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MSUD NEWSLETTER

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THE MILLION DOLLAR BIKE RIDE

JUNE 12, 2021

***By Herb Foster**, 2021 Team Scott Leader*

My name is Herb Foster but my friends call me Butch. I serve on the Board of Directors for the MSUD Family Support Group. I hope this message finds you safe and healthy during these very difficult times. The MSUD Board of Directors is focused on the current events pertaining to the Coronavirus and are here to help in any way we can.

'RIDE' Continued on page 6

TURN HOPE FOR A BETTER FUTURE INTO ACTION BY PARTICIPATING IN OUR MSUD REGISTRY WITH CORDS

Our Scientific Advisory Board has advised us that a strong MSUD registry must be our Number 1 priority. This is because researchers need to understand the challenges of living with MSUD, and only you can tell them. A patient registry tells researchers what is important to you as a person with (or family member of

'ACTION' Continued on page 18

MSUD REGISTRY

CORDS (COORDINATION OF RARE DISEASES AT SANFORD)

***By Alyssa Mendel**, Project Manager*

The Maple Syrup Urine Disease Family Support Group (MSUD FSG) launched its CoRDS registry in October 2020. As of this writing, 140 participants from around the globe have enrolled by filling out the MSUD questionnaire. This number will continue to grow as more people enroll in the registry.

Participating in the MSUD CoRDS registry gives participants the opportunity to contribute to

'REGISTRY' Continued on page 19

Inside This Issue:

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MSUD FAMILY SUPPORT GROUP NEWS

FROM THE PRESIDENTS' DESK

By Sandy Bulcher

2020 was dominated by Covid-19 and unfortunately it is not yet behind us. There is a sense of hope, though, that better days are coming. Like you, I am anxious to get together with friends and family without the fear or concern of spreading Covid. Some of those with MSUD have been vaccinated against the virus, others are waiting for the opportunity to get the injection, and some are concerned about receiving the vaccine. I encourage you to educate yourself about the vaccine and to talk to your metabolic doctor about the pros and cons of you or your loved one with MSUD receiving the vaccine to determine the best course of action.

Even though the MSUD Family Support Group Board was unable to meet in 2020 for our yearly face to face meeting, we continued our quarterly zoom calls and working toward our goals. One goal in particular that we achieved was launching the MSUD registry. We are thankful that so many of you took the time to complete your CoRDS registry profile which is the most important thing that you can do to advance MSUD research. Special thanks to Karen Dolins for her countless hours working in partnership with CoRDS to develop the registry. Also thanks to Denise Langosch, Kelly Langosch, and Hannah Dolins for reaching out to many of our families by phone and email and encouraging them to participate in the registry.

Another goal that we are currently pursuing is updating and improving the MSUD website. Soon, we anticipate revealing the new website which will have a new platform, format, and content. The MSUD logo will have a fresh look too- a more modern version of the previous logo. Watch for an announcement when the new website goes live! ■

EDITOR'S NOTE

By Dr. Karen Reznik Dolins, *EdD, RDN, CSSD*

Wow, I sure am glad Spring is here! My family made it through this oddest of winters and emerged healthy. I appreciate our good fortune. My husband and I were able to work from home. Hannah had to give up her part-time job but attended school remotely. Her sister teaches third grade in Maryland and was remote until mid-March. Her brother lives and works in Chicago. He did have to go into work most days, but stayed healthy as well. We are also fortunate in that we were able to get vaccinated against COVID-19! Please see Dr. Greg Rice's advice for the MSUD community on this topic.

This issue of the newsletter features several family stories. Two of our writers have undergone a liver transplant and speak of their experiences. We hear from another family living well with MSUD through medical management and an adult with MSUD who also manages it medically. We hear the highly unusual story of two siblings diagnosed with intermittent MSUD as adults. Sadly, the diagnosis came too late for one of the siblings. This case was written up in the New York Times, which will increase awareness of MSUD. We're happy to welcome our new family member Michael Neal.

'EDITORS NOTE' continued on page 4

MSUD HAPPY HOUR REACHES 1 YEAR MILESTONE

By Susan Needleman

This May will mark one year since the first MSUD Happy Hour. What is the MSUD Happy Hour, you ask? It is when MSUD Families, transplanted and not, of all abilities and ages, come together online 1-2 times a month, through Zoom. We share our perspectives on a wide range of MSUD and non-MSUD topics and offer each other's perspectives on challenges we have faced, while connecting with others with MSUD. Some topics we have covered are: how COVID has affected us, the COVID vaccine, different foods and formulas we eat and drink, how others treat us because we have MSUD, how we act when our levels are high, and how our week has gone. Participants always have a chance to bring up a topic they would like to discuss.

Meetings are always on Saturday night around 8:30PM EST. For more information and to find out when the next meeting is, please email Susan Needleman, (an MSUD adult herself), at slneedleman@yahoo.com.

Please note that these virtual meetups are not run by medical professionals, and are not intended to give medical advice, but to share and listen to personal experiences of other MSUD patients. You should always contact your clinic before making any changes to your MSUD treatment. ■

'EDITOR'S NOTE' Continued from page 3

This issue is rich in research news. It's heartening to know that researchers are interested in MSUD and continue to explore ways to improve care. Researchers are unanimous in urging us to develop a strong Registry, and I'm thrilled that almost 150 of you have participated. If you haven't registered yet, see the article describing the simple steps you can take to join.

Finally, if it's Spring then the Million Dollar Bike Ride can't be far away! Fellow board member Herb (Butch) Foster and I bought new bikes and are busy training for this event. Please be sure to read his article describing how you can help us raise critical research funds.

My thanks to those who helped with this issue of the newsletter including Sandy Bulcher for her fine eye which finds all my typos, Matt McIntosh for doing the layout, and Susan Needleman for her help with family stories. ! ■

NORD (NATIONAL ORGANIZATION OF RARE DISEASES) UPDATE

The recently enacted American Rescue Plan contains important provisions to help the rare disease community through the COVID 19 crisis.

Here are 5 changes the American Rescue Plan makes that matter to the rare disease community:

Increases funding and support to help Americans afford private health insurance through healthcare.gov or their state marketplace and provides protection from paying back excess subsidies due to income changes.

Provides 100% premium support for COBRA insurance through September 30 for individuals who have lost coverage due to involuntary layoffs or reduced hours.

Provides additional federal support for vital home and community-based services that enable many rare diseases patients to live in their homes rather than moving to a facility for care.

Expands state coverage to help uninsured Americans access COVID-19 vaccines and treatment and curb the spread of the virus.

Provides new incentives for states to expand their Medicaid programs and provide health insurance to millions of low-income Americans. ■

'RIDE' Continued from front cover

I have again been asked to step in as Team Leader for this year's Million Dollar Bike Ride (MDBR) sponsored by the University of Pennsylvania's Orphan Disease Center (ODC). Along with the entire MSUD Board of Directors, I appeal to everyone in the MSUD community to make an effort to get involved in this year's bike ride and help us raise much needed funds for research to find a cure and improved treatments for MSUD. Your participation and donations will be greatly appreciated by all families living with MSUD. We are a small group but together we can make a difference. My wife Diane and I have been involved in the MSUD community for almost 49 years since our son Scott was born. Our MSUD team is named Team Scott in his honor. Like many other families, we are witnessing much progress and hope in our fight for a cure and better lives for our children and loved ones with MSUD.

I along with my brother-in-law Steve Healy, Taryn Kessel and her husband, and Karen Dolins (another very dedicated board member) and her whole family have previously traveled to Philadelphia to participate live and represent our organization. Due to the pandemic, last year's event was held "virtually" but that did not dampen the enthusiasm of the event staff, the riders, and others. Many more riders across the country and in Canada rode locally in their communities for our MSUD team. It has been a great experience to come together with 900- 1000 cyclists to ride for our respective Orphan diseases and raise money for our respective research projects.

The MSUD Family Support Group has been amongst the most successful organizations participating in the event. In our previous three years we have raised over $300,000 to support pilot research focused on finding improved treatments and potential cures for MSUD. That is why we are so excited about being invited back to participate in the event.

The ODC has announced that this year's bike ride will once again be an all-virtual event. This means:

- We ask and encourage you to ride on your own (or safely socially-distanced from your cycling buddy), between

now and June 12th, and document your progress! Various cycling apps such as Strava can help you track and share your progress, allowing you to cycle at your leisure over the course of the next few weeks (or all at once!) Whether or not you choose to use an app we hope you will participate to show your commitment and spirit for the MDBR.

- Have a stationary bike at home? Cover your miles from the comfort of your home and share your status and progress with us along the way!

- Whether you're on your stationary bike or on the road, we will have special hashtags for sharing on social media and ask that you post your personal or team cycling updates throughout the next several weeks up to and including June 12th. We will be sharing, "liking" and re-posting your updates on our social media channels and website, as well.

As always, ALL registration dollars will contribute towards each team's grant fund, and up to $30,000 with be matched by U Penn. We encourage you to consider your registration fee as a (much needed) donation to your team's research grant.

Finally, let us all thank the Orphan Disease Center at the University of Pennsylvania for all they do and for inviting our organization to participate again for the fourth year in the bike ride. They match up to $30,000 of the money we raise and oversee the research projects we generate through our fundraising efforts. Please join us virtually and make this year's event our most successful! ■

For more information, visit: https://www.milliondollarbikeride.org/

Click here to make a donation to Team Scott: http://givingpages.upenn.edu/FamilySupportGroup

ADVOCACY UPDATE

By Jordann Coleman

2021 brings several pieces of legislation that are important to the MSUD and rare disease communities.

The Medical Nutrition Equity Act ensures public and private insurance coverage for medically necessary foods when prescribed by a physician. The bill is of vital importance to the MSUD community. It was previously introduced in 2018 and will be re-introduced to the 177th Session of Congress this spring. With a majority of the co-sponsors returning, we continue to work towards gathering more co-sponsors and support for this bill.

We need your support to move this bill forward. We need more MSUD stories to show how necessary the bill is to our community. Go to www.NutritionEquity.org to share why having coverage for medical nutrition is important to you and your family. You can also go to https://nutritionequity.org/contact-congress/ to send an auto-generated email to your members of Congress asking them to become an original co-sponsor of the bill. Please share with your friends, family & social networks and ask them to contact their Congressional members. Together we can make coverage for medical nutrition a reality.

The Newborn Screening Saves Lives Reauthorization Act. The Act reauthorizes existing federal programs that assist states in improving and expanding programs, support parent and provider education, ensure laboratory quality and effective surveillance, and facilitate adding of conditions to the Recommended Uniform Screening Panel (RUSP). You can also contact your members of Congress and ask them to support this bill. ■

MEDICAL ADVICE

COVID-19 VACCINATIONS AND MSUD

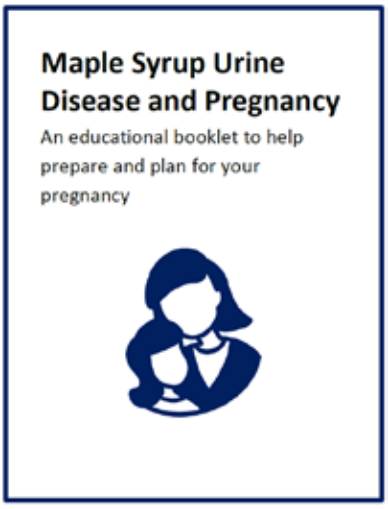
***Gregory M. Rice**, M.D.*
Associate Professor of Pediatrics, Division of Genetics and Metabolism
University of Wisconsin School of Medicine and Public Health

Patients with MSUD are considered high risk for complications from COVID-19 infection due to their metabolic disorder. COVID-19 vaccination significantly decreases the risk of serious complications from COVID-19 in vaccinated patients above the age of 16 years old. MSUD patients should discuss COVID-19 vaccination with their metabolic physician including the risks and benefits of COVID-19 vaccination. Parents of children with MSUD younger than 16 years old, should consider discussing with their own physician the risks and benefits of getting themselves vaccinated to decrease the risk transmission to their children.

Please see Center for Disease Control for more information. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html ■

MANAGING PREGNANCY WITH MSUD

***by Elaine Sim**, MS*
OHSU Graduate Programs in Human Nutrition



Today, more and more women with MSUD are reaching childbearing age, starting their own families, or are interested in doing so.

With careful planning, frequent monitoring, and individualized care, women with MSUD can have healthy, safe pregnancies.

A new educational booklet about pregnancy and the postpartum period for women with MSUD aims to bridge a gap between evidence and consensus-based recommendations for clinicians and the lack of educational resources for the patient population.

The booklet was developed using information from current literature, guidelines, toolkits, and meaningful suggestions from several women with MSUD who have had successful pregnancies.

The booklet includes information such as:

- A review of MSUD
- The impact of pregnancy and postpartum care on disease management
- Lab monitoring and anticipated dietary changes
- Practical tips, ideas, and examples for meeting goals and recommendations

The booklet is intended to help guide women with MSUD through pregnancy and the postpartum period, facilitate communication and relationship-building between patients and their metabolic team, and in doing so, create opportunities to discuss patient-specific needs.

Print and online versions of the booklet will be available soon from the MSUD Family Support Group. ■

FOOD AND NUTRITION

GENTLE NUTRITION ADVICE FOR MAPLE SYRUP URINE DISEASE

***Nikki Drilias**, RD, CD*
Certified Intuitive Eating Counselor
Metabolic Dietitian at UW Madison Waisman Center

The last year has been challenging for all of us in so many ways. Many of us have found ourselves at home more, moving our bodies less, and eating more. Many have gained a few pounds over the last year. This is not an article about weight loss, but rather, some tips from a friendly metabolic dietitian for making some improvements to your MSUD diet that will help you feel good, energized, and satisfied!

I must stress that my recommendations regarding MSUD are ONLY intended for when you or your child are WELL. And, as always, please talk with your metabolic team before making any changes to your MSUD diet.

Here is my best advice for improving your MSUD diet:

It's probably not your formula. You might think a formula change would be an easy way to cut calories and lose weight. It's possible. However, MSUD formula is meant to provide a significant portion of the protein and calories needed in your diet. Cutting calories by changing formula can backfire:

- Decreased formula intake – if you don't like the new formula you may struggle to meet your daily formula goals which could cause leucine levels to rise.
- Increased food intake – getting fewer calories from formula may leave you hungrier! This might make it more difficult to stick to your leucine goal.

Add some fat. Yep, I mean it. Did you know that a low protein diet is sometimes unintentionally low in fat? Much of the fat in a diet not restricted in protein comes from meat and dairy. Without these foods, the MSUD diet often ends up high in carbohydrate and low in fat as well as protein. Fat tastes good and helps us feel full and satisfied with our meal. I'm not recommending any drastic changes, but don't forget to add some fat sources like butter, olive oil, salad dressings, avocados, or coconut milk to your diet. Ask your dietitian to review your diet to help you determine if your fat intake is on track or if you could benefit from a little more fat.

Value veggies and focus on fruits. These nutritious foods are naturally low in protein and are a wonderful

part of the MSUD diet. The fiber and water in these foods help us feel satisfied. You can enjoy fresh, canned, frozen fruits or veggies. You can roast them, steam them, eat them raw! You can add seasonings, dips, dressings! The options are endless. Fruits and vegetables are a great, low protein way to add nutrients, fiber, and volume to the MSUD diet and best of all, can be enjoyed by the WHOLE family. A side of veggies or a salad would pair nicely with your French fries next time you're at a restaurant!

Plan ahead. I know, I know. But it's true! If you want to improve your diet, you really do need to plan ahead. Start small by making a list of a few favorite MSUD friendly snacks. But don't stop there. Make a plan to shop and prepare these items. You're much more likely to eat some veggies if you have some sliced peppers, carrots, cucumbers ready and waiting in the fridge with a low protein salad dressing dip.

Variety is the spice of life. There are a lot of interesting foods with 0 grams of protein. Have you tried sauerkraut or giardiniera (pickled vegetables)? What about hot sauce or horseradish? Or Thai curry paste? Adding new, bold flavors can be a great way to add variety without adding protein. Spend some time in the condiment aisle and try something new!

Save the soda! Sugary drinks like soda, juice, and sports drinks can be enjoyed in moderation when you're well, but be sure to keep them handy for when you're sick and need more calories without the protein.

Get moving! I recommend adding some physical activity to your day. Not for weight loss or calorie burn, but rather to get some fresh air, get your blood pumping, and boost your mood and energy levels. What's something you enjoy? A Zumba video? A hike with your family? A walk with your dog and a favorite podcast? Experiment to find something you enjoy and you'll be much more likely to do it again and again.

Mindless eating?? Do you find yourself eating when you're not hungry? Self-awareness around eating behaviors can be very eye opening!

Here are some great questions to ask yourself in this situation:

1. Am I actually hungry?
2. What am I feeling?
3. What do I need?
4. What do I want?

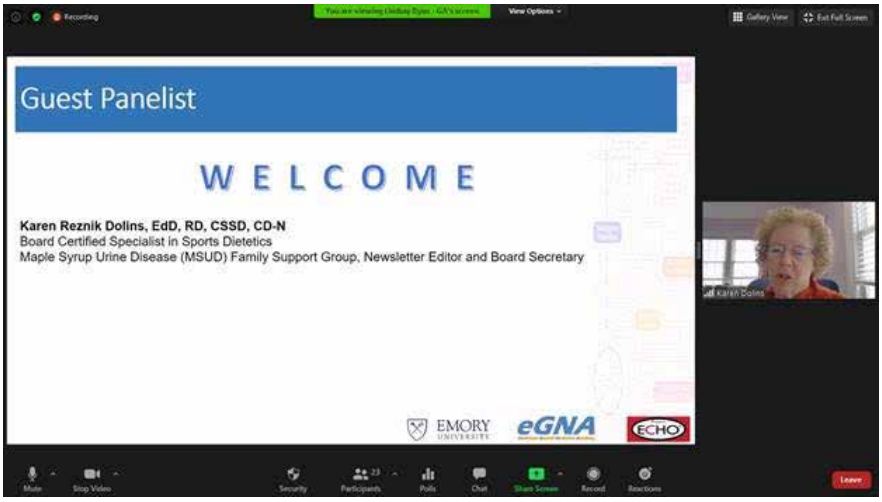
Weight and body mass index (BMI) are not the only markers of your health. I believe that we put too much emphasis on the number on the scale. Instead of aiming for a certain number, I recommend changes to your diet with the goal of feeling well, having more energy, maintaining muscle, and enjoying life!

Will adding veggies, eating satisfying food within your MSUD diet, and moving your body more lead to weight loss? Maybe.

Will these things improve your health even if you don't lose weight? Absolutely! ■

TEACHING DIETITIANS ABOUT MSUD: ELECTRONIC GENETIC NUTRITION ACADEMY

***By Lindsay Ryan**, MS, RD, LD*



While in school to become a registered dietitian nutritionist (RDN), I remember learning a little bit about inherited metabolic disorders (IMDs) including MSUD and thinking that they were fascinating! However, my training on these disorders and their treatment was very limited. I was lucky to have an incredible mentor that trained me when I started working with patients with IMDs.

The Electronic Genetic Nutrition Academy (eGNA) was the first online program developed to provide training to medical providers working with patients with IMDs. eGNA was started in 2017 with interactive case conference and journal club webinars, online discussion boards, and medical commentary videos from experienced providers. By 2021, eGNA has had more than 1100 healthcare providers (including doctors, RDNs, nurses, etc.) register for the program. eGNA expanded and created the Genetic Nutrition ECHO traineeship in 2020. In this program, 10-15 health care providers meet weekly for 3 months for in-depth, case-based training to provide better care to patients at their institutions, which may be located anywhere in the world.

Recently, Dr. Karen Dolins, EdD, RD, CSSD, CDN, joined us for our Genetic Nutrition ECHO session focused on MSUD. She provided personal insight into the life of a child with MSUD from a parent's perspective, along with wonderful professional tips for exercise and healthful eating in MSUD patients. In the future, we plan to expand eGNA further to include online self-paced courses to allow providers to seek training from any location and on their own time.

The eGNA Genetic Nutrition ECHO Traineeship program is supported by a grant from the Health Resources and Services Administration (HRSA) for the Southeast Regional Genetics Network, Grant #UH7MC30772. ■

A DIETITIAN PARENT'S PERSPECTIVE ON MSUD

***By Karen Dolins**, EdD, RDN, CSSD*

I was honored to accept an invitation to participate as a panelist on eGNA's ECHO session on MSUD. Clinicians value learning about the patient's perspective on living with a disease. As a parent who is also a dietitian, I was able to provide the group with a somewhat unique perspective. When the conversation turned to managing the nutrition of individuals with MSUD participating in sports, I was in my element as sports nutrition is my specialty area. For more information on this topic, see my article in this newsletter. I appreciated the opportunity to participate in this educational session and help professionals understand the needs of those living with MSUD.

If any providers are interested in participating in a future Genetic Nutrition ECHO session, please email eGNA@emory.edu. ■

HEALTHY LOW PRO MEAL + SNACKS

By Dana Angelo White

There are many ways to enjoy low protein cooking while maximizing other nutrients. Fiber, vitamins and minerals from antioxidant-rich foods helps to promote digestive and immune health and work to fight inflammation throughout the body. For some recipe inspiration here are some ideas for breakfasts, lunches, dinners, snacks and even a few sweet treats – all featuring these good-for-you nutrients.

Dana and Charlie

BREAKFAST

- 1 Rice Cake + 2 tbsp avocado (Leu: 110 mg) Total Protein 1g
- ½ cup cooked cream of rice cereal + 2 tsp honey + ½ cup blueberries (Leu: 120 mg) Total protein = 2g
- Dairy Free (coconut milk) yogurt with berries <1 gm protein

LUNCH/DINNER

- Lettuce wraps: ½ cup carrots, ½ cup cauliflower+ 1 tbsp teriyaki sauce (Leu: 140 mg) Total protein: 3g
- 1 cup Vegetarian Vegetable soup (Leu: varies with ingredients) approximately 2 grams total protein per serving
- 1 small baked potato topped with ½ cup roasted vegetables (tomatoes, onion, eggplant roasted in 1 tsp olive oil) (Leu: 190 mg) Total protein: 4g
- Vegetable stir fry: ½ cup carrots, ½ cup bell pepper, 1 cup cooked rice noodles + 1 tbsp teriyaki sauce (Leu: 220 mg) Total protein: 4g

SNACKS/TREATS

- 1 cup canned Pineapple (juice packed) (Leu: 40 mg) Total protein: 0.5g
- Banana bites: 1 medium sliced banana dipped in 1 oz melted semisweet chocolate (then freeze) (Leu: 150 mg) Total protein: 2g
- Rice Crackers with ¼ cup mashed Avocado + 2 dashes hot sauce (Leu:115 mg) Total protein: 2g
- Coconut milk yogurt Total protein: <1 g
- 1 cup air-popped popcorn (Leu: 118 mg) Total protein: 1g

Dana is the mom of 9 year old Charlie aka Charlotte or "Cha Cha" (classic MSUD, transplanted in 2012). Cha Cha loves to spend time in the kitchen dreaming up new recipes for her family + friends - she is becoming quite the little chef. For more recipes from Dana and Cha Cha, visit DanaWhiteNutrition.com ■


Zev Kessel, Classic MSUD age 11

EXERCISING SAFELY WITH MSUD

By Karen Dolins, *MSUD Mom and Board Certified Specialist in Sports Dietetics*

Children with MSUD want to live normal lives, and that includes participation in sports. More and more parents are asking their doctors and dietitians how to modify their children's nutrition plan to keep blood leucine levels in a safe range while they play soccer, tennis, baseball, and more. The nutritional needs of physically active individuals with MSUD have not yet been studied, but understanding some basic sports nutrition concepts can help guide us. This article will discuss the ways in which physical activity affects the need for calories, carbohydrate, protein, and fluid.

CALORIES

Muscles need energy to move. The amount of energy used is measured in calories. In MSUD, it is critical that energy balance is maintained to prevent breakdown of muscle which releases leucine and causes a rise in blood leucine levels. This means that the energy cost of activity must be balanced by the amount of energy (calories) taken in through food and formula.

CARBOHYDRATE

Active muscles use a combination of fat and sugar for fuel. Sugar is derived from carbohydrate foods which include the starches used in most low protein food products, fruits, vegetables, juice, sweetened beverages, jellies, and candy. Sports drinks provide sugar along with fluid and electrolytes, usually sodium and potassium which may be lost in the sweat. High intensity exercise (a sprint) is fueled mostly by sugar while lower intensity exercise (a walk) uses more fat. Fortunately, sugar is not limited in the MSUD diet and most low protein foods are high in this nutrient!

PROTEIN

While dietary supplement companies would have you think otherwise, protein is not typically used to fuel activity and a normal diet will provide enough protein to build muscle. Sports nutrition scientists advise those who are trying to build muscle to eat

enough protein to meet the body's needs but to get extra energy from carbohydrate foods. This is good news for the athlete with MSUD! You may have heard that leucine is especially important for building muscle. This is true, but with MSUD blood levels of this nutrient are almost always higher than they are in a person without MSUD. As long as you are taking your formula as prescribed (preferably 3-5 times daily), adequate protein will be available to build muscle. The bottom line is that muscle building is more likely to be limited by consuming too few calories or carbohydrates than by the protein restriction needed in the MSUD diet.

FLUIDS

Hydration is an important strategy for any athlete person, and the active individual with MSUD is no exception. The body is about 60% water by weight. Sweat causes some of this water to be lost, which puts strain on the body and has been found to impair athletic performance. For the exerciser with MSUD, this can also be dangerous. It is possible to estimate fluid needs by weighing oneself before and after activity (minimal clothing should be worn so you're not weighing sweat trapped in the fabric). A loss of one pound indicates a fluid loss of 2 cups. Athletes maintain hydration most effectively by knowing their fluid needs and drinking to a schedule rather than to thirst. Sports drinks can be particularly helpful for the athlete with MSUD as they provide calories as well as fluid and the sugar and electrolytes they contain helps keep fluid in the body.

TIPS FOR EXERCISING SAFELY WITH MSUD

- Make sure calorie intake is adequate by monitoring body weight.
- Include carbohydrate foods with all meals and snacks.
- Consume medical formula 3-5 times throughout the day to ensure adequate protein availability.
- Drink fluids throughout the day and consider sports drinks especially when exercising in hot and humid conditions.

Always check with your medical team and dietitian about making adjustments to your nutrition plan. ■

RESEARCH

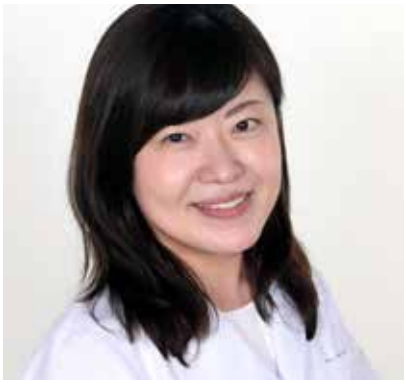
BOVINE GENE THERAPY FOR MSUD

***Karlla W. Brigatti**, MS*
Research Operations Director
Clinic for Special Children

The Clinic for Special Children is working with the University of Massachusetts Medical School Horae Gene Therapy Center and Tufts Cummings College of Veterinary Medicine to test an adeno-associated viral vector (AAV) gene therapy for MSUD in the calf model. This AAV-based approach is approved for other rare genetic disorders such as spinal muscular atrophy and is in clinical trials for scores of other rare disorders. One limitation in studying gene therapy for MSUD has been the lack of a good mouse model of the disease, since the mouse model with classic MSUD is nonviable and the existing one only has intermediate features. However, a naturally occurring bovine form of MSUD, first discovered in the 1980s among Black Hereford herds in Australia, closely mirrors the most severe form of MSUD in humans. These calves have a specific mutation in the BCKDHA gene, which encodes one of the three components of the BCKD enzyme complex that breaks down the branched-chain amino acids (BCAAs) leucine, valine, and isoleucine. Without treatment, these calves develop elevated branched-chain amino acids (BCAAs), metabolic encephalopathy, brain swelling, coma, and death within the first week of life. Our study first evaluated unaffected calves in 2020 to obtain baseline "normative" data similar to what is measured in patients and we plan to do the same assessments in affected calves. Funding from the MSUD Family Support group enabled some of this work.

The UMass/ Tufts team implanted three MSUD calf embryos. Two affected MSUD calves are due in late spring 2021 and the third is expected in the fall. Our team of scientists, veterinarians, and physicians from all three collaborating centers will come together to deliver the MSUD calves at the large animal hospital at Tufts and treat them with this potentially lifesaving gene therapy. The condition of the MSUD calves after birth will be closely monitored by large animal internal medicine specialists from UMass and Tufts, together with Dr. Kevin Strauss from the Clinic for Special Children. These calves will be treated with human-like doses of AAV gene therapy and fed adult MSUD formula for a period of time until the AAV gene therapy starts to work, which we estimate will take a few weeks to a month. During that time, we will monitor BCAA levels in the blood. Tests will be performed daily or as needed under the direction of Dr. Strauss. Behavioral testing, brain MRI, and outcome measures will be performed and compared to the unaffected calves. The effectiveness of this gene therapy approach for MSUD in cows will be complete by the end of 2021. These results will be important as proof-of-concept for this therapy in humans and provide important data to design and plan a human clinical trial for MSUD gene therapy. ■

CLINICAL PERSPECTIVE ON THE USE OF HUMAN AMNIOTIC EPITHELIAL CELLS TO TREAT MAPLE SYRUP URINE DISEASE



***By Chika Takano**, M.D., Ph.D.*
Nihon University School of Medicine, Tokyo, Japan.

The mainstay of treatment for individuals with Maple Syrup Urine Disease (MSUD) is diet therapy. Even if well-controlled by diet therapy, catabolic events may lead to metabolic crisis. The accumulation of leucine causes irreversible brain damage, adversely affecting the prognosis. Liver transplantation provides significant benefits, however this treatment carries significant medical complications associated with the invasive surgical procedure and requires lifelong immunosuppression. Importantly, there is a scarcity of livers available for transplantation. These limited treatment options represent a critical unmet medical need for these patients. To overcome some of these impediments, liver cell transplantation has emerged as an alternate to organ transplantation. Clinical studies have demonstrated that replacement of as little as 5-10% of the liver mass should theoretically be sufficient to demonstrate a therapeutic benefit. This less invasive cell replacement approach may in fact be more suitable for the treatment of congenital (present from birth) metabolic disorders; however, the limited source and quality of liver cells remains a problem. In search of an alternative to human liver cells, regenerative therapy using stem cells has thus become a focus in order to develop treatment options. Herein, we discuss pertinent issues necessary for clinical application of the human amniotic epithelial cell (hAEC), a type of placental stem cell, to treat MSUD.

HUMAN AMNIOTIC EPITHELIAL CELL

hAECs can be isolated from an amnion membrane, which is the most inner layer of the placenta, and have unique characteristics. First, as hAECs develop during a very early stage of pregnancy, the cells express stem cell marker genes, and under appropriate culture conditions, are capable of differentiation into different types of cells including liver cells. Second, the placenta is one of the immune-privileged organs (able to tolerate foreign bodies without generating an immune response), which allows these cells to avoid rejection following transplantation. Third, hAECs possess wide-ranging immunomodulatory functions, which can ameliorate local inflammations. Most importantly, hAECs are genetically stable compared to the other stem cell types and have not formed tumors following engraftment into immunodeficient mice or in human volunteers/patients.

Due to these advantages, hAECs have attracted attention as a new source of regenerative therapy. Several preclinical studies using mouse models have demonstrated the therapeutic potential of hAECs for congenital metabolic diseases including MSUD. Skvorak et al. (Hepatology. 2013;57(3):1017-1023.) reported that hAEC transplantation improved survival and normalized the bodyweight of intermediate MSUD (iMSUD) mice. Treated iMSUD mice survived more than 100 days, whereas untreated iMSUD mice died within 28 days of birth. The activity of branched-chain α-keto acid dehydrogenase (BCKDH), the enzyme which is defective in MSUD, doubled following hAEC transplantation and was maintained long-term in these immunocompetent iMSUD mice without signs of hAEC rejection. One of the proposed mechanisms of this approach was that some of the transplanted hAECs differentiated into functional liver cells and expressed BCKDH enzymes, resulting in improved branched-chain amino acid (BCAA) metabolism.

CLINICAL PERSPECTIVE

Transplantation of these cells into individuals with MSUD would be minimally invasive without the need for major abdominal surgery and would not carry the complications associated with orthotopic liver transplantation. As hAECs are widely available, in the future patients could be treated immediately without waiting for a deceased donor or incurring the risks for a living donor.

Based on previously established protocols for liver cell transplantation, we propose to transplant a similar number of cells as a single dose of the hAEC therapy and are seeking approval for clinical trials.

Multiple hAEC injections might be required to stabilize the uncontrolled BCAA levels in the treatment of adult patients. The optimal total cell dose could be determined for each case based on the patients' baseline BCKDH activity. Therapeutic efficacy would be evaluated using the measurement of the missing enzymatic activity as well as monitoring correction of amino acid levels.

In transitioning from bench to bedside, several questions must be answered. For example, the timing of cell engraftment and differentiation as well as the durability of the treatment need to be determined. Establishment of GMP (Good Manufacturing Practice) -grade cell products and cell banking system are also important issues. We are currently investigating cell transplantation using large animal models in order to determine the parameters for the clinical translation.

If you are interested in more details of this therapeutic approach, please also find the article I co-authored "Clinical perspective on the use of human amniotic epithelial cells to treat congenital metabolic diseases with a focus on maple syrup urine disease". * This is the first review to explore this approach from a clinician's perspective, as I am a pediatrician and participate in the management of individuals with MSUD. In Japan, MSUD has been part of newborn screening for 40 years. The frequency in Japan (1/500,000) is relatively lower than the estimated worldwide frequency. Our institute, Nihon University Hospital is one of the main institutions for congenital metabolic diseases, and we currently treat about 10 patients. Those identified with MSUD are able to access the necessary medical formulas at diagnosis, although the variety of the medical food is limited.

We believe that cell replacement therapy is a promising approach to treat MSUD and will continue to work on this research. It was our pleasure to be able to share some of our research with the readers of the MSUD newsletter! ■

* Takano C, Grubbs BH, Ishige M, Ogawa E, Morioka I, Hayakawa S, Miki T. Clinical perspective on the use of human amniotic epithelial cells to treat congenital metabolic diseases with a focus on maple syrup urine disease. Stem Cells Transl Med. 2021 Feb 6. doi: 10.1002/sctm.20-0225. PMID: 33547875.

RESEARCH FUNDED BY THE MILLION DOLLAR BIKE RIDES

2019 BIKE RIDE

Using a Yeast Model of MSUD to Understand Pathology

Dr. Ehud Gazit

MSUD affects metabolism in many ways. Improved understanding of the mechanisms by which MSUD affects physical and mental health is an essential step in developing improved treatments. To this end, Dr. Ehud Gazit has developed a model of MSUD in yeast. Yeast is a fungus (think mushroom) made of a single cell. His group is using this model to study what happens to cells when they are exposed to toxic levels of branched-chain amino acids (BCAAs), as occurs in MSUD. Their next step will be to try to identify specific compounds which will reduce the toxicity of the BCAAs.

Using a Mouse Model of MSUD to Examine Neuropsychiatric Manifestations of MSUD

Dr. Rebecca Ahrens-Nicklas

The team has developed a mouse model of MSUD to examine psychiatric and learning differences commonly observed in those with MSUD. They have observed differences in neurotransmitters in the brains of MSUD mice. They plan to challenge the mice with a high protein diet and observe chemical changes in the brain. The researchers will observe behavior changes and develop therapies which they hope will normalize brain differences in chronic MSUD and improve outcomes for patients.

2020 BIKE RIDE

Assessing Thinking, Behavior, Life Skills, and Quality of Life in Adults with MSUD

Dr. Jessica Gold
Summarized by Karen Dolins

Thanks to medical advances, like newborn screening, people with MSUD are living longer and healthier lives. These patients are now reaching previously unobtainable milestones. Many desire to live independently, have a job, and start a family. While the biochemical markers of these young adults have been carefully monitored, less is known about their thinking and quality of life. The purpose of this research study is to 1) look at thinking, behavior, and life skills, and quality of life in adults with MSUD and 2) measure how medical and personal factors impact these areas. The study will assess thinking and behavior skills through online questionnaires and neuropsychology testing, and life skills through online surveys. We will also conduct interviews to understand what it is like being an adult with MSUD. The results of the study will be used to learn how to best help adults with MSUD and how to best prepare for success in adulthood by ensuring appropriate support. Our study is based out of the Children's Hospital of Philadelphia. If you have any questions about this study or are an adult with MSUD ages 22-35 interested in participating, please contact Dr Jessica Gold at goldj@chop.edu. ■

'ACTION' continued from cover

someone with) MSUD and helps identify unmet needs.

The value of our registry increases with the number of participants enrolled. We strongly encourage you to make this YOUR #1 priority as well! If you participated in the NBS Connect Registry, we thank you. We are grateful for the work of the Emory University Metabolic Genetics team in developing the NBS Connect registry, which was used as a template for our CoRDS registry. As some questions are different, we hope you will continue your contribution by participating in this one as well.

It's easy! Click here to get started.

https://cordsconnect.sanfordresearch.org/BayaPES/sf/screeningForm?id=SFSFL ■

'REGISTRY' continued from cover

research into this rare disease by providing the patient's voice. Information from the registry may lead to better physician decisions and diagnoses, along with better industry models for drug development and other research.

As an additional incentive, the MSUD FSG provided ten $100.00 Visa Gift Cards which were raffled off weekly to those who had enrolled. CoRDS helped facilitate the campaign by using a randomization software to draw the names of a new winner each week for 10 weeks and sending the $100.00 gift prize via FedEx to the lucky recipient.

If you have not yet done so, we encourage you to fill out the Registry questionnaire. Your participation will help improve the lives of everyone with MSUD. It will allow the MSUD FSG and researchers globally know where people with MSUD live. Researchers planning a clinical trial or study will ask CoRDS to notify participants in the registry who will then be able to reach out to the researcher if they are interested in being a part of the trial or study. CoRDS does not give out identifiable information to researchers.

Researchers and clinicians can also access the de-identifiable data in the registry from the questionnaires participants complete about MSUD. This will allow them to develop improved treatments and identify important areas of research.

If you have not yet enrolled in CoRDS but would like to, visit https://cordsconnect.sanfordresearch.org/BayaPES/sf/screeningForm?id=SFSFL to access the Activation Form, which starts the enrollment process. After you have completed the Activation Form, you will be able to complete questions specific to MSUD either online or by mail. If you are unable or prefer not to use the online portal, call CoRDS at the number below. Staff will mail you a copy of the questionnaire and can enter your data into the secured registry on your behalf.

If you have any questions or need help enrolling, give CoRDS a call at 1-877-658-9192 or email us at cords@sanfordhealth.org. ■

FAMILY NEWS

CARTER COLEMAN

CLASSIC MSUD, 8 YEARS OLD

***By: Jordann Coleman**, mom*

Carter Bass Coleman was born November 17, 2012 in Walnut Creek, CA. Carter is our second child (older sister, Sasha, now 10 years old, and younger sister, Zara, 2.5 years, do not have MSUD). My pregnancy and birth with Carter was easy. When we brought him home after one night in the hospital, we were ready to start our lives as a family of 4. In our first few days at home, I noticed Carter wasn't much of an eater and seemed to always fall asleep when I would feed him. At the time, I figured he was getting enough, so didn't think much of it. On his 4th day of life, the day before Thanksgiving, we received a call from our pediatrician. I thought this was a new service he was offering parents with newborns so I cheerfully answered the phone. Our pediatrician's tone was serious and he asked how Carter was doing. After sharing that he had a rough night of sleep the night before and didn't seem to be a great eater, he told us Carter's newborn screen came back with an out-of-range result for MSUD. Fortunately, where we live there are two genetics programs within an hour so our pediatrician told us to immediately start driving in the direction of either hospital and he would call with further instructions. Numbly, I hung up and went downstairs to share the news with my parents and siblings, who had just arrived 30 minutes prior from out of town for the holiday. My husband and mother-in-law were out running errands for the holiday, so I had to call them so he could come back home and we could head out to the hospital. We decided to go to Stanford Hospital as it was 15 minutes from where my grandparents lived.

When we got to Stanford, we were immediately brought into the Emergency Department where they started drawing labs and putting him on an IV. After a short wait, one of the Geneticists met with us to explain that Carter's levels were so high on his Newborn Screen (over 700), that there was no

need to run a diagnostic test. They were going to immediately start treatment. Later, we found out Carter's levels upon admission were 2450, and were told he was likely hours away from slipping into a coma. The first couple of days were rough before he stabilized. Once stable, we worked with his team to figure out his leucine tolerance and work on this stamina for oral feeds. After a month in the NICU, we were finally able to bring Carter home a few days before Christmas.

Despite the challenges of MSUD, the early years were pretty good. Carter loves his formula so we fortunately never struggled much with eating. If anything we had a harder time getting him to eat enough protein. There were additional hospitalizations during cold & flu season, a few of which led to us having to cancel family trips. We learned early that life with MSUD can be unpredictable so we had to be prepared to roll with the punches as they came. Although we dealt with challenges, Carter was a happy baby who met all of his developmental milestones and brought a smile to the face of anyone he met.

As he grew older, the hospitalizations were fewer each year and we settled into our lives living with MSUD. Carter is now in 2nd grade, plays flag football, baseball, basketball and soccer. He loves animals and playing Fornite and Roblox. He is a charming boy with infectious energy. We think of our life as "normal"*. We put the asterisk after normal because we feel MSUD is a part of our life though not our entire life.

My experience as a parent for an MSUD child inspired me to become an advocate. I started with advocating for Newborn screening as I feel it's a vital tool to helping our community get the best start. I later started advocating for the Medical Nutrition Equity Act as I know that it will have a lasting impact on Carter later in life. Advocacy and getting involved with the MSUD Family Support Group has helped me channel my anxiety and fear over the disease into something positive. I am hopeful for the day Carter won't have to worry about his disease and can fully pursue his dreams. We won't stop working until we can make this a reality for our son. ■

THE NEAL FAMILY

By Tammy and Tim Neal

Hello, we are the Neals, and this January we welcomed our second baby with classic MSUD. Michael was diagnosed within 32 hours of birth because the healthcare team at Duke University Hospital was aware of the risk since his sister has MSUD and was able to run labs a day after his birth. With the early detection, Michael's amino acid levels remained stable, and he came home within about a week. Michael was welcomed by his three adoring older sisters, Lorelei 7, Noelle 5, and Heather 3. Noelle was diagnosed with classic MSUD five days after being born thanks to the newborn screening program in Ohio, where we lived at the time. Her leucine levels were very high upon diagnosis and she spent five weeks at University Hospitals in Cleveland, Ohio. Despite a great team of doctors and careful diet management, Noelle had numerous hospitalizations due to illness. When Noelle was three we decided that a liver transplant would be her best treatment option. As only this community knows, it was a difficult decision. We moved our family to North Carolina so that she could receive the transplant at Duke Children's Hospital. After only a month on the transplant list and two months before her 4th birthday, Noelle was transplanted. She is doing very well and transplant is something we will consider with Michael. We know how challenging this disease can be, but we are grateful that so far Michael is handling it well. For now, we just continue to pray for the continued growth and development of our baby boy. ■

Lorelei, Noelle, Heather, and Michael Neal

THE COVID-19 PANDEMIC - IN THE EYES OF AN MSUD ADULT

By: Susan Needleman *Age 30*

March 2020 is a month that would lie in infamy in the lives of many Americans as the month when the COVID-19 pandemic started. In the eyes of many with MSUD it took on additional worries. While all of our experiences during that month and the year that followed are different, I wanted to tell you mine.

Growing up I learned about pandemics of the past, the Black Plague, the Spanish Flu, etc. I always thought that if a pandemic happened today, it would be a horrible situation for everyone but especially someone with MSUD. Many of us with MSUD can go into a metabolic crisis just with typical viruses that go around all of the time. An illness that was so contagious that a pandemic starts just sounded to me like it would be a nightmare for me and the MSUD community. Then it happened.

When COVID started in America, I really thought if anything, it would just be like a bad flu season. With MSUD I am always very careful of germs, I wash everything down that could carry them, stay away from those who are sick, etc. So, at first, I really was not too worried. Then March, 2020, came. Suddenly people were stocking-up on food, and some businesses gave their employees the option of wearing masks, even though it was not recommended by the CDC yet. It did not really hit

me, though, until my house had a scare. Someone in my house was exposed to the virus at a time when the fatality rate was 25%. For the average person this would be a concern for everyone in the house, but for me, as someone with MSUD, it was terrifying. What if someone in my house did get COVID? My doctor said I should not be in the house with someone who had it. How would that work? What if I got it? What would my levels go up to? Would I have to be hospitalized? What if there were no beds at my regular hospital? Would I survive?

Luckily, no one in my house got the virus, but my life changed after that scare. Ever since that time, we still have not since that day had face-to-face contact with anyone outside the house. I started to take my blood on filter paper, sending it half-way across the country after my clinic said it was not safe to go into their blood lab (words I never thought I would hear said). Prior to this I would go 1-4x a month. Everyone in my house stopped going to stores, which I really did not see coming, I thought if anything someone would still go food shopping. That was no longer safe even. We started to buy our groceries and everything else we needed online. If we could not find it there, we either had to find an alternative on the site or not eat it anymore. The biggest struggle was getting an opening for it to be delivered because everyone was ordering online. For us this was the only option as there was no way we could risk exposing ourselves to COVID again.

Another worry of mine was my medical foods. Everyone was stocking-up on their foods. Some of my foods and formula are distributed in America but are made in other countries. What if these foods cannot ship to America because the border is closed? I started to stock-up as much as I could. I never ran out but at one point it was hard to get some foods because other countries lock downs were even longer than our ten week one where I live.

When anything gets delivered, whoever in the house unpacks it always washes and/or sprays it down with disinfectants and changes their clothes after, in case anything that just came, touched them. It is as if they take on and off hazmat clothes. Now as a family who was careful of germs anyways, this is something we had always done to some extent, but not as much. In fact, some people who prior to the pandemic thought that there was no need for cleaning everything like this were suddenly asking us for advice on how to disinfect. The biggest struggle with this was finding cleaning products at the start of the pandemic, when everyone was buying them, so they were always out-of-stock. As time went on, government restrictions lessened and a lot of people started to return to a new normal of their daily lives. We have not. We do not want to risk it.

Now for many the isolation that COVID caused was hard, not being able to see family and friends, go

to a store, events, etc. Some even disinfect less as the pandemic goes on, because it is too hard and it is going on for so long. For me, I feel I have been planning for a pandemic all my life and did not know it. With always being careful of not getting sick, having to disinfect is not anything new, more something I am used to. The pandemic has also caused everything to go virtual. Which in a way makes me feel like the world is catching up to me. I always wanted to be able to interact with people more online and join gatherings virtually. That way I would not have to worry about staying away from anyone who was sick there. I have been able to socialize more now than before the pandemic, I am just doing it virtually. I even started MSUD Virtual Meet-ups where I have been able to connect with more of you (see details on page 4). Some virtual things I do not think are going to go away after the pandemic, such as more people working from home and different types of virtual meet-ups, which I am grateful for. While I, like probably everyone else, wishes the pandemic never happened, I am glad for these virtual changes, just wished they had started for a different reason. ■

TRANSPLANT AND BEYOND

***By Lindsey Nicole Miller**, Classic MSUD Age 34*

It's been four years since I had my liver transplant. In 2012 I wrote about growing up with MSUD and Make-A-Wish for the Spring issue of this newsletter. This is my story since that time.

Everyone has certain times in their life that are memorable and 2016 was mine. I was on the transplant list waiting for a liver for eight years. In October 2016, my mom got a call from Pittsburgh letting us know they might have a liver and asking how soon I would be able to come if it was good. Unfortunately, they called back to say it wasn't. I was disappointed but they told me not to worry, as this means that I'm on their radar and I should get another call very soon.

Not even a month later, November 9th, I got my call from Pittsburgh telling me they had a liver for me.

We live in Port Royal, PA, about 3 ½ hours from Pittsburgh. My Mom was working in Baltimore, Maryland at the time, so Dad and I packed our bags and were on our way. Before leaving I had to call work to let them know that I wouldn't be in for a while. With my job as a full-time support clerk for Novitas Solutions, a Medicare insurance company. I was able to go on short-term medical leave. My manager and supervisor both knew I had been wanting this transplant for a while and helped me take the correct steps to make sure I was able to get short-term medical leave the right way. My supervisor Sandy asked if I minded if she told my coworkers the good news. I said of course! My sister Courtney worked for the same company and kept everyone informed about my progress. She also posted on Facebook and told people in person how I was doing, until my surgery was done, and I could do it myself.

I was told that I would have to stay in the Pittsburgh area for a while after discharge so I could get to the hospital quickly if I were to have a rejection to the liver or anything were to happen medically. I would be staying at Shadyside Family House, which is a hotel for hospital patients who are receiving treatment and need to stay in the area.

Once arriving at the hospital, Dad and I were informed that my liver was coming from a 32-year-old male in Baltimore, Maryland. Once my mom arrived at the hospital, the doctors explained the procedures and let us know, that a 13-year-old boy from Toronto, Ohio was getting my liver.

The day finally came, November 11th, 2016, that I would be getting my surgery. It was finally my day that I've been waiting for for eight years. The longest wait for me was waiting to be taken into the operating room. Mom and I were watching all the coolers trying to figure out which one had my liver. I was finally down to hours and minutes until I went into surgery. The doctors explained that the procedure would take about six hours or more depending on how the surgery went.

After surgery I needed to stay in the ICU. It was there that I ate new foods for the first time. The first two things I remember eating was chicken noodle soup and yogurt. I loved the chicken noodle soup. Now, I'm not a fan of yogurt but we believed that it was a taste and texture thing.

There are a lot of people on a transplant team. Blood is checked for things like EBV (Epstein Barr Virus which is like mono), Cytomegalovirus (CMV), electrolytes, blood count and prograf (anti-rejection medicine) levels. They do this often to make sure my body is accepting my organ. They even check my scar, which is an upside-down Y with staples, to ensure it is closed and to make sure it's healing properly. When I got my blood done before the transplant, I was positive for EBV but negative for CMV, which meant I had been exposed to EBV before the transplant. The man I received the liver from tested positive for both EBV and CMV, so they had to test me for this, too.

Both of my parents have really good jobs and were able to take turns being up in Pittsburgh with me. Once I was moved out of the ICU and placed on the transplant floor, my Mom and Dad would come up on the weekends to see me, knowing I was watched carefully by the medical team around the clock.

I also got to try bacon and pizza for the first time. Bacon was excessively salty and I wasn't a fan of it. When I tried pizza it tasted like cardboard. I was told hospital food is never good but I was disappointed with bacon, which was something I always wanted to try.

Because I had my transplant in November, I wasn't able to be home for Thanksgiving. I was a little disappointed but Mom and Dad came up and spent some of Thanksgiving with me so I could try turkey and stuffing. After the holiday, since I was doing well, I was allowed to go home on weekends and see my family. We made a point to try to come home every weekend except for one weekend at the end of November when my body started to reject the transplant and I had to go back to the hospital. I was devastated as I didn't think I'd be able to be home for my birthday on December 19 or Christmas. They had me on more steroids and upped my dose of prograf to get my numbers back to where they needed to be.

A week before my birthday, my mom and sister came up to see me. My sister brought up stuff from my coworkers and family. We didn't know when I was going to be out of the hospital so mom brought up my birthday stuff and I celebrated my birthday a week early. I got to open up a bunch of gifts. It was a memorable birthday celebration in a unique way.

As my birthday got closer, my numbers kept going down and doctors felt I could be discharged soon. On December 18th, they told me I would be discharged on the 19th; my birthday. I moved back to Shadyside Family House and had labs done every day. December 20th was my dad's birthday. We celebrated both of our birthdays in Pittsburgh. The doctors let me go home for Christmas, although I'd have to return. I was so thrilled that they were able to make all that happen. I called my Nan and told her I was coming home for Christmas and asked her not to say anything to anybody because I wanted to surprise everybody. My Nan, my Pap, and everybody else that showed up for Christmas were so glad to see me. After Christmas, Dad and I made our trip back up to Shadyside Family House where we stayed until we got the okay to come home. At the beginning of the year, I had to go back into the hospital because I contracted CMV and was put on more IV steroids and more medicine so my body could counteract the infection while trying to keep all of my other levels as good as possible. The best part of all this is that CMV and EBV remain dormant in my system. This meant my body is familiar with them and my medical records show how to treat it properly.

I went through several rejections and each time I had a liver biopsy. I had a total of three biopsies in the hospital. I got to realize when my biopsy went well and when a biopsy didn't go well. When something didn't seem right, it was vital that I said something. After my third biopsy the outcome felt different. It hurt to walk and hurt to lay on that side. I had to go through ultrasounds on my liver to find out what went wrong and how they could treat it. The doctors applauded my efforts to tell them that something didn't seem right. If I didn't say anything about how I was feeling they wouldn't have known to look further into it.

Between getting biopsies and the transplant, I went through so much anesthesia that it acted as chemotherapy. I already had thin hair and the anesthesia made my hair literally fall out. After being on the operating table for six hours or more, I developed an ulcer on the back of my head. I had to go through things like hair care treatments just to make sure my hair grew back.

Finally, we were in the home stretch. We were home sick and wanted to go back home for good instead of just some weekends. Mom's boss was understanding and gave her permission to work remotely in Pittsburgh so Dad could have a break. This was where their teamwork was vital. I was finally able to go home for good in February, about 3 months after I arrived.

I video chatted with my coworkers and I called my supervisor, Sandy, to let her know when I'd be able to come back to work. She made sure I was following the proper procedures to come back. By the end of February I was finally able to go back into the office. I still had to be diligent with my checkups. Everything I experienced was life-changing for not only me, but everybody who was involved in making this happen.

I try to completely remember everything I went through. I might have missed a few things here but we experienced so much, it was hard to keep up with it all. Facebook was my way of documenting everything.

My family had been waiting for this for quite a while and wish we had gone through this process sooner because it has made our lives so much better to manage. Previously I struggled to drink all of my medical formula. Now I feel normal when I eat different foods. My friends who have known me for years are still not used to me being able to eat anything. People who have come into my life can't believe everything I've been through and are able to see how strong I am. The most amazing thing ever is how the friends I grew-up with get to see how much better I am as a person.

I met a lot of good people because of my condition but the struggle was just too much. Transplant was more that transplant was more ideal for me and my family. ■

AN UNEXPECTED DIAGNOSIS – SEAN AND ANDREA'S STORY

By Monica Storozuk
Sean and Andrea's Mother

Our story is a tragic one of a beautiful life lost to MSUD and a diagnosis that came too late for one sibling, while offering hope to the other.

In 1983 my son Sean was born. He was a happy, seemingly healthy baby. At the age of 3 he began to have strange episodes in which he would stagger and fall and would not respond to his name. These episodes lasted five or ten minutes and then he would return to his usual self. Sean's pediatrician failed to follow up on these reported episodes. When Sean was 6 years of age, he was taken to the Emergency Department of a hospital while having an episode. A pediatric neurologist was consulted and misdiagnosed him with "benign paroxysmal vertigo" or "migraine of childhood".

When Sean was four years old, his little sister Andrea joined the family. As a newborn, she received the usual newborn screening tests (not provided at the time her older brother was born). Twice she "failed" the screening and was asked to return for another test. We were told that she would need to be tested until she "passed" the test. "What is the problem" I asked? "What is she being tested for?". At this point she had just passed the third test. The nurse told me that she was being tested for a rare disease. I remember her words: "fortunately she doesn't have it as the kids that have it have to eat only rice and pasta. They can't eat protein." I was so relieved that my beautiful baby did not have this rare disease.

Sean and Andrea grew up and had normal, happy, healthy lives. Sean had a few problems with school – he seemed to have trouble concentrating. At times I wondered about attention deficit disorder. But he graduated high school, continued with post-secondary education, and eventually worked in heath care. Andrea became a social worker, married and had a baby daughter.

When Andrea was 30 years old, she became ill while with her cousin Natassja. She was nauseated and feeling unwell, but more alarmingly, at one point she didn't recognize her cousin. Natassja was very worried and phoned for an ambulance. Andrea was seen by doctors at an emergency room and sent home. They said she had food poisoning and was dehydrated. Two days later, she had another episode where she lost touch with reality and was hallucinating. Again she went to the emergency room at a different hospital. This time she was admitted as a patient. Over the next ten days Andrea became increasingly ill. She was treated with a variety of medications, none of which helped. Her hallucinations increased, she began to have seizures and eventually went into a coma. The doctors in ICU diagnosed encephalitis. Tragically, they were unable to save her.

The next few months were a fog of pain and confusion as we waited for the medical examiner to review her case and hopefully provide an answer to her untimely passing. When we were told that no cause of death could be found, we were left with no answers to the "WHY" that hung over us all.

It was during this time that I received a call from my son-in-law. Sean was walking around in a strange state, not recognizing anyone and not making sense. "Call the ambulance!" I told him. Unbelievably, we were going through a similar nightmare less than three months after the loss of my daughter.

The rest of the story is covered in a New York Times article published recently (https://www.nytimes.com/2021/03/17/magazine/maple-syrup-urine-disease.html). I and my family fought tooth and nail to have Sean tested for every conceivable condition. We asked especially that Sean be tested for illnesses that Andrea had not been tested for.

As Sean got sicker day by day, and his unusual symptoms became longer and more frequent each day, we continued to advocate for him and the hospital pulled out all stops. Eventually Sean received a diagnosis: Intermittent MSUD DBT 2. The medical examiner's office tested Andrea's tissue and confirmed that she too had this illness. The genetics doctors could not have been more surprised. It was not a result that they anticipated. To their knowledge, no adult has received this diagnosis.

We now know that both Sean and Andrea have and had a rare variant of a rare illness. The story could end there. But there is something that continues to trouble us and inspires us to want to bring attention to their story: about half of all cases of encephalitis have no known cause*. Inherited metabolic illnesses, of which there are about 700, are not typically on the radar of doctors treating life-threatening conditions in adults. But should they be? Sean's story, covered in the New York Times, explains that Sean was admitted to Psychiatry as he was suspected of having a psychiatric illness. Could others who have psychiatric or neurologic symptoms actually have a metabolic disorder?

We hope that Sean and Andrea's story will raise these questions in the minds of those in the medical and scientific world and that the search for answers will lead to knowledge that will benefit others. ■

*https://www.hopkinsmedicine.org/news/media/releases/johns_hopkins_researchers_identify_conditions_most_likely_to_kill_encephalitis_patients

LIVER TRANSPLANT AND PREGNANCY: MY STORY

***By Amanda Wood**, Classic MSUD Age 35*

I received a liver transplant at Children's Hospital of Pittsburgh (CHOP) when I was 28 years old. I was in the hospital for a month due to complications including rejection, water in my lungs, and the need for blood transfusions. After my first transfusion I had an anaphylactic shock. I needed a second transfusion a couple of weeks later but was given Benedryl and Tylenol in advance and tolerated it well. After my transplant I needed to be on steroids for a year which led to medically induced diabetes. Once I was able to discontinue steroids my blood sugar was normal and I was able to stop taking diabetes medications. At that time, I was told that if I became pregnant I might develop gestational diabetes.

Before transplant my leucine levels ran high. One day

I went on a trip, came back, and was getting ready to leave for another when I ended up shattering my ankle. I was already considering transplant but that pushed me over to do transplant.

Everything happens for a reason. I believe that 100%. During the time between my transplant and pregnancy, life improved dramatically. Before transplant things got cloudy and I would get easily confused. After transplant I could focus better. I was excited to work without having to take time off because of high levels. I started to work at a school with children with disabilities but for financial reasons I moved to a job working for New York State at a group home for adults with disabilities. I love the fact that I was able to enjoy food and travel without worrying about my leucine levels. I got married and that was a great thing and one of the best days of my life. Even with all the ups and downs that came with transplant I have no regrets and would do it all over again.

My husband Joshua and I found out we were pregnant in March 2020 during quarantine when I was 5 years post-transplant. I did well at first, but at 20 weeks gestation I had headaches and noticed that my urine was dark. I thought my symptoms might have been related to the long hours I was working, but I also knew that this could be a sign of rejection so I called the team at Pittsburgh. They advised me to have bloodwork to evaluate whether this was related to my pregnancy. Shortly after I was told by a coworker that my eyes were yellow. I was told to go to the hospital for repeat labs to check my liver function and was diagnosed with acute rejection. As there was no liver specialist at my local hospital in Syracuse, New York, they coordinated my care with the team at CHOP. My liver tests started to improve but then worsened again. Due to the liver failure my bilirubin increased dramatically. This caused terrible non-stop itching which worsened at night. I needed to go to the hospital and was given the option of going to Rochester, about an hour from my home, or to CHOP which is what I decided to do. I was admitted to Magee Women's Hospital so the baby could be monitored. The team was able to reverse the rejection by increasing the dose of my immunosuppressant medications. I was told that I was in ductopenic rejection, which is associated with loss of the bile duct. I also developed gestational diabetes. It was now July and I was about 22 weeks pregnant. I wasn't due until December. I needed to be closely monitored for the rest of my pregnancy by both the obstetrics and transplant team to determine if an emergency C section would be needed, which meant staying in Pittsburgh. Fortunately, my stay at the Family House in Pittsburgh was covered by my health insurance.

My Mom stayed with me the entire time, but my husband was only able to visit once or twice a month. My water broke on September 24 when I was at 29 weeks 4 days gestation. We called an ambulance to take me to the hospital. I was not dilated and the team hoped to keep from delivering the baby, but the next day there was a drop in his heart rate. They performed an emergency C section and Joshua Michael Wood Junior (JJ) was born at 3 lbs. 4 oz.! He needed to stay in the neonatal intensive care unit for 68 days. Finally, we were allowed to go home on November 30th. Joshua continues to gain weight well. Due to COVID-19 we've been isolated from everyone but my mom who has been vaccinated.

Throughout this time my liver function continued to be monitored and my medications adjusted, but my amino acids were not checked. By February my liver function tests were back to normal. I now feel back to my usual self and have gone back to work.

Interestingly, there were 2 other women at CHOP who also went into rejection at 20 weeks gestation. The team said this has never happened before, and that research is needed to determine why this happens and how to prevent it.

Being a mom is one of the many things I wanted to do post-transplant and one of the biggest reasons I did it. Being a mom is tiring but it's the best job I have ever had. Being a working mom has been an adjustment and it's hard to leave him but when I am not working that time with him is even more important to me. My husband and my son are the best things that have ever happened to me. JJ is our world and we would not change that for anything. ■