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The Spectrum of Liver Transplantation: Addressing the Needs of Diverse Patient Groups

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch, and joining us today to discuss liver transplantation, which is a topic that appeared in *The New England Journal of Medicine* in November 2023, is Dr. Michael Lucey. Dr. Lucey is a Professor of Medicine at the University of Wisconsin School of Medicine and Public Health.

Dr. Lucey, welcome to the program.

Dr. Lucey:
Well, thank you very much for the invitation. I'm happy to be here.

Dr. Buch:
To start us off, Dr. Lucey, can you tell us how the MELD score is now more accurate and less biased? And what conditions add points to the MELD score?

Dr. Lucey:
So the MELD score was originally designed to try and predict mortality after a procedure to relieve portal hypertension, a procedure called TIPS, and then it was adapted from that position to predict mortality in patients on the transplant waiting list or who might be placed on the transplant waiting list, and so that's how it came about. And over the course of over 20 years, it's been found that it did not work well in every situation, so it has gone through a series of iterations. Some are just to improve its accuracy of predicting short-term mortality, and others are to avoid discriminating against particular groups. In the most recent iteration, the impact of creatinine has been changed, and a factor has been placed for the gender of the person whose test is being measured. And then there are some other changes as well. Over time, serum sodium was added to improve accuracy, and most recently, albumin has been added to improve accuracy.

Then regarding conditions, the most obvious condition that is not well captured by the MELD score is hepatocellular cancer, both standard hepatoma or hepatocellular cancer, but also other cancers of the liver. So in order to recognize the urgency of those patients, they are given extra MELD points, and how to do that has been changed at various times over the years because it has appeared we've been either too favorable or not favorable enough, and so that's under constant review. And then there are other conditions which are not captured well. So the so-called hepatopulmonary diseases, portopulmonary hypertension, and hepatopulmonary syndrome would be an example of that, and there are others as well.

Dr. Buch:
What strategies are being used to increase the number of livers available for transplantation?

Dr. Lucey:
Well, there are several approaches that might improve the available number of livers. One would be to improve the process whereby family members who have a person in an intensive care unit who is declared brain dead would be encouraged to allow those persons become donors. So the whole process of transition from potential brain-dead person to a brain-dead person who's a potential donor to an actual donor is one that is under review.

But then there are the questions about the persons who might have been donors but are not considered donors. So the standard donor is a donor who has been declared brain dead, but then there are persons who are dying or are almost dead who don't yet meet criteria for being brain dead, and according to the law, they have to be allowed to die, but they might become donors at that point, and they're

the so-called declared cardiovascular death donors, and so they form a small but important group. However, those livers have an interval of ischemia while the declaration of cardiovascular death has to be made, and so those livers have a greater risk of injury to the bile ducts in the recipient, so that's an issue for them.

And then there are a whole series of new maneuvers—which are detailed in the paper you refer to, the one that I wrote with David Foley and Katryn Furuya who are colleagues of mine here at the University of Wisconsin—a process to try to improve the viability of livers and also to improve our ability to identify those livers which will become viable if they're transplanted. Currently, many livers are declined for transplantation even after the family have agreed to donation because, on the rather crude basis for judging this, it appears they're unlikely to work, so there are whole series of new innovations to try to improve that process of both recognizing viability and encouraging viability, particularly in patients who have either been declared cardiovascular dead or in persons who are declared brain dead and whose perfusion is being maintained on life support.

Dr. Buch:
And then there's also that other field of living donor transplants. Can you tell us a little bit more about that?

Dr. Lucey:
Well, living donor liver transplantation is based on what might be called the Promethean nature of the mammalian liver. If you remember the Greek myth of Prometheus, he was an immortal, and he stole fire from the Gods, and the Gods punished him by having him change to a rock, and I think every day his liver was pecked away by a bird, sometimes depicted as an eagle, sometimes depicted as a blackbird, and every night it regrew. So that capacity of the liver to grow again after injury is what's being relied upon in living donor liver transplantation because with the right selection and the right care about estimating liver size in donor and recipient, a healthy person can have a partial hepatectomy, so up to half of their liver is removed. The removed part has its vasculature maintained, and so an intact vasculature is then placed in the recipient, and the donor's liver then grows back to approximately 90 percent of their original liver size and maintains the proper architectural integrity of the liver.

The liver is an exquisite architecture related to portal and arterial blood inflow. The blood flows through the sinusoids and exits through the terminal hepatic venule, also called the central vein. That exquisite architecture and then the passage of bile into the canaliculi, all of that is maintained when the liver regrows. So when this goes well, the donor liver is perfectly healthy six weeks after the transplant, and they have almost the same size liver as they ever had. And in the recipient, the same process occurs with the liver growing back to nearly the size of the original liver when the patient was healthy. So that's living donor liver transplantation.

Dr. Buch:
What are the trends that we're seeing in liver transplantation among patients with nonalcoholic fatty liver disease, now called MASLD?

Dr. Lucey:
So, first of all, congratulations on getting the names right. That's MASLD. We're trying to get away from defining something by what it isn't, so it's never a good way of defining something. So metabolic-associated stereotactic liver diseases are largely associated with type 2 diabetes and the metabolic syndrome, which we now see as type 2 diabetes, increased body mass, particularly around the middle of the abdomen, systemic hypertension, hyperlipidemia, obstructive sleep apnea, polycystic ovary syndrome, and, in a small proportion of patients, progressive fibrotic liver disease. However, the prevalence of metabolic syndrome is so high that the actual numbers of patients with advancing fibrosis due to MASLD is high, and it's projected to become the most common cause of need for a liver transplant. It hasn't reached there yet, but it potentially could. The challenges here are the challenges related to the metabolic syndrome in that patients with diabetes mellitus may often have microangiopathy and all the other complications of diabetes, which may themselves prevent or make difficult a successful transplant. But that's the trend. The trend is for more patients with MASLD to require a liver transplant and to be offered one.

Dr. Buch:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Michael Lucey about liver transplantation.

So, Dr. Lucey, if we zero in on alcoholic liver disease, how do you decide whether a patient should be placed on the list?

Dr. Lucey:
So alcohol-associated liver disease is a useful name because it points out that the disease is by and large linked to alcohol use disorder, what was previously termed alcoholism, but we're trying to get away from that term as well because it's the use of alcohol that makes the difference here. And there is a silent epidemic of alcohol use disorder in the United States at the moment. It has been exacerbated by COVID. And so now if I were to look into the patient population in the hospital of the University of Wisconsin, the patients with serious liver disease would be predominantly patients with alcohol use disorder, and so it is now the commonest reason

for liver transplantation in the United States. And the outcomes are by and large excellent, but it does not cure the alcohol use disorder, and so we still have to work to try to protect the patient from the damaging effects of alcohol after transplantation, and that's a big issue. But alcohol use disorder and alcohol-associated liver disease are very important elements to the whole liver transplantation story.

To be considered doesn't necessarily mean to be placed on the transplant waiting list, and so it's both a practical and an ethical issue as to what is the right way to proceed when a patient with threatened death from alcohol-associated hepatitis who might be saved by a liver transplant is under the care of a hospital and the medical facility.

At the moment, our ability to distinguish those patients who will recover and do well, even if they return to drinking, versus those persons who are likely to fail a transplant and die after the transplant, let's say, in the first year either because of a return to drinking or for other end-organ issues is not very good. And our group and several other groups around the country are currently in the early stages of an NIH-funded study to try to better understand that. But at the moment, we do the best we can by trying to see which patient has the familial and personal infrastructure to undergo transplant and live with the demands of a transplant and try to identify those patients most likely to establish abstinence because absence does make a difference, even though return to drinking occurs in maybe 40 or 50 percent of patients in this situation.

Dr. Buch:
What's the outcome of recipients who receive either hepatitis C or hepatitis B donated livers?

Dr. Lucey:
Well, let's take the hepatitis C first. Hepatitis C is one of the greatest medical happiness stories of the last 30 years. A new disease discovered the virus. It was first of all recognized as posttransplant or posttransfusion, non A, non B. Then the virus was identified. Then the viral structure was identified. Halting efforts at trying to cure it right up to finding drugs that absolutely cure it. So for patients who are in a brain-dead state, if they have hepatitis C but their liver is not severely damaged, they are reasonable candidates for transplantation because we can treat the recipient after the transplant and cure the hepatitis C. So hepatitis C is a very good option for cure after transplantation, and that applies to liver transplantation and also to kidney transplantation.

Hepatitis B livers don't come forward to us as often, so we don't have a very good experience with that. One could transplant those into patients with hepatitis B. There's no particular extra risk there. However, we don't see many patients in this country with hepatitis B requiring liver transplantation because of the efficacy of treatment pretransplant. Indeed, apart from hepatocellular carcinoma, consequential on hepatitis B, I think the numbers of patients getting transplanted in the United States for hepatitis B is very, very low.

This just brings out a point that's probably worth mentioning in that the profile of liver transplantation and the diseases being treated differs in different countries.

Dr. Buch:
In the last few moments of our discussion, Dr. Lucey, are there any additional thoughts you'd like to share with our audience?

Dr. Lucey:
I have two thoughts. The first is to emphasize that liver transplantation really restores the lives of people. So for many patients with a liver transplant, they are on medicines, but they are doing very well, so the listeners wouldn't necessarily know that a person has had a liver transplant. There is a smaller stratum of patients who have complications posttransplant, but I would not want the listeners to imagine that that is the only outcome. The main outcome of liver transplantation is the restoration of health. And that then leads me to my second point: to encourage families to donate.

Dr. Buch:
This has been a wonderful and practical review of liver transplantation, and I want to thank my guest, Dr. Michael Lucey, for sharing his insights with us. Dr. Lucey, thanks so very much for joining us today.

Dr. Lucey:
Peter, thank you for your questions, and it's been a pleasure.

Dr. Buch:
It's been my pleasure. For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit *GI Insights* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.