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Advances in the Treatment of Neurogenic Detrusor Overactivity

ANNOUNCER INTRODUCTION:
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DR. ROUTH:
Hello, and welcome to this webcast titled Advances in the Treatment of Neurogenic Detrusor Overactivity. We're here speaking today from the 2021 Society's for Pediatric Neurology meeting here in sunny Miami, Florida. And my name is Jonathan Routh. I'm a pediatric neurologist at Duke University where I serve as the Chief of Children's Surgical Services. I'm also an Associate Professor of Surgery Pediatrics and Population Health. I'm joined today by my colleague, Dr. Benjamin Wittam. Ben, do you want to introduce yourself?

DR. WHITTAM:
Hi, my name is Ben Whittam. I'm a Associate Professor of Urology at Riley Hospital for Children at Indiana University Health and I primarily focus on pediatric urology at that institution.

DR. ROUTH:
So before we get started, let's review our learning objectives for today. Upon the conclusion of this webcast, participants should be able to summarize therapeutic options for pediatric neurogenic detrusor overactivity and the efficacy for each of those, describe the definitions of therapy non-response, partial response, and complete response, identify therapy non-response rates to the various medication classes, and evaluate common adverse drug event frequency with medications approved by the FDA for NDO.

So, a quick word on pediatric neurogenic bladder in general. What exactly is neurogenic bladder? Well, we know from copious data that roughly 25% of children at any given point in their lives are going to experience some degree of voiding dysfunction. Pediatric neurogenic bladder can perhaps best be thought of as an extreme example of voiding dysfunction, specifically, where we know that there's a known and defined neurologic cause for that voiding dysfunction in that particular child.

DR. WHITTAM:
And I would say the most common etiology for pediatric neurogenic bladder would most likely be classified as spina bifida, spinal cord injury, and then some less common things like a transverse myelitis, or cerebral palsy, things like that. So we're going to be focused primarily on those etiologies for pediatric neurogenic bladder, primarily spina bifida, which I know in my practice is probably the most common thing that I see where I do see neurogenic bladder.

DR. ROUTH:
No, I would certainly tend to agree with you. It's - certainly we do have some kids with transverse myelitis, cerebral palsy, other causes, but by far the most common thing that we see a spina bifida.

In terms of neurogenic detrusor overactivity in pediatric neurogenic bladder in general, the key factor here really to keep in mind is that long-term urologic care and management of these patients is absolutely essential. We know from CDC data, on prior data National Spina Bifida Patient Registry Data, other sources that roughly 70 to 75% of all these children will require clean intermittent

catheterization, for example, among other things to manage their bladder and keep them safe over time.

DR. WHITTAM:
I think it's paramount to the management of these children. Now, you know, in the last 30 or 40 years since the advent of the ventri - the VP shunt to protect from hydrocephalus, you know, renal failure, was the most common morbidity and mortality. We've been able to reduce that significantly with the advances that we've had with different therapies that we're going to talk about shortly. So it's very important for urologic care long-term, not only in pediatrics, but even into adulthood, these children need to be followed regularly.

DR. ROUTH:
Certainly, medical and surgical, you know, options abound for these patients. And let's dive into that a little bit more.

Before we do though, I'd like to focus a little bit more specific on one particular form of neurogenic bladder or one particular symptom of neurogenic bladder and that's specifically neurogenic detrusor overactivity, or NDO. This is a common thing which we see in our neurogenic bladder patients, and it effectively manifests. Again, it can be thought of as a extreme example of the voiding dysfunction, which we'll see in some kids, which typically in a non-neurogenic child will present with urgency, frequency, and occasional accident. In the neurogenic bladder population, it's a very different beast.

DR. WHITTAM:
And it can act as many different things. We can see hydronephrosis. We can see recurrent urinary tract infections, incontinence, inability to empty, and in the event - and the worst case scenario, we can see renal failure.

DR. ROUTH:
Absolutely. So let's take a minute to talk about the goals and response we're looking for in terms of management of pediatric neurogenic bladder, particularly children of spina bifida. The one thing that we always try and teach our trainees is to shoot for the, you know, kind of pay attention to kids. And specifically, we're looking for the kidneys, making sure that the kidneys are staying safe, keeping them infection free, keeping them dry, when and if they decide to be dry. Because to be very clear, and I should also mention that these are in order: kidneys come first, infections come second, dryness comes third because no child has ever died from having wet underwear. However, kidney failure, definitely not a good thing and that we want to avoid. And then the fourth portion of that is going to social independence. As kids become older, we want them to be coming more and more independent and gradually taking over more and more of their care when they're able to do so.

DR. WHITTAM:
John, that's a great acronym, and I think I'm going to use that with my trainees. But I couldn't agree more. The problem is, is that kidney failure is silent. We don't see it as hydronephrosis, renal scarring, there's no symptoms beside that. And that's where detrusor overactivity in this neurogenic population is very important to be watching, because there are no symptoms realistically. So we have to be watching this closely, once again, why we need to be following these patients regularly. Infections, obviously, those are obvious when children are having infections. But I could not agree with you more about dryness and social independence. I think those are important, but they do come last. I always say I would hate to make a social problem into a medical problem. Absolutely, I can certainly cause you to go into renal failure. I don't want to do that.

DR. ROUTH:
Absolutely.

DR. WHITTAM:
I think that's where we have to focus our goals on, our number one, number two, and then I think it's a big drop off till we hit three and four.

DR. ROUTH:
I couldn't have said it better myself.

Typically, there's a variety of indications for interventions for pediatric NDO. And those can range anywhere from new onset incontinence, new onset infections, new onset hydronephrosis, or obviously more concerningly, decreases in compliance.

DR. WHITTAM:
Right. And we can also start to see higher detrusor leak point pressures. And I always worry more when I have to talk to you about new incontinence that wasn't there before. So those are all the things that make me start to consider is the therapy that I'm offering, is it efficient?

DR. ROUTH:
Right.

DR. WHITTAM:
I do think that - I don't think we've mentioned this yet, but how important urodynamics are in the role of all this, when we start to see these changes, we probably need to get some degree of data to tell us what's going on.

DR. ROUTH:
Absolutely.

DR. WHITTAM:
And I think that's what drives the next steps. But these are the - these things that you just listed. And I added to this is when I start to say, 'okay, something's not right. We need to do something.' And the first step is, and I'm sure it is in your hands, too is let's get urodynamics, has something changed? And if so how can I affect that change? How can I modify that to reduce the risk of kidney infect - kidney failure, infections, social incontinence, and dryness?

DR. ROUTH:
Right. Absolutely. And actually, in the protocol, as I mentioned, the standard protocol is that we do urodynamics at birth, at 1 year of age, at 2 years of age, at 3 years of age, that's, you know, moving forward to 5 years of age, and then you enter a dry spell. And we don't necessarily do urodynamics between ages 5 and 10, unless it's needed for cause. And at any point along the line in between those goalposts, if it needs to be done for cause because of those, you know, changes you were just mentioning, then we would perform an extra urodynamics, again to try and figure out what's going on to the child's bladder.

DR. WHITTAM:
I don't know about you, but I have a very low threshold to repeat urodynamics if something doesn't sound right.

DR. ROUTH:
Absolutely.

DR. WHITTAM:
I think that's when I know that some something's going on.

DR. ROUTH:
Absolutely. And in children who have begun on a therapy, let's say - and we'll get into more details in just a minute. But let's assume they start – they've started medication, we need to assess whether or not that medication is working. Is it's a complete non-response? We've not really budged their NDO, they've got just as many episodes as they were having before. Is it a partial response? Where we've seen some decrease in the NDO episodes and decrease in the overall bladder pressures, but they're not to the point that we want them to be.

DR. WHITTAM:
Or is it a full response? Is their system metric capacity improving? Or is there reflux? Do they have reflux? Has the reflux improved? All those things, there's no way of looking at a patient and seeing that. You've got to test it and I think that's where urodynamics are so important and vital to this.

DR. ROUTH:
Absolutely.

So let's talk for a minute about the current treatment paradigm for pediatric NDO. Really historically the cornerstone of therapy has always been antimuscarinics or more broadly, anticholinergics in general. This medication class has been around roughly since dinosaurs roamed the Earth I think. And despite their very common use in children, there's relatively few of them that are actually approved by the FDA for use in pediatric NDO. And specifically, we have oxybutynin, we have solifenacin, and that's about it. And everything else is given is typically given off label. These can be given classically orally, or in the case of oxybutynin particular, can frequently be given actually intravesically as an installation into the bladder. And the goal here is to decrease bladder storage pressures, reduce back pressure on the kidneys through the bladder, and also to reduce these incontinent episodes or NDO episodes that are occurring.

DR. WHITTAM:
These medicines have, as John alluded to, have been around since the beginning of time it feels like, but they're not totally benign medications. I mean, think we've had some serious issues with them. I know you and I both talked about this in meetings and over some beers here and there. But you know, everyone talks about dry mouth and urinary retention. So some of these kids can void, now they can't all of a sudden. Constipation. I think those are already some issues that we see in spina bifida population. So but I think some of the more alarming things from a physician and talking with parents have been some behavioral changes, mood alterations that have -

sometimes even hallucinations, which are alarming, not only to the family, but also to me. And so I've been very quickly to change medications when I see that because it is alarming. And I worry when I see those. I don't even want to begin to see those.

DR. ROUTH:
Absolutely. Antimuscarinics and anticholinergics, at the end of the day, they're smooth muscle relaxants. And the issue is that they're not necessarily specific smooth muscle relaxants. So the same smooth muscle that's present or the same class of smooth muscle that's present, but then the bladder is also present within the rectum, which is why you wind up getting constipation, it's present within the salivary glands, which is why again, dry mouth, you can visual changes, because the iris of the eyes the same. And likewise, kids can get in the summertime again, because sweat glands, again, are smooth muscle dependent. But I wholeheartedly agree with you. The most concerning factor that can occur these kids is when it does penetrate the blood brain barrier, and you have a cute little 6-year-old telling you all about the pink elephants dancing on the wall. That's not a conversation that you want to have with a child in clinic.

DR. WHITTAM:
Those are uncommon. I don't want to say that these are happening with all my patients. But you know, 1 out of 100 It's enough to make you remember it, because we're still talking about it right now. Right? It's an alarming.

DR. ROUTH:
Exactly. And another similar type of concern that we have with these kids is that we know in the setting of children who have VP shuts, it's very well documented among many children with spina bifida that we do see executive function challenges, particularly as they age, particularly the VP shunts perhaps begin to have some concerns, you know, or disconnected over time, and don't function well. And after repeated occurrences of VP shunts, you know, need to be revised, we do see challenges in terms of the executive function for these folks and into adulthood, perhaps an increased risk of dementia, which particularly for antimuscarinics, is concerning.

DR. WHITTAM:
There's been some data in the adult literature in elderly patients about increased risk of dementia. And we've not proven that or shown that in pediatric patients specifically with myelomeningocele or spinal bifida as they age, but that's - every meeting that I come to, everyone expresses that concern, but we don't really have another option.

DR. ROUTH:
Exactly.

DR. WHITTAM:
So right now, John, what do you do when you have a patient who comes in and sees pink elephants and is having trouble with their muscarinics? What are you thinking about your next line of therapy?

DR. ROUTH:
So the challenge that we usually have in that kind of situation, or that I kind of discuss with parents is do we want to complete halt that line of therapy? Or do what progress on to something different? Each parent is really going to have - each family I should say is going to have, you know, their own version of that. And it really depends on our previous point. Were they not responding at all, but you're getting side effects? In which case we're going to give up on this all together? Or were they having a good response, but the side effects are really intolerable?

DR. WHITTAM:
We reduce the dose.

DR. ROUTH:
Right.

DR. WHITTAM:
so we get we can we get that maximal tolerable dose? That's a hard time. It's a hard patient to figure out what the next steps are.

DR. ROUTH:
Absolutely. And along those lines, you know, I think it's worthwhile to kind of discuss briefly, you know, what some of the, you know, other new treatment options that are out there are. And again, this is really a significant advance in the field, as far as I'm concerned that we now do have, you know, a new medication, or a new class of medications, that's out there, that actually is now approved for use in children specifically with NDO. Mirabegron was approved, as you well know, by the FDA in March of this year. And it's arguably better tolerated among, you know, these kids. Again, by and large, side effects are not the problem when we put kids on mirabegron. Again, it's a newer medication, we don't have good long-term data to really look at and say it's, you know, tolerated well over time, simply because it hasn't been out of the market thus far.

DR. WHITTAM:
Right. But, you know, but the Phase 3 open-label trial that I think prompted the FDA approvals, you know, it wasn't a huge study. It was about 60-some patients or so who all were on intermittent catheterization with known neurogenic detrusor overactivity. So the exact patients that we worry about, they were talking about, they showed a pretty significant improvement in their system metric capacity. which was a primary outcome. And they actually did the power analysis to make sure that they're actually finding a difference when they're looking for it, which is, as you and I both know, is rare in urology or pediatric urology literature. But they also noticed an improvement in the number of incontinence episodes, the amount of volume they were cathing, and overall, showing they were able to relax the bladder in a better way, is what I sort of took out of this.

DR. ROUTH:
Right.

DR. WHITTAM:
And they're even on some of the quality of life questionnaires, they seem to see some improvement. Some were – showed no difference, but there was improvement, particularly looking at the difference that they saw pre and post mirabegron.

DR. ROUTH:
Exactly. And this, I think, was a huge advance, because being able to have a medication that can increase complian - the capacity of the bladder, that can decrease NDO episodes, decrease incontinence, and overall, you know, giving you a better happier bladder picture. Again, our primary concern here is what's going on with the kidneys. If you can reduce that bladder pressure and reduce those NDO episodes, you're reducing back pressure on the kidneys, which is going to keep them happier longer.

DR. WHITTAM:
And just like your acronym with kids, right? We got the kidneys protected, we're hopefully reducing infection, the number of incontinence episodes are reducing, which helps the social. So I think this is a - and it's an oral pill, or a liquid, if you can get it suspended, which has been a problem recently, but I'm sure they're going to work on that.

DR. ROUTH:
I'm sure.

To that end, why don't we actually focus in on a typical patient case to kind of, you know, try and see how this would this new sort of academic discussion we've been having would fit specifically into the manage of a given child.

DR. WHITTAM:
Who, if you're anything like me, you can sit here and lecture me for hours, but until I hear it in a patient situation, I don't know what to do.

DR. ROUTH:
So Adam is a 13-year-old boy who has been followed in a multidisciplinary spin – spina bifida clinic since diagnosis, which actually in his case occurred prenatally, which is often the case for our patients. He was counseled, or his parents, I should say, were counseled in terms of fetal care by a multidisciplinary team and he's been managed proactively with frequent monitoring over time. Now, thankfully, Adam has not had any urinary tract infections or any problems along those lines. But as is often the case, again, after age 5 is when we really start looking for attainment of continence in these children, and at age 6, he was actually diagnosed with neurogenic detrusor overactivity, NDO. And at that point, CIC and anticholinergics were initiated. He tolerated them well, but he remained incontinent. He was followed with serial ultrasounds that showed no significant changes, no concerns, no hydroureteronephrosis, and most importantly, no scarring. But nonetheless, the incontinence, you know, remained. So on urodynamics, we talked already about the importance of that in terms of kind of determining management, Adam has low pressure, he has a relatively smooth bladder wall, and he has no reflux. However, his bladder neck is relatively open, with significant leakage during neurogenic detrusor overactivity episodes. And so he's able to get to 75% of expected bladder capacity on an appropriate dose of an anticholinergic despite CIC, and he still has multiple NDO episodes. So he would certainly fall into that class of a partial response.

DR. WHITTAM:
Absolutely. How was he – so the first question is, if he came into my clinic with all that, which is great, thank you for teeing it up for me, it from it makes it really easy how to manage him, I would first off talk to family about, you know, I - can we potentially increase his muscarinic. If we go up a little bit on his anticholinergic therapy, increase the frequency of his CIC, maybe to reduce that. But it sounds like I'm sure you've done all those things at this point. And -

DR. ROUTH:
And in this case, he's actually already doing CIC every three hours, which for a school-aged kid is a challenge, and on top of that he is

having increasing constipation due to the side effects of the anticholinergics he's on. So what non-invasive therapies would you kind of, you know, think about at this point?

DR. WHITTAM:
Well, previously, I would have started talking to them about - it's more invasive, but consider Botox and saying, you know, 'Well, let's go to the operating room, we will inject your bladder, we will use about 10 units per kilogram,' based on his weight, so max of about 300 units is sort of what I do for neurogenic bladder. I'm sure it's similar for you. However, I think recently, mirabegron has been this stopgap right now, where I would say, 'Well, we're having a partial response on anticholinergic therapy.' He's kind of maxed out it sounds like, we're starting to get some of the bad side effects. So I think it's time - this is this is the perfect patient I think to say let's start at 25 milligrams of mirabegron and see where we go.

DR. ROUTH:
I wholeheartedly agree. I think this is a child who he's not having any signs of kidney problems. This is essentially an incontinence episode. You don't want to take this child to the operating room to do a large urinary reconstruction for a kid who really doesn't need it at this point. He's not getting his goals met by, you know, maximum medical management. And I agree with you take him to the operating room every 6 to 12 months for Botox injection isn't exactly ideal either.

DR. WHITTAM:
Well, arguably, as a three years ago, he was on maximal medical therapy. I think now, he's not on maximum medical therapy.

DR. ROUTH:
That's a great point.

DR. WHITTAM:
Because we do have FDA-approved medicine for this that we can now maximize his medical therapy.

DR. ROUTH:
That's a great point.

So just to summarize the key kind of takeaway points from today, we talked a little bit about the therapeutic options for NDO, antimuscarinics, mirabegron, Botox in select cases, about 20% of kids will go on to surgery. But again, kids like Adam, not that kid just yet.

DR. WHITTAM:
Well I do think that the heavy lifting from this is pretty much CIC and anticholinergics.

DR. ROUTH:
Absolutely.

DR. WHITTAM:
That those are going to be our primary medications and therapies. However, the patients that are having partial responses and complete response, I think that mirabegron's got a nice use at this point.

DR. ROUTH:
I wholeheartedly agree.

We just talked about therapeutic response rates and how to define those, non-response, partial response. You just mentioned complete responses, again, kind of where to go from there based on the algorithms, and also what sorts of non-response rates will look like for the various medication classes of antimuscarinics or beta-3 agonists like mirabegron. We talked a little bit about mirabegron toler - tolerability, again, the biggest problems I run across are occasional headaches. Based on the mechanism of action, we need to be concerned about the potential for high blood pressure. I personally haven't seen that. But it's a potential option that's you know, that can be - can occur and yet something we need to be worried about.

DR. WHITTAM:
My biggest caveat is we don't know long term.

DR. ROUTH:
Right.

DR. WHITTAM:
That's we have to follow. However, it's something that we've never had before. It fits in a place where we need a medication. So I'm okay

using it. I think the FDA is agreement - is an agreement that it's safe to use, and I think proven safe - its safety and efficacy, long-term tolerability and safety. I think is only time is going to tell and I think we're going to follow that.

DR. ROUTH:
I wholeheartedly agree. And with that, we thank you all very much for joining us today.

DR. WHITTAM:
Thank you.

DR. ROUTH:
And I appreciate your attention. Thank you.

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You've been listening to CME on ReachMD. This activity entitled: Advances in the Treatment of Neurogenic Detrusor Overactivity is jointly provided by Medical Education Resources and Novice Medical Education, and is supported by independent educational grants from Astellas Incorporated. To receive your free CME credit or to download this activity, go to reachmd.com/cme. Thank you for listening.