Panel Discussion

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Alan Buchman, M.D., M.S.P.H.
You, Dr. Fryer, talked about the high mortality on the waiting list for patients who are waiting for liver/small bowel transplant. You mentioned that so many patients are listed for both a liver and small bowel transplant, suggesting that these patients are referred too late. When would be the optimal time to refer a patient to an intestinal rehabilitation center, an intestinal transplant center, or one of the few programs that actually have both?

Jonathan Fryer, M.D.
My belief is that consideration should occur very early. I think it should be as early as when the patient first goes home on TPN when the physician knows that the patient is destined to long-term TPN. Although it is a somewhat crude parameter and surgeons (including myself) often fail at documenting exactly how much intestine is left, those measurements give the gastroenterologist a fair idea of who those patients will be.

As seen, some of these patients experience problems, though most do not have issues for several years. Patients should be sent to rehabilitation or transplant centers early.

Kishore Iyer, M.D.
One of the concerns among referring physicians and transplant centers has been that there is a disconnect that is not clearly understood. There is a very big difference between referring to an intestinal rehabilitation center and actually doing the transplant. The patient may never receive a transplant or may undergo the surgery within 6 months or a year, and for the vast majority of the patients who are referred, the goal is not to hang on to them in our own institution. Very often, for the stable patient on TPN, a short-term plan and long-term plan can be created and instituted in conjunction with the primary physician, whether a gastroenterologist or surgeon. That approach allows the physician to more easily recognize when such a patient is worsening, and it allows clinicians not to miss what is sometimes a very limited window of opportunity to intervene. It allows better overall outcomes.

Dr. Buchman
Would you mind giving us an update in terms of GLP2 and GLP1 and where you see that headed for the future?

Palle Jeppeson, M.D.
First of all, a study that just came out is very interesting because it shows that growth hormone is actually difficult to use. There is a high incidence of side effects to high-dose growth hormone, and a patient should actually take the growth hormone for a long time. The problem in the study is that the majority of patients are those with preserved colon, and those are the patients we can get off parenteral nutrition. I do not really believe much in the hormone story to be honest.

GLP2 works in patients with a jejunostomy where we can reduce the output by approximately a liter. It works mostly on fluid and not energy absorption. Then, we have GLP1, and animal studies suggest that it may have an additional effect with GLP2. We can help a lot of borderline patients with a jejunostomy to get them off parenteral nutrition. I do not have much faith in the hormone story, to be honest.

Dr. Buchman
Why don’t we do more living donor transplantations, and do we have any information about the donor outcome?

Dr. Fryer
Living donor transplantation is a highly debated discussion at any meetings that address this. We do not do more because...
attacks; the surgeon cannot transplant patients out of those problems.

**Dr. Buchman**

Part of the problem that we see in the United States is the fact that the care of these patients is very decentralized, and care of them in circa 1982 occurred in about one-half dozen centers in the United States. As care and expertise have become diluted, this is the one patient group for which overall care is worse today than it was 10 or 15 yr ago. In Denmark, two centers care for all intestinal failure and the patients therefore benefit clinically from the breath of clinical experience. For us, we have a large referral population.

A lot of patients who are referred already have liver disease, and some of them, for example, are sent with a bilirubin of 32 mg/dL. There isn’t too much to do at that point. I had a referral patient who did not eat, but she was never hungry because she got TPN 7 nights a week. She was sent home on TPN and no one ever bothered to do anything else, whether it was dietary therapy, growth hormone, or anything of that sort. If you do not eat, you are essentially a no-gut patient. In your experience this wouldn’t happen, but we see this sort of thing quite frequently in the United States.

**Dr. Fryer**

This problem is somewhat specific to our country because of the way that TPN is given. People lose their gut, they go home on TPN, and then they are in a black box. Some do well, and some return to the transplant centers with a serum bilirubin concentration of 20 mg/dL and elevated international normalized ratios (INRs), and they die of TPN-associated liver disease. Management of TPN may be the problem in the United States. We are trying to change the paradigm in this country and have people referred to centers of excellence that focus on intestinal TPN management and intestinal failure. Today, even the most complex patients are receiving care from individuals who are either busy or do not have a lot of experience with TPN. In addition, some of the TPN companies are very good, but some smaller TPN companies become engrossed in the business and miss early signs of some of the problems. Those problems can be identified earlier when care is centralized.

**Dr. Iyer**

There are two sides to the problem: there are those who are not being managed correctly and there are those who have limited options. The most gratifying successes come in patients who from the start were suboptimally managed. We recently had a teenager who was referred for liver/bowel transplant. She had a bilirubin of about 15 mg/dL, and liver biopsy showed some bridging fibrosis, but she had TPN 14 h a day 7 days a week and had a gastric tube from the newborn period that had never been used. It took us 3 months of commonsense medicine to get her off TPN and adjust her fluids, and to our surprise her liver improved. Quite clearly, she did not need a liver transplant. There is that patient on one hand who is clearly suboptimally managed and should not have ever been in the situation.

On the other hand, there are patients who have limited options from the start, such as a pediatric patient who was born term with no bowel. I did his transplant when he weighed 5.2 kg in the face of liver disease. He had 6 cm of jejunum. There was nothing to do but nurse the patient and liver along until he was better able to undergo treatment. There are comparable adult examples. We do suffer from really a somewhat disorganized management.

**Participant**

In your opinion, what is the appropriate time to seriously consider isolated intestinal transplantation? Is it when the liver enzymes bump? Is it when fibrosis sets in? Obviously, it was different 5 or 10 yr ago when small intestinal transplantation had lower success rates, the postoperative complications were horrible, and the life expectancy was terrible. That is not the case today, and you have demonstrated that with your statistics. From the standpoint of TPN-associated liver disease, what is the threshold for referral for consideration of isolated intestinal transplantation?

**Dr. Iyer**

I am going to deliberately be provocative. I think there is a small subset of patients for whom we might go as far as preemptive isolated intestinal transplant in 2006–2008. Most of the pediatric kidney transplants I do are preemptive kidney transplants before dialysis. I do not think the state-of-the-art intestinal transplantation is there yet, but we are not far. We are certainly not far if you have a patient who is, for example, a 23-yr-old with strong family support who has trauma and is left with 6 cm of jejunum. Should you wait for this patient to start to lose access or get liver disease before you would consider transplantation, or should you stabilize the patient, start him on TPN, and consider isolated intestinal transplant before complications set in? I am not completely certain the data are there, but it is not far. Beyond that, in 2006, TPN dependency has to be proven irreversible. The patient has to have no prospect of coming off TPN because if that is not met, the patient is not a transplant candidate. If you can prove, however, that the patient really has no possible means of coming of TPN, at the first hint of complications we should consider them for transplantation.

**Dr. Fryer**

I think those high-risk patients should be sent for intestinal rehabilitation, and every effort should be made for them to get off TPN. We have had good results using growth hormone and reducing TPN, and we have also seen benefits in improved liver function. The data are preliminary but promising. Patients should be referred early. If you cannot get them off of TPN and they are stable, watch them. If you cannot get them off TPN and they are declining and the liver seems to be the most important area that you have to watch, I would transplant them. I would do it early. We’re obviously not predicting
successfully, as 75% of them are coming when they need a liver and most of them die. We must transplant earlier but only when we have ruled out all other solutions.

Dr. Buchman
Just because patients are evaluated for transplant does not mean that they have to be transplanted. When we evaluate these patients, we learn a lot more about them in terms of their absorptive status and other factors. We do liver biopsies, for example. We find patients who may have normal liver tests but have some significant histologic abnormalities. Transplant is just a bridge from the management of TPN. It is not yet proven as a replacement for TPN, and I do not know if it ever will be. In the future, there are a number of groups in the United States and Europe who are looking at growing new intestine on various matrixes with different theories as to how best to do it. It is probably 15 or 20 yr out, but it is kind of exciting.