Beyond the Blue: What Fellows are Reading in Pediatric Sleep Apnea

Dr. Nitin Seam: Hello. I’m Nitin Seam, podcast editor for the American Journal of Respiratory and Critical Care Medicine. Today, we are discussing Beyond the Blue: What Fellows are Reading, which is a popular feature in the Blue journal. In Beyond the Blue, fellows as well as their faculty mentor discuss important articles in their area of interest that are not published in the Blue journal. In the June 15, 2015 American Journal of Respiratory and Critical Care Medicine, the University of Chicago Pediatric Sleep fellows Alex Gileles-Hillel and Mona Philby, as well as Pediatric Hematology-Oncology fellow Gabrielle Lapping-Carr, reviewed three important articles related to pediatric sleep apnea with their faculty mentor Dr. David Gozal. As background for our listeners, Dr. Gozal is a leading expert in pediatric sleep apnea and is the Herbert T. Abelson professor of pediatrics at the University of Chicago, as well as the ATS president-elect.

Dr. Gozal, please take us behind the scenes of why you decided to submit to Beyond the Blue.

Dr. David Gozal: Well first of all, thank you for the opportunity to talk a little bit about one of the areas that I love most in respiratory medicine, and of course it is pediatric sleep medicine. The reason that we thought it would be important is that there is a relative paucity of articles being published in the Blue on pediatric sleep-disordered breathing, and when they do they very much tackle areas that are very specific, and therefore we felt that for the more general readership of the journal, it would be very important to get a flavor of the large array of topics that could be potentially synergistic to the activities of pulmonologists, critical care physicians, and sleep medicine physicians that primarily deal with adults but sometimes are confronted with a pediatric case, and in this case we thought that it would be useful to bring this area to the forefront through Beyond the Blue.

Dr. Seam: So the three articles that were reviewed included one on quality of life after pediatric adenotonsillectomy for pediatric obstructive sleep apnea. Another was on asthma outcomes in kids receiving, again, adenotonsillectomy for obstructive sleep apnea. And finally, there was an interesting article on the incidence of OSA in sickle-cell anemia.

You mentioned picking things that are of relevance and interest to Blue journal readers, and pulmonary critical care sleep physicians at large. I was wondering if you could tell us a little bit more about your thought process behind picking these three specific articles.

Dr. Gozal: Well, of course we wanted articles that were very high quality, that we felt the methodology was very sound, that tackled or addressed specific issues that I think every physician is concerned about, and also addressed issues that can be transferred, or in the context of managing the aging pediatric population and the transition to adulthood, that there would be an overall interest of the readership, not just on the pediatric side but also on the adult side. Because at one time or another, a physician involved in the care of patients with any one of these diseases may be confronted with some of the issues that at the moment are pertinent to the topics that were covered in these three specific manuscripts.
Dr. Seam: Thank you for that explanation. I did want to step back a moment, since all of these articles obviously deal with pediatric obstructive sleep apnea, and again, many of our listeners are adult providers. So can you review some of the basics with our listeners regarding pediatric OSA? I guess I’d start, before asking you about diagnosis and treatment, about telling us what’s known about the pathogenesis in pediatric obstructive sleep apnea.

Dr. Gozal: So, it’s a little bit more complex probably than the adult, but overall the pathogenesis is quite similar. Let me just start by stating that, similar to adults, pediatric OSA is a very frequent disease. It is estimated that about 10-12%, on average, of the pediatric population presents with the major symptom of obstructive sleep apnea—habitual snoring—and that of those, at least using current diagnostic criteria in the sleep laboratory, at least 25-30% of those children that have habitual snoring will have the abnormalities that could essentially lead to the diagnosis of sleep apnea. So, globally speaking, the disease be affecting between 2-4% of the general pediatric population, which is clearly a very frequent disorder in this age spectrum.

The second important component of pediatric OSA is its pathogenesis. On one hand, with the emerging epidemic of obesity across all ages in Western societies and even in emerging economies, the prevalence of sleep apnea has been on the rise, and obesity is clearly a major contributor, a causative mechanistic contributor to increase the risk of sleep apnea. And in fact what we see is that in obese children, the prevalence of sleep apnea is markedly increased, and studies from different parts of the world would indicate a prevalence of around 25-40% of obese children—depending on the degree of obesity and some other factors.

But looking more specifically at the pathogenesis, it is a complex pathogenesis. Again, very similar to the adult. The three elements that I think are in play are: one, obviously an airway, the size of the airway. In children, the factors leading to this problem could be either craniofacial disorders but also a genetic predisposition for craniofacial elements that will be somewhat less developed than the normal child, and so this would create a predisposing component, but alone it is insufficient to account for the disease.

Similarly, neuromuscular factors such as control of breathing, such as the tone of the muscles and the responses of reflexes within the muscle of the upper airway and the muscles that govern both the dilator and the constrictor muscles are very important and clearly play a role. But alone, again, do not account for obvious cases except for in conditions such as neuromuscular disease, or cerebral palsy, for example.

And then the final element that I think is obviously important is the anatomical, but of the airway component, with inflammation, which is where in children the primordial and predominant contributor is the presence of upper airway lymphadenoid tissue proliferation and hypertrophy—otherwise, enlarged tonsils and adenoids.

So for example, we could be in a situation where a child with kissing tonsils may not have any snoring at all and no sleep apnea on polysomnographic assessment, and then a child with relatively very mild increases in the size of the adenoids or tonsils may have very severe sleep apnea due to the other factors contributing to a greater degree.

Dr. Seam: Thank you for spending a couple of minutes describing what clearly is a complex disease. And I would like to talk a little bit more about diagnosis and assessment of severity. In adults, we use a threshold apnea–hypopnea index to both diagnose OSA as well as assess whether it’s mild, moderate, or severe. In children, I understand it’s not as clear cut. If you could, please tell us how pediatric OSA is defined and then how severity is assessed.
Dr. Gozal: Well, first of all, the diagnosis at the moment relies, at least as a gold standard, on an overnight sleep study—very similar to what happens in adults. The use of home-based polygraphy, which has become very popular of course in adult patients, is not as extensively employed in children, although experience is being accumulated now more recently in the last 12 or 18 months that would suggest that with certain adjustments this might be possible.

Now speaking to the demarcation or classification of the disease, the upper airway of children is relatively less collapsible. It seems almost a little bit paradoxical. But the upper airway of a normal child is very resistant to collapse. So, because of this unique feature—the mechanisms of which I won’t go into detail, but suffice it to say that they have been tested quite extensively by several leading authors, including Dr. Carol Marcus at Children’s Hospital of Philadelphia. This work has led to the understanding that the normative data is different from that of adults, and so to that effect, an apnea–hypopnea index of less than 1 is considered completely normal; in fact, an AHI of 1 is already three standard deviations beyond the mean for a pediatric healthy child population.

Therefore, AHIs between 1 and 5 are viewed as mild obstructive sleep apnea, 5 to 10 are viewed as moderate, and more than 10 are viewed already as severe obstructive sleep apnea. So clearly criteria that are very different from those that are used in the adult population.

Dr. Seam: Thank you for that explanation. As you mentioned, you typically refer patients for adenotonsillectomy—in patients with enlarged adenoids or tonsils and who have all been kids—which is different than in adults, and I was wondering if you could tell us about treatment and when you refer for treatment in pediatric OSA, I guess based on severity.

Dr. Gozal: This is a little bit of a muddled area again, for which there is no definitive consensus. The American Academy of Pediatrics guidelines, the more recent one, clearly advocate that the initial, phase one treatment of a child with habitual snoring whose polysomnographic assessment indicates the presence of an AHI of more than 1—in other words, establishing the diagnosis of OSA—is preferentially, unless there is any other contraindication, to pursue an adenotonsillectomy.

However, we and others have a little bit disputed this contention, by virtue that the risk–benefits of adenotonsillectomy have not been as carefully weighted against in the context of this decision making. And so many centers around the world, and including here in the United States, have opted to at least attempt other approaches when the severity of OSA is very mild. And, for example, additional alternatives such as anti-inflammatory agents, be that intranasal corticosteroids or anti-leukotriene medications, have been implemented with relative success in the context of mild sleep apnea in children.

There’s only one study, a randomized controlled study, on adenotonsillectomy that was published about 18 months ago in the New England Journal of Medicine, and that study clearly showed a benefit of adenotonsillectomy, but we need to be cautious. There is substantial improvement in the severity of the sleep apnea measured by the apnea–hypopnea index, but there is still a relatively large proportion of children who after the adenotonsillectomy will see an improvement but not resolution, complete resolution, and normalization of their sleep study.

So, the jury I think is still out as to what is the actual efficacy of adenotonsillectomy, but it clearly remains, at least at this stage, the best option for those children with moderate and severe sleep apnea, and an option to consider in cases in which anti-inflammatory therapy does
not work well, or in cases in which the parents opt to go directly for adenotonsillectomy because of additional symptoms associated with morbidities of the disease.

**Dr. Seam:** Well thank you for going through that for us, and I believe you’re referring to the CHAT study that was published in the *New England Journal of Medicine* in 2013. So now that you’ve provided us this background, I’d like to talk a little bit about what we came here for: the Beyond the Blue, and as I mentioned before your fellows discussed three articles. But in the interest of time, I’d ask is there one article you were particularly interested in discussing, and if you could tell us about that paper.

**Dr. Gozal:** Great. Definitely the three articles, as indicated, were selected out of many because of their quality, and so you’re making my life a little bit difficult trying to select one of the three. But if I really have to make that choice for the sake of time, I would focus today, if possible, on the one by Dr. Rakesh Bhattacharjee in *PLoS Medicine*. The paper was a very interesting paper that really addresses the efficacy or the association of adenotonsillectomy and asthma outcomes, and so I think that it will be of great interest to all the readership of the journal.

I would like to bring a few other points that I think are important in relation to the *PLoS Medicine* paper.

The first one is that although this is obviously a retrospective longitudinal database, the numbers are very important. We’re dealing with a group of 13,500 children that have asthma that underwent in that period of time an adenotonsillectomy. We believe that the majority of those children underwent the surgery for the presence of symptoms that would be suggestive of sleep apnea—we don’t know for sure if they went through the process of the sleep study for the diagnosis, since at the time of the database, which covered the period of 2003–2010, there’s only a proportion of children that undergo sleep studies, and many of them do not get a sleep study before they go through the adenotonsillectomy.

So assuming that the adenotonsillectomy was done for the majority of cases for symptoms of sleep apnea, which is a reasonable expectation based on several surveys, then we have a very large group of children with asthma receiving adenotonsillectomy for symptoms of a priori sleep apnea. And, in parallel, we identify for each one of these children two age, gender and geographically matched children with asthma without adenotonsillectomy, so that we had 27,000 or so controls. Obviously these are very large numbers.

And what we looked at was two outcomes. One was to look as to whether the admissions or severity or the presence of any indicators of the severity of asthma as measured by occurrence of acute asthma exacerbation in the database or acute status asthmaticus was present, and second whether there were changes in the utilizations of asthma medication prescriptions. And on both of these we found that the children that underwent adenotonsillectomy for suspected sleep apnea, I’m assuming, had major improvements in the severity of their asthma, both from the context of admissions as well as the context of therapy. And in fact, they had started with much more severe asthma, and after adenotonsillectomy reverted to the same level of asthma severity as the matched controls that were identified.

So the overall conclusion of this study is that adenotonsillectomy for a priori obstructive sleep apnea improves the severity of asthma. But also it tells us that children with obstructive sleep apnea symptoms underlying the presence of asthma are more at risk of having a more severe course and severity of their asthma.
So I think that this is a very enlightening study, one that clearly provides a lot of ammunition to start thinking of the overlap possibility on the presence of both sleep apnea and asthma in children with asthma. And so that the presence of snoring and other symptoms of sleep apnea should not only not be ignored but should be actively and prospectively sought in the context of any encounter between children with asthma by their physician.

**Dr. Seam:** So I guess if I could talk a little bit more about that, then. It was a retrospective study describing the overlap between pediatric asthma and OSA, and you’d mentioned before the controversy of what to do with those cases when their AHI is greater than 1, should you try to maximize any other medical therapies before referring for adenotonsillectomy. And I wonder if this article that you referred to, did it have any effect on your opinion of whether, in patients with other comorbidities such as asthma, would maybe lowering your threshold or having an earlier referral for adenotonsillectomy—I was wondering what you thought about that.

**Dr. Gozal:** This is a great question, but I’d like to step back for a second. The first point that I think is important in this study and a few studies that have preceded it, is the realization that sleep apnea exists not as an isolated condition but actually overlaps with additional conditions, such as, for example, asthma or obesity or attention deficit disorder. And so in the context of asthma and sleep apnea, it has become over the last 3 or 4 years quite apparent that children with asthma may be at risk of manifesting a more severe course for their asthma, and therefore less ability to be symptom free or to have a better control of their asthma if they have concurrent presence of OSA.

On the same token, it is very likely, although it has not yet been shown conclusively, that children with asthma may be more at risk of having OSA, and that therefore the presence of inflammation in the airways may contribute to a higher prevalence of OSA in the pediatric asthmatic population.

So it’s a two-way street we think; we think that one may be affecting the other. And so it was an interesting question to see if indeed we treated this a priori sleep apnea in children with asthma, whether this would make any difference to their outcomes from the asthma standpoint. So this was really the hypothesis that was being tested in this paper, which followed on a previous study that was published 3 or 4 years before that, in which a cohort, a much more restrictive cohort of children with asthma who were poorly controlled turned out to have a very high prevalence of sleep apnea—around 60%. And in those that were treated for their sleep apnea, there was clearly an improvement in the course of their asthma symptoms, and a relatively improved control of the asthmatic disease severity.

So altogether the evidence pointed out that this relationship between sleep apnea and asthma might be modified by the imposition of a treatment for sleep apnea, such as an adenotonsillectomy, and which this is exactly what was tested using a longitudinal database that is available, through a very careful analysis of this database.

So this is one of the reasons for which the paper, I feel, would be of great interest to the journal.

**Dr. Seam:** It certainly is very interesting, the *PLoS Medicine* paper you described, published in 2014, adding to that body of literature describing this overlap and the question of treatment of OSA improving asthma outcomes. So again, retrospective, but something very interesting and something that I’m sure you’ll be following very closely.
I wanted to close the podcast and ask you for your final thoughts, and I’d ask you less related to the literature, but I wondered if you had any feedback about this experience in terms of your fellows. The Beyond the Blue segment does allow fellows to sort of get involved, in a way, in writing these manuscripts, and from my experience reading these, they do very detailed analyses, and I often learn something from them, and I just wondered if you could comment about your fellows’ experience and your experience through this process.

Dr. Gozal: This is a great question. So, two things came up. One is, I think this was a wonderful way for fellows to really delve deeply into a published paper and critically assess the evidence that was being presented, very similar to a journal club as part of their training, but in a formal way where their scrutiny and their input and their insights are going to be visible to all their peers across the globe.

So the exposure of the ATS journals in general and that of the Blue, of course, is worldwide, and so their thoughts and their insights and their interpretation of the paper that they were selecting and reviewing is an opportunity not only of being exposed and being visible but also to be very careful and to do this in a very critical and scientific fashion. And so the unique pressure building up to the publication was I think a wonderful opportunity to refine the process of their review to the maximum.

The second element was the selection process of the papers, and to do that and to put it in context of their own biases or preferences as fellows. So this gave them an opportunity to be more personalized in the way that they selected the paper, and I thought that this was a very pleasant experience.

And I think that the major learned lesson out of this was that the depth to which the fellows pursued their analysis led them to, I think, gain unique expertise through a very active process of learning. They gain unique expertise on the disease and the topic that they selected, because this forced essentially a review, a very in-depth review, of the literature, forced in-depth analysis of the data both in the paper and potentially of other papers in order to reach their conclusions. And I think it was an outstanding lesson of what is required of an evidence-based physician nowadays in order to make ultimately diagnostic or therapeutic decisions.

So I think that this was a wonderful mechanism that not only gives an opportunity for drafting and publishing in an outstanding journal, but more importantly is a very valuable lesson in both evidence-based medicine and in the implications of how to approach a scientific paper and make it understandable but also while being critical, and seeking very substantial details behind the scenes.

Dr. Seam: I want to thank David for joining me today to discuss his group’s contribution to Beyond the Blue, which is published in the June 15, 2015 issue of the *American Journal of Respiratory and Critical Care Medicine*. On a side note, I must also mention that David provides interesting insights on pediatric sleep apnea via his Twitter feed. You can follow him on Twitter: [@SleepKid](https://twitter.com/SleepKid). Finally, you can find this podcast, as well as our other article discussion podcasts, at [atsjournals.org](http://atsjournals.org), or you can subscribe via the iTunes store by typing *American Journal of Respiratory and Critical Care Medicine* in the search box. You can do that on the computer, or on your mobile device.

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