MAKING THE CHOICE

Medical Management or Liver Transplant for Urea Cycle Disorders: *The Family Experience*

A Guide for the UCD Community

Patients, Families and Healthcare Providers

www.CureUCD.org

Making the Choice
Medical Management or Liver
Transplant for Urea Cycle Disorders:
The Family Experience

For more information about
urea cycle disorders:

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INTRODUCTION TO THE GUIDE

Patients and families affected by urea cycle disorders (UCD) face profound concerns about the short and long-term effects of UCD on brain function and quality of life. While some families choose to continue with medical management, other families pursue liver transplant in hopes of preserving brain function and improving quality of life. Either choice is a leap of faith. Patients, families and their medical providers often struggle with uncertainties and a lack of information to help them navigate the complex issues involved in making choices about continuing with standard medical treatment or opting for liver transplantation.

To begin to address this problem, a pivotal study was proposed by the National Urea Cycle Disorders Foundation (NUCDF) on behalf of UCD patients and families to examine and describe the factors that influence families' decisions to continue medical management or choose liver transplant. The study was supported by the Patient-Centered Outcome Research Institute (PCORI®) and conducted by a collaborative team of experts. We deeply appreciate their commitment to this research—the first patient-centered outcome study on this topic. The purpose of this first-edition Guide is to help begin to disseminate the results of the study to UCD patients, families and healthcare providers.

The Guide is a labor of love dedicated to patients and families affected by urea cycle disorders. It was made possible through the generosity of families in the study sharing their very personal experiences with the study team in the hope of helping other UCD families on this journey.

Yours towards a Cure,

Cynthia LeMons

CYNTHIA LE MONS
Executive Director
National Urea Cycle Disorders Foundation

ACKNOWLEDGEMENTS

We would like to thank Dr. Mendel Tuchman, Dr. Nicolas Ah Mew, Dr. Anne Markus, Cynthia Le Mons, Maya Gerstein, and our study coordinators Jan Bartos, Kirk Williamson and Kan Gianattasio for their commitment to this research and compassion for the families who so generously shared their experiences about urea cycle disorders for the study.

We extend our deepest gratitude to the families and healthcare providers who graciously agreed to be interviewed and provided their knowledge, perspectives and insights with the goal of helping other UCD patients, families and providers.

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THE STUDY

Overview

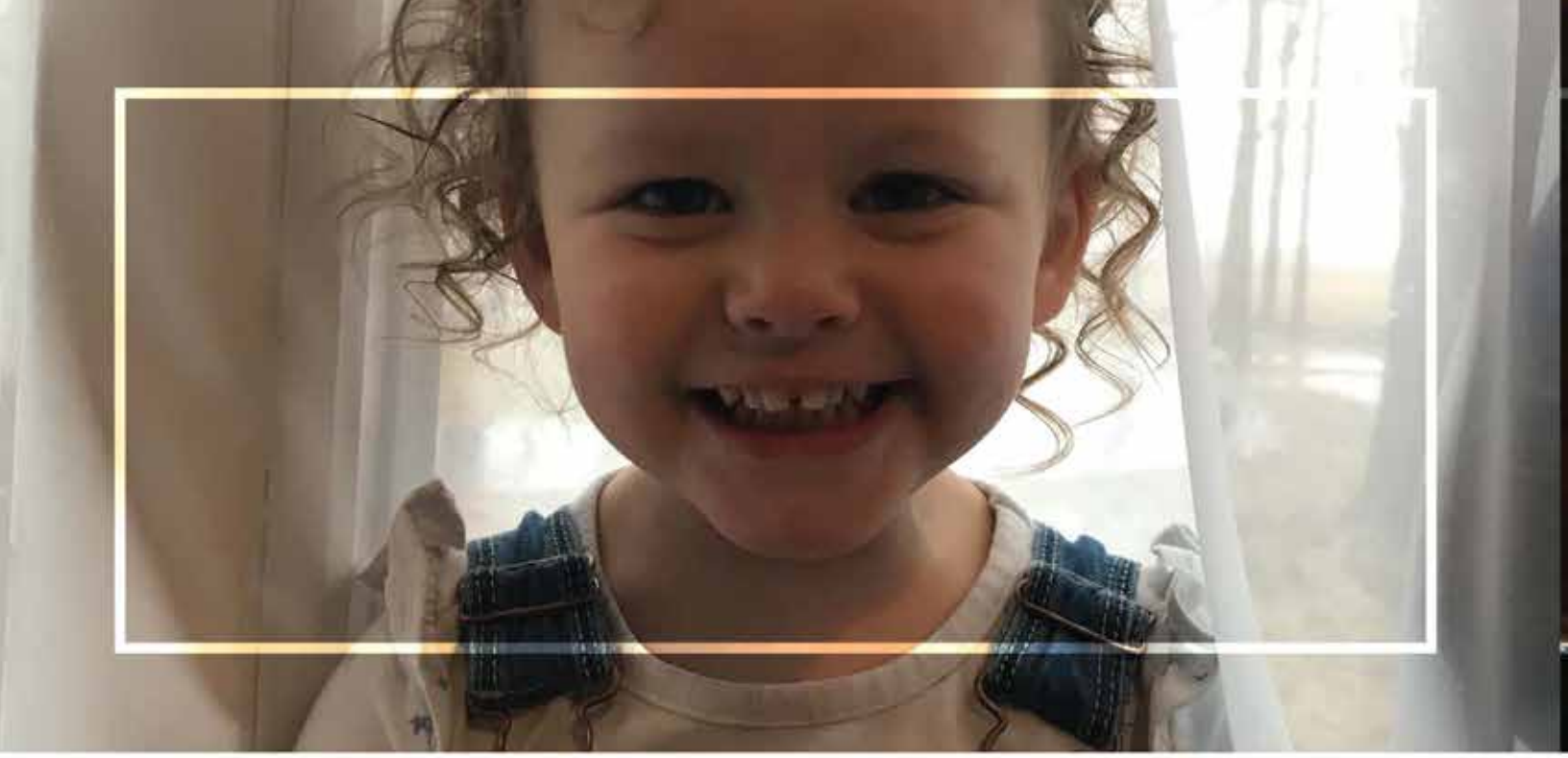
Framing the Issues

Urea cycle disorders (UCD) are rare inborn errors of metabolism caused by genetic mutations. The urea cycle consists of six enzymes and three transporters that are responsible for detoxifying ammonia in the bloodstream. Ammonia is produced normally in the body as a byproduct of protein metabolism. The urea cycle enzymes normally convert this toxic ammonia to a harmless substance in the blood called urea. In urea cycle disorders, this conversion is absent or deficient and, without treatment, ammonia builds up to toxic levels in the brain, causing neurological damage and ultimately death. Even with optimal treatment this condition, called "hyperammonemia," can result in early or chronic damage to the brain.

There are two major treatment options for UCD: 1) Medical management with modified diet, amino acid supplements and ammonia-scavenging drugs, or 2) Liver transplantation. Because the urea cycle is primarily located in liver cells, liver transplant corrects the enzyme deficiency, stops the risks of hyperammonemia, and ends the need for modified diet and ammonia-scavenging drugs.

Both these treatment approaches are associated with mortality and morbidity. Medical management carries the risk of recurrent episodes of hyperammonemia, complications due to treatments, chronic neurological damage, and death. Liver transplant carries the risk of potentially fatal surgical and postsurgical complications, as well as side effects of chronic immunosuppression.

The evidence comparing outcomes between these two treatment options is sparse. Therefore, patients and healthcare providers face a difficult dilemma: should the patient be managed medically, or should they undergo liver transplantation? Despite the complexity and critical impact surrounding the decision, no formal research has been conducted on how UCD patients and families make these treatment choices and the factors and issues that influence their decision to pursue one option over the other.



Study Overview

"Choosing Between Medical Management and Liver Transplant in Urea Cycle Disorders: A Qualitative Evaluation of Parent Decision-Making"

APPROACH

A qualitative evaluation of parent/caregiver decision-making was conducted in collaboration with NUCDF, Children's National Health System (Washington, DC), and George Washington University Milken Institute School of Public Health. A two-stage qualitative approach utilized semi-structured telephonic interviews and in-person and online focus groups with parents/caregivers of children affected by UCD, as well as healthcare providers. Analysis techniques were used to identify key patterns, themes and concepts, explore the relationship between these elements, and build a framework that describes how parents of children with UCD reach treatment decisions, and the key factors that influence this process.

STUDY GOALS

- Improve the understanding of the factors families consider when making decisions about liver transplant vs. standard treatment.
- Provide clinicians and other UCD care team members with a better understanding of the needs and priorities of UCD patients and families.
- Improve providers' ability to support families who are navigating the complex and challenging choice between medical management and liver transplant.
- Promote better delivery of care and information to UCD patients and their families about current treatment options.

STUDY TEAM

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Children's National Health System (CNHS)

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PARTICIPANT INTERVIEWS

To facilitate the study goals, the study team conducted interviews with UCD parents and healthcare providers who shared their experiences about issues they faced when making treatment decisions. Their insights helped the study team identify the common factors that families consider when weighing the decision between standard medical management and liver transplant.

This model collaboration between the study team, families and providers included:

- In-depth, individual phone interviews with 34 parents of children diagnosed with UCD about their experiences making the choice between continuing medical management or opting for liver transplant.
- In-person and web-based focus groups with 31 parents, hosted by NUCDF online and at the NUCDF Annual Family Conference.
- In-depth, individual phone interviews with 26 clinical providers, including metabolic physicians, genetic counselors and liver transplant team members, about their experiences counseling families about these choices.
- In-person and web-based focus groups with 19 clinical providers.

THE DILEMMA

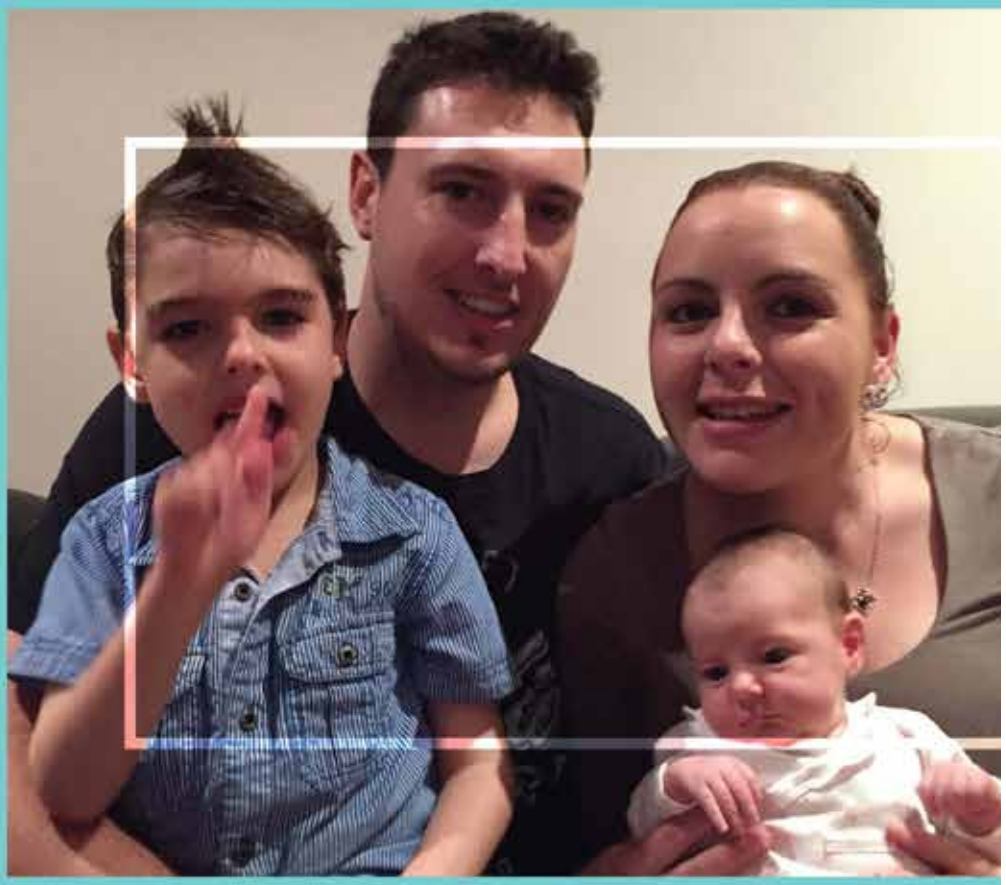
Weighing the Risk and Benefits Childhood Development

Perceptions Influence Decisions

The study found that parents put considerable effort into understanding and analyzing the risks and benefits of medical management and liver transplant. Due to the variability in severity of urea cycle disorders and differences in access to expert care, parents want to make the choice that is right for their own child. Because the data and scientific evidence is so limited, parents and providers often struggle to make informed decisions about medical management and liver transplant. To guide their choices, parents often rely on their own experiences and that of their providers and other families. What ends up driving a treatment decision is each family's personal perception of the risks and benefits of these treatment options, built on a very complex combination of clinical issues, personal factors, social factors and healthcare system issues.

> ***We wanted to be in the driver's seat...for his best interest and his life...it's the same thing as a risk benefit. You're making a pro and con list, and it's an unknown number of hyperammonemic episodes versus unknown complications from liver transplant. I think it's a hard decision, especially in those that might not be extremely sick right now.***
>
> ~ Parent

CHANGING EQUATION
Catalysts for Treatment Choice



Milestone Transitions

Feedback from the family interviews also highlighted the idea that certain changes during key developmental milestones throughout the life of the child act as a catalyst for parents to consider or reconsider liver transplant as a treatment option for their child. For example, as a child moves from infancy to early childhood, parents often must contend with new feeding challenges, such as a transition to solid foods. As their child moves to school age, they are faced with new challenges around managing the disorder in a school setting. When the child transitions into adolescence and early adulthood, parents are faced with new questions about their child's long-term independence and ability to live safely alone outside their parent's home and care. These are just a very few examples of new challenges that parents face during each of these milestone transitions.

The common theme cited by families is that these key transitions play an important role in "changing the equation" for families affected by UCD. Each milestone brings with it a whole new dimension to the disorder that may change the parent's and child's priorities and reframe the family's perception of the risks and benefits of medical management versus liver transplant.

> ***It's just a new chapter in our lives. In order for the possibility of her [daughter] being able to maybe go to college...just be able to think about things like that...If we can't get it [UCD] under control now, I don't know how we're going to be able to get it under control in the next couple of years.***
>
> ~ Parent

THE DRIVERS
Factors Affecting Treatment Choice

Key Drivers of Treatment Choice

Throughout the interviews with parents and providers, several factors were identified as drivers of treatment choice among UCD families. These factors included:

- **Clinical Factors** - Disease severity and disease stability.
- **Personal Factors** - Burden of the disease on the family and the affected child.
- **Social Factors** - Effects of UCD on family and school social experiences, as well as considerations for the affected child's independence.
- **Health System Factors** - Access to quality metabolic specialty care, cost and coverage of treatment, and physician approach to guiding treatment choices.

Clinical Factors

DISEASE SEVERITY

Severity of diagnosis was cited by both parents and providers as a key consideration in treatment choice. For those diagnosed with severe neonatal-onset UCD or who characterized their child as having zero enzyme function, liver transplant was often described as the child's "only option" or "best chance for long-term survival."

For those with late-onset UCD or partial enzyme function (widely variable from very mild to moderate severity), the choice between medical management and liver transplant was much more subjective and complex. In this latter group, families reported a lot of ambiguity in terms of the perceived risks and benefits of transplant versus continuing medical management.

Clinical Factors

DISEASE STABILITY

In the shared experiences and stories of different families, periods of instability for the child were often cited as a catalyst for parents to consider liver transplant. Regardless of diagnosis, parents may feel compelled to explore transplant when a child goes through a period of frequent episodes of hyperammonemia, or frequent emergency room visits and hospitalizations. Some parents also described transplant as a proactive or "preventative" measure to avoid any future instability (episodes of hyperammonemia) and as a way to protect and preserve the child's neurocognitive function. Many of these parents did not consider previous or current stability of their child's disease as reassurance of continued stability. The fear of the unpredictable nature of high ammonia alone was enough to compel some families to seriously consider liver transplant.

The following quotes, representing differing perspectives, come from two different parents who expressed their thoughts about transplant as a treatment option.

"From everything that I've heard, it should be for us more of a last resort scenario. My daughter's condition, for the most part, has been pretty well-controlled... In my mind, if that is still feasible for us, why would we take on the risks that are associated with the liver transplant?"

"Tons of reasons as to why we felt transplant was a better option, even though he was quite a stable kid so far, but everybody told me that might not be the case forever. That can change literally overnight, so that's why we decided to go for the transplant."

Personal Factors

BURDEN ON CHILD

The parents we spoke to also expressed a great deal of concern about the impact of UCD on their child's quality of life and their child's intellectual and social development. Parents said they asked themselves if transplant could offer their child an opportunity for a "normal life"—for lack of a better term—and "better quality" of life. For some, the answer was yes. However, others were less motivated to pursue transplant because they felt their child was thriving both socially and intellectually with medical management. One parent, who did ultimately elect to transplant, shared the following:

"That was one of the things in school. He learned how to count money, and that was a huge thing because he worked and worked at it. Then he had a high ammonia level...He remembered that he knew how to count money, but he couldn't count it anymore. We thought, oh, that quality of life's horrible...to lose functionality was devastating for him. That played into [the decision to transplant] too."

Personal Factors

BURDEN ON FAMILY

Parents spoke extensively about the day-to-day challenges of managing UCD, reporting it to be an enormous undertaking and a key focus of raising a child with UCD. All families we spoke to related to the challenges of 24/7 medical caregiving; feelings of fear, worry, anxiety and the emotional health of the family, as well as the difficulty coping with changes to "normal life" comforts like enjoying food and travel. Some families reported these daily burdens as a compelling reason to consider transplant. For others, the daily burdens of managing the disorder were not a factor driving them to pursue transplant.

In some cases, when parents felt a level of mastery and comfort handling their child's routine, the new and unfamiliar risks and burdens of transplant were a more frightening prospect than coping with the very difficult but more familiar challenges of dealing with the UCD.

Social Factors

SHARING FAMILY EXPERIENCES

With limited scientific data and evidence to help inform the choice between transplant and medical management, the experiences of other families are a powerful source of information and insight for families who are currently navigating this decision. Almost uniformly, the parents reported they made efforts to network with other families affected by UCD. Parents described being motivated to pursue transplant by positive stories from families who had gone through successful transplant, as well as by the experiences of other families who had delayed or foregone transplant and had a negative outcome.

A few parents described being deterred from transplant or encouraged to continue with medical management by the stories of others who had gone through the transplant procedure and been faced with severe complications, or by the stories of families who have had a lot of success in managing their child's disease with diet and medication.

"I probably wrote back and forth with about six, or seven, or eight different moms for a couple months. Just hearing their experiences, asking if they feel that dealing with transplant life is easier than a UCD life...A lot of their opinions really helped make my decision."

Social Factors

CONSIDERATION FOR THE CHILD'S INDEPENDENCE

Parents also raised concerns about their child's short term and long term independence as a factor in considering treatment choices. They questioned how treatment with diet and medications versus liver transplant might impact their child's ability to live more independently. This included smaller steps toward independence such as entering preschool or grade school, to more major milestones such as living as an adult outside the parent's care--for example, when attending college. For some, this was a major driver towards transplant, as they could not envision a future where their child could be truly independent while still relying on parental supervision and vigilence to manage their UCD.

Conversely, other parents felt they could envision and prepare their child for a safe and independent life outside the home with medical management of their UCD. One parent, who was still grappling with the decision to transplant, said the following about their child's future independence with the disease:

"For her independence, a transplant is necessary...when her ammonia level starts to rise, she can't make decisions on how to help herself... Living on her own and going away to college was not going to be an option."

DRIVERS OF TREATMENT CHOICE

System Factors

ACCESS TO QUALITY METABOLIC CARE

Another factor that triggered considering transplant was family experiences with their metabolic care team and their perception of the quality of metabolic care their child was receiving. Families who expressed concerns about the local metabolic team or the emergency medical care in their area were often driven to consider transplant in part because they lacked confidence that their child's disease would be managed appropriately by the providers and institutions that were available to them. Conversely, parents with a great deal of confidence in their metabolic care team's ability to manage their child's UCD were often less motivated to explore alternatives like transplant. Because expert care is not found everywhere, access to quality medical care, including which institutions and providers are available, is especially important to families living with UCD.

A parent whose child is currently managed medically said the following:

I'm confident that if she does get sick that we're in the right place. I trust the team here very much...The reason [liver transplant is] not forefront in my mind is because we are with [this] department, and we're with [this] doctor.

One parent who ultimately pursued transplant for their child commented the following:

All these little things were adding up for us. Okay, he didn't have a crisis for eight months, but they're not able to quickly handle it...if we weren't here watching like hawks all the time, would he survive?...When we went in there, my faith was that these people were going to save his life, and suddenly, I couldn't count on them to do it right....

System Factors

PHYSICIAN APPROACH TO TREATMENT GUIDANCE

During the interviews and focus groups, both parents and providers stated there was a great deal of variability in physicians' approaches to treatment and treatment guidance. Some physicians described themselves as pro-transplant for UCD, and promoted transplant consults for almost all their UCD patients. Other physicians viewed transplant as a "last resort," or only for patients diagnosed with more "severe" forms of the disorder. Still others took a more balanced approach or deferred the choice to the family. What is clear is that the approach and clinical perspective on transplant seemed to vary from physician to physician and from institution to institution.

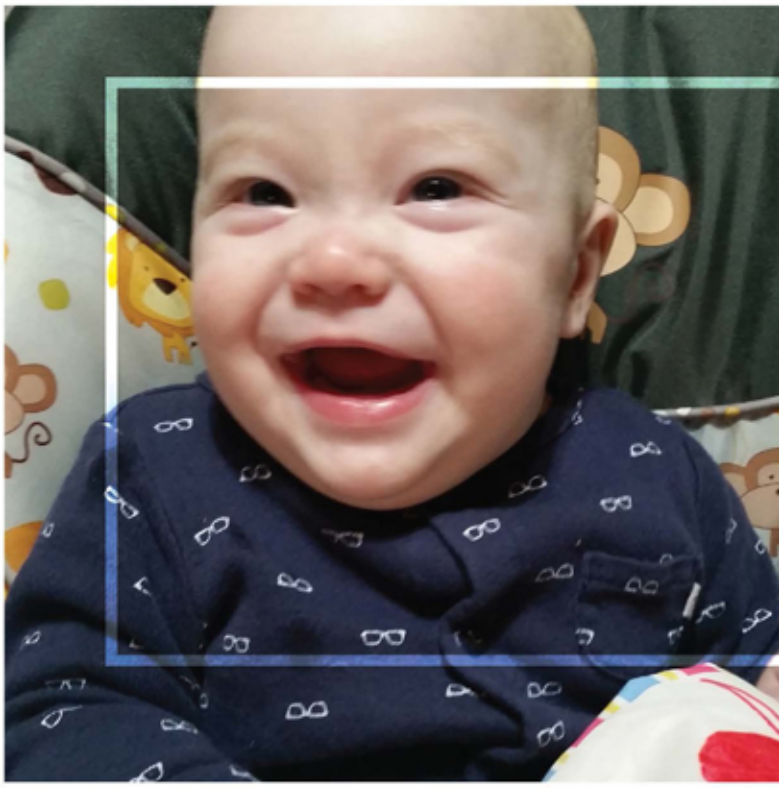
It is known that physician opinion is a very powerful driver of treatment choice for families and has a significant impact on the ways in which the family views the options that are available to them. In our study, it was observed that there is not a great deal of consensus among physicians about how to approach this choice and how to counsel families about this decision.

It is important to acknowledge this lack of consensus. The study team confirmed the need to better equip families with the resources they need to feel empowered and supported when making these tough treatment choices.

System Factors

COST AND COVERAGE OF TREATMENT

In terms of the cost and coverage of UCD care and treatment, we heard a lot about the high out-of-pocket costs of care and the burden families undertake when navigating their insurance benefits to secure the treatment and medications their child needs. This topic itself deserves further study from a healthcare policy perspective. From the stories collected, there was a very stark difference in the cost and coverage of medical management versus liver transplant, in favor of transplant. This was surprising to the health policy researchers on our study team who examine health policy for many different chronic disorders.



When we asked families about insurance coverage for needs associated with medical management, they reported lengthy and time-consuming disputes with insurance companies over medication, metabolic formula and nutrition benefits. Limited or insufficient coverage for formulas, amino acid supplements and medical foods was very common.

The study team was surprised at how different this picture looked when we spoke to families about insurance coverage for liver transplant. In all cases, it was fully covered with little out-of-pocket costs to the family.

Although no parent indicated cost of care as being the driving force in their decision to transplant or not to transplant, we found that the financial burden of standard care certainly contributed to the overall burden of disease on the family. The differences in coverage experiences and out-of-pocket costs between medical management and liver transplant were striking and problematic.

"It's too hard...the struggle between insurance, and where you work, and getting covered...it's a full-time job just to get medication...The nutrition many times is not considered medically necessary, but is medically necessary...Then you're constantly battling with your insurance company. It's hard enough emotionally to deal with the condition, but then to have to be bullied by insurance companies...The amount of money that we spent the first five years that [she] was diagnosed, we were living in poverty, but our income was well above poverty...we couldn't comprehend how it could cost this much money out of our pocket to be able to keep her alive...."

FINALLY, THE TIPPING POINT

A critical aspect of the decision process identified by the study team was the "tipping point." We learned from our discussions with parents and providers that parents who opted for transplant had ultimately reached a point when they felt they were no longer able to manage their child's disorder through diet and medication.

If, when, how, and for what reason this point is reached is uniquely personal and varies from family to family. Some families may never reach a point where transplant is a true consideration. But, for many families, this "tipping point" comes shortly after diagnosis. Other families face their personal "tipping point" after years of medical management and certain key shifts and changes in the child and the family's circumstances.

In conclusion, all the factors and issues reported in the study are pieces of a complex process that each family has to undertake when they navigate the choice between medical management and transplant through the lens of their own personal priorities and experiences.

With a more holistic understanding of the circumstances that motivate families to evaluate treatment options and to consider, pursue or exclude transplant as a viable choice for their child, providers may be better positioned to anticipate and respond to the needs and priorities of families affected by UCD.

ABOUT
THE NATIONAL UREA CYCLE DISORDERS FOUNDATION

NUCDF is the only nonprofit organization in the world solely dedicated to saving children and adults from the catastrophic effects of urea cycle disorders (UCD). NUCDF leads the fight to conquer UCD, and is the driving force behind critical research to improve the understanding and management of UCD, find new treatments, and ultimately a cure. NUCDF serves as a vital resource to medical professionals and a lifeline to affected families all over the world, providing information, guidance, support and Hope.

The Foundation promotes increased public awareness of UCDs to facilitate swift identification and diagnosis, provides information and education for healthcare professionals and affected patients and families, stimulates and supports pioneering research, and educates legislators on the needs of UCD patients and families.

NUCDF is committed to working with researchers and clinical professionals, advocates, policymakers, industry and the public to improve the quality of life for all those affected by UCD.

NUCDF is a founding member and partner in the Urea Cycle Disorders Consortium (UCDC), an international collaboration of research sites in United States, Canada, and Europe. The Consortium is part of the Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR) and the National Center for Advancing Translational Science (NCATS). The UCD Consortium is funded through a cooperative agreement between NCATS and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), with philantrophic funding from the O'Malley Foundation, National Urea Cycle Disorders Foundation, Kettering Family Fund, Dietmar-Hopp Foundation, and Rotenberg Family Fund.

Additional Resources and Support

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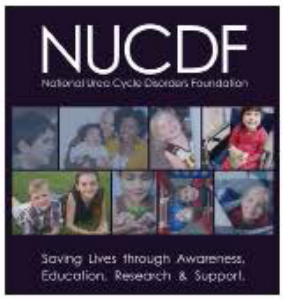

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