction and avoid unsuccessful surgery. There is increasing use of DISE for the evaluation of paediatric OSAS and it is generally considered a safe procedure. However, there is no consensus on the sedation protocol (dexmedetomidine, ketamine and propofol are the more common drug choices) and at least six different scoring systems have been used to report paediatric DISE findings to indicate the level and severity of obstruction. DISE is an invasive procedure that requires skilful providers, while facilities for cine MRI are limited. There is lack of data on the sensitivity and specificity of these tools and future research is needed to define the roles of these technologies.

**Treatment options**

OSAS in children is a heterogenous dynamic condition with diverse treatment options. Treatment strategies differ according to the underlying aetiology, severity, comorbidities and patient beliefs. However, the art of choosing the best option precisely for the patient at the right time is extremely challenging. Here, the ‘classical’ treatment options of AT and PAP for paediatric OSAS are discussed and various alterative surgical and non-surgical therapeutic choices are reviewed.

**AT and other surgical options**

AT has been considered as the first-line treatment for otherwise normal children aged ≥2 years old with enlarged adenoids or tonsils who suffer from OSAS. It is a safe procedure, with 93% of patients without perioperative complications and a success rate of 75% quoted for otherwise healthy non-obese children. However, AT produces resolution of SDB in only about one-third of obese children and careful assessment for risks and benefits is needed in children with craniofacial abnormalities, syndromal or neurological conditions with multilevel obstruction, and those with higher risks of complications. Tonsillar bleeding, upper airway obstruction, dehydration, nausea, vomiting and pain are known complications following AT. Intracapsular tonsillectomy or tonsillotomy with partial resection of tonsils instead of the classical complete tonsillectomy is becoming more commonly used for the treatment of children with SDB. Some studies showed that tonsillectomy resulted in a faster recovery and slightly lower risk of postoperative complications of bleeding and pain. However, more robust data from high-quality and long-term studies are needed to confirm its effectiveness and the risk of recurrence.

Children with risk factors for postoperative complications include young age less than 3 years, severe OSAS with an AHI score of >20 events per hour, cardiac complications, obesity, pre-existing structural comorbidities, or concurrent respiratory infections and should be subjected to at least a period of overnight in-patient observation postoperatively. Adiposity and elevated leptin in obesity may also affect the metabolism of analgesic drugs such as morphine during postoperative care.

Marcus et al. reported the results of the Childhood Adenotonsillectomy Trial (CHAT), the first large-scale, randomized controlled trial (RCT) of AT against watchful waiting for 453 children aged 5–9 years with mild-to-moderate OSAS. At 7 months, the AT group had better outcomes than the non-surgical group in terms of normalization of PSG parameters (79% versus 46%), higher symptoms and behavioural scores but there was no difference in attention and neurocognitive performance. The finding of almost half of the patients having a normalized AHI in the watchful waiting group at 7 months implied that a substantial proportion of patients can have natural improvement without intervention. Furthermore, there remained 20% of patients with abnormal PSG after AT. In two meta-analyses, AT was found to have better outcomes in PSG parameters and quality of life than watchful waiting, but long-term outcomes are lacking and there are still uncertainties on the best treatment options for specific age groups and severity of SDB.

There are ongoing research studies on more long-term outcomes of AT compared to watchful waiting, including the Pediatric Adenotonsillectomy Trial for Snoring for 3–12.9 years with mild obstructive SDB and the Pre-school OSA Tonsillectomy Adenoidectomy (POSTA study) focusing on neurocognitive outcomes of children aged 3–5 years.

Residual OSAS after AT is common and PAP is usually effective as a second-line therapy. In case of intolerance to PAP, careful evaluation of the upper airway with imaging or DISE will help to identify sites of obstruction for further surgical intervention. Lingual tonsillectomy, supraglottoplasty, tongue base suspension or reduction, expansion sphincter pharyngoplasty, tongue–lip adhesion, and bariatric surgery for obesity are some of the surgical options for management of OSAS in children.

Major surgical interventions like mandibular distraction osteogenesis or plastic surgery for mid-face hypoplasia require multidisciplinary involvement. If OSAS is...
severe and refractory, tracheostomy may be the only option to bypass the upper airway obstruction.

PAP therapy

Continuous PAP (CPAP) is considered as a second-line therapy indicated for residual OSAS post-AT or as a bridging therapy before surgery is available. It may also be one of the primary options for those who prefer not to undergo surgery, those with minimally enlarged lymph adenoid tissues not indicated for AT or those having comorbid conditions like obesity and craniofacial syndromes with multilevel obstruction.1,2,6,64 Bilevel PAP may be needed in patients with coexisting hypoventilation and neuromuscular weakness. The effectiveness of PAP therapy for adult OSAS has been well established but there are only limited small-scale studies available for children. There is evidence of improvement in PSG parameters and neurobehavioural outcomes in children receiving PAP for treatment of OSAS.65,66 In a study of obese adolescents with OSAS, 83% of PAP users had improved attention and academic performance compared with 86% of non-adherers who showed deterioration over time.67 However, the lack of appropriate equipment, difficulty in habituation and non-adherence are some of the practical problems.64,68 A systematic review of 20 studies by Watach et al. found an average PAP adherence to be a mere 56.9% and average PAP usage 4–5.2 hours per night in children and adolescents with OSAS.69 Female sex, younger age and developmental delay were identified as significant predictors for a higher chance of adherence to PAP therapy.58–70 In qualitative studies, the home and family structure, style of communication, social reactions and attitudes, adolescent perception of PAP benefits, and design of the machine and interfaces were some of the influential factors.68,71 Compliance can be improved by well-conducted PAP programmes with behavioural intervention, education, close follow-up, identification of barriers, and management of complications or discomforts of PAP.72,73 In-laboratory manual titration for an optimal CPAP pressure being the standard for PAP therapy in children is costly and labour intensive. There is more evidence to show that auto-PAP is safe and effective for titration and treatment, especially for initiation of CPAP therapy in older children.64,74

In children who are intolerant to PAP therapy, there are reports of case series to suggest humidified high-flow nasal cannula therapy may be an alternative; however, well-designed randomized studies are needed to delineate its effectiveness and role.75–77 The use of supplementary oxygen can improve SpO₂ but at the same time increase the duration of apnoea–hypopnoea events.78 In infants who are not candidates for PAP or surgery, low-flow oxygen supplementation could improve oxygenation and reduce obstructive AHI without an increase in CO₂.79 With limited available data, oxygen supplementation shall only be considered as an interim palliative treatment and subjected to careful titration to avoid hypercapnia.

Anti-inflammatory medications

Anti-inflammatory medications, mainly intranasal corticosteroids (INS) and oral montelukast (OM), have been used for primary and adjunctive treatment of paediatric OSAS. The rationale for use has been based on evidence of inflammation and the coexistence of rhinitis and asthma in OSAS.

Evidence of inflammation

It has been postulated that the repeated opening and closure of the upper airway in OSAS leads to mechanical stress and intermittent hypoxaemia, which activate and propagate the local and systemic inflammatory processes. Epigenetic alterations of the immune system with a decrease in regulatory T cells and obesity as a proinflammatory state are additional predisposing factors for chronic inflammation.80 The presence of nasal and oropharyngeal inflammation is evident by the detection of elevated inflammatory mediators such as leukotrienes and prostaglandins in exhaled breathe condensate and increased neutrophils in the sputum of children with OSAS.81,82 The elevation of serum C-reactive protein was one of the first inflammatory markers, suggesting chronic low-grade inflammation.83,84 Levels of proinflammatory cytokines, including TNFα, IL-6, IL-8, ICAM, VCAM and selectins, were found to be significantly higher in OSAS patients.85–87 Elevated inflammatory biomarkers are found to be associated with cardiovascular and neurocognitive risks in adult and children. Furthermore, an improvement in inflammatory markers is observed with the treatment of OSAS.83,88 In the past decade, research findings also accumulated to show that certain specific biomarkers may help to predict treatment outcomes and the associated end-organ morbidities.89 High-sensitivity C-reactive protein and IL-23 may serve as blood markers for the persistence of SDB after AT.90,91

Impact of rhinitis and asthma

Allergic and non-allergic rhinitis commonly coexist in children with obstructive SDB but are not found to be associated with severity.92,93 The nose is the port of entry that contributes more than 50% of the total airway resistance. Although obstruction of the nose alone is not the cause of OSAS, it adds negative pressure to the pharynx, leading to further collapse. The small narrow nasopharyngeal passage and the high prevalence of adenoid hypertrophy in addition to rhinitis predispose a child to SDB.94,95 The relationship of asthma and obstructive SDB is bidirectional. The risk of development of SDB is two times higher in asthmatic children compared with non-asthmatics and children with obstructive SDB are more likely to develop asthma.86,87 AT for SDB also appears to improve asthma control but it is uncertain if the control of asthma can improve SDB.98

Intranasal corticosteroids

INS are topical anti-inflammatory agents aimed at decreasing local inflammation of the upper airway and improving airway patency through a reduction in the size of adenoids in children.
with adenoidal hypertrophy and as a treatment of coexisting rhinitis in obstructive SDB. INS such as budesonide, fluticasone and mometasone are commonly used for the treatment of paediatric SDB but there are only a few high-quality controlled studies available. Brouillette et al. conducted an RCT with the application of nasal fluticasone propionate for 6 weeks in children aged 1–10 years with various severity of OSAS and adenotonsillar hypertrophy. The results demonstrated that the AHI score reduced from 10.7±2.6 to 5.8±2.2 events per hour in the fluticasone group but increased from 10.9±2.3 to 13.1±3.6 events per hour in the placebo group (p=0.04) with no change in adenotonsillar size. Another RCT done by Chan et al. recruited children aged 6–18 years with mild OSAS and compared intranasal mometasone furoate against placebo for 16 weeks. There was an improvement in PSG parameters, with the mean obstructive AHI score decreasing from 2.7±0.2 to 1.7±0.3 events per hour in the intervention group but increasing from 2.5±0.2 to 2.9±0.6 events per hour in the placebo group (p=0.039). There was a small reduction in oxygen desaturation index in the intervention group without changes in size of adenoids or tonsils and the results seemed to be more significant for the subgroup with allergic rhinitis. The 2020 updated Cochrane review included the above two placebo-controlled studies with a total of 75 patients for meta-analysis. The primary outcome of difference in AHI score (−3.18 events per hour; 95% CI −8.70 to 2.35) favoured the intervention but the result was not significant. The authors concluded that there was insufficient evidence to confirm the efficacy of INS alone as a treatment for OSAS in children. There were no significant adverse effects reported from both studies but long-term side effects of INS were not available. Liu et al. conducted another meta-analysis to include adult and paediatric studies. Other than outcomes in PSG parameters, the four analysed studies (including three paediatric studies) demonstrated an improvement of subjective quality of life outcomes, including Epworth Sleepiness Score, OSAS symptoms score, nasal symptoms and daytime alertness. Hitherto, there is still a lack of data on long-term neurocognitive and cardiovascular outcomes.

For patients being put on CPAP as a treatment of OSAS, rhinorrhea and nasal obstruction are common complaints leading to non-adherence. A systematic review showed that a 4-week adjuvant therapeutic course of INS might have benefits resulting in a longer average duration of use of CPAP per night but results were not significant. A more recent study showing additional INS treatment decreased the frequency of nasal symptoms among patients with OSAS initiating CPAP therapy and increased compliance to CPAP after 90 days of treatment. No similar studies were found in paediatric patients.

**Leukotriene receptor antagonists**

OM is a leukotriene receptor antagonist (LTRA) widely used for allergic diseases, including asthma and allergic rhinitis, which commonly coexist with paediatric OSAS. The 2020 updated Cochrane review on the effects of anti-inflammatory medications for the treatment of paediatric OSAS included two RCTs with a total of 103 children aged 1–18 years and compared OM against placebo from 6 weeks to 4 months. The results showed that OM had a short-term effect of a significant reduction of AHI by 3.41 events per hour (95% CI −5.36 to −1.45). However, it was uncertain if the small difference in PSG parameters demonstrated was clinically relevant and whether the effects could be sustained after the treatment period. Another meta-analysis was conducted by Liming et al. to study the effects of OM with or without INS for 6–16 weeks on children aged 2–5 years with mild-to-moderate OSAS. Five studies including 166 children on OM alone showed that 55% had improvement with a reduction of mean AHI by 2.7 events per hour (95% CI −5.6 to −0.3) pre-treatment and post-treatment. Besides, the lowest SpO2 was significantly higher post-treatment. Similar to studies on INS, it was unsure if the improvement in PSG parameters could be translated to benefits in clinical symptoms, sleep quality, daytime performance or long-term outcomes. Furthermore, parents and patients have to be warned about the side-effects of OM. In early 2020, the US FDA further strengthened the ‘black-box’ warnings on OM concerning serious mood and behavioural changes.

**Combination of INS plus LTRAs**

In the meta-analysis by Liming et al., studies on OM plus INS in 502 patients found a 70% improvement in mean AHI by 4.2 events per hour (95% CI −6.3 to −2.0). A retrospective review of 752 children aged 2–14 years with mild OSAS being treated with 12 weeks of combined INS and OM as initial treatment appeared to provide an effective alternative to AT, particularly in younger and non-obese children. Another prospective cohort study of 35 children aged 3–6 years with mild OSAS treated with combined intranasal fluticasone and OM for 4 months was conducted. Results indicated significant improvement in quality of life measures with the OSA-18 score. The combination of INS and OM for a period of 12 weeks could improve symptoms or normalize PSG parameters in children with residual SDB after AT. A comparative study of INS, OM or INS plus OM for 12 weeks was conducted and results suggested that the combination treatment might be more effective than either INS or OM alone.

In practice, expert consensus and clinical guidelines suggest the consideration of a trial of INS and OM for a period 1–6 months in children with mild-to-moderate OSAS and adenotonsillar hypertrophy, especially if parents refuse surgery. Patients shall be followed-up regularly to monitor clinical response and side-effects and resort to surgical or PAP therapy if drug treatment fails. There could be benefits in residual OSAS after AT and as an adjunctive therapy for patients on CPAP therapy. Yet, the definitive role, indications and duration of INS and OM in the treatment of paediatric OSAS remain unclear. There are insufficient long-term data on end-organ outcomes and the sustainability of treatment effects as well as uncertainties about its effectiveness in children with...
other comorbidities. Larger scale and extended studies on the efficacy and safety of INS and OM and on predictive factors are needed to guide clinicians to select the precise treatment for patients who will benefit most.

**Systemic corticosteroids**

Al-Ghamdi et al. reported that a 5-day course of systemic oral prednisolone of ~1 mg/kg per day was ineffective in treating OSAS caused by adenotonsillar hypertrophy.112 In a recent study including 12 children with severe OSAS and adenotonsillar hypertrophy receiving a short 5-day course of oral betamethasone (0.1 mg/kg) in addition to intranasal betamethasone, a significant reduction in sleep clinical record scores and minimal SpO₂ was observed at 3 weeks post-treatment. The author commented that this could be considered as an interim treatment before surgery.113 However, this small-scale study reporting only short-term results cannot support the routine clinical use of systemic corticosteroids.

**Antibiotics**

Antibiotics have been used for the treatment of recurrent tonsillitis but there is limited evidence to support the use for adenotonsillar hypertrophy or paediatric SDB. Two RCTs using oral azithromycin for 30 days to 6 weeks in children with adenotonsillar hypertrophy were compared with placebo or intranasal fluticasone, suggesting only temporary improvement in clinical symptoms related to obstructive events. The risk of prolonged courses of antibiotics causing drug resistance outweighs the marginal benefits of such practices.114,115

**Other medications**

Adjunctive pharmacotherapy has been suggested to improve wakefulness in adult patients with excessive daytime sleepiness associated with OSAS. Modafinil and armodafinil are central nervous system stimulants and solriamfetol is a dopamine/norepinephrine reuptake inhibitor. However, these are not approved for paediatric use.116–118 Other medications, like selective serotonergic uptake inhibitors, methylxanthines or protriptyline, are not recommended for the treatment of OSAS.117

A clinical trial with dimethyl fumarate, an immunomodulatory agent for multiple sclerosis, reported promising results in the reduction of severity of OSAS in adults.119 The combination of a norepinephrine reuptake inhibitor (atomoxetine) and an antimuscarinic (oxybutynin) administered orally to adults before bedtime demonstrated improvement in genioglossus muscle activity and upper airway patency, resulting in reduced OSAS severity.120 No paediatric data are available for these novel treatments.

**Weight reduction**

The prevalence of OSAS in obese children and adolescents is estimated to be 60%. Adiposity, lymphoid hypertrophy in the upper airway and proinflammatory state are some of the predisposing factors.121 Residual OSAS post-AT in obese children is high, ranging from 33% to 77%.122 CPAP demonstrates improvement in PSG parameters but it is difficult to sustain long-term adherence. The few available studies support the notion that weight loss is beneficial, particularly for morbidly obese adolescents and children. Surgical weight loss appeared to be more effective in the reduction of BMI and resulted in a lower prevalence of persistent OSAS of 10–18%, which was lower than that observed with behavioural weight loss of 33–38%.122

**Dental treatment**

Chronic upper airway obstruction and mouth-breathing in children with OSAS lead to forward head postures, craniofacial abnormalities (e.g. maxilla–mandibular retrusion, increased anterior facial heights) and abnormal dental morphological features (e.g. maxillary/mandibular crowding, high arch and narrow palate).123,124 Dentists may play a role in the early detection of OSAS in children and dental/orthodontic treatment options have emerged in the past decade for children with OSAS who exhibit orofacial abnormalities.125 These include rapid maxillary expansion (RME), mandibular advancement appliance or maxillo-mandibular surgeries.123 RME can help to increase nasopharyngeal and oropharyngeal space for children with upper jaw restriction. In a systemic review of 17 studies reporting outcomes for 314 children, there was a 70% reduction in AHI values and 25% achieved a resolution of OSAS within 3 years after RME.126 In a recent meta-analysis with three RCTs including a total of 66 patients receiving a mandibular advancement appliance surgery, there was significant improvement in PSG parameters and symptoms compared with placebo for all severity of OSAS. Subgroup analysis suggested that it was more effective if treated before the end of puberty for a duration of 6 months or longer.127 Daily usage for longer periods could advance the mandible faster and is particularly suitable for children with class II malocclusion (retrognathia), while prolonged wearing in class I (normal) dental occlusion may result in unfavourable dental and facial changes. A combination of AT and dental interventions might be more effective in patients than performed separately.128 Mandibular distraction osteogenesis is one of the maxillo-mandibular surgeries performed for children with congenital craniofacial abnormalities such as Pierre Robin sequence or Treacher Collins syndrome.123 These interventions should be co-ordinated by a multidisciplinary team, preluded by and followed-up with sleep studies.

**Oral myofunctional therapy**

In the past two decades, there has been increasing research and clinical application of oral myofunctional therapy (OMT) in the treatment of OSAS. OMT involves the re-education of facial and oral muscles to achieve appropriate daytime and night-time positioning, strong sucking, mastication, and swallowing
Choosing the best treatment plan for an individual patient

In a network meta-analysis, the effectiveness of various interventions for paediatric OSAS were compared. Fourteen comparative studies involving 1064 otherwise healthy children with adenotonsillar hypertrophy were included. The study concluded that a surgical approach with AT was still the most effective intervention compared with no treatment in terms of improvement in AHI.\(^{131}\) However, residual and recurrent OSAS after AT is common and can be attributed to multiple factors. Despite the availability of algorithms and consensus guidelines, further research is needed on the classification of severity, the evaluation of long-term outcomes of the various treatment options, and on the investigation of objective predictors, e.g. inflammatory biomarkers, so to aid in choosing the most effective option for a given individual.\(^{91}\)

Conclusions

OSAS in children is a heterogenous condition with multiple contributing factors. The decision of treatment has to be individualized and a combination of therapeutic options is often required. A multidisciplinary team management approach involving a paediatric pulmonologist, an otolaryngologist and orthodontist is often needed.

### Key practice points

#### Diagnosis and assessment

- Polysomnography is the reference standard for the diagnosis of paediatric obstructive sleep apnoea syndrome (OSAS). In resource-limited settings, overnight pulse oximetry, validated sleep questionnaires and clinical examination charts can be used as alternative screening tools.
- Adenotonsillar hypertrophy is the most common contributing factor. Assessment for comorbid conditions, including craniofacial abnormalities, obesity, neuromuscular diseases and allergic airway diseases, is needed to guide the choice of optimal treatment.
- Drug-induced sleep endoscopy and cine MRI of the airway are advanced tools that may help to identify the site(s) of airway obstruction in children with complex comorbidities or residual OSAS post-adenotonsillectomy.

#### Treatment options

- The management plan must be personalized and often requires more than one treatment modality with involvement of a multidisciplinary team.
- In non-obese, otherwise healthy children with adenotonsillar hypertrophy, management depends on severity:
  - Adenotonsillectomy is the first-line treatment option for moderate-to-severe OSAS.
  - A period of watchful waiting with follow-up is a reasonable option for mild OSAS.
- Intranasal corticosteroids and oral montelukast, used alone or in combination for a few weeks to 6 months, can be considered as an empirical treatment for mild OSAS or as an adjuvant therapy for those with allergic rhinitis, asthma and nasal symptoms associated with positive airway pressure therapy.
- Positive airway pressure therapy is an effective option for selected patients. The provision of appropriate equipment and support with a well-coordinated programme for initiation, education and follow-up are essential to ensure adherence.
- Weight reduction programmes are particularly important for morbidly obese children and adolescents.
- Dental treatment and myofunctional therapy are additional therapeutic options for patients with primary or secondary craniofacial abnormalities.

#### Follow-up

- Residual and recurrent OSAS after adenotonsillectomy is common. Follow-up is needed for long-term neurocognitive and cardiovascular adverse outcomes.

#### Future

- Research studies on inflammatory markers may provide non-invasive tools in the future for screening, diagnosis, precise management and monitoring.
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