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• Deadline for entries: 6/12/2020 •

Virginia Chapter

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

Introducing: Virginia Chapter Immunization Representative

Hello! My name is John Ring and I was named Chapter Immunization Representative (CIR) for VA-AAP in August, 2019. The 'job description' I received is broad; ideally, I am to do the following: provide two-way communication between the Chapter and the National organization; participate in development of immunization-related programs, both educational and clinical; provide 'technical assistance' to Chapter members re: immunizations, e.g. medical and administrative (including VFC); and develop relationships with multiple stakeholders, e.g. VA-DOH personnel, state legislators and staff, other concerned groups and the media, in order to further the Chapter's immunization agenda. Fortunately, I do this work in the context of our Chapter Immunization Committee; chaired by Chapter Vice President – Dr. Michael Martin – these colleagues expand my personal expertise greatly. Another source of information and help is the National AAP CIR Listserv, including its Steering Committee and the Staff that support its function; no one knows our business like our fellow providers and the opportunity to 'noodle' with other Chapters – learning from their successes and their failures – *is invaluable*.

Each quarter – through Virginia Pediatrics – I intend to do three things: summarize noteworthy immunization-related activities at the State and National level, underscoring our Chapter's participation; present one or two immunization-related developments that I think will be of interest to you; and pose an immunization-related question, on which I would appreciate your answer. So …

- We have responded to three Requests for Applications: from the VA-DOH, to re-develop our State Immunization Coalition; from the AAP Chapter Quality Network, to develop and implement a quality improvement program to increase immunizations rates in older adolescents; and from the AAP Visiting Immunization Expert Initiative, to host a visit, with associated convening functions, from a National expert re: HPV and LAIV. We have provided input on legislation that would make immunization schedules promulgated by definitive bodies – ACIP/CDC, AAFP and AAP – the requirement for school entry in the Commonwealth; this would obviate the need for action by the General Assembly every time the requirements were changed. A broader legislative agenda is being formulated – one we hope will gain traction now that VA has unified government. At the request of the VA-DOH, we are reviewing and editing materials that will be sent to rising sixth-graders re: immunizations required for school entry; this will also enhance the value of this key health maintenance encounter.

cont. page 3 …

Inside this issue …

Dates to Remember

2020 Peds at the Beach Conference
July 17-19, 2020
Hilton Virginia Beach Oceanfront

SAVE THE DATE!
14th Annual Pediatric and Adolescent Sports Medicine Update for Primary Care
June 10, 2021
**this year's event is cancelled due to Covid-19*

Get in touch

We welcome your opinions and ideas. Please contact
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President's Message

Sandy Chung, MD, FAAP, FACHE
Virginia Chapter, AAP President

I wrote most of this message before the arrival of COVID-19. I know that we are all being inundated with issues because of the pandemic and its effects on our day to day lives at work and at home. We are working hard as a Chapter to advocate for pediatricians, pediatric providers, families and children in the face of this unprecedented emergency. Advocacy for child health and pediatricians is one of central activities for the Virginia Chapter of the AAP. As we all know, children are not little adults and it is imperative that as the experts in child health, that we educate, advocate and lead the way when our legislators and regulators are dictating what needs to be done for children and adolescents.

After a very busy General Assembly session, this year resulted in several new laws that will benefit children, families and pediatricians. I wanted to share those with you in this message.

We are excited that the Governor included full funding for the Virginia Mental Health Access Program (VMAP) which increased access to mental health care for children and adolescents in our state. It includes educational training for primary care providers (PCPs), a phone line that PCPs can use to consult child psychiatrists, telepsychiatry services and care navigation for families. The House and Senate were very supportive of VMAP and kept the full funding in the state budget. With this funding, we will be able to roll out services across the state over 2020-2021. Please keep an eye out for announcements about when services are available in your region. You can also find this information at the VMAP website at vmapforkids.org.

We are very pleased that a key immunization bill was passed that moved the decision making about what vaccines should be required for school attendance to the Virginia Department of Health, taking it out of the politics (prior to this bill the legislators had to decide if a vaccine would be included). This should allow Virginia's requirements to stay up to date more readily. At this point the following vaccines will be added – two doses of varicella, Hepatitis A, Meningitis, Rotavirus and HPV for males.

As many already know, gun safety legislation played a significant role this year. Legislation that will protect children including requiring background checks on all firearm transactions, requiring lost or stolen guns to be reported to authorities within one day, prohibiting the subjects of protective orders from possessing guns, tax credits for gun safes, and increasing the penalties for allowing access of a loaded, unsecure firearm to someone 14 years or younger.

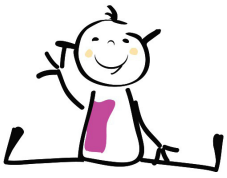
We also now have secured essential health benefits for all health insurance plans in Virginia except for short term plans which are limited to 3 months in duration. Essential health benefits include preventative screenings included in Bright Futures, including vision, hearing, and developmental screenings.

Including the laws above, here are some other laws of interest for child health and pediatricians:

- *Physicians are protected and given civil immunity when they participate in wellness programs.*
- *Children under 18 years are prohibited from using tanning facilities.*
- *Bills that would have allowed pharmacists to prescribe medications for children have been successfully opposed.*
- *Virginia is joining the Regional Greenhouse Gas Initiative to cap and reduce power sector CO2 emissions in an effort to address environmental health.*
- *Insurers must cover medically necessary formula and enteral nutrition products.*
- *Excess food for the free and reduced meal programs can now be redistributed to student who quality instead of being thrown away.*
- *The Department of Education will provide policies for schools to adopt for transgender children.*
- *Funding to increase children's access to school meals was passed.*
- *The Virginia Food Access Investment Fund was created which will help ensure access to healthy food through grocery stores for our underserved populations.*

These are just a few of the many laws passed this session. For a complete list, check the website: lis.virginia.gov

By the time you read this, I am sure that the pandemic will be in a different place than from the day that I am writing this message. As I end my presidency of the Chapter this summer, I thank you for all of your tireless hard work, strength and dedication to the children of the Commonwealth of Virginia. I urge you to continue to stay engaged and to speak up for kids!



Immunization Representative

The measles epidemic may be winding down in most places, but this influenza season promises to be particularly challenging, especially for children. The season started early (July), with Influenza B identified as the predominant causative agent, thus making complications more likely in children less than five years of age. For the week ending January 4th, CDC reports 32 pediatric deaths – 21 with Influenza B. More child deaths have occurred at this point in the season than in the record year 2017-2018. Dr. Anthony Fauci (Director – NIAID) said "…the trajectory of the cases is really on a trajectory very similar to two of the worst years we have on record". We all know that children with chronic illnesses are of particular concern; however, data indicates that even well children have a substantially decreased risk of influenza death when immunized (Flannery B. "Influenza Vaccine Effective Against Pediatric Deaths". ***Pediatrics***. 2017;139(5):e20164244). This year's vaccine, though it does not include the causative strain (B/Victoria) documented to date, will still confer some immunity. Case numbers may rise as children return to school. Extensive information regarding prevention, diagnosis and treatment of influenza in children is available on the AAP website: www.aap.org. Based on your own practice experience, how satisfied are you with the VFC program in VA? *Please contact me [jcringmd@aol.com; 703.380.9100] with questions, comments or concerns pertinent to my role as CIR: VA-AAP.*

John C. Ring, MD, MPH, FAAP graduated from the University of Minnesota Medical School. He completed a Residency in General Pediatrics (University of Minnesota) and Fellowships in Cardiology (University of Minnesota) and Critical Care Medicine (George Washington University - Children's National Medical Center). He practiced over 25 years in academic medical centers as a member of medical school faculties (University of Minnesota, University of Tennessee and Temple University). At mid-career, he broadened his professional focus to emphasize multiple aspects of population health - access, financing, provision and quality of care. Additional training and education included the Primary Healthcare Policy Fellowship (U.S. Department of Health and Human Services), the Robert Wood Johnson Health Policy Fellowship (National Academies Institute of Medicine and U.S. Senate Committee on Health, Education, Labor and Pensions) and the MPH Program (Johns Hopkins University – Bloomberg School of Public Health). He directed the Board on Health Care Services (National Academies – Institute of Medicine), the Office of Policy Research and Development (American Heart Association) and the Program – Pediatric Quality Improvement (Geisinger Health System). AAP involvement – seminal in refocusing his career – included multiple leadership positions in TN-AAP, culminating as Chapter President, and membership on National-AAP Committees (Drugs and Federal Government Affairs). He lives with his wife – a school nurse – in Alexandria, VA; they have two adult sons.

The Virginia AAP Chapter is your advocate and your resource.

During the COVID-19 Pandemic we worked hard with the Governor's office, national AAP, the Virginia Department of Health, and communities to find ways to protect children and families, give pediatric providers the tools they need to take care of people, and help our communities get through this unprecedented crisis.

We have several practical ways to help you now and in the future, including: Group Chats with Your Colleagues via Email Listserves, Resources for Your Families that can be found at virginiapediatrics.org/covid-19/, and our *VA-AAP Pulse emails.*

Several Chapter members led grassroot efforts to make the public aware of our situation. This includes letters to Governor, PPE local exchange programs, group PPE purchasing, and doing op-eds and media interviews. It's important to always keep up your advocacy efforts so that children and their healthcare providers are not left out of decisions being made by others.

Your active participation is vital to our mission.
Get plugged in: LMunn@ramdocs.org
Please encourage your colleagues to become active members!

2020 Legislative Wrap Up

Lauren Schmitt
VA-AAP Lobbyist

The 2020 Virginia legislative session adjourned on Thursday, March 12. They had to extend the session by five days to finish all of the legislation and the budget. It was an incredibly successful General Assembly session for the VA-AAP. We are excited about all of the important policies that have passed and how these will improve the lives of our patients. This was also the first time we used our online advocacy tool, VoterVoice to help members contact their legislators. We had great participation rates and believe this made a huge impact on our advocacy efforts. Read below for a recap of our victories and what issues still need our continued advocacy. Warning: this is a long update because we were so busy this year, but it is worth the read!

Statewide Expansion of VMAP

We are thrilled that our top priority, the Virginia Mental Health Access Program, was fully funded in the budget to expand statewide. The VA-AAP was instrumental in creating VMAP and ensuring it received state funding. The VMAP is a statewide mental health access program designed to help health care providers take better care of children with mental health conditions by increasing access to child psychiatrists, psychologists, social workers, and care navigators. You can read more about VMAP here: https://www.vmapforkids.org

Big Victory on Immunizations

Our biggest legislative victory this session was the passage of HB 1090 (Delegate Hope), which will ensure that the list of mandated vaccinations for school entry is science-based and not subject to politics. It brings Virginia's list in line with the current ACIP recommendations by adding vaccines for Rotavirus, Meningitis, Hepatitis A and HPV for boys. The most important component of the bill is that it allows the Department of Health to add future vaccinations to the list without getting approval from the General Assembly. The opponents to this bill were very organized and vocal. But thanks to the advocacy efforts of our members and other physicians, we were successful in moving this common-sense legislation forward. It now goes to Governor Northam for his signature.

Compromise Reached on Pharmacists' Scope of Practice

Senator Dunnavant and Delegate Sickles introduced legislation this year that would have greatly expanded pharmacists' scope of practice and allowed them to provide vaccinations, test for the flu, strep and UTIs and many other services they are not qualified to do. We immediately expressed our concerns to the patrons about how this would potentially impact children. Fortunately, and thanks to your advocacy, both patrons were receptive to our concerns and amended their bills to only apply to people ages 18 and older. Other amendments were made to address concerns of the Medical Society of Virginia. The compromise version passed the legislature and is headed to the Governor for his signature.

Funding to Expand Access to School Meals and Healthy Foods

We supported the Governor's proposed funding to increase children's access to school meals. This money will eliminate the reduced-price meal category and allow those students to eat for free at school in every division in Virginia. The legislature maintained the full $10.6 million for this important initiative.

SB 1073 (McClellan) and HB 1509 (Del. McQuinn) create the Virginia Food Access Investment Fund, which will help ensure access to healthy food through grocery stores for our underserved populations. The budget included $1.25 million for this fund.

Firearm Safety and Child Access Prevention

After hearing from our members, we determined that preventing gun violence and preventing child access to firearms is a top priority for the VA-AAP. We supported legislation this year for which there is data and research to support and will directly impact the children we serve. Bills related to background checks, child access prevention, dating violence, funding for violence prevention and extreme-risk protective orders. All of the initiatives we supported were successful and passed the legislature. One bill in particular, HB 1083 (Hayes), was heavily amended, but we are still pleased some progress was made.
HB 1083 (Hayes) is a child access prevention bill that as introduced, would have made it a Class 6 felony to recklessly leave a loaded, unsecured firearm in the presence of a child under the age of 18. The current law had it as a Class 3 misdemeanor and applied to children under the age of 14. After discussions with Senators who had concerns, a compromise was reached and the bill now changes it to a Class 1 misdemeanor, but keeps the age to 14. While we would prefer stronger language and the age to be 18, we were happy to see this bill move forward in some form.

HB 888, carried by Speaker Filler-Corn, creates a retail sales tax exemption for the purchase of a gun safe for $1,500 or less. We have supported this bill for a few years now and are excited it has now passed both the House of Delegates and Senate for the first time.

Protecting Essential Health Benefits

We are thrilled that SB 95 (Sen. Favola) passed both houses. This bill will require catastrophic health insurance policies and association health plans to include preventive services as part of their essential health benefits plans. Currently, many of these plans do not include preventive services and parents are unaware of this when they purchase the product. This will help ensure more children have access to these critical services.

Agreement on Surprise Billing

Legislators were determined this year to

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resolve the issue of "surprise billing" for patients who go to an in-network hospital but receive care from an out-of-network provider. The physician community introduced bills sponsored by Delegate Luke Torian and Senator Barbara Favola that were identical to the proposal we had last year and would only apply to emergency services. The health plans had bills that would have implemented a fee schedule based on the health plans' in-network rate or 125% of Medicare (whichever is lower) for both emergency AND non-emergency services. We were able to successfully defeat the health plans' fee schedule, but legislators and the patient advocates insisted we address both emergencies and non-emergencies.

A proposal was then offered based on the Washington State model, which applies to emergencies and non-emergencies services at an in-network hospital IF the services involve surgical or ancillary services and are provided by an out-of-network provider. After researching this proposal and discussing with our physician colleagues in Washington, we determined that this was a good option for physicians and certainly better than any of the other proposals on the table. The physician community supported this new bill and were pleased when the legislature passed it unanimously.

The bill contains the following components:

- Pays providers a "commercially reasonable amount" that is undefined so there is no benchmark that can then impact in-network payments.
- For the purposes of arbitration and for determining the "best offers" for the baseball style arbitration, a data set will be created based on commercial health insurance claims (excluding Medicaid and Medicare) and will be prepared using the All Payer Claims Database, in collaboration with providers and health insurers, for use by providers, facilities, insurers, and arbitrators. The data set will include: Median in-network allowed amount | Median OON allowed amount | Median billed charges

The bill includes "baseball style" independent dispute resolution and takes patients out of the middle of the billing process. It is also a huge win for us that it does not put a benchmark in the Code and allows the arbiter to consider physician charges when determining a fair payment.

Environmental Health

The VA AAP has supported a package of bills this year that ensure a safe environment for children's health today and their future tomorrow. HB 981 (Herring) and SB 1027 (Lewis) will allow Virginia to join the Regional Greenhouse Gas Initiative (RGGI), which is a regional carbon cap and trade program to reduce carbon emissions from electricity generation. We also supported the Virginia Clean Economy Act (HB 1526 and SB 851) carried by Delegate Sullivan and Senator McClellan. This legislation lays out a clear and achievable path for Virginia to transition to a 100% clean electric grid by 2050.

Disappointing Outcome on Tobacco Legislation

The VA AAP supported several bills this session that would have strengthened our tobacco laws to prevent more children from ever using nicotine products. These bills would have increased the cigarette tax, required licensure for retail establishments selling tobacco and prohibited the sale of any flavored tobacco products. Unfortunately, the House subcommittee that heard these bills chose to carry them over to 2021 and not move forward at this time. We are confident these bills will be back next year and we look forward to advocating for them in the interim.

Indoor Tanning

HB 38 (Samirah) will prohibit the use of indoor tanning salons for children under the age of 18. Our chapter has worked on this bill for many years now and it is great to see it finally pass the legislature.

Smoking in Cars

HB 578, carried by Delegate Guzman, now makes it illegal to smoke in a car when a child under the age of 15 is present. The current law applies to children under the age of 8. We supported this bill because we know the effects of secondhand smoke are so harmful to children and secondhand smoke can be up to 27 times more concentrated in the confines of a car.

Lauren Schmitt: VA-AAP Lobbyist Background

Lauren B. Schmitt is Vice President of Government Relations with Commonwealth Strategies. Lauren has worked with Aimee Perron Seibert for many years lobbying in Richmond since 2010. She works with a number of clients, including non-profit organizations, professional societies and corporations. Lauren works on several policy issues, with a focus on health care and children's issues. Lauren most recently served as the Deputy Legislative Director for Governor Ralph Northam, in which she lobbied for the administration's top priorities during the 2018 General Assembly Session. Contact: 118 N 8th Street | Richmond, VA 23220 | Lauren@commonwealth-strategy.net | 804-484-4751

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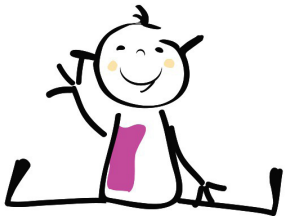

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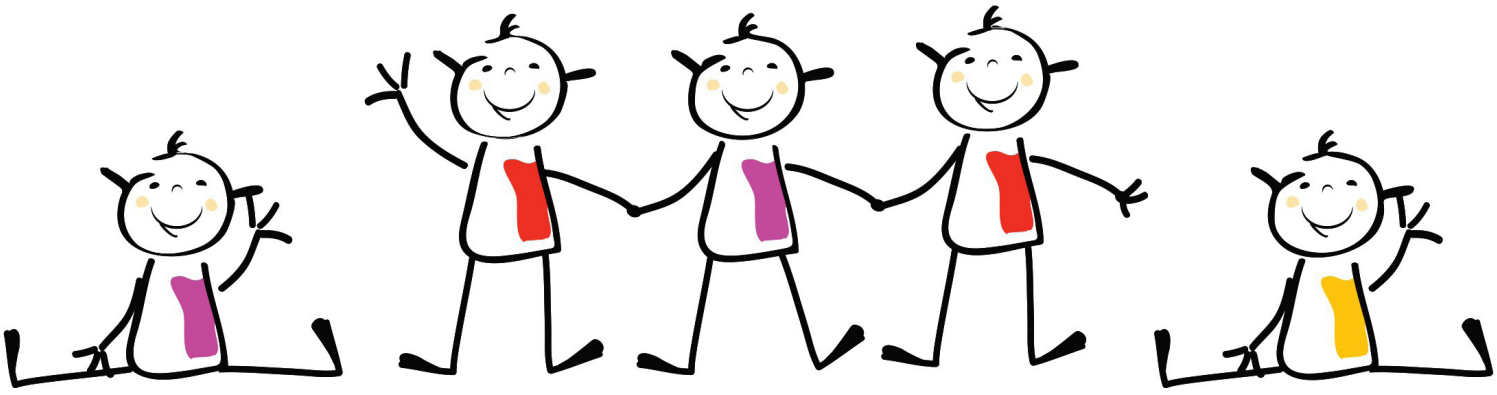

Cystic Fibrosis: The Best Story in Medicine

Deborah K. Froh, MD
Associate Professor of Pediatrics
Director, Cystic Fibrosis Center
UVA Children's Hospital

Objective: *1. Identify the pathway to development of the neweset CFTR modulator drugs.*
2. Summarize key results of the clincial trials, particularly, the dramatic pulmonary benefits.
3. Determine the potential to alter the course of CF disease to most patients.
ACGME Competencies: *Patient care, Medical Knowledge*

In October 2019, the FDA approved a groundbreaking new therapy that will be able to help almost 90% of persons with cystic fibrosis. The latest in a series of drug advances, this medication (elexacaftor-tezacaftor-ivacaftor, brand name Trikafta) is a "CFTR modulator," meaning that it acts on the faulty CFTR protein to improve its function. Treating the basic cellular defect is an obvious advance compared to the multiple familiar therapies aimed at end-organ effects including chronic airway infections, mucus obstruction, and inflammation. Moreover, the specific target of the new triple combination therapy is the CFTR associated with the most common CF mutation, F508del, or "deltaF508." In the U.S., about 85-90% of persons with CF have this mutation in one or both of their CF alleles; nearly half of the patients are homozygous for it.

The path to this latest advance was laid 30 years ago, in 1989 when the gene for cystic fibrosis was identified. The corresponding protein, CFTR, is active in numerous epithelia (hence the multiorgan system involvement in CF) and serves primarily as a chloride channel. In the airways, lack of CFTR function results in reduced chloride transport and poor hydration of the airway lining fluid, inability of the cilia to move freely, and mucus stagnation.

Over 2,000 different gene mutations have been associated with CF. The first clinical success for a CFTR modulator came in 2012, with FDA approval of ivacaftor ("Kalydeco") for persons carrying G551D, a gating mutation, meaning that CFTR is present at the cell surface but is not responsive to signals to open the channel. In clinical trials, ivacaftor was found to produce a rapid and dramatic increase in lung function (based on FEV1), reduced frequency of pulmonary exacerbations, reduced pulmonary symptoms, and even increased weight. In the 8 years since its initial approval, ivacaftor has also been shown to be helpful for other mutations in the gating category, as well as for "residual function" mutations where the CFTR channel is at the surface and has partial but reduced function or where CFTR function is normal but CFTR amount is greatly reduced. Over the years, ivacaftor has continued to prove itself, and is now available to patients as young as 6 months. So why have you likely not heard of it? This is because these mutations are present in less than 10% of people with CF.

Naturally, the biggest need was to address F508del-CFTR, given the mutation's predominance. This, however, was more challenging to fix because the altered genetic code results in a major misfolding of the 3D structure of the protein, such that the cellular quality control mechanisms target it for destruction, and no CFTR reaches the surface membrane. Thus it cannot be helped by ivacaftor alone, as ivacaftor can only serve as a "booster" to channel function. A combination medication would be needed, and this led to the dual medications Orkambi (lumacaftor-ivacaftor) and Symdeko (tezacaftor-ivacaftor) approved in 2015 and 2018, respectively. However, these agents were far from the final answer for F508del, as their clinical effects were relatively modest; for example, the lung function increase was only 3-4% predicted FEV1, significantly less than the 10-12% predicted FEV1 increase that had been seen with ivacaftor treatment of G551D positive CF. In fact, the effect on F508del was only enough to impact patients who are homozygous, leaving behind a multitude of patients (~40% of all CF patients) with a single F508del (and no second mutation that is ivacaftor-responsive).

The newest CFTR modulator builds on the dual combination by adding a third ingredient. The elexacaftor (new component) and tezacaftor both aid F508del-CFTR in reaching the cell surface, by binding to two different sites and presumably improving protein folding; the ivacaftor can then boost channel opening and add to the effect. The triple combination therapy showed stunning results in clinical trials, even for patients with just one copy of F508del. Demonstrating a direct and systemic effect on CFTR, sweat chloride values dropped markedly, by an average of 40-45 mmol/L, actually bringing them to a level below the diagnostic threshold of 60 mmol/L. Among the pulmonary results: [(1)] FEV1 percent predicted increased on average by 13.6 points, which occurred within 2 weeks and was sustained for the duration of the study at 24 weeks. [(2)] The rate of pulmonary exacerbations was greatly reduced, by about 3-4 fold. [(3)] Respiratory symptom scores were dramatically improved.

Putting these findings in perspective, the natural rate of decline in FEV1 is about 2% predicted per year with existing supportive therapies, thus many patients are seeing their best lung function in years. Additionally, pulmonary exacerbations are estimated to account for about 50% of overall lung function decline currently, so the reduction in these would naturally have further impact long term, in addition to the obvious benefits of sparing patients and families the life disruption, stress, and cost of hospitalizations. The longer term experience with ivacaftor for eligible mutations (gating and residual function) suggests that effective CFTR modulation is associated with reduced though not absent lung function decline, reduced mortality or need for transplantation, and possibly decreased infection rates with *Pseudomonas aeruginosa*.

This newest drug advance has only been available since October 2019, but already we are seeing remarkable changes in our patients taking it, improvements that they were not seeing previously even with a grueling regimen of daily breathing treatments and other supportive thera-

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pies. We are amazed by stories of "the mucus purge" that can begin after just one dose of medication, the sense of breathing easier, or disappearance of cough. There is even the prospect that some of the standard baseline respiratory medications might be able to be reduced, and there is a formal study planned to look into this. Perhaps most of all, there is a new feeling of hope throughout the CF community, that maybe life with CF need not be so hard or so short. The current estimated median survival of 47 years is likely to rise significantly, and CF morbidity and mortality may shift 15-20 years by some estimates.

So, are we there yet? No, the work continues. First, the eligibility for the triple combination drug currently begins at age 12, and this needs to decrease for maximum impact on disease course. Studies are already underway for age 6-11 years, and in planning stages for age 2-5 years. Second, despite the remarkable improvements noted, patients who already have advanced lung disease will not normalize and will still need respiratory disease management. Special attention is being paid to the need for new strategies to treat the difficult and often multiresistant CF lung infections which are a major contributor to morbidity and mortality. Third, about 10% of CF patients have no mutations that are currently modulator eligible. Even gene editing strategies are being explored and showing some promise, and would be independent of specific mutation (you may have heard of CRISPR-Cas, the genetic "cut and paste" tool).

The new availability of highly effective, truly transformative CFTR modulator therapy for potentially 90% of people with CF is the crowning achievement of 30 years of following the science, cultivating a vigorous pipeline for organized clinical trials of potential therapies, and meantime focusing on optimal care for our patients.

"I think this is the best story in medicine!" - Dr. Froh

References:

1. *Middleton PG, Mall MA, et al, Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. N Engl J Med 2019, 381: 1809-19.*
2. *Heijerman HGM, McKone ER et al, Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet 2019, 394: 1940-1948.*
3. *Collins, FS. Realizing the dream of molecularly targeted therapies for cystic fibrosis. N Engl J Med 2019; 381: 1863-1865.*

How a Person Gets CF

To have CF, you must inherit two copies of the CFTR gene that contain mutations – one copy from each parent. That means that each parent must either have CF or be a carrier of a CFTR gene mutation.

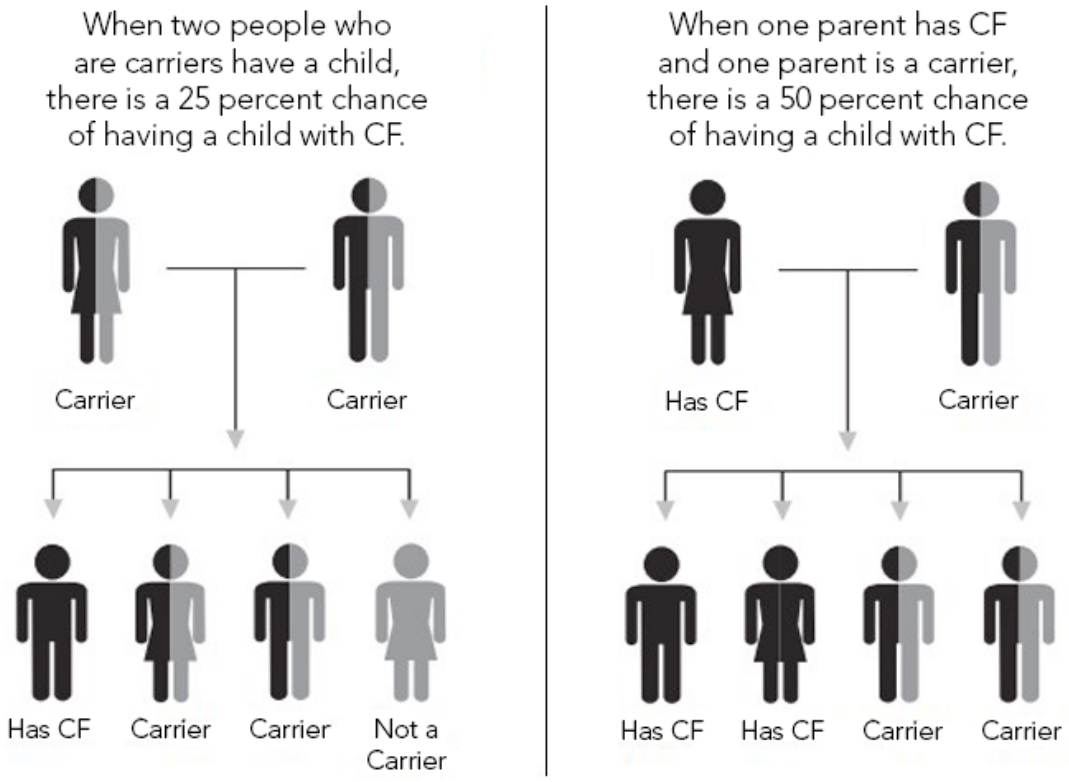

image credit : www.cff.org/What-is-CF/Genetics/CF-Genetics-The-Basics/

Evidence Based Treatments for Anxiety in Children and Adolescents

Laura A. Shaffer, PhD
Licensed Clinical Psychologist
Associate Professor of Pediatrics
UVA School of Medicine

Objective: *Identify treatments for youth anxiety with the best research support.*
ACGME Competencies: *Patient Care.*

Anxiety disorders are the most common class of mental disorders in children and adolescents. Approximately one-fourth of adolescents aged 13-18 years old in the United States experience anxiety at some point, and specific anxiety disorder prevalence rates for younger children range from 2.2% to 9.5%. Primary care is often the first place parents take their children with mental health concerns such as anxiety, and the rate of psychological problems identified by pediatricians has more than doubled over the last 20 years. It can be a challenge to know what treatments to recommend and how to know if children are receiving these if services are provided outside the pediatric practice. What follows is an overview of evidence-based interventions for pediatric anxiety to help guide treatment referrals and discussions with patients and their families.

Evidence-based practice in psychology (EBPP) is the integration of the best available research with clinical expertise in the context of patient characteristics, culture, and preferences. The American Psychological Association Council of Representatives adopted this definition in August 2005; it is very similar to the definition of evidence-based practice used by the National Academies Health and Medicine Division. The purpose of EBPP is to promote effective psychological practice and enhance public health by applying empirically supported principles of psychological assessment, case, formulation, therapeutic relationship, and intervention. We now have enough research to rely heavily on empirically supported psychological treatments for anxiety in children and adolescents.

Evidence based treatments for child and adolescent anxiety focus both on symptom reduction and functional improvement. Treatment efficacy based on symptom reduction is more established in the literature, whereas the more stringent approach of measuring how well treatments address functional impairment has emerged more recently. Charmaine Higa-McMillan and her colleagues published a review of 50 years of treatment for child and adolescent anxiety in which they look at both as well as practice elements common to effective treatments (Higa-McMillan, C. K., Francis, S. E., Rith-Najarian, L., & Chorpita, B., 2016). See Table 1 below for an overview of their findings.

Table 1. Evidence Based Treatments for Child and Adolescent Anxiety

	Best Research Support	Good Research Support
Symptom Reduction	Cognitive Behavior Therapy (CBT) Exposure Modeling CBT with Parents Education CBT plus Medication	Family Psychoeducation Relaxation Assertiveness Training Attention Control CBT for Child and Parent Cultural Storytelling Hypnosis Stress Inoculation
Functional Improvements	Cognitive Behavior Therapy (CBT)	CBT with Parents CBT plus Medication Exposure

Higa-McMillan, C. K., Francis, S. E., Rith-Najarian, L., & Chorpita, B., 2016

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Cognitive Behavior Therapy (CBT) has the strongest research support for both anxiety symptom reduction and improvements in child functioning. The basic premise of CBT is that thoughts, feelings, and behavior are inter-related such that altering one can help alleviate problems in another. For example, a child sitting for a test in school who thinks to herself "I'm going to fail this and won't make it into honors next year," would likely feel anxious and might have difficulty remembering material she studied. Alternatively, a child who thinks to herself "I've got this!" may feel calmer and be able to perform better on the test. Much of CBT focuses on identifying automatic thoughts that contribute to anxiety and challenging distorted cognitions and destructive patterns of behavior that generate or reinforce anxiety.

Two interventions that are often used in CBT and also have strong evidence as treatments on their own for reducing symptoms of anxiety are exposure and modeling. Exposure involves either in vivo or imaginal exposure to feared objects, activities, or situations in a safe environment. This can be done by gradually working up a hierarchy of difficult tasks (graded exposure) or starting with the most difficult task for the child or adolescent (flooding). Modeling, as it sounds, involves a therapist, peers, or others demonstrating a non-fearful response in anxiety provoking situations to promote imitation.

There are some specific components of treatment that are present in at least one quarter of the best-supported treatments (Higa-McMillan, et al., 2016). Exposure and modeling were among these. Other essential practice elements were cognitive strategies (i.e., reframing or self-talk), relaxation, psychoeducation for children and adolescents, psychoeducation for caregivers, self-reward or praise, and problem solving. Being aware of these elements can be helpful for pediatricians and caregivers trying to determine whether or not children and teens are receiving evidence based therapy for their anxiety. Therapists should be able to explain to caregivers and pediatricians what they are working on and what elements they are including in treatment. If a pediatrician is not in direct communication with the therapist, she or he may be able to get some sense of whether or not the youth is receiving any of these evidence based interventions by asking youth and caregivers to describe what strategies they are learning in therapy. By guiding families in requesting and recognizing evidence based treatments as they seek help for their children and adolescents with anxiety, we can help reduce distress and improve functioning for a growing segment of our youth.

The New ALTE: Updates in the Management of Infants with Brief Resolved Unexplained Events

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Objectives: *1. Define BRUE and explore how it compares to ALTE.*
2. Discuss management recommendations for patients with BRUE.
3. Evaluate recent literature examining management and outcomes of patients with BRUE.
ACGME Competencies: *Patient Care, Medical Knowledge, Pratice-based Learning and Improvement*

Background

Apparent life-threatening event (ALTE) was a term developed in 1986 at the National Institutes of Health Consensus Conference on Infantile Apnea and Home Monitoring.' The purpose was to replace the term "near-miss SIDS" and to create a definition so that these patients could be better studied. ALTE was defined as "an episode that is frightening to the observer and that is characterized by some combination of apnea (central or obstructive); color change (usually cyanotic or pallid but occasionally erythematous); marked change in muscle tone (usually limpness); choking or gagging." With years of research, it was concluded that ALTE and SIDS are separate entities, and ALTE is not a predisposing risk factor for SIDS. The term, however, remained challenging as ALTE described non-specific, subjective symptoms where the underlying cause ranged from normal infant physiology to serious etiologies such as child abuse, metabolic disorders or sepsis. Balancing workup for these "never-miss" diagnoses with judicious use of hospitalization and testing was difficult, and there was wide variation across hospitals throughout the country.'

A New Definition

In 2016, the AAP published new guidelines re-naming ALTE to "Brief Resolved Unexplained Events" (BRUE).[3] BRUE is defined as "an event occurring in an infant <1 year of age when the observer reports a sudden, brief, and now resolved episode of >1 of the following: cyanosis or pallor; absent, decreased or irregular breathing; marked changed in tone (hyper- or hypotonia); altered level of responsiveness.

Moreover, clinicians should diagnose a BRUE only when there is no explanation for a qualifying event after conducting an appropriate history and physical examination." This new definition is more precise, less subjective and attempts to eliminate the fear surrounding the diagnosis by removing the term "life threatening." There is also an attempt to exclude normal newborn physiology from the diagnosis (such as choking and turning red). The most significant difference between ALTE and BRUE is that the BRUE definition excludes patients who have a clear cause of the event or who are still symptomatic at the

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time of presentation. If after initial evaluation another diagnosis is made, the diagnosis of BRUE is excluded and the patient should be managed according to the apparent diagnosis rather than as a patient with BRUE would be managed.

Lower-Risk BRUE Management Guidelines

The 2016 guidelines also risk stratify infants with BRUE and provide management recommendations for patients who qualify as lower-risk. In addition to having no concerning features on history and physical exam, a patient with lower-risk BRUE must be older than 60 days and born at least at 32 weeks gestational age with a corrected gestational age of at least 45 weeks. Furthermore, a lower-risk event must be the first event of its kind and not part of a cluster of events, must have lasted less than 1 minute and not required CPR by a medical professional. If all of these criteria are met, then the event qualifies as a lower-risk BRUE and this patient is less likely to have a serious underlying condition or have recurrent events. Lower-risk patients may be managed according to the lower-risk algorithm, which states that most diagnostic testing is not necessary. Performance of an EKG and pertussis testing in the appropriate clinical setting can be considered. The guidelines also notably state that patients with lower- risk BRUE do not need to be admitted to the hospital solely for the purpose of cardiorespiratory monitoring.

Higher-risk BRUE Patients

Due to the paucity of data, the guidelines were unable to provide management guidelines for higher-risk patients. Since publication of the 2016 guidelines, studies have demonstrated that 79-95% of patients with BRUE are higher-risk, making the management guidelines only applicable to a minority of patients.[4, 5] To address this shortcoming, a framework for managing higher-risk patients was published in 2019, which is based on both current evidence and expert consensus.[6] Unlike the management guidelines for lower-risk patients, these recommendations cannot be considered official clinical practice guidelines, but instead are considered an outline to guide the management of these patients. This framework divides patient evaluation into two tiers. The first tier is meant for evaluation of all patients with higher-risk BRUE and is intended to detect both rare conditions in which diagnosis or treatment is time-sensitive (such as child abuse or pertussis) or common conditions in which prompt diagnosis can prevent unnecessary additional testing or recurrent events (such as viral respiratory infection, feeding difficulties). This initial evaluation includes monitoring with pulse oximetry for four hours, screening for child abuse, performing a feeding evaluation, and diagnostic testing (EKG, pertussis, respiratory viral panel, hematocrit, lactate, bicarbonate and blood glucose). The second tier of evaluation is guided by more patient-specific characteristics and is directed towards diagnoses that are less sensitive to delayed diagnosis. This secondary evaluation involves subspecialty consultation and targeted diagnostic testing based on the history and physical exam. Depending on the resources of the health system as well as based on physician and caregiver shared decision-making, this evaluation may take place in the hospital or with coordinated outpatient care.

Moving Forward

Since the publication of the BRUE guidelines, several studies have been published examining patient outcomes and the new management recommendations. One study calculated the risk of mortality after experiencing a BRUE using meta-analysis from ALTE studies and concluded that the risk of death following BRUE is no higher than the baseline mortality rate for all infants.[7] The authors concluded that this finding supports the return-to-home approach for lower-risk infants. Another study compared management of patients with ALTE/BRUE before and after publication of the BRUE guidelines using a multi-centered children's hospital database. There was a significant reduction in hospitalizations and fewer diagnostic studies were performed on these patients after publication of the guidelines. There was no increase in revisit rates suggesting that changes in practice of doing less does not necessarily result in worse outcomes, however additional outcome studies are needed.

The BRUE guidelines help diminish variation in management and reduce unnecessary resource utilization for lower-risk patients. Because these guidelines provide a more precise definition, there is hope that with additional research we will be able to better understand which higher-risk patients will benefit from more testing and in which patients we can safely do less testing and hospitalize less so that we can take better care of all of patients with BRUE.

References

1. *National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring, Sep 29 to Oct 1, 1986. Pediatrics. 1987;79(2):292-299*
2. *Tieder JS, Cowan CA, et al. Variation in inpatient resource utilization and management of apparent life-threatening events. J Pedatr. 2008 May;152(5):629-35, 635.el-2. doi: 10.1016/j.jpeds.2007.11.024*
3. *Tieder JS, Bonkowsky JL, Etzel RA, et al. Subcommittee on Apparent Life Threatening Events. Brief resolved unexplained events (formerly apparent life-threatening events) and evaluation of lower-risk infants. Pediatrics. 2016;137{5):e20160590*
4. *Meyer JS, Stensland EG, Murzycki J, Renzi Gulen C, Evindar A, Cardoso MZ. Retrospective application of BRUE criteria to patients presenting with ALTE. Hospital Pediatrics. November 2018, hpeds.2018-0044; DOI: https://doi.org/10.1542/hpeds.2018-0044*
5. *Ramgopal S, Soung J, Pitetti RD. Brief resolved unexplained events: Analysis of an apparent life threatening event database. Academic Pediatrics. 2019; 19(8): 963-8.*
6. *Lawrence MJ, Quinonez RA, Bronkowsky JL, et al. A framework for evaluation of the higher-risk infant after a brief resolved unexplained event. Pediatrics. 2019; 144(2):e20184101.*
7. *Brand DA, Fazzari MJ. Risk of death in infants who have experienced a brief resolved unexplained event: A meta-analysis.J Pediatr. 2018 June;197:63-7.*
8. *Ramgopal S, Bonkowsky JL, Etzel RA, et al. Changes in the management of children with brief resolved unexplained events (BRUEs). Pediatrics. Sep 2019, e20190375; DOI: 10.1542/peds.2019-0375*

PANDAS: An overview of the past, present and future of Pediatric Autoimmune Neuropsychiatric Disorders Associated with group A Streptococcus Infections

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Objective: *The intent of this article is to describe the clinical manifestations of Pediatric Autoimmune Neuropsychiatric Disorders Associated with group A Streptococcal infections (PANDAS), and its more recent inception, Pediatric Acute-onset Neuropsychiatric Syndrom (PANS); to discuss possible etiologies and pathophysiology; and to provide a framework for treatment strategies.*
ACGME Competencies: *Patient Care, Practice-based Learning and Improvement, Medical Knowledge*

In 1998, investigators at the National Institute of Mental Health first described the clinical characteristics of a novel group of patients with obsessive-compulsive disorder (OCD) and tic disorders, designated as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (group A b-hemolytic Streptococcal [GABHS]) infections (PANDAS).[1] While physicians, patients and families may experience children with dramatic behavioral symptoms after GABHS infection, the link between correlation and causation has been difficult to prove, and the pathophysiology of PANDAS has been fervently debated. The intent of this article is to describe the clinical manifestations of PANDAS and its more recent inception, Pediatric Acute-onset Neuropsychiatric Syndrome (PANS); to discuss possible etiologies and pathophysiology; and to provide a framework for treatment strategies.

The original clinical definition of PANDAS as described by Swedo, *et al* includes 5 criteria:

1. Pre-pubertal symptom onset
2. Temporal association between symptom exacerbations and GABHS infections
3. Episodic course of symptom severity
4. Presence of OCD and / or a tic disorder
5. Associated neurologic abnormalities

Group A strep pharyngitis, the most common clinical manifestation of GABHS, occurs in all ages but is most common among school age children, peaking at 7-8 years of age. This parallels the described pre-pubertal symptom onset of PANDAS, typically after age 3 years. In order to be considered a case of PANDAS, GABHS must be proven by rapid antigen testing, bacterial culture, or positive antibody results on serologic testing. Antistreptolysin antibody is positive in 20-50% of PANDAS cases and peaks at 3-5 weeks after GABHS infection, while anti-DNase B is positive in 80% of PANDAS cases and peaks at 6-8 weeks.[2] Antibody titers begin to fall rapidly over next 6 months. As would be expected with a clinical syndrome triggered by a common infection, PANDAS is episodic in flares. Parents often report an "explosion" of symptoms within 24-72 hours of acute strep infection, including findings of OCD or tic disorder meeting DSM V criteria, motoric hyperactivity, choreiform movements, and irritability and anxiety, particularly separation anxiety. These symptoms can be severe and impair all aspects of a child's function, with school absence and decreased academic performance as one common example. The psychiatric and neurologic symptoms recede over weeks to months. About 50% of patients will have a second or more episode, developing a "sawtooth" pattern over time.[1]

GABHS infection alone is not sufficient to cause PANDAS; the prevalence of GABHS is very high, while PANDAS diagnoses are rare, suggesting the imperative of an intermediary step. To date, no specific biomarkers have been identified; however, there is biologic plausibility that GABHS infection may trigger systemic, immune-related symptoms. The classic model for this is rheumatic fever in which molecular mimicry between GABHS antigens and "self" peptides leads to transient arthritis due to the formation of immune complexes, chorea due to binding of antibody to basal ganglia cells, and carditis due to antibody binding and infiltration of T cells in the heart. We also know that nephritogenic strep antigens in the kidney leads to immune complex deposition, triggering complement activation and inflammation leading to post-streptococcal glomerulonephritis. It follows that neuropsychiatric symptoms described in PANDAS and temporally related to GABHS infection may also be immune derived and / or modulated by inflammation.

A 2008 collaborative case control study led by members of the Tourette Syndrome Study Group looked at 40 patients with PANDAS and 40 patients with OCD or tic disorder whose symptoms were not related to GABHS infection at the time of diagnosis.3 Subjects were followed over 2 years and underwent throat cultures once per month, anti-strep antibody testing every 3 months, and testing for GABHS during exacerbations of OCD and tic symptoms. While the PANDAS group had more exacerbations than the control group, 87.5% of exacerbations in the PANDAS group were not related to GABHS, and none of the exacerbations in the control group were related to GABHS. It follows that GABHS cannot, therefore, be the sole inciting factor for PANDAS symptoms.

This finding led investigators to describe the broader syndrome of PANS in 2014:4

I. Abrupt, dramatic onset of OCD or severely restricted food intake
II. Concurrent presence of additional neuropsychiatric symptoms (with similarly

cont. page 13

severe and acute onset), from at least 2 of the following 7 categories:

1. *Anxiety*
2. *Emotional lability and / or depression*
3. *Irritability, aggression, and / or severely oppositional behaviors*
4. *Behavioral (developmental) regression*
5. *Deterioration in school performance (related to ADHD-like symptoms, memory deficits or cognitive changes*
6. *Sensory or motor abnormalities*
7. *Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency*

III. Symptoms are not better explained by a known neurologic or medical disorder

This more inclusive definition is agreed by PANS / PANDAS experts to have multiple possible etiologies, ranging from psychological trauma or underlying neurological, endocrine, and metabolic disorders to post-infectious autoimmune and neuroinflammatory disorders, cerebral vasculitis, neuropsychiatric lupus, and others.[5]

One downside of the broad inclusion criteria for PANS has been that pathophysiology has been difficult to determine, and targeted treatments therefore challenging to identify. A 2017 PANS / PANDAS Research Consortium published a 3 part treatment guideline based on expert opinion derived from treating collectively over 1000 patients with PANS / PANDAS.[6-8] Their 3-pronged treatment strategy includes psychiatric and behavioral interventions to support symptom management; an escalating regimen of immunomodulatory therapy beginning with NSAIDS and progressing to corticosteroids, IVIG, plasmapheresis, and disease modifying anti-rheumatic drugs; and treatment and prevention of infections, including anecdotal support for long-term antibiotic prophylaxis to prevent GABHS infection. Unfortunately, studies supporting these treatments are mainly limited to observational case series or retrospective surveys. The few randomized controlled trials that have been done suffer from small enrollment numbers, lack of appropriate blinding, and absence of control for confounding variables. Specifically, a 2018 systematic review of the literature found inconclusive evidence to support treatment of PANS / PANDAS with NSAIDS, steroids, IVIG, plasmapheresis, or antibiotics.[9] This said, there is no compelling case that immunomodulation cannot produce benefit in some patients, and thus the risk-benefit calculus is highly subjective.

Rationally, supportive therapies through behavioral interventions and psychiatric management makes sense for these children who are experiencing symptoms that are very distressing and often disruptive to the entire family. Referral to neurology may aid in treating tics, and specialized eating disorder clinics may also help some children. In addition, it is appropriate to evaluate for inflammation and to search further for a source if laboratory markers such as elevated C-reactive protein or erythrocyte sedimentation rate are identified. Patients with acute evidence of inflammation as evidenced by delirium, psychosis, encephalitis or seizures should be immediately referred to neurology or the emergency room. Those with less obvious inflammation but histories of chronic pain or hyperesthesia may benefit from a 4-6 weeks tapering course of naproxen. Finally, it is reasonable to identify and treat infections, specifically GABHS. If GABHS is found through rapid antigen testing, culture or rising antibody titers, treatment with amoxicillin for 10 days is appropriate. For recurrent GABHS a 5 day course of azithromycin may be considered; despite a resistance rate of GABHS to azithromycin of around 12%, the drug's mechanism of action with inhibition of RNA protein synthesis allows intracellular penetration not seen with amoxicillin. [10]

While controversy over PANS / PANDAS abounds, it cannot be denied that a group of children with similar symptoms are suffering. The way forward should begin with a better defined clinical syndrome(s), and it is likely that ultimately PANS / PANDAS will turn out to be not one but many similar illnesses with unique genetic and environmental triggers. With strict inclusion criteria to define subsets of PANS / PANDAS, it may be possible to identify sensitive and specific diagnostic – and perhaps therapeutic – targets. Larger, high-quality treatment studies that are blinded, randomized, and placebo controlled are needed, particularly of those treatments associated with higher risk (e.g. immunomodulatory therapies, antibiotic prophylaxis). To be most informative, these studies may need to define very strict inclusion criteria to avoid type II statistical errors. Current research efforts at PANS / PANDAS centers across the country in anti-neuronal antibodies and metabolomics may provide future direction.

References

1. *Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Swedo S, et al. Am J Psychiatry. 1998 Feb;155(2):264-71.*
2. *Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). Murphy ME, Pichichero ML. Arch Pediatr Adolesc Med. 2002 Apr;156(4):356-61.*
3. *Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: a prospective blinded cohort study. Kurlan R. Pediatrics. 2008 Jun;121(6):1188-97.*
4. *Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. Chang K, et al. J Child Adolesc Psychopharmacol. 2015 Feb;25(1):3-13.*
5. *Overview of Treatment of Pediatric Acute-Onset Neuropsychiatric Syndrome. Swedo SE, et al. J Child Adolesc Psychopharmacol. 2017 Sep;27(7):562-565.*
6. *Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part I-Psychiatric and Behavioral Interventions. J Child Adolesc Psychopharmacol. Thienemann M, et al. 2017 Sep;27(7):566-573.*
7. *Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies. J Child Adolesc Psychopharmacol. Frankovich, et al. 2017 Sep;27(7):574-593.*
8. *Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part III – Treatment and prevention of infections. J Child Adolesc Psychopharmacol. Cooperstock M, et al . 2017 Sep;27(7):594-606.*
9. *Treatment of PANDAS and PANS: a systematic review. Sigra S, et al. Neurosci Biobehav Rev. 2018 Mar;86:51-65.*
10. *Macrolide and Clindamycin Resistance in Group a Streptococci Isolated From Children With Pharyngitis. DeMuri GP, et al. Pediatr Infect Dis J. 2017 Mar;36(3):342-344.*

Updates in Pediatric Neuromuscular Disorders

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Objective: *Identify new treatments for Duchenne Muscular Dystrophy and Spinal Muscular Atrophy.*
ACGME Competencies: *Patient Care, Medical Knowledge, Practice-based Learning and Improvement*

These are exciting times in the world of pediatric neuromuscular medicine, with new treatments and therapies, and ever-increasing life expectancy for children with rare motor disorders.[1-3] Disorders that have historically been without treatments now have new hope.[4-6] And as one recent article stated: "treating pediatric neuromuscular disorders: the future is now."[7] Recent advances in care of children with Spinal Muscular Atrophy, Duchenne Muscular Dystrophy, and new trials for patients with Charcot Marie Tooth, Myotonic Dystrophy, Friedreich's Ataxia and neuromuscular junction diseases have offered new possibilities for patients and families living with these conditions. We will highlight two disorders seen in neuromuscular clinic.

Spinal Muscular Atrophy (SMA) is the leading genetic cause of death in infants, with a life expectancy of less than 2 years, which until recently had no treatment. It is characterized by progressive motor loss, and challenges with feeding, breathing and motor milestones. SMA is caused by a variation of the survival motor neuron gene which leads to a lack of survival motor neuron protein, a protein essential for the health of motor neurons coming from the anterior horn of the spinal cord to innervate the muscles. SMA affects 1 in 10,000 or so infants, and 1 in 50 people in the United States is a carrier for this disease, which is inherited in an autosomal recessive manner.

New treatments have revolutionized opportunities for children living with SMA. In December 2016, the FDA approved Nusinersen, an antisense oligonucleotide given via intrathecal injection. The dose is 12 mg, given in four loading doses over two months, and then one dose every four months. Nusinersen (brand name Spinraza) works by binding to RNA to fix a splicing error in the back-up survival motor neuron gene (SMN2), to increase production of survival motor neuron protein.[8, 9] In our clinic, we have seen children make remarkable progress with this medication, have decreased hospitalizations, decreased need for respiratory support, and improved motor function. Another antisense oligonucleotide, given orally, is currently in trials with promising results.[10]

In May 2019, the SMA community had another breakthrough with the FDA approval of onasemnogene abeparvovecxioi (brand name Zolgensma), a gene therapy to treat children under 2 years of age with bi-allelic variation in SMN1 gene. Zolgensma is given in a one-time IV infusion, and replaces the missing SMN1 gene by giving it inside a viral vector, the AAV9 virus.[5, 11] Children are infused with the gene contained in the virus, to "infect" their cells with the new survival motor gene. Results for this new treatment have also been remarkable, and in the patients who have received this treatment at UVA, we have seen significant progress.

Duchenne Muscular Dystrophy (DMD) is the most common muscular dystrophy, and the most common genetic cause of death in boys. DMD affects about one in 5,000 boys and young men, leading to progressive muscle weakness, causing loss of ambulation, and then loss of arm function, followed by respiratory weakness and cardiomyopathy. DMD is caused by a variation in the dystrophin gene, leading to lack of dystrophin protein throughout the body. This protein is essential for muscle structure and function, and lack of dystrophin leads to severe, progressive muscle weakness.

Eteplirsen (brand name Exondys 51) is a new treatment for DMD. This exon-skipping medication splices RNA, allowing a "skip" over the variant/non-functional section of code, to allow a read-through and creation of a truncated dystrophin protein similar to what is seen in patients with Becker Muscular Dystrophy (caused by an in-frame variation in the dystrophin gene).[12] Eteplirsen is given intravenously, weekly, at a 30 mg/kg in a 35 to 60 minute infusion. The data show small improvements in dystrophin on muscle biopsy. The FDA approved this medication September 2016. This medication can be used in boys who have a deletion in the dystrophin gene that is amenable to Exon 51 skipping. At UVA, the medication is initially given in the UVA Children's Hospital Infusion Center, and then the patient's transition to weekly home infusions. A similar medication, Golodirsen (brand name Vyondys 53), was approved by the FDA December 2019, and can be used in patients who have a deletion in the dystrophin gene that is amenable to Exon 53 skipping.[13]

Boys with DMD are also treated with glucocorticoids, specifically prednisone or deflazacort (brand name Emflaza), to prolong ambulation, arm function, and cardiopulmonary function.

In addition, trials are currently underway for gene replacement therapy, using an AAV viral vector to give a microdystrophin (the dystrophin gene is very large, and so trials are looking at giving pieces of the gene) to boys, and results have been promising.

These treatments are expensive, as pharmaceutical companies' price medications for rare disorders at extraordinarily high cost in order to recoup R&D expenses. The Institute for Clinical and Economic Review (ICER) provides overviews on drug-pricing and cost-benefit analysis for various treatments: https://icer-review.org/material/sma-report-at-a-glance/ https://icer-review.org/material/dmd-evidence-report/

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Updates in Pediatric Neuromuscular Disorders

Children with Neuromuscular Disorders receive comprehensive care in the UVA Children's Hospital **Pediatric Neuromuscular and Muscular Dystrophy Association Care Center**. We see children with diagnoses including SMA, DMD, Becker Muscular Dystrophy (BMD), Limb Girdle Muscular Dystrophy (LGMD), Fascioscapulohumeral Muscular Dystrophy (FSH MD), Friedreich's Ataxia (FA), Charcot-Marie-Tooth (CMT), Myotonic Dystrophy (DM1), congenital myopathies, collagen VI disorders and a range of other muscle concerns. Children receive full multi-disciplinary care and their growth, development and health are monitored closely. Studies have found that children seen in an interdisciplinary setting who receive careful monitoring and appropriate therapies have improved health outcomes.[1-3]

Multidisciplinary team available: Our teams feature providers from Developmental Pediatrics, Neuromuscular Neurology, Cardiology, Pulmonology, Orthopedics, Physical Medicine & Rehabilitation, Prosthetics/Orthotics, Physical Therapy, Occupational Therapy, Speech/Language/Feeding Therapy, Nutrition, Education, Psychology, Social Work, Respiratory Therapy, Dental, Nursing, Palliative Care and Genetic Counseling.

Our pediatric neuromuscular clinic is a certified Duchenne Care Center (www.parentprojectmd.org/care/find-a-certified-duchenne-care-center/) and a Muscular Dystrophy Association Care Center (www.mda.org/care/mda-care-centers).

In addition to clinical care, pediatric neuromuscular medicine contributes to the missions of the UVA Children's Hospital through education and research as well. We serve as a clinical training site for residents from Pediatrics, Neurology & Physical Medicine & Rehabilitation (PM&R), as well as medical students from UVA School of Medicine. Our clinic trains fellows from Developmental Pediatrics, Neuromuscular Neurology, and Child Neurology who receive their experience with pediatric neuromuscular disorders through this clinic, so that trainees are prepared to assess children with motor delays in early childhood. Nursing and therapy students also receiving training in neuromuscular disorders in this clinic. We give lectures on neuromuscular disorders to Pediatrics, Neurology, Developmental Pediatrics, Neuromuscular Neurology, Cardiology, and PM&R residency programs, as well as in the medical school.

In order to promote health and flourishing of children with neuromuscular disorders, we seek to build a robust research program with the goal of improving care for children with neuromuscular disorders. We are currently partnering with engineers from the departments of biomedical engineering, engineering systems, and computer engineering to study motor function in children with weakness, and we have on-going studies examining quality of life, mood, cardiac function and use of palliative care supports in patients in this clinic. We believe that the future is bright for these children, although significant challenges remain.

References

1. *Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for Standard of Care in Spinal Muscular Atrophy. Journal of Child Neurology. 2007;22(8):1027-1049.*
2. *Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurology. 2018;17(3):251-267.*
3. *Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurology. 2018;17(4):347-361.*
4. *Corey DR. Nusinersen, an antisense oligonucleotide drug for spinal muscular atrophy. Nature Neuroscience. 2017;20(4):497-499.*
5. *Day JW, Chiriboga CA, Crawford TO, Darras BT, Finkel RS, Connolly AM, et al. Avxs-101 gene-replacement therapy (GRT) for spinal muscular atrophy type 1 (SMA1): pivotal phase 3 study (STR1VE) update. Journal of Neurology Neurosurgery and Psychiatry. 2019;90(E7).*
6. *Charleston J, Schnell F, Dworzak J, Donoghue C, Lewis S, Rodino-Klapac L, et al. Long-term treatment with eteplirsen promotes exon 51 skipping and novel dystrophin protein production in Duchenne muscular dystrophy patients. Neuromuscular Disorders. 2016;26:S153-S153.*
7. *Dowling JJ, Gonorazky HD, Cohn RD, Campbell C. Treating pediatric neuromuscular disorders: The future is now. American Journal of Medical Genetics Part A. 2018;176(4):804-841.*
8. *Chiriboga CA, Swoboda KJ, Darras BT, Iannaccone ST, Montes J, De Vivo DC, et al. Results from a phase 1 study of nusinersen (ISIS-SMNRx) in children with spinal muscular atrophy. Neurology. 2016;86(10):890-897.*
9. *Khorkova O, Wahlestedt C. Oligonucleotide therapies for disorders of the nervous system. Nature Biotechnology. 2017;35(3):249-263.*
10. *Chiriboga CA. Risdiplam SMN2 splicing modulator Treatment of spinal muscular atrophy. Drugs of the Future. 2019;44(8):643-658.*
11. *Al-Zaidy SA, Mendell JR. From Clinical Trials to Clinical Practice: Practical Considerations for Gene Replacement Therapy in SMA Type 1. Pediatric Neurology. 2019;100:3-11.*
12. *Charleston JS, Schnell FJ, Dworzak J, Donoghue C, Lewis S, Chen L, et al. Eteplirsen treatment for Duchenne muscular dystrophy Exon skipping and dystrophin production. Neurology. 2018;90(24):E2146-E2154.*
13. *Muntoni F, Frank D, Sardone V, Morgan J, Schnell F, Charleston J, et al. Golodirsen Induces Exon Skipping Leading to Sarcolemmal Dystrophin Expression in Duchenne Muscular Dystrophy Patients With Mutations Amenable to Exon 53 Skipping. Neurology. 2018;90.*