Advancements in Newborn Screening for Inborn Errors of Metabolism

Speakers: Rebecca Sponberg, NP

Maura Bowen: Okay, let's say you're working night shift. You've just finished your rounds and everyone in the NICU is tucked in tight, but just as you start to think it might be a quiet night, you get a call from the emergency department to look at a three-day old newborn, who was just brought in by the squad. He's lethargic, he's tachypneic, and minimally responsive. His perfusion and capillary refill are poor, and the poor little guy is a mottled gray color, so you take him to the NICU to work him up for neonatal sepsis, because 80 percent of the time that's the diagnosis, but when his lab comes back, you notice something odd. His acidosis is all metabolic, and not respiratory, and when you order an ammonia level, it comes back sky high, and that's when you know, you're not dealing with a sepsis diagnosis.

Instead, it's probably an inborn error of metabolism, and that's a game changer. IEMs, or inborn errors of metabolism, are rare medical conditions that result from the absence or abnormality of an enzyme or its co-factor, which can lead either to accumulation or deficiency of a specific metabolite, and optimal outcomes for children with IEMs depend on recognizing signs and symptoms and promptly evaluating and referring to a tertiary care center familiar with evaluation and treatment. Delay in diagnosis may result in acute metabolic decompensation or progressive neurologic injury or death.

So, luckily, newborn screening programs have changed the way we identify and treat patients with IEMs, and many other serious conditions that occur in the newborn period. So, the goal of newborn screening is to detect disorders that are threatening to life or long-term health before they become symptomatic.

So, rather than providing definitive results, newborn screening will identify which newborns require further testing. Newborn screening programs have expanded in the U.S. and globally over the last ten years, with many new advances in identification and long-term management of patients with these rare diseases.

I'm Maura Bowen with Abbott Nutrition Health Institute's Power of Nutrition Podcast, and I'm excited to have Rebecca Sponberg with me today. Rebecca is a pediatric metabolic nurse practitioner from Children's Hospital of Orange County, and she's dialing in from Long Beach, California, here in the United States. I'm in a studio in Columbus, Ohio, and that may explain why your recording sounds slightly different today. Welcome, Rebecca.

Rebecca Sponberg: Thank you for the invitation.

Maura: So, Rebecca, before we start, can you tell us a bit about your background?'

Rebecca: Sure, I was born and raised in Long Beach, California. I earned my Bachelor's of Science in Nursing Degree from the University of Pittsburgh. I chose to specialize in pediatrics, and gained a few years of experience in a transplant

Rebecca: …pediatric ICU in Washington, D.C., before completing my pediatric nurse practitioner Master's program at the University of Virginia. I began my NP career at CHOC in their Division of Metabolic Disorders. I am the lead Newborn Screening Coordinator, and we receive around 120 metabolic newborn screening call-outs per year. Once we identify a patient has the IEM, I can follow them in our clinic and have my own channel of patients.

Maura: Excellent. Thank you for your background. Now, in the introduction to this recording, I defined inborn errors of metabolism, but I'm hoping you can elaborate and discuss how we determine if a child has an IEM.

Rebecca: Individual inborn errors of metabolism, they are rare disorders, with some ranging from one in 15,000, such as phenylketonuria, or PKU, to one in 500 or one in a million for others. However, collectively, the incidence may approach one in 800 to one in 2,500 first. The majority are inherited in an autosomal recessive pattern so the parents are the healthy carriers with a single mutation and do not realize there is a 25 percent risk with each pregnancy that the child could inherit both mutations and develop symptoms of the condition.

Most IEM identified by newborn screening involved genetic mutations that cause issues in a particular enzyme to be made. This enzyme deficiency leads to issues in the metabolism or breakdown of either protein, such as a specific amino acid, fatty acids, or carbohydrates into energy at the cellular level. Newborn screening is a screening tool that is very sensitive, meaning we have to set the cut-off level for a specific analyte low enough that we do not miss any cases. This causes it to not be as specific, so we do have quite a few false positive cases per month, or may pick up a carrier for a condition, who is not at risk of developing symptoms.

We use additional ratios and second-tier tests, which can even include basic genetic sequencing performed on the original newborn screen blood spot sample to try to reduce the number of false positives.

These screen positive cases should be referred to a metabolic center that can then provide education to the family and order the appropriate confirmatory testing, which should include both biochemical or blood, urine, or enzymatic testing, and, ultimately, we need the complete genetic testing.

Maura: Can you tell us a little bit more about newborn screening, and, especially how it's changed over the years.

Rebecca: Newborn screening started with the work of Dr. Robert Guthrie's bacterial inhibition assay that could screen patients for phenylketonuria or PKU in the early 1960s. He is considered the father of newborn screening, and his work was spurred on by his niece, who was diagnosed at 15 months of age with PKU, and already had severe intellectual and developmental delays at the time of diagnosis.

Newborn screen emphasizes the importance of quick identification and rapid treatment as PKU patients can have normal IQ levels if we can get their Phenylalanine levels into goal range within the first two weeks of life. Most conditions are added to the newborn screen through the efforts of families and advocacy groups to nominate their child's condition to the recommended uniform screening panel or RUSK Committee for review.

Rebecca: Wilson and Jungner's Principles of Screening provide additional criteria to determine if a condition is appropriate for newborn screens, such as is there an early symptomatic phase; is there a diagnostic test and treatment available; and, is there consensus on who needs treatment?

Expanded newborn screening occurred in 2005 as tandem mass spectrometry allowed us to quantify individual amino acid levels and acylcarnitines, which is the measurement of different length of fatty acids that are attached to a carnitine molecule.

This huge testing breakthrough allows us to screen for 50 metabolic conditions all at once from a few drops of blood on a filter card, and results can take as little as 24 to 40 hours to be reported.

Since expanded newborn screening started in 2005, we can even pick up maternal conditions or mothers who are affected with a mild form of IEM and were not originally screened by expanded newborn screening, and this can be identified through low carnitine levels or placental and breast milk transfer of metabolites to the newborn.

Maura: Can you tell us – is newborn screening the same in every state here in the United States?

Rebecca: No, unfortunately, it's not the same in every state, so the U.S. Health Resources and Services Administration established the RUSP, a list of core conditions that all newborn screen programs should include in order to minimize variability across states. There are currently 26 core conditions. In California, we have a policy that our Department of Public Health has to add a new RUSP core condition to our newborn screening program within two years after it is accepted by the RUSP Committee. Other states are not testing for all the core conditions, as they may not have a certain timeframe in which to add it to their programs.

Even the collection of newborn screen samples can be different between states. In California, we complete one newborn screen filter card between 12 to 48 hours of life. Some other states complete a second newborn screen card in the second week of life as it takes a longer time for some metabolites to accumulate.

Maura: And, is that the same all over the world?

Rebecca: Unfortunately, no. Newborn screen is not the same all over the world. We are fortunate in the U.S. to have such a widespread newborn screen program, but some countries may only include a handful of the most common conditions for their specific population, or it may vary some each region. Other medically disadvantaged countries lack both metabolic providers and metabolic treatment options, which would cause an ethical dilemma of "should they identify" conditions if they are not able to offer treatment. We need to continue to improve health equity for children with IEM across the globe.

Maura: After you identify a child has an inborn error of metabolism, what happens next? How do you manage the disorder?

Rebecca: We usually have multiple approaches for each type of IEM condition. Our metabolic dietitians are so important in helping families begin metabolic formula and low protein foods, which allow us to limit the ascending substrate, for PKU, Phenylalanine Hydroxylase enzymes can't break down Phenylalanine to Tyrosine, which makes Tyrosine an essential amino acid in this condition. Our PKU formulas have no Phenylalanine and extra Tyrosine supplementation to help normalize Tyrosine levels and keep Phenylalanine.

VLCAD deficiency is a fatty acid oxidation disorder where long chain sats cannot be metabolized and used for energy in the form of ketones and ATP. By using a formula that is rich in medium chain triglycerides, we can limit the long chain sats in the diet and bypass the enzymatic block.

There are also detoxifying agents we can use in the form of nitrogen scavenger medications to reduce the risk of hyperammonemia in urea cycle disorders. In other conditions, including isovaleric acidemia, we can also use carnitine or glycine supplementation to bind with toxic organic compounds, which can then be excreted safely in the urine.

Vitamin cofactors can be used to boost any residual enzyme activity. Sapropterin is a cofactor medication we use for milder PKU patients that can increase their protein tolerance by 30 to 75 percent. There are new enzyme replacement therapies, or enzyme substitution therapies. We have started the PKU enzyme substitution injections in some of our classical PKU patients, and their protein tolerance increased from ten grams a day to 65 grams, and are now on an unrestricted protein diet.

For most severe forms of IEM, especially organic acidemias or urea cycle disorders, for require organ transplantation to prevent metabolic decompensation, severe intellectual disabilities, and death.

Maura: You know, it seems like management has changed a lot over the years. Can you elaborate on how care, and particularly nutrition management, has changed over the past five to ten years, for example?

Rebecca: Now that we are identifying most patients through newborn screening, we have discovered more patients on a very wide spectrum of disease severity. One of the biggest challenges is deciding how much nutrition management do these milder cases need, and would they have good outcomes without implementing such burdensome diet restrictions for the patient and family?

Benign hyperphenylalaninemia is an example that some of our patients may need PKU formula during the rapid growth of infancy, but then, some can tolerate a partially controlled or unrestricted protein diet during childhood and adolescence, while maintaining their Phenylalanine levels in goal range.

However, our hyperphenylalaninemia patients with child-bearing potential need to be educated that they will need metabolic nutrition management during pregnancy to prevent maternal PKU syndrome, while supporting the higher protein demands of pregnancy.

Rebecca: For some IEM conditions, we can use a genotype or specific mutation to correlate what type of severity or phenotype may occur, and then determine what level of nutrition management needs to be initiated. Even the U.S. PKU guidelines were changed in the last 15 years to promote diet for life as our adult PKU patients with uncontrolled PHE levels can have debilitating anxiety, depression, and other psychiatric issues.

I would say we have made some great progress with the palatability of metabolic formulas in the past few years, and I recently had an adult PKU patient resume formula after trying some new formula samples. Our dietitians are great at staying up to date on all the latest products, and it's wonderful to be able to offer samples to families before starting the insurance approval process.

Maura: Can you tell us – are you seeing new research in this area?

Rebecca: Absolutely. Our team is involved with multiple research trials for new medications and even potential cures for IEM conditions, using gene therapy or gene editing techniques. It is an exciting time to be in this field, and I can't wait to see how many conditions can be cured throughout my career.

Maura: And what advice do you have to help clinicians apply this to their practice?

Rebecca: If a patient or family member has a child with a positive newborn screen, please remind them that this is just the screening tool, and we will need to complete more tests to determine if they have the actual condition. If you need to order confirmatory testing for a patient, and can't get ahold of your metabolic team, you can always use the ACMG's ACT sheets and algorithms to get started. If you want to see what conditions are being screened for in your state, or provide additional information to families about the screen's positive condition, babysfirsttest.org is a wonderful resource. If you are interested in maybe a career in metabolics, or want to take a deeper dive into a condition, the NIH's Gene Review is an excellent resource for healthcare providers.

I also want to highlight that the American College of Obstetricians and Gynecologists, or ACOG, recommends expanded carrier screening to be offered to all pregnant individuals. These are genetic testing panels that include between 200 to 500 conditions, with many IEM conditions on the panel, and ideally, it should be performed prior to pregnancy. If a pathogenic or disease-causing mutation is found for an IEM in the mother, then the partner should be testing and genetic counseling offered to learn about their risk and reproductive options.

If a fetus is at risk for a severe IEM, there are ways to confirm the condition through prenatal testing, such as amniocentesis. Our metabolic team has been able to create a post-delivery plan for the infant to rapidly initiate treatment and have significantly improved outcomes in these patients.

Maura: This is really great, and before we close, Rebecca, are there any closing comments you'd like to share with our listeners?

Rebecca: Yeah. I am just so thankful to work with a wonderful multidisciplinary team made up of biochemical geneticists, genetic counselors, dietitians, nurse case managers, medical assistants, and our social worker to care for these medically complex and challenging patients. It truly takes a village, and I'm thankful for the trust our families give us as we work together to help their children thrive.

Maura: Wonderful. Thank you, Rebecca for your insights, and thank you for joining us today.

Rebecca: Thank you so much for having me and allowing me to spread more awareness on metabolic newborn screenings.

Maura: And, for our listeners, if you're looking for more podcasts, we have dozens and dozens across a variety of different nutrition science topics, and you can find them on ANHI.org by clicking Resources at the top of the page, then podcasts and videos. We're on Spotify and Apple podcasts too, and we hope you'll listen, like and share these recordings with your colleagues.

Thanks everyone.

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