Intestinal rehabilitation for children with intestinal failure is cost-effective: a simulation study

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Henk Groen*
Esther Neelis*
Marten Poley
Joanne Olieman
René Scheenstra
Paul Krabbe
Gerard Dijkstra
Edmond Rings
* Both authors contributed equally to this work

ABSTRACT

Background

Children with intestinal failure (IF) depend on parenteral nutrition (PN). The goal in the treatment of IF is to wean children off PN through intestinal rehabilitation (IR). Although the healthcare burden of IF is enormous, to our knowledge there has been no previous cost-effectiveness analysis in pediatric IF including IR.

Objective

We sought to determine the cost-effectiveness of IR in terms of costs and life-years.

Design

We simulated the treatment of IF in children in a discrete-event model. Data for this model were derived from patient records, the Dutch Registry of Intestinal Failure and Transplantation, the Intestinal Transplant Registry, and the literature. The time horizon of the model was 40 y. Simulated patients were enrolled at a rate of 40 patients/mo for 10 y. Actual costs were calculated for hospital admissions, surgical interventions, endoscopies, PN, and immunosuppressive medication. We evaluated the cost-effectiveness of IR by comparing 1 scenario with IR with 1 scenario without IR. In the scenario with IR, a proportion of patients who represented those with the ability to wean off PN were assigned to IR. In the scenario without IR, all patients progressed to home PN (HPN). In both scenarios, a proportion of patients receiving HPN were eventually eligible for an intestinal transplantation.

Results

IR prolonged survival; the mean number of life-years per patient was 19.4 in the scenario with IR compared with 18.2 in the scenario without IR. Average total costs per patient were €819,292 in the scenario with IR compared with €1,176,830 in the scenario without IR (equivalent to 1,129,230 US$ and 1,622,025 US$, respectively, in January 2014); costs mainly included hospital admissions and PN.

Conclusion

On the basis of our simulations, we concluded that IR improved the survival of children with IF and was associated with cost savings. Therefore, we consider IR to be a cost-effective treatment for children with IF.

INTRODUCTION

Intestinal failure (IF) in children is defined as a critical reduction of the gut mass or its function below the minimum level necessary for the absorption of nutrients that are required to grow and develop.[1] The most common cause of IF in children is short bowel syndrome (SBS). IF can be reversible but this depends on factors such as the underlying disease and length of the remaining small bowel. Chronic or irreversible IF is rare with a reported prevalence of 9.56/1 million Dutch children.[2] To maintain adequate growth and nutritional status during IF, parenteral nutrition (PN) is necessary. In the case of chronic or irreversible IF, PN can be provided at home (home PN, HPN). However, PN can be complicated by serious and possibly life-threatening complications, including liver disease and catheter-related sepsis.[3] Therefore, intestinal rehabilitation (IR) is the accepted treatment strategy with the aim of weaning patients off of PN. IR consists of a systematic approach to stimulate the adaptation of the small bowel and includes the optimization of parenteral, enteral, and oral feeding, while maintaining growth, preventing eating disorders and complications, and maintaining a good quality of life (QoL).[4] For patients with life-threatening complications that are due to PN, an option is intestinal transplantation (ITx).[5] However, ITx is not the initial therapeutic choice because survival rates after ITx are lower than those achieved on PN.[6-8]

The care of patients with IF is complex and requires prolonged hospital admissions, multiple surgical procedures, frequent outpatient visits, and specialized nutritional support. Therefore, from a socioeconomic perspective, the healthcare burden of IF is enormous. Estimated annual HPN costs have differed widely, ranging between 75,000 and 290,000 US$/patient in 2006.[9] IR is also expensive and might not always be successful. A Dutch study reported an average total cost of €269,700 (including follow-up) in 2010 for infants with SBS, which mainly compromised the costs of hospital admissions.[10] In 2008, Spencer et al.[11] reported average total costs of care for children with SBS during the first 5 y of >1.6 million US$. Studies that investigated the costs of ITx in the United States (in 2006 and 2011) have reported that, on average, an isolated small-bowel transplantation costs 135,000 US$.[9,12] These high costs may be partly explained by late referrals to expert centers and a limited implementation of successful practices such as the use of taurolidine locks to prevent catheter-related sepsis.

Thus, pediatric IF is a major clinical problem in terms of morbidity, and it is associated with high costs. Still, little is known about the cost-effectiveness of IF treatment. A British cost-effectiveness analysis of ITx in children revealed conflicting results, and therefore, no firm conclusions could be drawn.[13] A recent Dutch cost-effectiveness study of ITx in adults showed that ITx improved the life-years of adults with irreversible IF for relatively low costs.[14] To our knowledge, there has been no previous comprehensive cost-

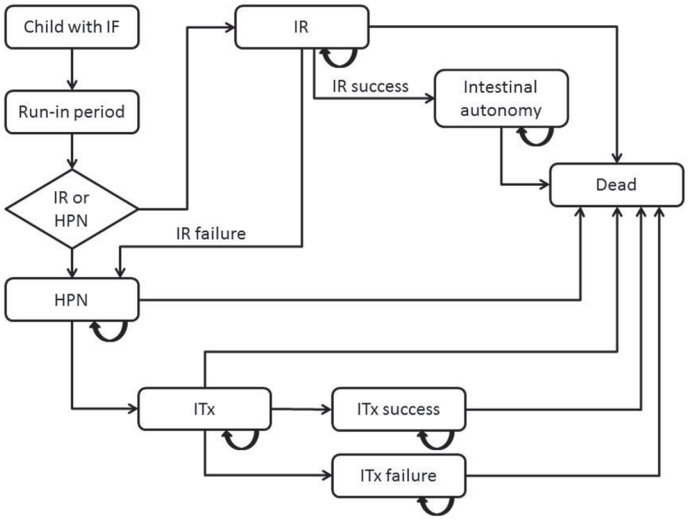
effectiveness analysis in pediatric IF including rehabilitation. On the basis of the results of IR, especially in terms of intestinal autonomy[4,15], it may be instinctively assumed that IR is a cost-effective treatment option. However, this assumption needs to be substantiated by evidence if IR wants to make a legitimate claim on scarce healthcare resources. Therefore, the purpose of this study was to estimate the cost-effectiveness of IR.

METHODS

Discrete event model

We simulated the treatment of IF in children in a discrete-event simulation model. Within such a model, patients move through the model experiencing events at any discrete time period after the previous event. Models such as these may be used to extrapolate costs and outcomes beyond the follow-up of clinical trials.[16,17] As shown by the graphical illustration of our model (**Figure 1**), the clinical course of patients was represented as a series of consecutive steps or states. On the basis of a similar model of ITx in adults[14], the clinical states included in the model were HPN, intestinal autonomy (successful IR), graft failure, and sustained graft function, whereas death was the final outcome. We modeled 2 scenarios; 1 scenario included the possibility of IR, and 1 scenario was modeled without IR. In the scenario with IR, a proportion of patients who represented those with the ability to wean off PN were assigned to IR, which could be successful (progression to intestinal autonomy) or unsuccessful. Patients who could not be weaned off PN progressed to HPN. In addition, all patients who did not have the ability to wean off PN from the start because of irreversible IF (e.g., because of an enteropathy) were assigned to the HPN

Figure 1. States (boxes) and transitions (arrows) in the simulation model consisting of IR, HPN, and ITx



Legend: The model started with a run-n period; all patients received a few days of PN before they were assigned to HPN or IR. In the scenario with IR, a patient with the ability to wean off PN was assigned to IR. IR could have been successful and lead to intestinal autonomy or unsuccessful (IR failure). In the latter case, patients progressed to HPN. In addition, patients who did not have the ability to wean off PN from the start because of irreversible IF were assigned to the HPN state. When ITx was indicated, patients were moved to receive an ITx. The ITx could have been successful or unsuccessful (ITx failure). Curved arrows indicate that patients could have remained in a certain state for multiple units of time.

Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; IR, intestinal rehabilitation; ITx, intestinal transplantation.

state. In both scenarios, a proportion of patients receiving HPN were eventually eligible for ITx. Patients were included immediately from the onset of IF while in the hospital. All children were dependent on PN for at least a few months.

Treatment choices were modeled by fixed probabilities or by comparing multiple time-dependent probabilities. The amount of time that simulated patients remained in each treatment state (transition time) was determined with the use of probabilistic Weibull functions, on the basis of the available data. The value for the duration in each treatment state for each individual patient was randomly drawn from the distribution of the associated Weibull function. In case of multiple possible outcomes, transition times were determined independently for each outcome, and the outcome associated with the shortest time was chosen. The time horizon of the model was 40 y. Half-cycle adjustment was applied to all counts that were generated by the model. To produce stable outcomes, the model was replicated 500 times. In each replication, all outcomes were calculated for the entire cohort of included patients. The model was constructed with the use of AnyLogic modeling software (version 7; AnyLogic Co.).

Model variables

Data for our model were obtained from patient records, the Dutch Registry of Intestinal Failure and Transplantation, the Intestinal Transplant Registry, expert opinions, and the literature (**Table 1**). In the Netherlands, the University Medical Center Groningen is the national center for ITx. HPN for children is provided by 3 specialized teams who are located in the Children's Hospitals of Amsterdam Medical Center, Erasmus Medical Center, and Radboud University Medical Center. IR is provided by these centers and the University Medical Center Groningen.

The number of new children with IF in the Netherlands was estimated at 15-20 individuals/y. However, we performed the simulations with an enrollment of 40 patients/mo as comparable with a multi-country population. This method was used to provide more stable outcomes, but it did not affect cost-effectiveness results because the results are presented as the difference between the different treatment options. Patients were enrolled over a period of 10 y, which implied that, overall, 4,800 patients were enrolled.

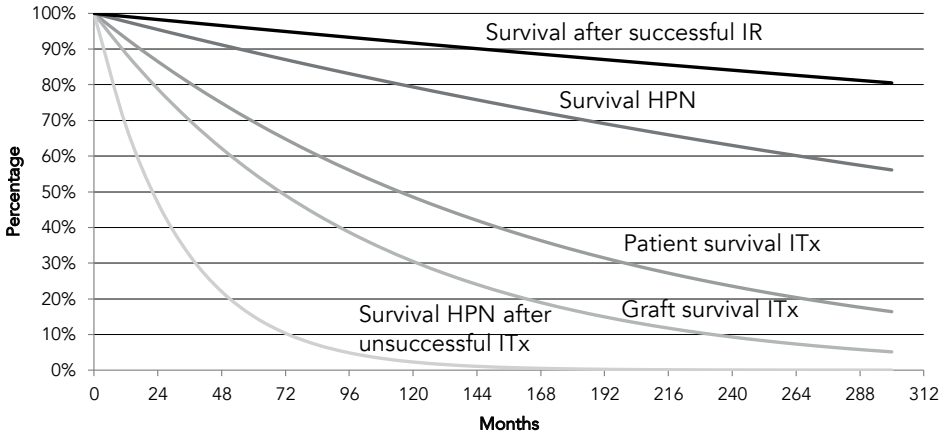
For our model, we assumed that 60-70% of the children had SBS, 10-20% had motility disorders, and 10-20% of the children had an enteropathy in agreement with previous reports from the literature.[7,18] Selections for IR and ITx were determined by fixed percentages of patients suitable for IR (67%) or ITx (10%). Children were eligible for ITx if their expected remaining survival time while receiving HPN was 12 mo. Survival while receiving HPN was based on data from the literature[6] and our own data. Graft and patient survivals after ITx were based on Intestinal Transplant Registry data. Survival data

Table 1. Model variables and parameters for IF in children[1]

Variable	Value	Source
Annual inflow of IF patients, *n*	480	NA
Proportion indication for IR, %	67	DRIFT
		Dutch HPN centers
		[7,18,19]
Duration of IR, d	279 (12-503)	HPN centers
Mortality during IR, %	2.6 – 11	HPN centers
		[20]
Proportion successful IR, %	80	HPN centers
		[20]
		[21]
Proportion indication for ITx, %	10	DRIFT
		Expert opinion

Abbreviations: [1] DRIFT, Dutch Registry of Intestinal Failure and Intestinal Transplantation; HPN, home parenteral nutrition; IF, intestinal failure; IR, intestinal rehabilitation; ITx, intestinal transplantation; NA, not applicable.

Figure 2. Survival curves applied in the simulation model for patient survival after successful IR (survival after successful IR), patient survival with HPN, patient survival after ITx, graft survival after ITx, and survival with receipt of HPN after an unsuccessful ITx (graft failure)



Abbreviations: HPN, home parenteral nutrition; IR, intestinal rehabilitation; ITx, intestinal transplantation.

were extrapolated to 40 y (**Figure 2**). The probability of dying while waiting for ITx was considered negligible.

Costs

We set out to calculate the treatment costs of patients who received IR and of patients who were receiving HPN but were not offered IR (**Table 2**). To this aim, we used data of

Table 2. Costs of pediatric IF treatment[1]

Treatment	Average cost
IR, €	
First year, total	265,132
Hospital admissions	206,759
Interventions	10,304
Diagnostics	1787
Outpatient visits	766
HPN administration	51,028
Dieticians' consults	980
Subsequent annual costs, total	30,262
Autonomy, €	
First year, total	8085
Subsequent annual costs, total	658
HPN, €	
First year, total	233,715
Hospital admissions	171,444
Interventions	5971
Diagnostics	1580
Outpatient visits	908
HPN administration	46,371
Dieticians' consults	1295
Subsequent annual costs, total	45,890
ITx, €	
First year, total	217,593
Transplant surgery	11,852
Other interventions	19,904
Blood products	621
Hospital admissions	167,718
Interventions/Diagnostics	855
PN	6742
Outpatient visits	3848
Medication	7592
Subsequent annual costs, total	42,443

Legend: [1]All data were derived from the HPN centers, with the exception of the costs of ITx, which were based on data from the ITx center.
Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; IR, intestinal rehabilitation; ITx, intestinal transplantation; PN, parenteral nutrition.

31 children who received IR (29 children with SBS and 2 children with an enteropathy, all of whom were able to wean off PN) and of 10 children who were receiving HPN (all of whom were suffering from motility disorders or enteropathies and were not able to wean off PN) and were attending the IF outpatient clinic at the Erasmus MC - Sophia Children's hospital between August 2003 and January 2014 (median PN duration: 583 d).

Children who received IR in our center frequently visited the outpatient clinic (every 2-12 wk depending on the age and condition of the patient). Their nutritional intakes and growths were evaluated, and laboratory values were monitored. Radiology and surgery (including intestinal-lengthening procedures) were performed when necessary. The nutrition (both PN and enteral nutrition) was adjusted, and medication (such as antibiotics or cholestyramine) was given when indicated. Children who were receiving HPN but were not eligible for IR also visited our outpatient clinic regularly (every 4-12 wk depending on the age and condition of the patient). Their growth and laboratory values were monitored, and PN was adjusted when necessary. Both children who were receiving IR and children who were receiving HPN were seen by the multidisciplinary team, which consisted of pediatric surgeons, pediatric gastroenterologist, dietitians, specialized nurses, and pharmacists.

For both groups, we retrospectively obtained data from the onset of IF regarding hospital days (either intensive care unit, high-care unit, general ward or daycare), surgical interventions (including intestinal-lengthening procedures in the IR group), diagnostic radiology, outpatient visits to the multidisciplinary IF team, dietary consultations (either inpatient or outpatient), and PN. Costs of intestinal autonomy (i.e., costs in the period after weaning off PN after successful IR) were calculated separately on the basis of the same variables. Data regarding ITx, including hospitalization, ITx procedure with blood products, other surgical interventions, radiology, visits to the ITx team, dietary consultations, PN, and immunosuppressive medication, were obtained for 5 children (with enteropathy (n=3), SBS (n=1), and motility disorder (n=1)) who underwent ITx in the Netherlands.

After this data collection, costs were calculated by multiplying the volumes of healthcare use with the corresponding cost prices. According to guidelines for costing studies in healthcare[22], we calculated integral cost prices for the variables. Because tariffs are not accurate measures of costs, we set out to calculate real economic costs. Costs of hospital days, surgical interventions, visits to the IF team, and dietary consultations were largely based on cost prices of the hospital. All costs compromised both personnel costs (including costs of medical specialists) and nonpersonnel costs (including materials, equipment, and overhead costs such as housing, utilities, cleaning, management). Personnel costs were based on the Collective Agreement for University Medical Centers. Cost prices of diagnostic radiology were based on national tariffs determined by the Dutch Healthcare Authority, which included both an amount to cover the hospital costs and an amount to

cover the services of the medical specialist. Costs of PN were calculated with the use of mean intakes that were obtained from the hospital records every 3 mo. The cost price of PN was based on the delivery rates in 2014 in our hospital and also included personnel costs, disposables, equipment, overhead, and transportation to the patient. Costs of immunosuppressive medication were calculated with the use of the pharmacists' purchase prices.

All costs were reported in euros (€) and were calculated for the year 2014 (with a few exceptions, which referred to the year 2012, because more recent cost prices were not available at the time). Costs were divided into the first year after start of IF and follow-up y. With consideration of the fact that the last year often did not constitute a full year, we adjusted for this variance and used corrected costs in the simulation model.

Cost-effectiveness

During the execution of the model, detailed information was collected about the time spent in the various treatment states. To estimate life-years for the scenarios with and without IR, we added up the number of patients in the different states (IR, intestinal autonomy, HPN, and ITx) per year. We evaluated the cost-effectiveness of IR by comparing life-years and costs of 500 replications of the model with and without IR as a treatment option. To calculate the incremental cost-effectiveness ratio (ICER), which was defined as the difference in costs divided by the difference in life-years, we combined life-years and number of patients with costs for the scenario with IR and for the scenario without IR. The ICER expresses the costs for the gain of a life-years. Costs and effects (i.e., life-years) that were to occur in the future were discounted to their current values.[23] This calculation was done to reflect the fact that individuals prefer current benefits over those in the future and prefer future costs over current costs. We discounted future costs by 4.0% and effects by 1.5% according to the Dutch guidelines for costing studies in healthcare.

Sensitivity analysis

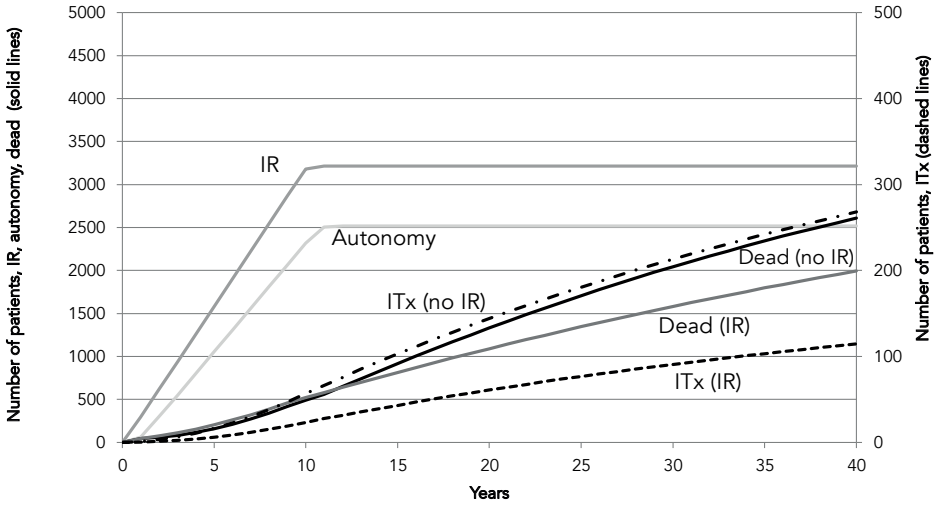
In addition to the base case scenario, we performed sensitivity analyses with a variable percentage of successful IR (60% rather than 80%), a variable percentage of indication for ITx (20% rather than 10%), the expected survival of patients who were receiving HPN to be eligible for ITx (18 mo rather than 12 mo), and variations of cost estimates (costs of IR and autonomy increased by 25%, and costs of HPN and ITx decreased by 25%).

RESULTS

Effectiveness

The number of patients who were treated with IR and, therefore, also the number of patients who achieved intestinal autonomy, increased during the 10 y in which patients were enrolled (**Figure 3**). These numbers were stable shortly after the end of the enrollment period because of the short median time of IR (279 d). The number of patients who were receiving PN were the same in the scenario with IR and the scenario without IR because all patients received a few days PN before they were assigned to either HPN or IR treatment. The number of patients who were receiving HPN declined steadily after the enrollment period because of ITx or death (**Figure 4**). At the end of the simulation period of 40 y, there were 933 patients left in the HPN group (19% of enrolled patients) in the scenario with IR and 2161 patients left (45% of enrolled patients) in the scenario without IR (Figure 4). In the scenario with IR, 1860 patients achieved intestinal autonomy (58% of the number of patients who were undergoing IR) (Figure 3). A total of 115 patients underwent ITx in the scenario with IR compared with 268 patients in the scenario without IR (Figure 3). The mean number of deceased patients was 1995 individuals (42% of the total enrolled) in the scenario with IR and 2610 individuals (54% of the total enrolled) in

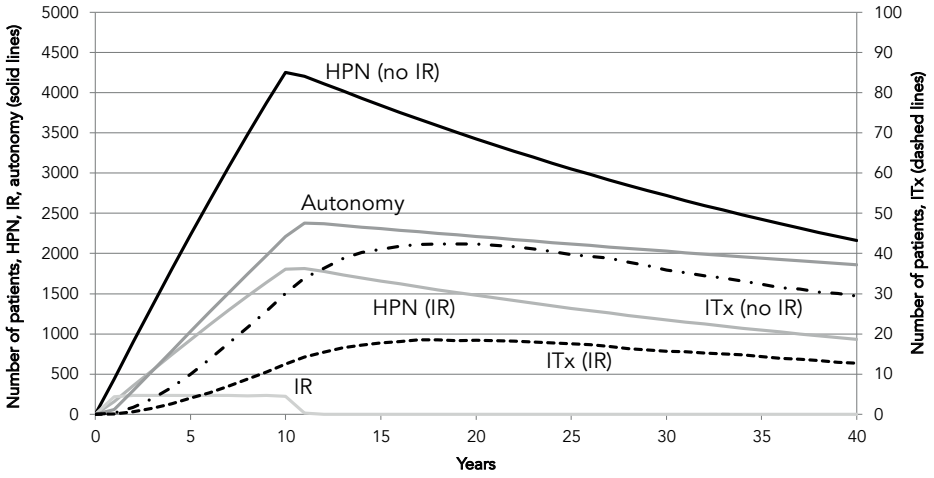
Figure 3. Cumulative number of patients over time in various states in the simulation model



Legend: HPN and IR are plotted on the left y-axis. ITx is plotted on the right y-axis. The 2 uppermost gray lines represent the cumulative numbers of patients undergoing IR and the cumulative numbers of patients who achieved intestinal autonomy, respectively. Dashed lines represent the cumulative number of patients who were undergoing ITx in the scenario without IR (dashed-dotted line) and in the scenario with IR (dashed line), both of which are plotted on the right y axis. The black line represents the cumulative number of deceased patients when the scenario without IR was applied. The lowest grey line represents the cumulative number of deceased patients in the scenario with IR.

Abbreviations: HPN, home parenteral nutrition; IR, intestinal rehabilitation; ITx, intestinal transplantation.

Figure 4. Distribution of patients over time in various states in the simulation model



Legend: HPN and IR are plotted on the left y-axis. ITx is plotted on the right y-axis.
Abbreviations: HPN, home parenteral nutrition; IR, intestinal rehabilitation; ITx, intestinal transplantation.

the scenario without IR (Figure 3). In addition, the mean number of life-years per patient was 19.4 in the scenario with IR and 18.2 in the scenario without IR (discounted).

Costs

The total first-year cost of IR was €265,132, whereas the cost in subsequent years was estimated at €30,262/y (**Table 2**). Costs mainly compromised hospital admissions (80% for the first year and 57% for subsequent years) and PN administration (19% for the first year and 39% for subsequent years). When patients achieved intestinal autonomy, costs were €8,085 in the first year and, on average, €658/y in the subsequent years. The cost of HPN was €233,715 in the first year, which mainly arose from hospital admissions and PN administration. Costs of hospital admissions were higher for patients who were receiving IR than for patients in the HPN group. The cost of ITx in the first year was €217,593, which was also mainly composed of hospital admissions. Average total costs (discounted) per patient were €819,292 in the scenario with IR compared with €1,176,830 without IR.

Cost-effectiveness

Compared with the scenario without IR, the scenario with IR resulted in an overall increase of 9690 life-years (**Table 3**, undiscounted). The mean number of life-years per patient was 19.4 in the scenario with IR compared with 18.2 in the scenario without IR. The scenario with IR resulted in total cost savings of greater than €4 billion. This amount resulted in cost savings of €435,000 for each additional life-year gained by IR. When we applied discounting, the ICER per life-year gained was €280,600.

Table 3. Effects and costs of treatment of children with IF with and without IR[1]

Outcome	With IR (IR + HPN + ITx)	Without IR (HPN + ITx)	Difference IR vs. no IR
Patients, n			
IR	3215	0	
HPN	4800	4800	
ITx	115	268	
Life-years (undiscounted)			
IR with subsequent autonomy	76,319	0	
HPN	49,478	115,406	
ITx	534	1235	
Total	126,331	116,641	9690
Mean life-years per patient, years (undiscounted)	26.32	24.30	2.02
Costs (undiscounted), €			
IR with subsequent autonomy	1,145,631,157	0	
HPN	5,278,540,318	10,584,334,490	
ITx	78,847,425	148,774,459	
Total	6,517,939,258	10,733,108,949	4,215,169,691
Average total costs per patient (undiscounted), €	1,357,904	2,236,064	878,160
Life-years (discounted at 1.5%)			
IR with subsequent autonomy	55,994	0	
HPN	36,946	86,319	
ITx	382	887	
Total	93,322	87,206	6116
Mean life-years per patient, years (discounted at 1.5%)	19.44	18.17	1.27
Costs (discounted at 4%), €			
IR with subsequent autonomy	906,814,494	0	
HPN	2,938,481,774	5,579,390,683	
ITx	42,306,644	69,394,567	
Total	3,932,602,912	5,648,785,250	1,716,182,338
Average total costs per patient (discounted at 4%), €	819,292	1,176,830	357,538

Legend: [1]Mean patient numbers and life-years and average total costs of all patients are shown.
Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; IR, intestinal rehabilitation; ITx, intestinal transplantation.

Sensitivity analysis

Because the percentage of success of IR can differ in centers and countries, an analysis with a percentage of success of 60% was also performed. As expected, total life-years were lower and total costs were higher, than with a percentage of success of 80% (**Table 4**). This analysis resulted in estimated costs savings of €499,752 for each additional life-year gained by IR. When discounting was applied, this amount decreased to €308,073.

Table 4. Sensitivity analysis of the percentage of success of IR, indication for ITx, and expected survival of patients who were receiving HPN to be eligible for ITx[1]

Outcome	With IR (IR + HPN + ITx) Successful IR = 60%	With IR (IR + HPN + ITx) Indication ITx = 20%, expected survival on HPN 18 mo	With IR (IR + HPN + ITx) Indication ITx = 10%, expected survival on HPN 18 m
Undiscounted			
Life-years	122,357	126,985	126,295
Costs, €	7,876,761,479	6,621,022,818	6,516,486,576
Difference vs. no IR			
Life-years	5716	8775	9768
Costs, €	-2,856,347,470	-4,289,133,613	-4,208,000,731
Discounted			
Life-years	90,676	93,803	93,306
Costs, €	4,579,636,971	3,981,877,095	3,933,994,328
Difference vs. no IR			
Life-years	3470	5443	6162
Costs, €	-1,069,148,279	- 1,754,249,084	-1,714,533,344

Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; IR, intestinal rehabilitation; ITx, intestinal transplantation.

When we selected a higher percentage of patients for ITx (20% instead of 10%), the total amount of life-years slightly increased, and the total costs slightly decreased. The result was that the costs per life-year gained (both undiscounted and discounted) basically remained unchanged. When we increased the expected survival of patients who were receiving HPN to be eligible for ITx to 18 mo, the results were comparable with the basic situation of our model.

Variations in costs of IR, autonomy, HPN, and ITx had a modest effect on the cost-effectiveness. With consideration of a worst-case scenario of increased costs of IR and autonomy by 25% and decreased costs of HPN and ITx by 50%, IR was still cost-effective with estimated costs savings of €148,603/life-year gained (discounted).

DISCUSSION

This study yielded insight into the costs of pediatric IF and the cost-effectiveness of IR. The study revealed that the annual costs of pediatric IF are very high ranging from €234,000 to €265,000 for the first year and €46,000 to €30,000 for subsequent years. According to our simulations, IR prolonged the average patient survival by 1.2 y over a 40-y period. The cost savings that were achieved per life-year were estimated at €280,600. Because our simulation showed that IR improves patient survival while saving costs, we consider IR to be a cost-effective treatment of children with IF. These results are relevant to both the medical community and health authorities, who, in different roles, have a joint responsibility for the efficient spending of scarce resources, which has become a top priority in today's healthcare systems.

To our knowledge, this is the first study to have evaluated the cost-effectiveness of IR. In general, studies on costs of pediatric IF have been scarce. However, there have been a few studies on the costs of pediatric SBS, which is the main cause of IF in children. A previous study from our center reported that the average total cost for children with SBS was €269,700.[10] The cost, which included costs that were related to first admission and follow-up, was for follow-up that varied between 9 mo and 5.5 y (median: 1.5 y). This average total cost is comparable with our current results as was the distribution of these costs (see Table 2). In our study, the bulk of costs were related to hospital admissions, especially the first admission which included the start of IF. Children with IF are frequently admitted to the hospital and often for a prolonged period. In addition, PN for children is mostly customized and, therefore, more expensive than PN for adults. Costs of hospital admissions were higher for patients receiving IR than for patients in the HPN group, especially in the first year. This difference might be explained by the fact that children who were receiving IR were mostly patients with SBS who often needed several operations. These factors may have consequently led to longer hospitalizations and higher costs. More recently, Longworth et al.[13] showed that the average costs of stable SBS patients (N=24) was £159,000/patient over 30 mo based on 1998 and 1999 prices, which was equivalent to ~ €190,000 in 2014. The lower costs in their study might be explained by the fact that the median PN duration before inclusion was 9 mo, and these data before inclusion in the study were not included in the calculation of the costs. A study in the United States[11] reported an average total cost of 1.6 million US$ over a 5-y period for children with SBS. However, this calculation was based on billable charges and not on actual costs, which made a comparison with our study difficult.

In addition to the studies that have evaluated the costs of pediatric SBS, some studies have been performed on the costs of ITx. Abu-Elmagd et al.[12] reported an average cost of 132,285 US$ for an isolated intestinal transplant. Another study reported an average

cost of an isolated intestine of 135,000 US$.[9] However, these costs were based on the US situation and on an average of adults and children and did not provide details as to the allocation of costs. A British study in children reported average treatment costs of transplanted children of £275,000 (equivalent to ~ €329,000 in 2014) over 30 mo[13], which is quite comparable to our results.

To make our study generalizable to other countries, we precisely described the variables and costs that we used for our model. The changing of these variables to figures that are relevant to another country can give an impression of the outcomes for other countries. However, it still remains difficult to compare costs between different countries because of differences in prices and differences in how the care for children with IF is organized and charged.

When looking at the cost-effectiveness, IR improved the average patient survival by 1.2 y over a 40-y follow-up period. This increase in patient survival may seem marginal and might be due to the fact that IR is not successful for all children who are eligible for IR. Some children will not gain extra life-years, whereas other children will gain > 1.2 life-years. Survival in this study was based on the literature[6] and was extrapolated to 40 y. As a result, we may have underestimated the survival of children with IF because recent publications have shown survival rates of 84%[24] and 90%[7] after 15 and 14 y, respectively. The survival data from these publications were based on both children who were receiving HPN and were not able to wean off PN and children who were undergoing IR. When these data would be applied to our model, survival would improve in both HPN and IR groups, and thus, we expect that the cost-effectiveness of IR will not change. In addition, it is not certain whether these survival rates will apply for 40 y.

The number of children who were undergoing ITx may have influenced the costs of ITx and, therefore, also the outcomes of our model. At the same time, indication rates may differ in countries. On the basis of the strict application of indications in the Netherlands, we assumed that 10% of the children met the indications for ITx. When we evaluated the cost-effectiveness of IR with the assumption of an ITx-indication rate of 20%, the costs per life-year gained remained basically unchanged. Another factor that may have an influence on the number of children who are undergoing ITx is the estimated prognosis for HPN that is necessary to be eligible for ITx. In our model, we used an expected survival of patients who were receiving HPN of 12 mo before patients could have undergone ITx. The increase of the expected survival of patients who were receiving HPN from 12 to 18 mo did not change the outcomes. Lastly, we performed a worst-case scenario analysis with increased costs of IR and autonomy, and decreased costs of HPN and ITx. Despite these changes, IR was still cost-effective. These findings suggest that IR is not only cost-effective in the Netherlands but may also be cost-effective in other countries or

settings where higher numbers of patients for an ITx are common and where costs may be different.

There are 4 points to consider when interpreting the results of our model. First, costs of IR and HPN were based on only 41 children, and costs of ITx were based on 5 children after ITx. Although small, we believe that our patient population of 41 children reflects the whole spectrum of children with IF in the Netherlands. Because ITx has been performed in only 5 children in the Netherlands, it was not possible to calculate costs for more children after ITx. In addition, the costs in subsequent years, which covered the 40-y time horizon of the model, had to be estimated on the basis of a relatively short follow-up period. Second, we calculated only direct and indirect costs inside the healthcare sector. We did not include indirect costs outside the healthcare sector, such as inability of parents to work, because this aspect fell outside the scope of the current study. We also excluded costs of laboratory tests, intercollegial consultations, and medications (other than immunosuppressive medication); however, these costs made up only a minor proportion of the total costs. Further, we did not calculate costs of the enteral nutrition because these costs were also a minor proportion of the total costs, and it is likely that these costs do not differ much in the different treatment options. Third, our model did not include outcome measures such as QoL , growth, and the number of complications. The inclusion of QoL, would have made it possible to calculate quality-adjusted life-years, which are a more generic outcome measure used in cost-utility analysis, but the evidence on QoL in children with IF has been both scarce and ambiguous. Growth was not included in the model because the aim of optimal growth (i.e., maintaining growth within a target height range) was the same for all groups (IR, HPN, and ITx). Complications were only indirectly included in the model when they led to costs (e.g., because of hospital admission or surger) or death. Fourth, although information that was used for the model was obtained from the literature or from actual data in our own population, some assumptions were necessary. Therefore, we performed sensitivity analyses to test the robustness of the results to certain assumptions that were made, and we were transparent about the decisions that were made regarding the methods of the study.

In conclusion, our model shows that IR improves the survival of children with IF and is associated with cost savings. Therefore, we consider IR a cost-effective treatment of children with IF. In the future, this model could also be used to evaluate the cost-effectiveness of ITx in children with IF.

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