What Is “Abnormal” in Pediatric Sleep?

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Summary

Sleep-disordered breathing in general and, more particularly, the obstructive sleep apnea syndrome are highly prevalent conditions in children. Although the diagnosis appears relatively straightforward using a sleep study (polysomnography), this labor-intensive and expensive procedure is used in only a minority of cases across the country because of the relative unavailability of pediatric sleep centers. However, the definition of an abnormal sleep study is not a trivial process and requires a methodical delineation of normative data, implication of “abnormal” variables to specific outcomes, and demonstration of cost-effectiveness of such approach. Unfortunately, such studies are lacking; there is no real consensus on any of these important aspects, which in turn leads to delays in diagnosis and treatment. Such paucity of validated data, however, is an opportunity to explore alternative options that would enable incorporation of biomarkers into well defined and validated algorithms. There is no doubt that novel approaches to the evaluation of community-based and clinically referred pediatric populations should enable more pragmatic and reliable diagnostic approaches for pediatric sleep-disordered breathing. Key words: pediatric; obstructive sleep apnea syndrome; polysomnography; sleep-disordered breathing. [Respir Care 2010;55(10):1366–1374. © 2010 Daedalus Enterprises]
Table 1. Frequent Clinical Symptoms and Findings in Pediatric Obstructive Sleep Apnea

<table>
<thead>
<tr>
<th>Symptom/Findings</th>
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<tr>
<td>Habitudinal snoring (audible snore &gt; 3 nights/week)</td>
</tr>
<tr>
<td>Elevated C-reactive protein (&gt; 0.4 mg/mL)</td>
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<tr>
<td>Elevated liver enzymes in obese children</td>
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<tr>
<td>Low-density lipoprotein cholesterol &gt; 80 mg/dL</td>
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<tr>
<td>High-density lipoprotein cholesterol &lt; 40 mg/dL</td>
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<tr>
<td>Fasting insulin &gt; 25 μU/mL in obese children</td>
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<tr>
<td>Enlarged adenoids (&gt; 50% of airway cross-sectional size)</td>
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<tr>
<td>Enlarged tonsils (≥ +2)</td>
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<tr>
<td>Left-ventricular hypertrophy</td>
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<tr>
<td>Systemic hypertension</td>
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<tr>
<td>Obstructive apnea-hypopnea index &gt; 2 events/h of total sleep time</td>
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<tr>
<td>Respiratory arousal index &gt; 2 events/h of total sleep time</td>
</tr>
<tr>
<td>Nadir S\textsubscript{PO2} &lt; 90%</td>
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<tr>
<td>Mouth-breathing and limited nasal air flow</td>
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<tr>
<td>Chronic rhinorrhea</td>
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<tr>
<td>Retrognathia</td>
</tr>
<tr>
<td>Cor pulmonale</td>
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<tr>
<td>Academic difficulties</td>
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<tr>
<td>Excessive daytime sleepiness</td>
</tr>
<tr>
<td>Weight gain</td>
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<tr>
<td>Obesity (body mass index z score ≥ 1.65)</td>
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<tr>
<td>Truncal obesity</td>
</tr>
<tr>
<td>Enlarged neck circumference</td>
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<tr>
<td>Recurrent ear infections</td>
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<tr>
<td>Hyperactive behaviors</td>
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<tr>
<td>Depression</td>
</tr>
<tr>
<td>Low self esteem</td>
</tr>
<tr>
<td>Social withdrawal</td>
</tr>
<tr>
<td>&gt; 5 visits per year to primary care physician for respiratory symptoms</td>
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<tr>
<td>Difficulty breathing during sleep</td>
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<tr>
<td>Excessive sweating during sleep</td>
</tr>
<tr>
<td>Frequent awakenings and restless sleep</td>
</tr>
<tr>
<td>Breathing pauses reported by parents</td>
</tr>
<tr>
<td>Night terrors</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Morning headaches</td>
</tr>
<tr>
<td>Fatigue, tiredness, reduced physical activity</td>
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</table>

What is “Abnormal” in Pediatric Sleep?

Sleep. Multiple parameters, such as chest and abdominal wall movement, heart rate (electrocardiogram), and air flow (using either a sidestream end-tidal capnograph, nasal-pressure cannula, or oronasal thermistor), need to be measured during the overnight sleep recordings. Preferably, respiratory inductance plethysmography should be used, since such approach can allow for extrapolation of air flow when the other 2 sensors are not available. Arterial oxygen saturation (S\textsubscript{PO2}) is assessed via pulse oximetry, with simultaneous recording of the pulse waveform, and with minimal averaging (ie, 3 s).

The bilateral electro-oculogram, 6–8 channels of electroencephalogram, chin and bilateral anterior tibial electromyogram, and analog output from body-position sensor are also monitored. Snoring is measured via tracheal sounds monitored with a microphone sensor. A digital time-synchronized video recording should be performed during the NPSG. The proportion of time spent in each sleep stage will be expressed as percentage of total sleep time, and central, obstructive, and mixed apneic events should be counted. In most pediatric sleep centers obstructive apnea is defined as the absence of air flow with continued chest wall and abdominal movement for a duration of at least 2 breaths. Hypopneas are defined as a decrease in oronasal flow of > 50% with a corresponding decrease in S\textsubscript{PO2} of > 4% and/or arousal. The severity of the disease is defined as the number of apneas and hypopneas per hour of total sleep time (apnea-hypopnea index [AHI]). The diagnostic criteria for OSAS differ among different centers, and may include an AHI > 2–5 events/h of total sleep time, with a nadir S\textsubscript{PO2} of at least < 92% in the presence of habitual snoring and daytime symptoms.

Several factors have hampered more extensive implementation of such recommendations, with the most important among those being the inconvenience for both parent and child to spend the night in the laboratory, the rather onerous and labor-intensive nature of this diagnostic procedure, the relative scarcity of laboratories with expertise in sleep disorders in children, and, as a corollary to this issue, an inordinately extended waiting period between referral and testing.

Based on these considerations, the initial question that has been raised revolves around the importance of diagnosing and treating OSAS in a timely fashion. In other words, what are the morbid consequences of OSAS? While some of these consequences will be addressed elsewhere in more detail, it is now well established that OSAS may lead to serious and measurable end-organ dysfunction, primarily affecting the cardiovascular and central nervous systems. However, multiple layers of added complexity in the process of determining the best approach to diagnosis need to be considered. For example, not every child with OSAS, even when the condition is severe, will manifest any of the complications.

Before we are to rank patients according to severity and risk, and consequently prioritize treatment, we need to improve our understanding of the individual and environmental determinants of susceptibility to the 4 major components of OSAS, namely, episodic hypoxia, intermittent hypercapnia, increased intrathoracic pressure swings, and sleep fragmentation. Of note, the conventional numerical measures derived from NPSG (eg, obstructive AHI, oxyhemoglobin desaturation index, and arousal index) are relatively poor predictors of morbidity, even if dose-dependent relationships have emerged between morbidity and these sleep measures. Notwithstanding, we should point out that polysomnographic approaches allow for objective quantitation of most of the abnormalities related to inter-
miment upper-airway obstruction during sleep, such as hypoxia, hypercapnia, and arousals.

Sleep studies can also provide qualitative or quantitative reporter information on intrathoracic pressure swings, via AHI, paradoxic breathing, heart-rate variability, or esophageal pressure measurements. Additionally, some of the morbidities may develop over a long period of time until they become manifest, and such occurrences are also contingent on interactions between the disease and individual susceptibility factors, such that accurate recordings of all of the abnormalities that play a role in such morbidity may not, despite their accuracy and objectivity, strongly correlate with the degree of end-organ dysfunction. However, we are unaware of a consensus whereby specific polysomnographic criteria have been recommended and will reliably identify those children requiring treatment and those in whom treatment is either not indicated or can be postponed. Thus, it seems of paramount importance to discuss these issues in this contextual setting, and put forth novel ideas regarding alternative diagnostic methodologies.

Diagnosis of Pediatric Obstructive Sleep Apnea

For the sake of simplicity, we will restrict our discussion by addressing only those children with habitual snoring who are otherwise healthy. In other words, children with craniofacial or genetic syndromes or neuromuscular diseases should be discussed separately and will be excluded from the scope of this paper. For the sake of some degree of consensus, we will refer to habitual snoring as the presence of snoring loud enough to be recognized by the parents and occurring at least 3 nights per week. Since this definition is not universally adopted, and since different cultural settings will view the presence of snoring sounds as either worrisome or as not requiring attention, it becomes evident that use of questionnaire-based tools that uniquely inquire on “snoring” is fraught with a high probability of failure to identify children at risk for end-organ morbidity (ie, those children with OSAS who need to be treated).

In recent years, several questionnaire-based approaches have been developed and enable some degree of predictability in the detection of OSAS or some of its consequences, such as sleepiness or hyperactive behaviors. However, we should emphasize that such tools have not been extensively evaluated beyond the program where they were developed, nor has their validity been assessed across different countries or settings (ie, community vs referral populations). Notwithstanding, the overall predictability of these instruments is relatively poor, usually yielding low areas under the curve in receiving operator characteristic (ROC) curves. Even in the clinical setting where symptomatic children are being evaluated, the overall accuracy of the prediction varies greatly, with a median around 60–70%. This relatively poor predictive ability has therefore prompted the recognition and recommendation to refer symptomatic children for NPSG to either confirm or negate the putative diagnosis of OSAS. Because of the high cost and inconvenience associated with laboratory-based NPSG, abbreviated and simpler overnight studies using nocturnal home video recordings have been examined and so far have fallen short of improving the diagnostic yield.

Unfortunately, although normative reference values have been published in the context of NPSG over the last decade, the exact NPSG criteria for definition of OSAS have been difficult to delineate (see below). I am of the opinion that one of the major reasons for the lack of consensus in the diagnostic criteria is due to the relative dichotomy between NPSG-derived measures and clinical symptoms. In other words, even though significant correlations have been reported between the clinical severity of symptoms and consequences of OSAS and NPSG measures, the magnitude of variability in such relationships precludes reliable pairing of these 2 components. Children who are very symptomatic may present a “normal” NPSG in the presence of habitual snoring, and, conversely, relatively asymptomatic snoring children may have concurrent and severe respiratory disturbances in their NPSG. These observations have led some investigators to develop a priori sensitive, albeit poorly specific, clinical scores that would enable the diagnosis of OSAS without the need for NPSG. While the conceptual framework of simplifying the diagnosis of OSAS is clearly attractive, both from the pragmatic and healthcare-cost perspectives, none of these instruments has been critically tested against NPSG or the probability of end-organ morbidity that would justify its use in referring for treatment.

Is the NPSG theAccepted Standard for Diagnosing OSAS?

There is no doubt that NPSG recordings provide unbiased and objective information about a variety of sleep-related events, such as sleep architecture, cardiac and respiratory patterns, and gas exchange. Thus, it is attractive to assume that if reference values are obtained, subsequent delineation of pathological criteria should be a straightforward procedure. This supposition was based on the initial assumption that distribution of reference values will follow a Gaussian pattern. Unfortunately, that assumption has not been corroborated. Furthermore, evidence demonstrated that, even in the context of habitually snoring children, the obstructive AHI, the most widely used variable to judge the severity of OSA, was not distributed in a Gaussian fashion among 674 habitually snoring children referred for NPSG for suspected OSAS. Indeed, Chan and Ng showed that simple linear regression approaches
were insufficient to linearize the AHI, and that a relatively complex mathematical process, namely, a negative binomial regression model with an offset of total sleep duration, was required to enable linearity of the AHI. Similarly, only a few studies have critically examined the distribution of nocturnal oximetry values in healthy children, and subsequently defined criteria for pathological values and severity range using pertinent statistical models.

Notwithstanding such a priori obstacles, the association between OSAS disease severity (defined through current NPSG-derived parameters) and OSAS outcomes is relatively weak, as previously mentioned. We should remember that an optimal diagnostic policy is one that minimizes the expected total cost and burden of diagnosing a patient, where the cost is the sum of 2 components: measurement costs (the costs of performing the required diagnostic tests); and the costs associated with misdiagnosis (ie, the costs incurred when the patient is either incorrectly diagnosed or when, more pertinent to our discussion, the diagnosis is missed). In this context, there is a clear tradeoff between these 2 types of costs. Based on such considerations, the difficulty of linking the measurements derived from a test (eg, AHI) to either the severity of symptoms or to the prediction of actual morbidities would make it superfluous to persist in our efforts to explore further in this direction. Instead, we should probably focus our attention on the development of novel and better-performing diagnostic methods that address either the problem of the weak association between symptoms and test findings or, alternatively, that permit reliable extrapolation from the test findings as to the presence or absence of end-organ morbidity.

In summary, the cumulative evidence indicates that among the conventional NPSG-derived measurements we are unlikely to identify any measurements that permit valid prediction of sleep-disordered breathing-associated outcomes. Such an a priori “gloomy prediction” should rather be viewed as a unique opportunity for development of reliable diagnostic alternatives.

### Other Potential Diagnostic Alternatives

In an effort to simplify the diagnosis and make it more accessible and convenient to patients, unattended home-based overnight oximetry studies have been explored. The major constraint to such approach is that it enables reliable screening for identification of only the subset of patients with more severe OSAS, and that such goal is achieved only in part because there is clearly a group of severe OSAS patients in whom marked oxyhemoglobin desaturations are not present. Furthermore, validated mathematical algorithms that enable automated and valid recognition of such positive severe cases have not been developed, and multicenter studies aiming to define the role of such approach and identify its limitations in the diagnostic algorithmic cascade have yet to be conducted.

An alternative, less onerous, and potentially useful approach would consist of home-based multichannel studies. This approach has been implemented with relative success in adults and has led to a consensus statement by the American Academy of Sleep Medicine. However, the frequency and severity of the events is markedly higher in adults, such that the ROC performance curves using these simplified approaches would be less likely to be affected. Also, multichannel monitors in the home are flawed by the absence of reliable assessments of sleep disruption and have not been critically tested in children. Of course, technological advances have permitted portable full NPSG systems, and while such approaches are clearly of value in research settings, it is unclear whether they provide any specific additional benefits to the cost balance considerations discussed above. We should also mention that the electrocardiogram signal or other tools providing non-invasive assessments of changes in autonomic nervous system tone have been proposed as potentially valuable and simple strategies, particularly when interfaced with simultaneous acquisition of oximetry, since they would allow for detection of both hypoxic events and arousals. The addition of other relatively non-obtrusive sensor technologies that record snoring, body position, air flow, and actigraphy to moment-to-moment autonomic recordings and oximetry may be promising, and certainly deserve further exploration.

### Biomarkers and OSAS Diagnosis

Based on the conceptual framework that OSAS will result in unique signatures in the expression of either genes or proteins, exploration of such signatures using novel technologies, such as genomics, proteomics, lipidomics, or metabolomics, would seem a worthwhile effort. The biological plausibility of this approach became apparent when we reported on the dose-dependent changes in vascular endothelial growth factor plasma concentration in children with sleep-disordered breathing. These findings with a single biomarker spurred subsequent exploration of predictable changes in either the gene expression of peripherally circulating white blood cells or in urinary proteins, with the intent to identify the most promising biomarkers and their overall applicability for home or pediatrician/primary-care physician office screening. The overarching concept of such preliminary studies was that the presence or absence of specific markers in a particular cluster would be closely linked to the diagnosis of OSAS and that some of the markers could also reveal OSAS-associated end-organ morbidity. If such assumptions are verified, they should permit delineation of specific algorithms for population screening (low cost, high sensitivity technique).
Obstructive apnea and hypopnea index > 2 events/h of total sleep time
Respiratory arousal index > 2 events/h of total sleep time
Nadir $S_{O_2}$ < 90%
Excessive daytime sleepiness
Academic difficulties
Hyperactive behaviors
Arterial blood pressure > 85th percentile
Enuresis
Obesity (body mass index z score > 1.67)
Adenoids ≥ +2 and/or tonsils ≥ +2

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
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<tbody>
<tr>
<td>C-reactive protein &gt; 0.4 μg/mL.</td>
<td>High-density lipoprotein cholesterol &lt; 40 mg/dL.</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol &gt; 80 mg/dL.</td>
<td>Fasting insulin &gt; 20 μIU/mL.</td>
</tr>
<tr>
<td>Elevated norepinephrine/creatinine ratio (&gt; 85th percentile)</td>
<td>Recurrent otitis media and/or status post tympanostomy tubes</td>
</tr>
<tr>
<td>&gt; 5 visits per year to primary care physician for respiratory symptoms</td>
<td>Adenoids ≥ +1</td>
</tr>
<tr>
<td>Tonsils ≥ +1</td>
<td>Tonsils and/or allergic rhinitis</td>
</tr>
<tr>
<td>Family history of OSAS</td>
<td>Nadir $S_{O_2}$ ≥ 90% but &lt; 93%*</td>
</tr>
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* If supported by a history of habitual snoring, we could, as a not validated example, propose the use of any 5 major criteria or of any 3 major and any 3 minor criteria as potentially and reliably indicating the presence of obstructive sleep apnea (OSA) that requires referral for treatment.

(Adapted from Reference 56).

and specificity) and potentially enable priority assignments for treatment and outcome monitoring in those children considered at increased risk.

A very recent study from our laboratory lends compelling support to the aforementioned propositions. Morning urine samples from 120 children were analyzed using differential in-gel electrophoresis (2D-DIGE). We found that unique sets of proteins were either increased or decreased in the urine of children with OSAS. ROC curve analyses using more than one of the putative biomarkers showed that if all 4 proteins were employed, the presence of levels exceeding the cut-offs for ≥ 2 of the proteins yielded a 100% sensitivity and 96.5% specificity to predict OSAS.55

### Novel Unifying Algorithms for Diagnosis of OSAS in Children

The aforementioned arguments markedly restrict the ability of statistical approaches for accurate diagnosis of OSAS, and particularly its severity, when using NPSG criteria alone or in combination with the patient history and physical examination. Therefore, we have clearly stated the goal that alternative diagnostic methods that encompass accurate determination of OSAS disease and its severity are needed if our discipline is to progress.

In the interim, and until such goals are accomplished, we have proposed an alternative approach that we believe should be critically examined by a multicenter prospective trial.56 The structure of this approach is rather straightforward, and utilizes conventional and readily available tests. The rationale, similar to other diseases, is a combination of several criteria, which could include, for example, the presence of specific symptoms related to OSAS, the use of NPSG measures that would employ consensus-derived cut-offs, and incorporation of measurable outcomes. The latter would include functional measures (eg, school performance changes over time, excessive daytime sleepiness questionnaire score, behavioral issues, dynamic memory test results, quality of life), and results of laboratory tests (eg, serum levels of high-sensitivity C-reactive protein, tumor necrosis factor alpha, fasting insulin and glucose, lipid profile, adhesion molecules). This approach, which is summarized in Table 2, could be viewed as analogous to that of the Jones criteria for the diagnosis of rheumatic fever.57,58 In this context, habitual snoring would be a mandatory requirement and could be defined, for example, as the presence of loud snoring ≥ 3 nights a week.

There would be a set of major criteria, which could include a number of polysomnographic findings, as well as a number of cardinal symptoms of OSAS, as well as a number of reported problems that have been thus far causally associated with OSAS in children. As mentioned, these could include recent onset of school performance problems,59 behavioral issues such as hyperactivity and inattention,60,61 excessive daytime sleepiness,62,63 bed-wetting,64,65 hypertension or altered endothelial function,8,66,67 and obesity.68-70

For minor criteria, we would propose inclusion of high-sensitivity C-reactive protein greater than a defined cut-off,71,72 high-density and low-density lipoprotein cholesterol,72 fasting insulin,72 elevated urinary norepinephrine,73,74 a history of recurrent otitis media or need for tympanostomy tube placement,75 previous adenotonsillectomy for OSAS-like symptoms, history of asthma or allergic rhinitis,76-79 family history of OSAS (one parent or > 3 close family members, including siblings, formally diagnosed with OSAS),80,81 or increasingly frequent respiratory illnesses leading to consultation with a primary care physician.
In addition, the presence of tonsillar and adenoid hypertrophy, as derived from a set of standardized visually derived assessment scores, would also be included, and its severity would ascribe their assignment to either minor or major criteria.

While this proposed approach has yet to be prospectively validated, we believe that it provides the conceptual framework aiming to improve the recognition of those clinically referred children who would be most likely to benefit from treatment. Nevertheless, how many major and how many minor criteria need to be included in the diagnostic algorithm, such as to optimize the ROC curve characteristics of such approach, will definitely need a multicenter prospective study working alongside a panel of recognized experts in this area. In addition, some of the minor criteria may not be as applicable to specific populations with intrinsically lower susceptibility, in whom the probability of such criteria being present may be lower. In addition, use of additional criteria such as size of adenotonsillar tissues in relation to the upper-airway size or the degree of nasal resistance may be considered as well, if appropriately validated in other cohorts.

Another not yet validated but potentially viable alternative is included in Figure 1. While rather simplistic and unsubstantiated clinical algorithms have been proposed, the current putative approach distinguishes between screening children in schools versus those being evaluated in the context of clinical referrals. However, the algorithm essentially merges these 2 possibilities after an initial inquiry step in the screening mode, and attempts to incorporate clinical elements only. This proposition is intended for consideration in habitually snoring children who do not have obvious neuromuscular, craniofacial, or genetic syndromes.

**Summary**

OSAS in children is a frequent disease, for which optimal diagnostic methods have yet to be developed. There is currently no definitive set of polysomnographic criteria that will reliably discriminate those children who have OSAS and require treatment, so combinatorial algorithms need to be explored to optimize early and dependable identification of those children. Alternatively, novel unbiased diagnostic approaches that are both sensitive and specific, require less effort, and are more affordable need to be identified to permit prospective screening of the large number of habitually snoring children.

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57. Jones TD. The diagnosis of rheumatic fever. JAMA 1944;126:481-484.
I should caution, however, that the effects we’ve seen are clearly better in younger children. When the child is older, the tonsillar tissues are more fibrotic and the effect of the anti-inflammatory agents appears to be lessened. However, these agents work very well in younger children.

**Discussion**

**Carlin:** What types of anti-inflammatory treatments are available for children? What’s in your medication armamentarium for children?

**Kheirandish-Gozal:** There is no FDA-approved pharmacologic therapy right now for children. Basically we use agents that we have tested in some of our studies. I conducted a randomized double-blind placebo-controlled crossover trial in which children received intra-nasal budesonide for 6 weeks, then had 2 weeks of wash-out, and then were switched to the other arm, so everybody eventually received the medication. Six weeks of intra-nasal budesonide statistically significantly improved mild OSA.

Several years ago Dr Goldbart and others conducted an open-label study with montelukast, and found that adenoid size shrank with 12 weeks of oral montelukast, along with improvements in the severity of OSA in mild cases. We also performed a combination study that found that with 3 months of combined montelukast and intra-nasal budesonide, children who had residual sleep apnea after adenotonsillectomy improved, and most normalized their sleep studies.

We currently have an ongoing randomized double-blind placebo-controlled trial with montelukast as a monotherapy for more severe OSA in children. We’re hoping that these anti-inflammatory medications, and potentially others in the future, will target the adenoids and tonsils and improve or even effectively treat pediatric OSA.

Quan: I’m going to ask you a controversial question.

**Kheirandish-Gozal:** Oh, please do.

**Quan:** The pediatric literature shows that they do a lot of PSGs [polysomnograms] and the age range is 1-18 years, but at some point the child crosses over into adulthood, and it may not be at an absolute time. At what point would you say we should apply the adult criteria—whatever it is, because we’re not so sure what sleep apnea is either? When does the child become an adult?

**Kheirandish-Gozal:** In my opinion, when puberty hits is when the problems start in defining the appropriate criteria. Most of our studies are in patients less than 9 or 10 years of age, for 2 reasons. The first is that the peak incidence of OSA in children is between 4 and 10 years, as was shown many years ago by multiple studies, and is associated with the higher propensity for enlarged adenoids and tonsils during that age. Later on, the parents say they grow out of it, which may not be true.

The other reason we don’t go beyond 12 years of age is because puberty complicates the relationships between adenotonsillar hypertrophy and puberty and post-puberty-associated changes in airway physiology. Furthermore, the population of kids that we studied in Kentucky were mostly overweight or obese and Caucasian. Now we are in the south side of Chicago and the majority are overweight or obese, but mostly African-American. Once puberty starts, these kids gain weight, hormones are all different, and it becomes very difficult to decide whether the changes in the measurements are because of puberty and hormone changes or OSA, so we try to stay below the age of puberty. There is absolutely a critical need for delineating normative data in adolescents as a function of pubertal changes, and preferably longitudinally.

**Quan:** So have you had any experience using CPAP [continuous positive airway pressure] in kids? Kristin Archibald in Arizona is very interested in that.
with children. We don’t do split-night studies at all, and our policy is that every child has to have their first diagnostic sleep study to make the decision about CPAP, and then titration happens in a second sleep study, after various interventions.

We have a 2-hour session of one-on-one with parent, child, and technician for mask fitting and explaining how to use it. We play all kinds of games and use various cognitive-behavioral techniques to improve acceptance and adherence. For some kids you just have to tell them, “You’re going to look like an astronaut.” You have to get the child to wear it. Actually, it’s very difficult for some children because of the issue of embarrassment; if they go to a sleepover, they don’t want to take a machine with them.

For adherence policy, we look at the downloads from the devices when they come for follow-up. That has been the approach and assessment, because we really can’t ask the child, “Are you using it?” because their parents are standing right there and of course they’re going to say yes. Our group has not done any adherence studies on CPAP use in children, but the adherence that we found as part of a study on liver dysfunction in children with OSA was encouraging.

I should mention that we prefer BPAP (bi-level positive airway pressure) in younger children, but it’s very hard to get the insurance to agree to that, so we have to prescribe CPAP first, then show that it didn’t work as well as we wished, so they can get the BPAP approved.


Carlin: Could you comment on the needs of children with Down syndrome and how the various forms of therapy (eg, surgical options, anti-inflammatory medications) fit into the treatment plan?

Kheirandish-Gozal: The rule is simple in children. If the child has any chronic craniofacial abnormalities, as in Down syndrome, you try to fix the obstacle imposed by the adenoids and tonsils first, because with those structures in the way it’s hard to achieve effective positive pressure. The behavior issues and the difficulties with implementing CPAP/BPAP in children with Down syndrome and others with behavioral disorders led us to attempt more radical and complex surgical interventions, as those currently done at Cincinnati Children’s, which have resulted in very favorable outcomes.

Mokhlesi: Your question was about anti-inflammatories medications?

Carlin: Or any solution. How do you manage the child with Down syndrome?

Mokhlesi: I just interpret the sleep study, since I don’t treat children in clinic. In terms of adenotonsillectomy in children with Down syndrome, my limited experience with patients coming back to our lab for a repeat study in 6 weeks or 6 months after surgery has been some improvement in the AHI, but there is residual OSA. The problem with that population is that they tend to be obese in addition to the craniofacial differences and a short neck.

Kheirandish-Gozal: And a large tongue for the size of the oral cavity.

Mokhlesi: And everything else. We have not been very successful even in doing CPAP titration in that group. As far as young adults I see in the clinic who have Down syndrome, my experience has also been limited in terms of getting good success with CPAP adherence. The parents typically state that adherence is excellent, but when I download the CPAP data for objective adherence monitoring, it looks horrible. I can’t get them to use it.

Kheirandish-Gozal: The adherence criterion we use is at least 7 nights a week, for at least 6 hours each night. I think the Cincinnati Children’s group are great experts in Down syndrome issues and OSA. Obviously, Down syndrome patients have facial abnormalities, but they are sometimes more cooperative than other kids and tend to be very helpful. There’s also obesity. I think it just puts the whole package together.

Gay: I’ll just add anecdotally that the way they come to me is after being identified by their cardiologists with cardiac complications. We gave tracheostomies to the last two I encountered that way, and they did beautifully. They were able to address their cardiac issues too, and then we could bring them back as they got older and potentially remove the tracheostomy.

Kheirandish-Gozal: I think in the past 10 years we’ve had 2 tracheostomies. We don’t advocate tracheostomies because of many different issues: the complications that come especially with the age of the child. Some adults prefer to have a tracheostomy, and just close it when they want to talk; they’re comfortable with that. Children have more difficulties; parents can have problems caring for a trached child, and then weaning them off the trach can be a problem. Unfortunately, not many of my colleagues know how to wean off in a systematic way, following a clinical protocol, so everybody goes by practice. Tracheostomy is not something we advocate, but sometimes you have no choice.

Patil: Following up on these pediatric patients after they’ve had adenotonsillectomy but still have residual sleep apnea—the issues of CPAP are pretty difficult in that population. There’s one novel therapy that’s still
in the pilot stage; Brian McGinley at Johns Hopkins has been exploring trans-nasal insufflation or high-nasal-flow therapy. Essentially, it’s the delivery of air via humidified nasal cannula, at flows of up to 30 L/min while the patient is sleeping. In the pilot studies\textsuperscript{1,2} it seemed to be more effective in kids than in adults. So that might be an alternative to CPAP some time down the road.


Mokhlesi: Regarding the Bhattacharjee data that residual AHI correlates with obesity,\textsuperscript{1} is there any evidence from your group about weight loss? Does that work, and would it be easier for a child to lose weight because the parents can control them, compared to an adult?


Kheirandish-Gozal: No, not really, because the parents are often obese too; the entire family eats the same food. I’ve never seen a very fit parent coming in with an obese child. Unfortunately, we don’t have any data on losing weight, because of several issues. We don’t have enough children being treated with a weight-reduction protocol in our database. We didn’t follow them specifically for that purpose. And for that we would need to collaborate with an endocrinology/obesity management group and put a program together. The only good weight loss that we’ve seen is in inpatients, because we have control over the food. Only when the food is controlled have we seen an improvement, but these are individual cases. It’s a great point.

Parthasarathy: In your paper,\textsuperscript{1} how many of those proteins were stress-related and how many were not related?


Kheirandish-Gozal: They originally came up with 17 proteins, and that paper describes all the details. However, of the 17, they were able to narrow it down to 12 proteins that were consistently altered, and from there they devised assays to measure the urine levels of 4, which in turn yielded outstanding predictive ability. I have some data from another study\textsuperscript{1} that Dr Khalyfa led in our group, and found extensive involvement of inflammatory pathways as far as gene expression, and the immense connectivity of this pathway in this disease.