Luke Musselman, 18 years old
PANS with severe OCD, High Functioning Autism
Submitted by Melanie Musselman, Clifton, KS 785-692-4526 3ml@bluevalley.net
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First of all, we want to introduce you to our son Luke Musselman and give you an idea of how accomplished he was before he developed this debilitating condition, PANS (Pediatric Acute Onset Neuropsychiatric Syndrome). Before Luke's PANS with severe OCD (Obsessive Compulsive Disorder) set in, he didn't even need an IEP (Individual Education Plan) at school for his High Functioning Autism. It wasn't until the spring of 2016 at age 14 when the OCD became too much for him to handle that he had to have an IEP. He was mostly an A student and excelled in spelling, geography and math. He loved the weather and maps. He was in 4-H and active at church. He was basically a normal kid. In fact, some have told me they didn't know he even had Autism. He was fully functional and independent, until he wasn't.

- **February 2016:** The first signs of OCD with him retracing homework assignments. It would literally take him 3 to 4 hours to complete approximately six Algebra problems. The OCD progressively became worse. He had a hard time eating and it would take him 3 to 4 hours to finish a meal by himself.
- **March 2016:** His first appointment with a psychiatrist in Manhattan, KS to get started on psychiatric medicines. He was prescribed Zoloft. He couldn't keep up with his homework assignments and school in general. He was evaluated by the school psychologist and qualified for an IEP because of his extremely slow processing speed, cognitive decline and difficulties in handwriting.
- **May 2016:** His first appointment with a psychologist in Manhattan, KS who specialized in OCD. He progressively became worse and more shut down with OCD after school ended. He became very resistant to take his prescribed medicines and it was hard to even get him out of bed in the mornings or for him to keep a regular schedule.
- **June 2016:** 11 days at Stormont Vail-West in Topeka, KS, the psychiatric hospital to get started back on medications consistently and six days at Children's Mercy South in Overland Park, KS. When he came to Children's Mercy he was just 81 lbs.! And at just 5'5" that is extremely underweight. We were extremely worried for his overall health and knew he couldn't sustain like that. He was in the eating disorders unit at Children's Mercy although they classified his condition as disordered eating because of the OCD. He required an NG (Nasogastric) tube and finally allowed us and nursing staff to help him eat. The NG tube supplemented his nutrition with Ensure Plus protein shakes overnight. **Ultimately, we feel that Luke should have been referred on to a PANS/PANDAS specialist when we left Children's Mercy in Kansas City. But because this is a controversial diagnosis not many medical professionals even recognize it as a true condition! It is a very misdiagnosed or underdiagnosed condition.**
- **July 2016:** Qualified for Medicaid on the SED (Severe and Emotionally Disturbed) Waiver. Our company was Amerigroup.
- **July, August and September of 2016:** He had therapy three times a week from a psychologist from in Manhattan who we first sought treatment from in May. He also received occupational therapy, speech therapy and physical therapy in Manhattan, KS.
- **August 2016:** He started school and had a full time para at school that helped him walk to and physically helped him get class to class. She took his notes in all of his classes. He had a case worker from Pawnee Mental Health, our local mental health agency, come to school and helped feed him his lunch.
- **October and November 2016:** We had care attendants coming from Pawnee Mental Health to help us at home with him and it became too much for all of us to handle. We couldn't take care of him at home anymore because the OCD was too strong, the rituals were too much for him to handle.
- **November 23, 2016:** He went to a residential treatment facility, Lakemary in Paola, KS the day before Thanksgiving. They are a Psychiatric Residential Treatment Facility (PRTF) and school which specializes in Autism and other intellectual and developmental delays. He gained weight there and made it up to about 100 pounds but they didn't have the specialized OCD treatment which he actually really needed. After he

was in the PRTF for a while and we did our own research, we asked the Clinical Director of the PRTF point blank, "Is this PANS or PANDAS?" He answered an astounding NO, because our son had already been on an antibiotic, which he had NOT. The doctor presumably confused our son with another patient.

- **March 2017:** We consulted Dr. Roger Kobayashi, an Immunologist with Allergy, Asthma and Immunology Associates in Omaha, NE about a possible PANS and/or PANDAS diagnosis. I faxed him 47 pages of Luke's prior medical, psychological and psychiatric history and from his records approved him for the Cunningham Panel of bloodwork. The Cunningham Panel can help identify the level of autoimmune antibodies associated with Neuropsychiatric Disorders and the capability they have to stimulate and trigger neurologic behavior. It was developed to assist physicians in their diagnosis of PANS and PANDAS and is the only test of its kind in the world. The Cunningham Panel™ of Tests determines the "likelihood of the patient's condition being auto-immune in nature," including possible PANDAS and PANS. Moleculera Labs in Oklahoma City, OK is the only lab in the world that tests the Cunningham Panel.
- **March and April 2017:** Moleculera Labs received Luke's blood sample. We got the results from Dr. Kobayashi's office in April that based on Luke's bloodwork with the Cunningham Panel he needed to be seen by Dr. Kobayashi. But due to Luke's limited functioning and extreme OCD with transitions including getting in and out of vehicles and going through doors, we couldn't get him up to see Dr. Kobayashi until 3 months later.
- **May 2017:** Because he wasn't getting enough of and not the right treatment at Lakemary, we sought treatment from KCCAT (Kansas City Center for Anxiety Treatment) for Luke's severe OCD and anxiety. KCCAT came to Lakemary for their initial evaluation and a few sessions. But according to Lakemary because he was in a PRTF, they didn't have to comply with another treatment team coming to Lakemary for more therapy when they provide it there. But in my son's case, Lakemary wasn't providing the correct kind of specialized treatment that Luke needed.
- **July 2017:** After Luke's appointment with Dr. Kobayashi, July 26, he confirmed what we had thought all along. Luke had PANS! This is what we suspected all along after doing research about the condition. But, from the beginning many doctors including at Children's Mercy in Kansas City dismissed it. Luke was started on the recommended treatment protocols including Prednisone (steroid) for 19 days, 30 days of Cefdinir and rotating between the antibiotics of Amoxicillin and Keflex (Cephalexin), 21 days each. Since then through more bloodwork, Luke also has an underlying infection of Mycoplasma Pneumonia. So because of that his antibiotic rotation has changed to Azithromycin and Cephalexin.
- **August 2017:** Along with the antibiotic regimen, ERP (Exposure Response and Prevention) therapy is recommended for OCD symptom reduction. Because of Luke's progress with the antibiotics and Lakemary's inability to provide the right treatment, Luke was able to be discharged from Lakemary and come home on August 24, 2017. Amerigroup paid for the approximately $13,000 a month for him to be at Lakemary.
- **September 2017:** Integrated Behavior Technologies, Inc. (IBT) from Basehor, KS provided in home therapy 5 mornings a week. They started in September. He was also attending high school in the afternoons at our local public high school.
- **January 2018:** After four months of treatment with IBT, they pulled out of their morning therapy January 9 because Luke became physically aggressive to us his parents during their morning sessions. The IBT Behavior Psychologist was still helping to navigate on Luke's behaviors at home and school. At that time, because of his extreme challenges, he was approved for PRTF again. But there was no facility open and plus, as we learned before, a PRTF is not the correct treatment environment for him. Pawnee Mental Health staff helped Luke with his morning routine and getting him to school for his half day. They pick him up from school and are with him in the evening until bedtime. Started oral steroid per Dr. Kobayashi to help with symptoms.
- **February 2018:** New Pediatric Neurologist in Salina, Dr. Britton Zuccarelli. She prescribed higher dose of oral steroid burst and taper starting at 60 mg. per day and going down each week.

- **May 2018:** Luke finished the school year and started going to one regular class a few days a week. He participated in a class group project with good results. Through recommendations of Dr. Kobayashi in Omaha, Luke had IV steroids, May 25 & 26, to help his ongoing symptoms of severe OCD, aggression and ODD, as well as not being able to perform ADLs (Activities of Daily Living).
- **June 2018:** Intensive ERP (Exposure Response Prevention) therapy in Kansas City with IBT Behavior Psychologist, June 5-8, 12-14.
- **August 2018:** Luke attended Pawnee Mental Health STARS Camp at Rock Springs Ranch. Salina Pediatric neurologist prescribed IVIG (Intravenous Immunoglobulin) for ongoing severe PANS symptoms. Started school, going at the start of 2nd hour to the end of school with four general education classes and two special education classes.
- **October 2018:** Five day High dose (2 g/kg of Luke's body weight) IVIG infusion at Salina Regional Health Center in Salina, by ordering Pediatric Neurologist, Dr. Zuccarelli, October 8-14.
- **November 2018:** Appointment with Dr. Kobayashi**,** November 12. Follow up after IVIG, determined 5 more infusions were needed. Dr. Kobayashi conducted a case study of patients from his practice in treating PANS/PANDAS and with a total of 6 infusions some patients, were symptom free.
- **December 2018:** Appointment with Pediatric neurologist to cosign on IVIG, December 4. She got the order from Amerigroup saying that the order had been approved. The only problem was, it didn't match the order submitted by Dr. Kobayashi. According to Amerigroup officials we spoke with, their pharmacy executed "internal override" of the denial by Blue Cross/Blue Shield, Luke's primary insurance and the order was generated. In trying to sort out the problem with Amerigroup in getting the IVIG order resolved, the pediatric neurologist's office felt we made excessive contact with them and they spent too much time on Luke's case. They felt like Luke's case could not be adequately handled by the neurologist anymore because she had approximately 1000 other patients. In the meantime, Luke needed another IVIG treatment and it was being held up by insurance. We also lost our doctor in the process. Luke spent New Year's Eve in the ER due to manic and aggressive behavior and had to spend the next day in the Crisis Respite House with Pawnee Mental Health.
- **January 2019:** First appointment with Dr. Shirley Wang, Rheumatologist, in Overland Park. She worked quickly and submitted the order for IVIG to Luke's new Medicaid insurance MCO, United HealthCare. Luke's next IVIG was 9 days after our appointment which is almost unheard of. Usually as was the case earlier, it takes a while to get it approved. He had low dose IVIG (1 g/kg of Luke's body weight) at Salina Regional Health Center, Outpatient Infusion Center, over two days.
- **February-March 2019:** Intensive ERP (Exposure Response Prevention) therapy in home with same Behavior Psychologist from KC, 3-4 hour sessions on three different days. ERP therapy is the evidenced based therapy for OCD. Through the Behavior Psychologist's research about PANS/PANDAS, patients have the most effective recovery with a combination of medical and behavior health therapies done together.
- **February-April 2019:** Luke continued getting low dose IVIG once a month at Salina Regional Outpatient Infusion Center. At the April appointment with Dr. Wang, she wanted to take a pause with the IVIG and see how he would do over the summer without it.
- **May 2019:** Intensive ERP therapy in home with Behavior Psychologist from KC and a behavior therapist with Pawnee Mental Health. The session was about six hours in one day and Luke got very agitated. One of Luke's triggers with OCD is checking the weather when there is severe weather and there was some that day.
- **June-July 2019:** Luke struggled tremendously and regressed over the summer with no monthly IVIG and no set schedule. He couldn't get up in the morning and was overly tired. He would go to the bathroom in his pants very frequently or even on the floor. His OCD rituals and aggression continued. We added a functional medicine doctor with a variety of supplements to Luke's treatment protocol.
- **August-September 2019:** Another appointment with Dr. Wang in August. Due to his extreme regression over the summer, she submitted the IVIG order again. Insurance approved two more IVIG infusions. Luke

had them in August and September. The same low dose of 1 g/kg of body weight. We knew there was no way he could go to school without resuming IVIG. Luke started school in all regular classes in high school except study skills in the special education room.

- **October 2019:** Dr. Wang suggested we explore another possible treatment, Rituximab infusion, because of the difficulty of getting IVIG approved by insurance. Rituximab is a medication used to treat certain autoimmune diseases and types of cancer. She recommended we get another opinion from a neurologist. Luke saw a new neurologist in the KC area. He was not a PANS friendly neurologist like Luke's previous neurologist was. Because of Luke's overall good physical health, he would not sign off on Rituximab. He said he would recommend IVIG to be continued since we were seeing progress. We told Dr. Wang we wanted her to pursue IVIG again.
- **November 2019-February 2020:** Dr. Wang had to go through a peer to peer review to get more IVIGs for Luke approved again. She was successful and Luke was able to get one per month, November through February. Little by little Luke is gaining more independent functions again such as going to the bathroom and decreased accidents. The rages are subsiding. Although sometimes, the OCD rituals to heighten immediately after the infusion. Then, they get better again.
- **February 2020:** Dr. Wang mentioned that after the last approval of IVIG, our Medicaid MCO UHC, indicated that after those last three infusions that would be it. So I don't know what our next step is. If another Prior Authorization can be submitted or not. So we may be up in the air again without IVIG which has helped Luke steadily become more independent and back to his normal personality. We consulted Dr. Kobayashi about ordering IVIG from his office. We started the process and initiated the insurance approval through both BCBS and United Healthcare Medicaid.
- **March–July 2020:** Luke struggled getting to school on time before in person classes were moved to online because of COVID-19. He was going to be in HS track again but it was cancelled because of the pandemic. He did not do very well with online classes to finish the school year. His anxiety was extremely high at this time and he had an ER visit on March 10 because of manic episodes. Over this time, Luke experienced symptoms of high anxiety, severe OCD rituals, manic episodes, behavior regression by going to the bathroom in his pants or on the floor, both urination and feces, all of those became very common and constant over the summer. At the end of the school year, he was probably about 3 weeks behind with his assignments. Luckily, the teacher and administration decided that students would receive the same grades for 4th quarter as what they did in the 3rd quarter. We waited and waited for insurance approval for IVIG. Dr. Kobayashi also did a peer-to-peer review with UHC Medicaid and it was denied. So, we pursued the State Fair Hearing process with the State of Kansas. It is a phone hearing and is conducted like an actual legal proceeding. We have been through a State Fair hearing before trying to get Luke's increased behavior health hours covered by Medicaid with Pawnee Mental Health.
- **July 2020:** We submitted the most up to date research for the Medicaid State Fair hearing regarding PANS/PANDAS and most importantly records from Luke's symptom logs proving how IVIG was indeed helping Luke's abilities to return and his OCD/Anxiety to decrease. The written testimony I submitted today from Dr. Suzanne Gazda, Neurologist from San Antonio, TX, I also submitted for evidence for our State Fair Hearing. As well Dr. Kobayashi, who we are going to hear from today, was going to testify that day on Luke's behalf as his doctor. At literally the eleventh hour, I was informed by email on Friday at 4:10 p.m. that Luke's IVIG had been approved by UHC ahead of the hearing on Monday, July 13!! This process took FIVE LONG MONTHS for his IVIG to be approved!!
- **July-August 2020:** Dr. Kobayashi ordered 8 IVIG treatments every 3-4 weeks which were July 23-24, August 13-14 in Lenexa, KS at the Optum Infusion suite. Normally, Dr. Kobayashi's IVIG patients do home infusion but our home county, Clay County, doesn't have a licensed home infusion nurse, so we had to either go to Lenexa, KS or Omaha, NE for the infusions. We chose Lenexa, KS. He made significant progress in just the first two treatments and was able to start school normally. Our school has been in person with masks and

our school staff has worked hard to put the proper protocols in place to keep the students safe and still be in class.

- **September-October 2020:** IVIG infusions in Lenexa, KS, September 3-4, 24-25, October 22-23. He made the most progress with IVIG between treatments 3-5 as opposed to now treatments 5-7. He is still making incremental progress but made the biggest jump between treatments 3-5.
- **November-December 2020:** IVIG infusions in Lenexa, KS, November 12-13, December 3-4, 21-22. In November and early December, he has experienced a minor setback with symptoms of fatigue, and he has had a hard time getting to school on time. However currently, he has all As in his classes for the semester which is phenomenal from where he started. His gen ed classes are War and Literature, Choir, Biology, Horticultural Science, Geometry and US Government. He lost a year in school but is now a Senior and will graduate in May 2021. His next appointment with Dr. Kobayashi is December 30 to reevaluate if he feels Luke needs more IVIG.

Through all of our searching for answers over this four-year ordeal, other than Dr. Kobayashi and Dr. Wang, we have felt we have been the only advocates for our son. For every diagnosis and treatment, it seems like we have to keep pushing the medical and behavior health community and have to keep fighting for our son.

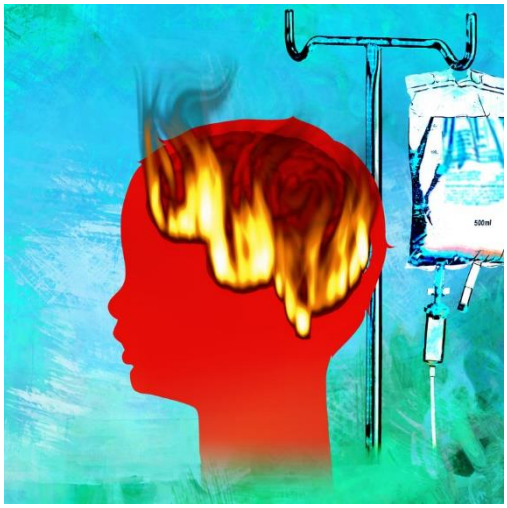
Estimated costs of treatment for Luke of PANS/PANDAS: Between behavior health, PRTF and IVIG, the very conservative estimated cost to treat his condition is $564,000. Of that IVIG cost was approximately $180,000. This total doesn't include other medications and the enormous amount of miles driven to appointments and seeing Luke when he was 3 hours away from home at the PRTF. **We are asking the Kansas Legislature to establish an advisory council on PANS/PANDAS to educate the medical providers and insurance companies in the state about the condition and the recommended protocols for treatment. IVIG and other off label medications and infusions are not "experimental and/or investigational" as some insurance language dictates for PANS/PANDAS. My son has PROVEN he has improved and became functional again with antibiotics, steroid (both oral and IV) and IVIG. Ultimately, insurance coverage of specialist-recommended treatments is imperative for children with PANS/PANDAS in Kansas. In closing, two dramatic statements are what I have learned with my son's traumatic illness.**

- **Early treatment is absolutely necessary for the best chance of a full recovery. Our son was 1 ½ years into the illness before he was properly diagnosed and treated by Dr. Kobayashi. Permanent brain damage can occur with prolonged brain inflammation and PANS/PANDAS going untreated.**
- **I firmly believe if my son had received the proper treatment soon after symptoms; he never would have had to go away from home for 9 months to the PRTF! When we showed our first neurologist the video of him in January 2017 at the PRTF when he could hardly talk, she said he should have given him antibiotics and IV steroids, right away. He lost a year in school. He's lost a year of his life basically, maybe more.**
- **Now with your help, by establishing the advisory council and better insurance coverage, Luke and other children can get back what this condition has taken away from them, the return to their lives as they know them.**

New Research moves PANS and PANDAS out of the Shadow of Mental Illness

https://www.suzannegazdamd.com/blog/new-research-moves-pans-and-pandas-out-of-the-shadows-of-mental-illness?fbclid=IwAR3uprL7nq03_zsl4jUGCClh1ZbAgrA0HE1WCyjd7KsyZ0UFLSh6uGhH6Lg

6/24/2020



Some fascinating and extremely important new research was recently published in the American Journal

of Psychiatry reporting on results from a study conducted by Yale University investigators. The study

ascertained in children with PANDAS (pediatric autoimmune neuropsychiatric disorders associated with

streptococcus infections) a type of antibodies that bind to particular brain cells called interneurons, which

are neurons that modify the signaling of other nearby cells.

What this significant research* provides is the clinical science that clearly shows us the physiological mechanisms at work behind the damage to the brain itself in PANS and PANDAS patients. The implications are huge relevant to shifting perceptions about these conditions in order to better identify the most appropriate treatments and enhance diagnostic procedures in order to improve the quality of life for the individuals in our care.

A few facts.

PANS (pediatric acute-onset neuropsychiatric syndrome) and PANDAS are infection-induced autoimmune conditions that disrupt a patient's normal neurologic functioning, resulting in a sudden onset of obsessive compulsive disorder (OCD) and/or motor tics as well as a host of

other life-altering symptoms including:

- anorexia (food restriction/failure to eat)
- anxiety; irritability and outbursts
- hyperactivity
- sleep disturbances
- mood swings
- large and small motor skill dysfunction
- urinary frequency and additional issues.

While typically associated with children, these disorders also can occur in adults. It is estimated that 1 in 150 children, up to age 18, may have PANS or PANDAS although these figures are likely to vastly underrepresent the true incidence as so many cases often go misdiagnosed for years. The PANDAS Network (http://pandasnetwork.org/statistics/) indicates that the age of onset (self-reported) is:

1 to 3 years - 11%
4 to 9 years - 69%
10 to 13 years - 19%
14+ years - 1%

In PANS and PANDAS it is hypothesized that in response to an infection, the immune system essentially becomes confused as to how it should respond. As I have discussed in previous blogs, this miscommunication in the brain may be related to something called "immune tolerance" whereby our immune systems have become overwhelmed from the endless assault by the extremely toxic environment in which we live. Subsequently, cross-reactivity develops and causes the body to attack the brain (https://www.suzannegazdamd.com/blog/what-causes-our-body-to-attack-the-mind) through misguided signals and responses to antibodies and autoantibodies.

What the new study showed and why IVIG should be considered in treatment protocols.
Significant too was the finding that in cohort participants receiving IVIg (intravenous immunoglobulin) the binding of interneurons was decreased. This latest research used serum (the part of our blood that contains antibodies) from seven children diagnosed with PANDAS who recently took part in an IVIG treatment trial at the National Institute for Mental Health. They introduced this serum into the brains of laboratory mice; they also for comparison introduced serum from healthy children who did not have PANDAS into the brains of a different

group of mice. The brains of the mice in both groups were examined to determine which of the cells bound with the antibodies. They then repeated this experiment using serum taken after the children with PANDAS had undergone IVIG treatment in order to see if IVIG treatment changed the way that the antibodies interacted with the brain.

The results.

The PANDAS children had high levels of antibody attachment in the basal ganglia to cholinergic neurons and those treated with IVIG had reduced antibody bindings, suggesting that IVIG is a potentially very effective treatment due to this therapy's multiple mechanisms of action. I have detailed in other articles **https://www.suzannegazdamd.com/blog/ivig-in-autoimmune-disease-therapies** how these mechanisms in IVIg work and the relationship as well as the importance of the brain's basal ganglia for movement, coordination, behavior control, memory, development of tics, OCD, anxiety and more. While the new research bears additional investigation, it does indicate that IVIg holds great promise as a means of intervening in the harmful mechanisms that contribute to PANS and PANDAS conditions.

The changing paradigms and out of the shadows of mental illness.

Dr. Susan Swedo at the National Institutes of Mental Health (NIMH) first reported on PANDAS in 1998. Since that time a tremendous amount of data has been accumulated, but we know that more research must be initiated in order to best help the patients as well as their families. It is imperative that PANDAS and PANS cease to be considered a "rare" disorder and that these children as well as adults are no longer misdiagnosed.

There clearly is mounting evidence that tells us a very large subset of mental illness, including schizophrenia, bipolar disorders, depression and others, is immune-mediated and related to inflammation. The time has come to change the conversation about the origins of many neuropsychiatric diseases to one that is centered on the immune-driven mechanisms. Only then we can identify the most appropriate, safe treatments targeted toward this dysregulated immune system that fueling systemic and neuro-inflammation and "brain on fire." With early

recognition and the right integrative medicine protocols, I believe we truly can help the many individuals suffering with PANS, PANDAS and related autoimmune encephalopathy conditions to achieve positive outcomes through treatment.

In hope and healing,
Dr. Suzanne Gazda
2020 appointee, State of Texas PANS Advisory Council
(https://gov.texas.gov/news/post/governor-abbott-appoints-fourteen-to-pediatric-acute-onset-neuropsychiatric-syndrome-advisory-council)

Suzanne Gazda, M.D. of San Antonio is a senior partner of the Neurology Institute of San Antonio and owner and director of Gazda Integrative Neurology. She is also co-director of the PANS and PANDAS Center of South Texas. She is a member of the International Society of Environmental Medicine, American Academy of Neurology, American Society of Antiaging Medicine, Texas Neurological Association, ILADS, and the Institute of Functional Medicine. Gazda received a Bachelor of Science in Pharmacy from The University of Texas at Austin and a Doctor of Medicine from The University of Texas Health Science Center Medical School.

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IVIG in Autoimmune Disease Therapies

https://www.suzannegazdamd.com/blog/ivig-in-autoimmune-disease-therapies

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Never before have we been faced on such a global scale with the realization of just how important it is to nurture a healthy immune system. While we have learned many lessons from these trying times of COVID 19, there are still a myriad of questions that remain to be answered. However, two undeniable facts have quite clearly emerged: individuals age 65 and older and those who have impaired immune status (e.g. history of cancer, other immunosuppressive condition) are at higher risk of developing severe symptoms if infected.[1]

Many new as well as older therapies are being utilized and studied in the treatment of this virus. Convalescent plasma or immunoglobulins have been used to improve the survival rate of patients with SARS and now IVIg has entered the forefront as a potential treatment for COVID 19. IVIg is a remarkably safe protocol for our autoimmune patients and one that may offer another layer of protections not just for COVID, but for other pathogenic infections as well given its unique properties that provide helpful autoantibodies including IgG.[2]

What conditions can be treated with IVIg?

There are numerous applications in both neurology, rheumatology and other fields of medicine where IVIg can be effective treatment option for patients with these and many other diseases* that include:

- Autoimmune Encephalitis (AE)
- Chronic B-cell lymphocytic leukemia
- Chronic inflammatory demyelinating polyneuropathy
- Guillain-Barre syndrome
- Infections following bone marrow transplants
- Inflammatory muscle diseases including dermatomyositis, polymyositis, and juvenile dermatomyositis
- Immune deficiencies such as common variable immunodeficiency (CVID) and primary immunodeficiency
  disorders associated with defects in humoral immunity.
- Immune thrombocytopenia (ITP)
- Kawasaki disease
- Multifocal neuropathy
- Neurological diseases such as myasthenia gravis or multiple sclerosis (MS).
- Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)
- Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)
- Pediatric HIV type 1 infection
- Rheumatic diseases including systemic lupus erythematosus (SLE), Sjogren's

disease, rheumatoid arthritis
(RA), vasculitis and other related autoimmune disorders.

How does IVIg work?
Commercial preparations of IVIg are derived from a pool of donors; as such, IVIg products contain smaller amounts of IgA and IgM antibodies as well as Th2 cytokines and cytokine antagonists that may also contribute to therapeutic effects. Numerous targets for IVIg include: T-cells; cytokines; immune cell trafficking; B-cells; complement; and Fc-receptors.

IVIg has been demonstrated to inactivate auto-reactive T-cells by competing for and interrupting their interaction with antigen presenting cells. The balance of cytokines also appears to be restored by IVIg with studies showing that IVIg contains antibodies and antagonists to pro-inflammatory cytokines. In addition, IVIg is thought to interfere with and prevent the passage of auto-immune T-cells into the blood-nerve barrier. The effects of exogenous antibodies on B-cells have been well studied; IVIg is thought to down-regulate antibody production by B-cells, interfere with B-cell proliferation via a blockade of cell surface receptors and prevent the activation of certain subtypes of B-cell. In addition, IVIg can affect innate immunity by interrupting the steps in the complement activation cascade and blocking Fc-receptor mediated activity, which results in down-regulation of macrophage activity. In conclusion, IVIg has numerous modes of action, which culminate in the down-regulation of the immune response; many of which may be relevant to neuromuscular disorders and immune neuropathies.

Combination therapy as a valuable modality in autoimmune disease.
In their concept paper, “Reversing Autoimmunity Combination of Rituximab and Intravenous Immunoglobulin,” the authors presented a unique treatment approach using a combination of B-cell depletion therapy (BDT), specifically rituximab (RTX) and intravenous immunoglobulin (IVIg), based on a specifically designed protocol (Ahmed Protocol).[3] Twelve infusions of RTX are given in 6–14 months. Once the CD20+ B cells are depleted from the peripheral blood, IVIg is given monthly until B-cells repopulation occurs. Six additional cycles are given to end the protocol.

There are several primary reasons as to why and how IVIG can be beneficial in treatment for any autoimmune disease:
1. IVIg works to enhance immune protection in a microenvironment of infectious triggers and toxins, all resulting in high levels of inflammation and immune dysregulation. IVIg has a multimodal method of action (MOA). A number of studies have shown the benefits of IVIg and its anti-inflammatory effects as well as an ability to regulate immune balance. IVIg additionally has the capacity to eliminate clinical autoimmunity, restore a state of tolerance, and reinstate physiologic homeostasis.
2. The synergy between IVIg and and BDT’s (like Rituxan) are remarkable. When the effects of RTX begin to wear off, IVIg exerts immune restoration by increasing regulatory T-cells (Tregs), regulatory B-cells (Bregs), macrophages, dendritic cells, and promoting more CD138+, normal plasma cells in addition to multiple other immune enhancing mechanisms. With the reduction and/or absence of inflammation, the tissue

microenvironment now has the opportunity to return to physiologic homeostasis.
3. IVIg also works to reduce and eradicate harmful autoantibodies.
4. IVIg can enhance B-cell-depleting therapies (BDTs) by its multiple MOAs culminating in profound anti-inflammatory actions as it also provides immune protection.
5. IVIg is considered highly safe and has multiple MOAs in virtually all autoimmune diseases.
Ideally, the full prescribing dose, e.g. 2 grams/ kg, should be used in the course of treatment (predicated upon individual patient criteria, tolerance or other considerations).

It is estimated that approximately one in five Americans now has a diagnosed autoimmune disease. Each year, within our own practice and the medical community as a whole, we continue to face an increasing number of challenges as the incidence of chronic disease rises commensurate with the need for appropriate therapies. New challenges such as COVID 19 should collectively encourage us to consider all available measures in order to provide our patients optimal care with a low-risk profile. IVIg affords us this opportunity and is one that we believe should continue to be explored and included as appropriate in our treatment protocols.

In health,
Suzanne K. Gazda, MD

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***Additional resources**
For more information about IVIg and other health conditions for which it may be used see:
https://emedicine.medscape.com/article/210367-overview#a2

References:

1 **https://www.nm.org/conditions-and-care-areas/infectious-disease/covid-19/high-risk-groups/autoimmune-disorders**

2 **https://www.ncbi.nlm.nih.gov/pubmed/32218340**

3 **https://www.frontiersin.org/articles/10.3389/fimmu.2018.01189/full**