Cost-effectiveness of Intestinal Transplantation Compared to Parenteral Nutrition in Adults

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Abbreviations

CIF: chronic intestinal failure

CRBSI: catheter-related bloodstream infections

HPN: home parenteral nutrition

ICU: intensive care unit

ITx: intestinal transplantation

KTx: kidney transplantation

MVTx: multivisceral transplantation

UD: underlying disease

Abstract

Background: Intestinal Transplantation (ITx) is the most expensive abdominal organ transplant. Detailed studies about exact costs and cost-effectiveness compared to home parenteral nutrition (HPN) therapy in chronic intestinal failure (CIF) are lacking. The aim is to provide an in-depth analysis of ITx costs and evaluate cost-effectiveness compared to HPN.

Methods: To calculate costs before and after ITx, costs were analyzed in 12 adult patients. To calculate costs of patients with uncomplicated CIF, 28 adult, stable HPN patients were studied. Total costs including surgery, admissions, diagnostics, HPN therapy, medication, and ambulatory care were included. Median (range) costs are given.

Results: Costs prior to ITx were €69 160 (60 682-90 891) in year 2, and €104 146 (83 854-186 412) in year 1. After ITx, costs were €172 133 (122 483 – 351 407) in the 1st year, €40 619 (3 905 – 113 154) in the 2nd year, and dropped to €15 743 (4 408 - 138 906) in the 3rd year. In stable HPN patients, the costs were €83 402 (35 364 - 169 146) in the 1st year, €70 945 (31 955 – 117 913) in the 2nd year, and stabilized to €60 242 (29 161-238 136) in the 3rd year.

Conclusion: ITx, although initially very expensive, is cost-effective compared to HPN in adults by year 4, and cost saving by year 5.

Introduction

Chronic intestinal failure (CIF) is defined as the long-term inability to absorb sufficient nutrients to sustain life and/or growth.¹ Causes include both structural and functional loss of intestinal surface.² The first-line treatment is home parenteral nutrition (HPN).¹ HPN improves quality of life and reduces costs compared to hospital treatment.^{3,4} It is important that these complex patients are managed by a dedicated multidisciplinary team.^{1,5} This approach has led to remarkable improvements in outcome, with centers reporting 80% 5-year survival in adult patients with benign indications.²

Nevertheless, CIF therapy is very expensive, costing between \$70 000 and \$300 000 per year.^{3,6–13} This is because patients require treatment for i) the underlying disease (UD); ii) HPN therapy (e.g. HPN and fluid/electrolytes bags, lines, pumps, home care, etc.); iii) HPN-related complications (venous access problems, metabolic complications, etc.)¹⁴; and iv) unrelated diseases.

Despite optimal treatment, some HPN patients develop life-threatening complications such as recurrent catheter-related bloodstream infections (CRBSI), extensive venous thrombosis compromising access or intestinal failure-associated liver disease. These patients with complicated intestinal failure have a poor prognosis and require a life-saving intestinal transplantation (ITx) after a careful multidisciplinary evaluation.^{15,16} Due to its complexity, ITx is the most expensive abdominal transplant procedure with costs varying between \$35 000 and \$85 000 in Europe^{11,17} and between \$130 000 and \$275 000^{10,18} in the US. However, many studies do not provide detailed information on cost distribution and evolution. Furthermore, most studies use estimates rather than direct billing information. Most importantly, the cost-effectiveness of ITx compared to HPN has not been investigated. Given the major financial burden that the treatment of CIF represents for healthcare systems, it is important to investigate

this topic. The aims of this study are i) to perform a detailed cost analysis of ITx and HPN and ii) to investigate the cost-effectiveness of ITx compared to HPN for the treatment of CIF.

Methods

To calculate the cost of stable CIF (including HPN), we studied long-term (>5 years), adult (>18 years), CIF patients treated at our center between January 1st, 2000 and December 31st, 2015. This group was subset (minimum 5 years follow-up) from a previously published study from our center.¹³ Costs were collected, including admissions, diagnostics, treatments, consults, home care, HPN and medication. The costs were assigned by cause (i.e. either HPN, UD or an unrelated disease). Cost registration was started from the first day of intestinal failure. Admission rate was defined as total admissions in a year divided by the total number of patients in that year (admissions/patient).

To calculate the cost prior to ITx, we investigated those patients in follow-up at our institution before undergoing ITx between January 1st 2000 and December 31st 2015. Costs in the 2 years prior to ITx were collected using hospital and home care billing records. The 2 years prior to ITx were defined as -2 (day 720 – 366 pre-ITx) and -1 (day 365 – day 1 pre-ITx).

To calculate the cost of ITx and follow-up, we studied all patients who underwent ITx from a deceased donor at our center (both patients already treated at our center as well as referred patients) between January 1st 2000 and December 31st 2015. All patients were followed at our center postoperatively. All costs were collected and tabulated according to cause. The cost of pre-ITx screening was recorded separately. In case of graft loss, patients continued to be analyzed as an ITx patient despite returning to HPN (intention-to-treat analysis). This include all subsequent HPN costs and medications required. In case of a patient dying, all costs up to the date of death were counted towards the total of that year. This was then multiplied by a factor (pro-rated) to compensate for the rest of the year where the costs would be 0. For instance, if the patient died after 3 months the annual costs would be estimated by multiplying by a factor

4. Year 1 was defined from the day of ITx until day 364 with subsequent years labeled Year 2 to Year 5.

To calculate the cost-effectiveness of ITx compared to HPN for stable CIF patients, we used the median annual cost in stable CIF patients after reaching a plateau as a reference. In order to do this, the first year in which costs stabilized was identified. The average was then taken of all annual costs up to year 5. This represented the reference annual cost in stable CIF patients. Each year after transplant was compared to this reference value to determine the extra cost of ITx and the potential 'break-even point' (i.e. the time point when the initial investment is recovered) after which ITx would be considered cost-effective.

In both groups, financial data were corrected for inflation to 2015 and rounded to the nearest Euro. This was achieved by multiplying all costs in a specific year by an indexation correction factor (i.e. Corrected value = uncorrected value x (national index value 2015 x national index value year X)). Home treatment costs were retrieved from the home-nursing companies. Medication costs were calculated using the national Belgian tariffs (www.bcfi.be) (last accessed on 29th of May 2019). All costs reported are the total societal costs. All data was recovered retrospectively from a prospectively maintained database of HPN and ITx patients.

Statistical analysis

All values are given as median with associated min-max range unless otherwise stated. For statistical analysis, *Paired* sample t-test was used for normally distributed, paired samples. Wilcoxon signed-rank test was used for paired, nonnormally distributed data and Mann-Whitney U test for unpaired, nonnormally distributed values. Differences between groups were considered significant at a two-sided *P* value of <0.05. Statistical analyses were performed with GraphPad Prism 8.0 (GraphPad Software, Inc., San Diego, CA).

Ethical approval was provided by the Leuven Institutional Review board (Reference number: S60961).

Results

Cost of stable CIF

Twenty-eight patients received more than 5 years of HPN at our center. The causes of CIF were short bowel syndrome (57%, n=16), intestinal dysmotility (24%, n=7), mechanical obstructions (14%, n=4) and mucosal disease (5%, n=1). Additional characteristics are summarized in Table 1.

First year (after onset of CIF): The total cost was €83 402 (35 364 - 169 146), 70% of which was spent on HPN (€58 651 (41 116-130 121), 22% on UD (€18 253 (357-88 334)) and 8% on unrelated diseases (€6498 (2420-43 517)) (Figure 1). Of the total HPN costs, 73% were direct costs (disposables, HPN bags, lines, home care etc.) at € 42 574 (27 240-111 463) while the remaining 27% was spent treating complications (all for CRBSI) (€16 073 (8124 - 57 683)). In all, 13 admissions were HPN related (25% of the total 52 admissions) (Figure 2). However, the majority of admissions were related to the UD (58%, n=30). The most frequent causes for UD admission were intestinal obstruction (27%), surgery (23%) or reevaluation of HPN therapy (20%). Finally, 17% (n=9) of admissions were for unrelated causes: infections (75%), respiratory failure (12.5%) and myocardial infarction (12.5%). This resulted in an additional €3428(1258-6429) in costs. The admission rate in this first year was 3.5/patient.

Second year: The total cost decreased significantly to €70 945 (31 955-117 913) ($P = 0.0047$). HPN accounted for 74% (€52 500 (2520-92 227)): direct HPN costs accounted for 75% (€39 875 (30 952-73 884)) while 25% was spent on complications (€13 181 (1569-18 343)). 18% of the total costs (€11 859 (570-77 118)) was caused by treating the UD.

Third year: The costs dropped further to €60 242 (29 161-238 136). Direct HPN costs accounted for 80% of total cost (€ 37 136 (28 759-41 275)), which also dropped significantly compared to year 1 ($P = 0.017$). In this period, weekly HPN volume declined significantly from 5.7 to 5.0

liters ($P = 0.022$). HPN complications were responsible for 20% of costs at €9339 (2652-58 804). From year 1 to 3, UD costs dropped by 49% to €9289 (514-131 248) ($P = 0.003$).

In total, a 28% reduction in costs was observed in year 3 compared to year 1 ($P = 0.006$). The average annual cost of CIF from year 3 to 5 was €60 369 (Figure 1). In all years, HPN accounted for the majority of costs of CIF treatment in adults.

Cost prior to ITx (-2Y and -1Y)

Six patients were in follow-up at our institution before undergoing ITx. The median age was 35 years (23-55). Four patients underwent isolated ITx, 1 had a combined Liver-ITx and 1 multivisceral transplantation (MVTx). Further details are listed in Table 2.

In year 2 before ITx (-2Y), the total cost per patient was €69 160 (60 682 – 90 891). In this period, there were 5 (3-45) admissions per patient (Admission rate= 8.8). This resulted in a total of 57 days (34-110) spent in hospital, with admissions lasting 10 days (1-87) (Figure 3A). Ambulatory costs amounted to a total of €44 954 (32 341-85 127) and were distributed as follows: HPN treatment {58% (€26 073 (21 256-68 732))}; outpatient treatment {14% (€ 6294 (1250-14 230))}; medication {18% (€ 8092 (4134-19 567))}; and home care {10% (€4495 (2176-13 789))}. HPN use during this period was 5 infusions per week (4-7) at 7 liters per week (5-12). Hospitalizations costs were €24 206 (21 765-98 147) and distributed as follows: treatment of UD {53% (€12 829 (8113 – 75 972))}; treatment of HPN complications {36% (€8714 (4295-67 815))}; and treatment of nonrelated diseases {11% (€ 2663(0-17 384))}. Most frequent causes for unrelated diseases admissions were infections at 55% ($n=21/38$ admissions), including pneumonia, urosepsis and cellulitis.

In year 1 before ITx (-1Y), the total cost per patient was € 104 146 (83 854-186 412). There were 7 (3-50) admissions per patient. This resulted in a total of 52 days (40-109) spent in hospital with stays lasting for 6 days (1-71). The admission rate was 13.7(Figure 3B). Treatment of HPN related complications accounted for 62% of the hospital costs (€40 034 (23 765-87 429)), 30%

for treatment of UD (€ 19 371 (7003-24 620); and 8% for the treatment of unrelated diseases € 5166 (0.00-10 385). HPN use was similar compared to year-2 prior to ITx at 5.5 infusions (4-7) and 8 liters per week (6-14). Of the ambulatory care budget, 63% (€24 808(11 171-49 119)) was spent on HPN, 6% on outpatient treatment (€2210 (823-12 177)), 10% on medication (€3867(1231-8912)) and 22% on home care (€8691 (3296-13 409)).

Cost of screening for ITx

The cost of pretransplant screening was €8148 (4563 – 10 266). Work-up included imaging, cardiac and pulmonary function testing, endoscopy and psychosocial assessment. Additional investigations specific to ITx such as vascular access mapping were also performed. After this, listing for transplant was agreed upon during a multidisciplinary meeting.

Cost of ITx: First hospitalization and year 1

There were 12 patients who underwent ITx at our institution with a median age of 44 years (23-57). Indications for listing were HPN related problems (n=9; liver failure, recurrent sepsis and loss of vascular access) or impending fatal progression of the UD (n= 3; recurrent bleeding and ultra-short bowel). Six patients underwent isolated ITx (50%), 3 had a combined Liver-ITx (25%) and 3 MVTx (25%). The 5-year all-cause survival was 83% with a follow-up of 4.1 years (0.3-13.5). Two patients (5 and 6) died in the first year due to invasive aspergillosis. All remaining patients were alive at time of last follow-up (Figure 4).

The cost of the first hospitalization: Total costs were €141 129 (80 302-385 224). The cost of surgery was €23 957 (12 360 – 33 436) which included the organ procurement. Patients spent 11 (2-50) days in the intensive care unit (ICU) which cost €25 392 (7578-112 257) at €2380 per day. After discharge from ICU, patients spent an additional 89 days (45-158) on the ward (€83 632 (30 332 – 229 265), on average €940 per day). Of the total costs, 60% was for hospitalization (€55 899 (13 087-223 308)); 17% for medication (€ 16 821 (5268-128 892));

20% for diagnostics (€16 241 (4308-87 123)); and 3% for medical consults (€2363 (732-24 531)). Patients spent a median of 98 days in hospital (56-208).

Remaining cost of year 1: After discharge from hospital, ambulatory care was gradually tapered¹⁹. Patients were readmitted 11 times resulting in 34 hospitalization days. The admission rate (including first admission for ITx) was 10.6 (Figure 3B). Cost of readmission was €23 065 (0-171 239). The majority of readmissions (79%) were short (<5 days) for reevaluations, surveillance endoscopies or other investigations. The remaining 21% of readmissions were longer than 5 days (see Table 3). During these longer readmissions, patients spent 16 (5-130) days in hospital. An additional €6857 (0.00-18 493) was spent on ambulatory care (clinics, endoscopy and imaging). Home medication cost €5495 (1962- 10 433) in the first year.

The total cost in year 1 was €172 133 (122 483-351 407) (Figure 5). The cost of the first year in case of a liver-including graft (n= 6) was €172 133 (122 483-351 407) which was similar to an isolated ITx (n= 6) at 169 233 (126 101-314 936). However, the length of stay after liver-including ITx was significantly longer at 143 days (112-208) compared to isolated ITx (81 days (56-204); $P = 0.056$). The total cost of treatment for the 2 patients that died was €314 936 and €307 079 respectively (patient 5 and 6). This was higher than the median cost although this was not statistically significant ($P = 0.36$). Four patients received an additional kidney transplantation (KTx) due to additional kidney failure (Table 2). The total costs were not significantly different at €174 344 (126 101-351 407) compared to ITx without KTx (€172 133 (122 483-314 936)).

Cost of ITx: year 2 until year 5

In the 2nd year, the cost dropped to €40 619(3905 – 113 154) (Figure 5) ($P < 0.0001$). Patients were admitted a total of 26 days (0-71). The admission rate dropped significantly to 4.3 (0-5 admissions per patient) compared to year 1 ($P = 0.0017$). Most admissions (61%, n=20) were shorter than 5 days and were for surveillance endoscopies, investigations or for minor

complications. Six patients required longer (>5 days) hospitalization, which accounted for 39% of readmissions (n=13). These readmissions lasted 12 days (5-34).

Subsequent years (3 to 5). By the 3rd year, costs declined to €15 743 (4408 - 138 906) ($P < 0.0001$ compared to Y1) and €14 112 (3152 – 67 337) in the 4th year. The costs further declined in the 5th year at €8832 (3270-38 723 (Figure 5). In year 3, patients were spending a median of 14 (0-120) days in hospital and this dropped to 9.5 (0-50) in year 4 and to 8 days (0-37) in year 5 (Figure 1). The number of readmissions also declined from 3 (0-13) in year 3, to 1 (0-6) by year 5. No patients died in this period.

Cost comparison between stable CIF and ITx

In CIF patients, the costs stabilized by the 3rd year at €60 242 (29 161- 238 136) (Figure 1). This was reflected in the low hospitalization rate of 0.61 per patient per year (Figure 2). On the other hand, ITx patients cost significantly more in the first year (€172 133) (122 483-351 407) ($P < 0.0001$) (Figure 6). The difference between the median annual stable CIF costs (year 3-5) and the first year after ITx was €111 764, i.e. the ‘initial investment’. By year 2, ITx patients cost €44 893 which was significantly lower than stable CIF ($P = 0.0052$). In the following years, the cost of ITx in adults continued to drop until reaching €8832(3270-38 723) in year 5 (Figure 6A). In ITx, 84% (57-92%) of total 5-year costs were spent in the first 2 years after ITx (Y1 + Y2). By contrast, CIF stabilized to €60 369 (58 186- 62 679) due to continued need for parenteral nutrition. As costs continued to decline in the years after ITx, the ‘investment’ was recovered by year 4 (cost-effective) and became cost saving compared to HPN by year 5 (Figure 6B).

Discussion

This in-depth analysis examined the costs before and after ITx and the cost-effectiveness of ITx compared to HPN in patients with stable CIF.

Costs prior to ITx

Unsurprisingly, the costs before ITx of these complicated patients are high, exceeding €130 000 per year. This was double compared to stable CIF.¹³ This is due to 3 factors. First, HPN therapy was higher in both volume and frequency, most likely due to lower remaining enteral absorptive capacity. Indeed, the most frequent cause of complicated CIF was short bowel syndrome.^{1,16} Second, higher frequency of HPN leads to more catheter manipulations which increases the access complications.²⁰ Finally, UD costs were also higher, as these patients have more complex underlying pathologies. For example, these patients have higher incidences of hepatic failure and ICU admissions compared to stable CIF patients.^{21,22}

Costs of ITx

In the US, ITx has been officially approved for reimbursement since 2001, although financing is still suboptimal.^{23,24} In Belgium, a fixed reimbursement is provided with more funds given for liver including grafts.

In our study, the cost of the first admission for ITx was €147 437. By comparison, a liver transplantation at our center costs about a third (€47 498). Two previous European studies reported lower costs.^{11,18} One study estimated the costs at €72 332 for the first posttransplant year. However, these data were extrapolated based on liver transplant figures rather than on direct ITx cost.¹⁷ Another study, estimated the costs of surgery and 30 days admission at around \$35 000-45 000, depending on the type of graft.¹¹ However, no details were provided on how these costs were calculated. Furthermore, this study is from 2003 which makes direct comparison difficult due to inflation and rising healthcare costs.

Comparing US and European data is challenging due to marked differences in financing.²⁵ US studies reported total first-year costs varying from \$132 285 to 275 000.^{6,18,26} However, these have also not been corrected for inflation and rising healthcare costs.²⁷ In fact, the most recent

US data indicate that an isolated ITx costs around \$1.1 million, much higher than a kidney (\$414 800), pancreas (\$347 000) or liver transplantation (\$812 500).²⁸

There are several reasons for the high costs of ITx. Many patients are malnourished before surgery which increases morbidity.²⁹ Also, surgery is challenging due to adhesions and complex anatomy from previous operations, which leads to more frequent complications.³⁰ Furthermore, the incidence of rejection and infection is higher after ITx.^{31,32} As a result, patients receive more immunosuppression and antimicrobial prophylaxis. Owing to the lack of noninvasive markers for rejection, endoscopic surveillance biopsies are performed in most centers.¹⁵ Even after discharge, patients are frequently readmitted to treat complications.³³

An extensive cost variation was noted in our cohort. This was also seen in other centers where median costs were \$275 000 but with outliers up to \$1.8 million.¹⁸ This is probably due to several factors. First, the type of grafts influences the costs. Recovery after isolated ITx is usually shorter compared to liver-including grafts. The latter are more complex and are usually performed in sicker patients, and therefore prone to more complications.³⁴ In contrast to other reports, in our cohort, the costs of liver-including ITx were similar to isolated ITx.^{6,11,26}

However, despite the high costs of ITx, they were concentrated in the first 2 years. During the first year, the majority of patients had unscheduled readmissions (Table 3). Similarly, another study found that 91% of patients were readmitted in the first year.³³ However, after this initial period, costs dropped sharply. This is due to cessation of HPN and improvement health status requiring far less admissions. This was also reported by Andersen et al.³⁵ The only remaining costs were for medication and ambulatory follow-up care.

There is high incidence of kidney failure in CIF and ITx patients and in the latter is an independent risk factor for poor outcome.³⁶ Therefore, we have a low threshold to add a kidney graft in case of significant – not yet terminal – pretransplant kidney dysfunction. In our

data adding a kidney to an ITx graft added a negligible additional cost while probably avoiding costly dialysis in some ITx patients.

Cost-effectiveness of ITx

Although ITx costs were high in the first year, these rapidly dropped thereafter. From year 2 onwards, ITx became cheaper compared to conservative management on the waiting list. In other words, rapid ITx is not only lifesaving but also cost saving.

Compared to HPN therapy in stable CIF, we found that ITx was cost-effective in adults by year 4 after recovering the higher initial cost. By year 5, ITx became cost saving compared to HPN. This is despite comparing ITx patients, who by definition have complicated CIF, to a highly selected group of stable CIF patients with an excellent 5-year survival (93% in this study *versus* 80% in literature¹). The cost-effectiveness issue of ITx *versus* HPN is comparable to KTx *versus* dialysis for end-stage renal disease. Studies show that it takes between 2.5 to 4 years for KTx to become cost saving.³⁷ Preemptive KTx leads to lower costs and better results compared to after start of dialysis.³⁸ Likewise, it is likely that early referral for ITx will increase cost-effectiveness, in addition to improving outcomes.¹⁶

There are a few limitations to acknowledge. This was a retrospective study and we cannot exclude missing data. We could not access the billing information of all patients prior to ITx as they were not yet treated at our center. However, healthcare costs in Belgium are fixed nationally and thus no differences exists across the country. Cost-effectiveness in pediatric ITx could not be calculated due to insufficient numbers.

Studying all patients with complicated CIF was beyond the scope of this study. We only included patients who eventually underwent ITx. However, some patients will never be listed and some will die on the waiting list or be delisted for some reason. In our center, there were no patients listed for ITx who died on the waiting list or had to be delisted, most likely to early multidisciplinary discussion on complicated CIF patients, which has been shown to

significantly reduce mortality in patients with complicated CIF.¹ This would further increase the potential cost-effectiveness of ITx as those waiting on the list remain alive and continue to use large amount of resources.

Another limitation is that healthcare reimbursement varies between countries which makes direct cost comparison difficult. However, although the absolute values vary, the evolution and distribution of costs will likely be similar. Additional indirect costs such as loss of productivity by patients or their family were beyond the scope of this study, but are an important factor to be considered.³⁹ Due to an absence of a validated quality of life measurement tool for CIF patients, no cost per quality of life adjusted life years – QALY – could be measured.⁴⁰ However, in a simulation study this was calculated to be €31 787.¹⁷ Finally, since GLP-2 analogues like teduglutide are not available in Belgium, the situation is likely to be different – but even more in favor of ITx. Indeed, the cost (~€250 000 per year) far exceeds the cost of ITx and it needs to be given indefinitely.⁴¹ HPN is currently the first line treatment in CIF because on average, survival is higher compared to ITx.^{1,16} However, ITx results in experienced centers are now approaching those of long-term HPN.^{19,42} If survival rates are similar in both therapies, cost-effectiveness, in addition to improved quality of life.^{40,42} would represent an additional incentive to carefully broaden the indication of ITx to stable CIF.

In conclusion, this study shows that ITx, although initially expensive, becomes cost-effective by year 4 and cost saving by year 5 compared to HPN in adults. These findings should be considered when revising intestinal transplant criteria.

References:

1. Pironi L, Arends J, Bozzetti F, et al. ESPEN guidelines on chronic intestinal failure in adults. *Clin Nutr*. 2016;35(2):247-307.
2. Pironi L, Goulet O, Buchman A, et al. Outcome on home parenteral nutrition for benign intestinal failure: A review of the literature and benchmarking with the European prospective survey of ESPEN. *Clin Nutr*. 2012;31(6):831-845.
3. Marshall JK, Gadowsky SL, Childs A, et al. Economic analysis of home vs hospital-based parenteral nutrition in Ontario, Canada. *JPEN J Parenter Enteral Nutr*. 2011;29(4):266-269.
4. Baxter JP, Fayers PM, McKinlay AW. A review of the quality of life of adult patients treated with long-term parenteral nutrition. *Clin Nutr*. 2006;25(4):543-553.
5. Baxter JP, McKee RF. Organization of managed clinical networking for home parenteral nutrition. *Curr Opin Clin Nutr Metab Care*. 2006;9(3):270-275.
6. Sudan D. Cost and quality of life after intestinal transplantation. *Gastroenterology*. 2006;130(2 suppl 1):158-162.
7. Curtas S, Hariri R, Steiger E. Case management in home total parenteral nutrition: A cost-identification analysis. *J Parenter Enter Nutr*. 1996;20(2):113-119.
8. Howard L, Ament M, Richard Fleming C, et al. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. *Gastroenterology*. 1995;109(2):355-365.
9. Reddy P, Malone M. Home Parenteral and Enteral Nutrition. *J Parenter Enter Nutr*. 1998;22(5):302-310.
10. Evans RW. Financial, Economic and Insurance Issues Pertaining to Intestinal Transplantation: When is too much not enough? In: *Intestinal Failure*. Blackwell Publishing Ltd.; 2009:363-377.

11. Schalamon J, Mayr JM, Höllwarth ME. Mortality and economics in short bowel syndrome. *Bailliere's Best Pract Res Clin Gastroenterol*. 2003;17(6):931-942.
12. Cade A, Puntis J. Economics of home parenteral nutrition. *Pharmacoeconomics*. 1997;12(3):327-338.
13. Canovai E, Ceulemans LJ, Peers G, et al. Cost analysis of chronic intestinal failure. *Clin Nutr*. 2018;38(4):1729-1736.
14. Howard L, Ashley C. Management of complications in patients receiving home parenteral nutrition. *Gastroenterology*. 2003;124(6):1651-1661.
15. Fishbein TM. Intestinal Transplantation. *N Engl J Med*. 2009;361(10):998-1008.
16. Grant D, Abu-Elmagd K, Mazariegos G, et al. Intestinal Transplant Registry Report : Global Activity and Trends. *Am J Transplant*. 2015;(15):210-219.
17. Roskott AM, Groen H, Rings EHHM, et al. Cost-effectiveness of intestinal transplantation for adult patients with intestinal failure : a simulation study. *Am J Clin Nutr*. 2015;101(1):79-86.
18. Langnas A, Chinnakotla S, Sudan D, et al. Intestinal transplantation at the University of Nebraska Medical Center: 1990 to 2001. *Transplant Proc*. 2002;34(3):958-960.
19. Ceulemans LJ, Braza F, Monbaliu D, et al. The Leuven Immunomodulatory Protocol Promotes T-Regulatory Cells and Substantially Prolongs Survival After First Intestinal Transplantation. *Am J Transplant*. 2016;16(10):2973-2985.
20. Bozzetti F, Mariani L, Bertinet DB, et al. Central venous catheter complications in 447 patients on home parenteral nutrition: an analysis of over 100.000 catheter days. *Clin Nutr*. 2002;21(6):475-485.
21. Burghardt KM, Wales PW, De Silva N, et al. Pediatric intestinal transplant listing criteria - A call for a change in the new era of intestinal failure outcomes. *Am J Transplant*. 2015;15(6):1674-1681.

22. Pironi L, Forbes A, Joly F, et al. Survival of Patients Identified as Candidates for Intestinal Transplantation: A 3-Year Prospective Follow-Up. *Gastroenterology*. 2008;135(1):61-71.
23. Evans RW. Financial, Economic and Insurance Issues Pertaining to Intestinal Transplantation: When is too much not enough? In: *Intestinal Failure*. Blackwell Publishing Ltd.; :363-377.
24. Sudan D. The Current State of Intestine Transplantation: Indications, Techniques, Outcomes and Challenges. *Am J Transplant*. 2014;14(9):1976-1984.
25. Papanicolaos I, Woskie LR, Jha AK. Health Care Spending in the United States and Other High-Income Countries. *JAMA*. 2018;319(10):1024.
26. Abu-Elmagd KM, Reyes J, Fung JJ, et al. Evolution of clinical intestinal transplantation: Improved outcome and cost effectiveness. *Transplant Proc*. 1999;31(1-2):582-584.
27. Moses H, Matheson DHM, Dorsey ER, et al. The Anatomy of Health Care in the United States. *JAMA*. 2013;310(18):1947-1963.
28. Bentley TS, Hanson SG. 2017 U.S. organ and tissue transplant cost estimates and discussion. *Milliman Res Rep*. 2017:1-16.
29. Matarese LE. Nutrition interventions before and after adult intestinal transplantation: The pittsburgh experience. *Pract Gastroenterol*. 2010;34(11):11-26.
30. Grant WJ. Surgical Complications of Intestinal Transplantation. In: Alan N. Langnas, Olivier Goulet, Eamonn Quigley, Kelly A. Tappenden, eds. *Intestinal Failure*. Oxford, UK: Blackwell Publishing Ltd.; 2009:290-296.
31. Berger M, Zeevi A, Farmer DG, et al. Immunologic challenges in small bowel transplantation. *Am J Transplant*. 2012;12(suppl 4):S2-S8.

32. Silva JT, San-Juan R, Fernández-Caamaño B, et al. Infectious Complications Following Small Bowel Transplantation. *Am J Transplant*. 2016;16(3):951-959.
33. Kwon YK, Etesami K, Sharp AL, et al. Hospital Readmissions After Intestinal and Multivisceral Transplantation. *Transplant Proc*. 2016;48(6):2186-2191.
34. Middleton SJ, Pither C, Gao R, et al. Adult small intestinal and multivisceral transplantation: Lessons through the “retrospecto-scope” at a single UK centre from 1991 to 2013. *Transplant Proc*. 2014;46(6):2114-2118.
35. Andersen DA, Horslen S. An analysis of the long-term complications of intestine transplant recipients. *Prog Transplant*. 2004;14(4):277-282.
36. Huard G, Iyer K, Moon J, et al. The high incidence of severe chronic kidney disease after intestinal transplantation and its impact on patient and graft survival. *Clin Transplant*. 2017;31(5).
37. Evans RW, Kitzmann DJ. An economic analysis of kidney transplantation. *Surg Clin North Am*. 1998;78(1):149-174.
38. Axelrod DA, Schnitzler MA, Xiao H, et al. An economic assessment of contemporary kidney transplant practice. *Am J Transplant*. 2018;18(5):1168-1176.
39. Winkler MF, Smith CE. Clinical, Social, and Economic Impacts of Home Parenteral Nutrition Dependence in Short Bowel Syndrome. *J Parenter Enter Nutr*. 2014;38(1 suppl):32S-37S.
40. Ceulemans LJ, Lomme C, Pirenne J, et al Systematic literature review on self-reported quality of life in adult intestinal transplantation. *Transplant Rev*. 2016;30(2):109-118.
41. Vanuytsel T. Disease modifying therapy in short bowel syndrome: finally coming of age? *Lancet Gastroenterol Hepatol*. 2019;4(5):328-329.
42. Abu-Elmagd K. The concept of gut rehabilitation and the future of visceral transplantation. *Nat Rev Gastroenterol Hepatol*. 2015;12(2):108-120.

Figure Legends

Figure 1. Median HPN costs per patient per year. HPN, home parenteral nutrition.

Figure 2. Admission rate and causes among HPN patients. HPN, home parenteral nutrition.

Figure 3. 5-year all cause survival after ITx. ITx, intestinal transplantation.

Figure 4. Median admission days and admission rates before and after ITx. ITx, intestinal transplantation.

Figure 5. Total annual cost before and after ITx. ITx, intestinal transplantation.

Figure 6. Cost of ITx vs HPN in adults. HPN, home parenteral nutrition; ITx, intestinal transplantation

Table Legends

Table 1. Stable HPN patient characteristics.

	Value (Range)
Mean Age	59 years (34-85)
Gender distribution	18 Female (69%), 10 Male
Median duration of HPN (years)	6.8 (5.1-15.1)
Number of infusions per week	4.0 (1.5-7)
Mean Total kcals per week	5875 (2385-10890)
Mean Glucose kcals per week	3363 (1365-7320)
Mean Lipid kcals per week	1641 (400-3600)
Type of access	Tunnelled catheter: 24 (86%) TIVAD: 4 (14%)

HPN, home parenteral nutrition; TIVAD, totally implantable venous access device

Table 2. ITx patient characteristics.

Patient	Gender (M/F)	Age (at time of ITx)	Cause IF	Indication ITx	Graft type	Pre-ITx cost data available
1	F	56	Ischemia	Liver Failure + Recurrent sepsis	cLi-ITx	Yes
2	F	57	Ischemia	Liver Failure + Recurrent sepsis	cLi-ITx	No
3	F	26	CIPO	Recurrent sepsis + Liver fibrosis	ITx	Yes
4	F	41	Volvulus + EH	Loss of vascular access	ITx + KTx	Yes
5	M	43	ST (APS)	Recurrent Bleeding	MVTx	No
6	F	40	Ischemia	Recurrent sepsis	ITx	No
7	F	36	Volvulus	Liver Failure + Recurrent sepsis	cLi-ITx	No
8	F	57	CD + KF	Recurrent dehydration + Kidney failure	ITx + KTx	No
9	M	29	CD	Liver Failure + Recurrent sepsis	ITx	Yes
10	M	23	Splanchnic Thrombosis (NET)	Recurrent Bleeding	MVTx	Yes
11	M	47	ST (Cirrhosis)	Liver Failure + Recurrent sepsis	MVTx + KTx	No
12	M	55	Ischemia	Ultra-short bowel	ITx + KTx	Yes

ITx, Isolated Intestinal Transplantation; cLi-ITx, combined Liver-Intestinal Transplant; MVTx, multivisceral transplantation; KTx, kidney transplantation; CIPO, Chronic intestinal pseudo-obstruction; NET, Neuroendocrine tumor; CD, Cohn's Disease; ST, Splanchnic thrombosis; ALP, antiphospholipid syndrome; EH, Enteric hyperoxaluria

Table 3. Cause for readmission in the first year after ITx.

Patient identification	Cause of admission	Days admitted	Timing (in days) after initial discharge
1	Closure ostomy	12	112
3	High-output ileostomy	10	65
6	ACR Grade III + invasive aspergillosis	130	54
7	Toxic tacrolimus levels	9	24
8	Obstructive urolithiasis in transplanted kidney	8	202
	Urosepsis	29	261
9	Closure ostomy	12	93
10	Mechanical Obstruction	21	72
	Gastro-enteritis	16	172
	Gastro-enteritis	7	264
11	Mycotic aneurysm	20	33
	Acute kidney failure	18	82
	Acute kidney failure	5	105
	ACR Grade I	33	148
12	Acute kidney failure	18	35
	Fluid/electrolyte disorder	6	58
	Closure ostomy	11	224

ACR, acute cellular rejection; EBV, Epstein-Barr Virus

Figure 1: Median HPN costs per patient per year

Figure 2 : Admission rate and causes among HPN patients

Figure 3: Days admitted and admission rate before and after ITx

Figure 4 : All cause survival after ITx

Figure 5: Total annual cost before and after ITx in adults

Figure 6 : Cost of ITx vs HPN in adults