Candidacy for Intestinal Transplantation

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A recent report from the American Small Bowel Transplant Registry (2003) has highlighted the significant progressive increase in graft and host survival to over 80% at 1 yr, suggesting that a new era has dawned, and that soon transplantation may offer an attractive alternative to any patient with permanent intestinal failure. In order to investigate the potential candidacy for small bowel transplantation in Western Europe, 854 home long-term parenteral nutrition (TPN) patients and their physicians were surveyed in nine countries. Their results demonstrated that only a small proportion of patients were considered candidates, but that candidacy was higher in the pediatric population (34% vs 16%, respectively). Despite the general acceptance in the United States that the development of the complication of liver failure in home TPN patients is an indication for urgent transplantation, “immediate candidacy” was only made by physicians in 36% of such adults and 43% of such children. This study reveals that there remains reluctance in Europe to refer patients for transplantation, even when life-threatening complications have developed. Further investigations need to be performed to determine whether this was because of inaccessibility to a transplant center or unfamiliarity with the procedure and its outcomes.

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It is very difficult, nay impossible, to establish set indications for a procedure that is new and rapidly evolving. A good example of this is small bowel transplantation (SBTx). As with the first heart transplant by Christiaan Barnard in the 1960s (1), the procedure was, by definition, initially experimental, and the indication could only be to save life in patients who were about to die and had no further treatment options. With intestinal failure, there was, like renal failure, an alternative support measure, namely, long-term parenteral nutrition (TPN, or home TPN [HPN]). Consequently, SBTx only became life-saving after patients with intestinal failure developed “TPN-failure.” Although SBTx was attempted in the 1950s, it was only with the employment of powerful immunosuppressive agents in the early 1980s that long-term survival was achieved in France, Germany, and Canada and consideration could then be given to developing indications. However, as I will relate below, the success of the procedure continues to improve, and so too will the indications.

The first major boost for SBTx in the United States was the establishment of criteria for TPN failure by Medicare in 2000, which enabled insurance coverage for a larger number of candidates (2). Annual case volume rose by 50%, and 75% of transplant cases worldwide are now performed in the United States (3). TPN failure was defined by Medicare as any one of the following, impending (jaundice, LFTs ↑) or overt liver failure (cirrhosis, portal hypertension), thrombosis of central veins (at least two), frequent central-line sepsis (more than two per year, fungemia, shock, ARDS), and frequent severe dehydration. However, these criteria were developed against a background of survival that was significantly inferior to present day statistics. The 2003 report of the North American Small Bowel Transplant Registry “A New Era Has Dawned” was recently published by David Grant et al. (3). Sixty-one programs provided data on 989 grafts in 923 patients. They noted that 80% of all current survivors had stopped parenteral nutrition and resumed normal daily activities. The modified Karnofsky performance score showed that 80% of patients had high performances of between 90 and 100%. During the last 5 yr of analysis, they noted that survival was best in patients waiting at home, those of younger age, those given antibody induction immunosuppression, and those transplanted in centers with an experience of at least 10 cases per year. Figure 1 illustrates the Transplant Registry’s data on graft survival rates separated into three eras. There has been a steady, significant ($p = 0.001$) improvement in survival from 1991 to 1998. One-year graft survival rates were 81% in those induced with antithymocyte globulin and then maintained on tacrolimus, indicating that survival rates are now approaching those for liver transplantation. More recent outcome data from our own institution, which is the most active program worldwide with a total of 53 transplants for 2004, shows a 1-yr patient survival of 92% and a graft survival of 89% (4). These figures beg the question of whether the indications for SBTx should be broadened from “TPN-failure.”

Following TPN failure, the next indications to consider are those associated with prediction of TPN-failure or long-term survival. Prospective analyses of HPN patients have shown that ultra-short bowel of less than 20–30 cm is associated with high risk of liver failure and poor survival in children and adults. Similarly, infants with total intestinal
agangliosis or microvillus inclusion disease have low life expectancy (3). Transplantation in this situation has been termed “preemptive,” and is being increasingly applied in the major centers. With continued improvements in outcome and as the risks-benefits balance swings to the right, “soft” considerations, such as quality of life, can become realistic coindications. Despite the life-saving capacity of HPN, quality of life is poor because of lifelong dependency on daily 8–18 h IV infusions and frequent hospitalizations (5,6). With the emphasis on TPN failure as the indication for SBTx, quality of life issues have not been systematically followed after SBTx. Central-line problems are replaced by immunosuppression problems, but initial reports all point to a general improvement in quality of life (7–9). Finally, the Transplant Registry analysis not surprisingly observed that outcome was better in patients transplanted from home, as opposed to hospital. By extrapolation, this means that the better your health, the better the outcome from surgery, something that is true for any form of surgery. We can therefore predict preemptive transplantation will be increasingly used to improve overall outcomes.

Timely to this discussion, is the publication by Pironi and colleagues in this issue of the *American Journal of Gastroenterology* of the results of a questionnaire on patient candidacy, contraindications, and physician attitudes toward SBTx sent to 41 centers in nine European countries (10). Candidacy was defined along the lines developed by Medicare and Medicaid (2) and the American Society of Transplantation (11) with specific modifications. “Preemptive” indications, the high risk of death attributable to the underlying disease resulting from desmoid tumors associated with familial adenomatous polyposis (FAP), congenital mucosal disorders such as microvillus inclusion disease, and ultra-short bowel syndrome with residual small intestine <10 cm in infants and <20 cm in adults, were also included. Assessment of quality of life was loosely defined and based on factors such as frequent hospitalizations, narcotic dependency, or any other causes of high morbidity, together with the impairment of social function associated with pseudo-obstructive disorders and high stomal outputs. Also covered in the quality of life assessment was the patient’s unwillingness to accept long-term TPN. The final count was 854 HPN patients, consisting of 688 adults and 166 children, estimated to be about 70% of the HPN population. For statistical analysis the indications and contraindications were combined to form a scoring system ranging from the presence of a clear indication with no contraindication and a clinical judgment by the physician taking care of the patient as to the patient’s potential or immediate candidacy, ranging to no indication, a relative contraindication, and the impression that the patient was not a satisfactory candidate by the physician. The results demonstrated that candidacy was identified twice as frequently in pediatric patients (34%) as compared with adults (16%). The probable explanation for this was that the basis for candidacy was more commonly risk of death because of underlying disease than TPN failure in children (60%) compared with adults (26%). Poor quality of life was considered an indication for transplantation in only 12% of adults and children. Perhaps the most important observation was that only 15% of candidates were considered by their primary physician to need urgent transplantation for the management of their disease. Furthermore, only 36% of adults and 43% of children with liver failure were described as needing immediate transplantation.

The survey achieved its first goal in identifying the candidacy rate for SBTx based on TPN failure, preemptive considerations, and quality of life: approximately 0.5 persons per one million of the adult population and 1.5 per million of the pediatric population. Applied to the U.S. population, this would identify 109 adult and 113 pediatric candidates, which is higher than the present worldwide annual transplant rate of about 150. As the use of HPN and transplantation is higher in the United States than in Europe, one would expect the actual candidacy rate in the United States to be higher than these estimates. This calculation, together with the direct observation that only 15% of candidates are considered by their European physicians to need transplantation, shows there is a large gap between candidacy and SBTx—if the selection criteria employed in the present survey are valid. Examination of the data on Table 3 reveals that all of the primary indication criteria were weak (i.e., <50%) predictors of the physician’s decision to refer patients for immediate transplantation. The strongest indicator for transplantation in adults was the combined “multiple indication criteria” (38% of candidates), which presumably contained the sickest patients, and in children, it was TPN failure (44%). At the other extreme, frequent dehydration and poor quality of life were never considered reasons for transplantation.
The question then becomes, were the indication criteria used in the survey incorrect, or were the primary physicians reticent in referral for transplantation? Indications such as frequent dehydration and recurrent catheter sepsis are weak indicators as these problems can, and have, been managed by HPN physicians successfully for years. Quality of life (QOL) was not properly assessed in this survey, as it was based simply on morbidity, which was already covered by the other criteria. In any form of disease management, QOL is extremely important, but probably should not be used as an independent criterion for transplantation. On the other hand, the physician reservations for referral of patients with liver failure are difficult to support, given the lack of alternative treatments and the improving outcomes from transplantation. There is also concern that physicians are waiting too long to refer patients, as patients with multiple indication criteria were most frequently considered transplant candidates. A strong argument can also be made for recommending early transplantation for patients “at risk” of developing liver failure, such as those with ultra-short bowel or severe fatty liver, as a number of studies have demonstrated that nonfibrotic disease is reversed by isolated SBTx, thus obviating the need for a combined liver graft (12). Although there is evidence that the intestine graft survives longer if combined with a liver, overall survival may be less because patients will be sicker by the time the liver fails. Furthermore, graft failure is easier to manage in isolated intestine transplantation, as the patient can return to TPN while awaiting retransplantation, whereas liver-SBTx patients would need an immediate multivisceral transplant to survive.

The results of this survey show that there is discord between current guidelines for SBTx and physician practice in Europe. It is likely that the same is true in the United States. Consequently, there is an urgent need for regulatory authorities to set up expert committees to review the outcome-based evidence and establish more robust criteria for SBTx. Furthermore, it needs to be recognized that this is a dynamic situation where outcome is continually changing. Consequently, such criteria will need to be modified and updated at regular intervals.

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