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ORIGINAL ARTICLE

Waitlist characteristics of patients at a single-center intestinal and multivisceral transplant program

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Summary

Intestinal transplantation (ITX) can be a successful treatment for patients with irreversible intestinal failure and associated severe complications. Because of long waiting periods and organ shortages, the precise identification of eligible patients and their early referral to centers that perform ITX is important. We retrospectively analyzed all patients who were referred to our center between 2000 and 2011 concerning their referral criteria, waitlist characteristics, and outcome. A total of 87 patients (47 male patients, 40 female patients; median age 39.8 ± 13.4 years) were referred to our center. All patients presented with intestinal failure caused by short bowel syndrome or motility disorders. About 80.5% of patients were evaluated for isolated ITX, modified multivisceral (mMVTX), or multivisceral transplantation (MVTX). About 56.3% were listed at EUROTRANSPLANT, 33.3% suffered from severe secondary organ failure requiring MVTX, and 34.5% were transplanted. 14.3% (all MVTX-candidates) died on the waitlist as a result of infectious complications. The high proportion of MVTX candidates underlines the need for early referral to specialized centers. MVTX-candidates have a high waitlist mortality for different reasons. However, the current allocation policy for MVTX does not mirror the severity of disease and may therefore contribute to high waitlist mortality.

Introduction

Intestinal transplantation (ITX) is the only causal therapy for patients with irreversible intestinal failure (IF) who fail total parenteral nutrition (TPN) [1]. Although the general acceptance of ITX has taken much longer than for other solid organ transplantations [2], the increasing short- and long-term survival rates (78–85% and 56–61%) [3] have caused ITX to become the standard of care for patients with IF [4] rather than just an experimental procedure. ITX is considered for patients who develop TPN-associated complications, such as major central venous catheter (CVC) complications or cholestatic liver dysfunction, and are therefore placed at a significantly increased risk of death on TPN [5,6]. In this context, ITX has become a life-saving procedure for patients with TPN failure. However, recent data suggest that the indications for ITX be expanded to include its use as a pre-emptive and rehabilitative procedure [7], which would avoid the development of TPN failure and help recover patient autonomy [1,8].

Defining the optimal timing for ITX remains difficult, especially because patients under TPN tend to deteriorate quickly and many eligible patients will have developed end-stage liver disease by the time of referral and require

combined liver and intestine (ILTX) or multivisceral transplantation (MVTX). Impending liver dysfunction is one of the main criteria defining TPN failure and warranting waitlisting for ITX. Subsequently, early referral to a specialized center is essential for a timely evaluation for transplantation, but does not necessarily result in an increased number of patients undergoing ITX [9]; the implementation of various diagnostic examinations allows for a clear identification of patients who would benefit from ITX/MVTX or who appear to be unsuitable for transplantation, but may benefit from other surgical strategies for intestinal adaptation. This latter group of patients may require TPN weaning. In addition, a nutritional care team may help to improve and individualize the TPN composition and thereby reduce the accumulated risk of TPN-related complications. However, given the selective donor criteria and a general organ shortage, graft availability represents a major problem [10]. Data from the United Network for Organ Sharing (UNOS) indicate that waitlist mortality for ITX, and especially MVTX, exceeds that of other organ transplant-candidates [11] as a result of the onset of liver disease, the need for combined organs, and chronic hospitalization [12,13].

Nevertheless, for early transplantation to be considered as an alternative to TPN, the mortality rate, quality of life, and annual rejection rates below 35% [14] should be evaluated. Many treatment centers manage only a few cases of IF, which makes the overall understanding of TPN-associated complications and standardization of treatment, such as catheter care and TPN composition, even more difficult.

The objectives of this retrospective study were as follows: (i) to identify characteristics and referral criteria contributing to the high waitlist mortality rate; (ii) to analyze key steps for the identification of this patient subpopulation; and (iii) to offer solutions to improve the outcomes of these patients with respect to waiting time, concomitant morbidity, and the allocation scoring system.

Subjects and methods

The intestinal and multivisceral transplant program at the Charité in Berlin was established in 2000. Between this time and August 2011, 87 patients (47 male patient, 40 female patient) with a median age of 39.8 ± 13.4 years were referred to our center (Fig. 1). All these patients presented with IF caused by short bowel syndrome (SBS) or motility disorders. The data were collected prospectively and obtained for this study by a retrospective review of medical records, and the following clinical variables were assessed: gender, age, underlying disease, number/type of previous operations, length of remaining intestine, remaining colon/ileocecal valve, time on TPN, reasons for evaluation, indication for listing at EUROTRANSPLANT (ET), time on waitlist, number of organ offers.

All patients were assessed by a multidisciplinary team consisting of members of the departments of surgery, hepatology, gastroenterology, radiology, anesthesiology, and psychology. Patients were considered suitable for transplantation if a diagnosis of irreversible IF was established and if life-threatening complications under TPN were evident and unresolvable. In addition, transplantation was expected to produce a survival benefit. Indications and contraindications to ITX are listed in Table 1.

All patients with irreversible SBS and significantly impaired venous access, recurrent line infections, and mar-

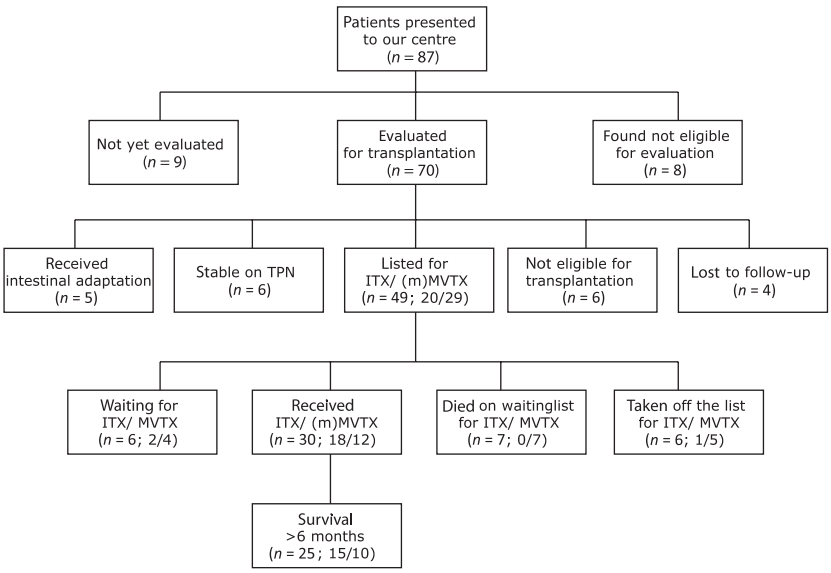

Figure 1 Summary of all patients, who were referred to our center to be evaluated for a potential intestinal transplantation.

Table 1. List of indications and contraindications for ITX and MVTX, that were adopted in this study.

	Indication	Contraindication
General	TPN-failure	Uncomplicated long-term TPN
	Persisting weight loss	*De novo* carcinoma
	Frequent episodes of severe dehydration, despite i.v. fluid substitution additional to HPN	Severe cardiopulmonary comorbidities
	Combined organ failure	Inoperability
		Severe multiorgan failure
Intestine/ underlying disease	Intra-abdominal invasive desmoid tumors	Rapid aggravation of underlying disease
	CIPO	Ability for intestinal adaptation
	USBS (<50 cm)	
	Frozen abdomen	
Central vein catheters	>2 CVC-infections/year	Complete loss of venous access
	Thrombosis in >2 central veins	
	Severe or recurrent sepsis episodes due to CVC-infections	
	Hypercoagulation	
HPN-associated liver dysfunction	Total bilirubin >3 mg/dl	Severe liver dysfunction
	Hepatic bridging fibrosis	
	Hepatic cirrhosis	
	Portal hypertension	
Quality of life	Recurrent hospitalization	Nonadherence
	Chronic pain syndrome	Patient's unwillingness for TX
	Inability for long-term HPN	

TPN, total parenteral nutrition; CVC, central vein catheter; CIPO, chronic intestinal pseudoobstruction; USBS, ultrashort bowel syndrome; TX, transplantation.

ginal signs of cholestatic liver disease were primarily listed for isolated ITX. Patients with motility disorders involving the stomach received a modified multivisceral graft (mMVTX: stomach, duodenum, pancreas, and small intestine), otherwise an isolated intestine. Patients with irreversible SBS and a frozen abdomen and patients with histological signs of bridging liver fibrosis (stage F2/F3) or cirrhosis (F4) required an ILTX or MVTX. Steatosis was not considered an indication for inclusion of a liver graft. In the case of stage F2, further histological features, including mononuclear inflammatory infiltrate in the portal areas, disarray of lobules with significant inflammation, ballooning of hepatocytes and apoptotic bodies, and macrovesicular steatosis, were considered as additional factors determining the indication for inclusion of the liver graft. The stage of fibrosis was assessed semiquantitatively according to the Scheuer classification [15] (F0: no fibrosis; F1: portal fibrosis without septa; F2: portal fibrosis and few septa; F3: fibrosis with architectural distortion, but no obvious cirrhosis; F4: liver cirrhosis) to determine the grade of fibrosis and to set up the indication for combined transplantation and MVTX.

Table 2. Indications for listing patients for either isolated intestinal, modified multivisceral, or complete multivisceral transplantation.

Indication for waitlisting for TX	ITX (20)	(m)MVTX (29)	*P*-value (Fisher's exact test) ITX vs. (m)MVTX
TPN-associated cholestatic liver dysfunction	7	29	<0.0001
CVC-infections	20	29	n.s.
Renal insufficiency	0	13	0.0003
Pancreatitis	0	13	0.0003

TX, transplantation, ITX, intestinal transplantation; mMVTX, modified multivisceral transplantation; MVTX, multivisceral transplantation; TPN, total parenteral nutrition; CVC, central vein catheter.

Statistical analysis

Means, standard deviations, and frequencies were used as descriptive statistics. For the comparison of differences between two groups, the unpaired Student's *t*-test, or the nonparametric Mann–Whitney test were calculated. For the comparison of clinical parameters, contingency tables were used and statistical differences calculated using Fisher's exact test or chi-squared test, respectively. A two-tailed *P*-value <0.05 is considered as statistically significant. Because of small patient numbers, most of the data presented are not significant and can only depict tendencies.

Results

A total of 87 patients were referred to our center between June 2000 and August 2011 to be assessed for ITX or (modified) MVTX (Fig. 1). Of these patients, 70 were evaluated for transplantation, and eight were found to be ineligible because of a profound underlying disease or cardial comorbidity ($n = 4$), nonadherence ($n = 1$), or inoperability ($n = 3$). Nine patients were in a stable condition without TPN and were not evaluated for transplantation. After evaluation, 49 patients were listed at ET, 29 of whom required either typical or modified MVTX. Patients with recurrent CVC-infections (>2 catheter infections/year), CVC-associated sepsis or endocarditis, or impaired venous access with marginal signs of cholestatic liver disease were listed for either isolated ITX or mMVTX. In contrast, patients who suffered from advanced TPN-associated hepatopathy or additional secondary organ failure, such as renal insufficiency or pancreatitis, were listed for MVTX (Table 2).

Six patients were stable on TPN after evaluation and were not listed. Their state of health was improved by modification in the TPN composition, which reduced the risk of cholestatic liver disease. Furthermore, they received antimotility agents to slow the gastrointestinal passage time. Two patients received a percutaneous endoscopic gastrostomy to reduce reflux and vomiting and improved their quality of life (Fig. 1).

During evaluation, we identified five patients who were suitable for intestinal adaptation and were no longer dependent on TPN. Six patients were found not to be suitable for transplantation at the end of the evaluation process caused by the advanced state of disease and imminent multiorgan failure (MOF; Fig. 1).

Thirty patients were transplanted by the end of the observation period. Six patients were removed from the list as a result of aggravation of the underlying disease ($n = 3$), *de novo* carcinoma ($n = 1$), or nonadherence ($n = 2$); therefore, six patients were on the waitlist at the end of the study period (ITX $n = 2$; MVTX $n = 4$).

In total, seven patients died on the waitlist, all had been listed for MVTX caused by bridging liver fibrosis ($n = 4$), frozen abdomen ($n = 2$), or infiltrating desmoid tumor ($n = 1$). The cause of death was severe sepsis with MOF in all cases. The underlying infections leading to MOF were pneumonia ($n = 3$), endocarditis following CVC-infection with subsequent myocardial infarction ($n = 3$) and enterococcus-sepsis after CVC-infection ($n = 1$). The resulting waitlist mortality rate for MVTX-candidates was 24.1%, compared with 0% for ITX- and mMVTX-candidates. The total waitlist mortality rate amounted to 14.3%.

To evaluate the causes of death for waitlisted patients, we evaluated characteristics that may have led to the different outcomes, such as 'transplantation', 'stable on TPN', 'death on waitlist', and 'waiting for TX'.

Underlying disease

The main reasons for irreversible IF included mesenterial ischemia (35.6%) and chronic intestinal pseudoobstruction (CIPO) (12.6%). The underlying diagnoses in relation to the main endpoints of the present study are shown in Table 3.

Residual length of intestine and enteric anatomy

In a statistical analysis, we compared the three groups (ITX-recipients, MVTX-recipients, and patients who died on the waitlist) concerning the remaining gut length, the presence of the ileocecal valve, and bowel continuity (Table 4). Four patients with CIPO (2 ITX; 2 mMVTX), who had a functional SBS and a complete remaining small bowel, were excluded from this analysis. There was a significant difference ($P = 0.04$) concerning the remaining bowel length between ITX-recipients (31.5 ± 19.9 cm) and patients, who died on the waitlist (17.2 ± 11.8 cm), but not concerning the presence of a stoma or the absence of enteric continuity.

TPN-associated cholestatic liver disease

All patients who were evaluated for transplantation received a liver biopsy to assess their state of TPN-associated hepatopathy. MVTX-recipients presented significantly more often with a bridging fibrosis or cirrhosis by the time of assessment than ITX- or mMVTX-recipients. The latter hardly had an advanced cholestasis (bilirubin >3 mg/dl) and did not require an additional liver transplantation (LTX) (Table 5).

Time on TPN

We analyzed whether the time on TPN may have influenced the progress of cholestatic liver disease in our

Table 3. List of underlying diseases of all patients, who were referred to our center in association with the final endpoints of this study.

Underlying disease	Patients	Median age	Stable on TPN	ITX	(m)MVTX	Died on list	Waiting
Mesenterial ischemia	31	43.3 ± 12.6	0	8	1	3	1
CIPO	11	31.9 ± 11.0	0	2	2	0	0
Crohn's disease	9	38.5 ± 8.6	1	0	3	0	1
Gardner's syndrome	7	43.5 ± 10.8	1	0	1	2	1
Peritonitis	9	45.2 ± 13.0	0	1	3	1	1
Adhesive ileus	6	43.2 ± 10.8	0	2	1	0	1
Intestinal malrotation	4	23.0 ± 7.7	1	2	1	0	0
Volvulus	3	20.0 ± 13.0	1	2	0	0	0
Road accident	2	27.0 ± 12.7	0	0	1	0	1
Sprue	2	63.5 ± 9.2	1	0	0	0	0
Polyposis coli	1	50	0	0	0	0	0
Amyloidosis	1	44	1	0	0	0	0
Radiotherapy	1	45	0	0	0	1	0

CIPO, chronic intestinal pseudoobstruction; TPN, total parenteral nutrition; ITX, intestinal transplantation; mMVTX, modified multivisceral transplantation; MVTX, multivisceral transplantation.

Table 4. Intestinal characteristics in patients with short bowel syndrome, excluding four patients with functional short bowel syndrome due to motility disorder such as chronic intestinal pseudoobstruction.

Patients with SBS	Median length of remaining small bowel (cm)	Patients with remaining ileocecal valve	Patients with remaining colon	Patients with a stoma before TX	Patients with bowel continuity before TX
ITX (n = 16)	31.5 ± 19.9	n = 1 (6.25%)	n = 12 (75%)	n = 4 (25%)	n = 12 (75%)
MVTX (n = 10)	25.7 ± 18.1	n = 0 (0%)	n = 7 (70.0%)	n = 5 (50%)	n = 5 (50%)
Died on list (MVTX) (n = 7)	17.2 ± 11.8	n = 1 (16.7%)	n = 7 (100%)	n = 4 (57.1%)	n = 3 (42.9%)
	P-values				
ITX vs. MVTX	0.453	1.0	1.0	0.234	0.234
ITX vs. died on WL	0.0463	0.520	0.273	0.182	0.182
MVTX vs. died on WL	0.261	0.411	0.228	1.0	1.0
Statistical test	Unpaired *t*-test (Welch's corrected)	Fisher's exact test	Fisher's exact test	Fisher's exact test	Fisher's exact test

SBS, short bowel syndrome; CIPO, chronic intestinal pseudoobstruction; ITX, intestinal transplantation; MVTX, multivisceral transplantation; TX, transplantation; WL, waitlist.

Table 5. Laboratory signs and clinical symptoms defining TPN-associated cholestatic liver disease in patients, who were transplanted or died on the waitlist, respectively.

	Bilirubin >3 mg/dl	Fibrosis grade 2 + 3*	Cirrhosis
ITX + mMVTX (n = 20)	15% (n = 3)	0	0
MVTX (n = 10)	80.0% (n = 8)	80.0% (n = 8)	20.0% (n = 2)
Died on WL (n = 7)	57.1% (n = 4)	85.7% (n = 6)	14.3% (n = 1)
	P-values		
ITX + mMVTX vs. MVTX	0.001	<0.0001	0.1034
ITX + mMVTX vs. died on WL	0.0496	<0.0001	1.0
MVTX vs. died on WL	0.593	1.0	0.2593
Statistical test	Fisher's exact test	Fisher's exact test	Fisher's exact test

ITX, intestinal transplantation; mMVTX, modified multivisceral transplantation; MVTX, multivisceral transplantation; WL, waitlist. Grade of fibrosis assessed according to the Scheuer classification [15].

patients, but the data were not significantly different (Table 6).

Time on waitlist

Because of a general organ shortage and selective donor criteria for ITX and especially for MVTX, the waiting times are long. The seven MVTX-candidates who died on the waitlist, seemed to have spent less time on the waitlist and received less organ offers than successful MVTX-recipients; however, the results did not reach statistical significance (Table 6).

Isolated ITX-recipients, compared with MVTX-recipients, were allocated less organ offers despite a longer waiting time before successful transplantation. Again, results did not differ significantly.

Reasons for organ refusal

The main reasons for declining organ offers included a mismatch of body mass index (BMI) between donor and recipient, an extended intensive care unit (ICU) stay of the donor, and donor age (Table 7). Organ refusal caused by BMI-mismatch always comprised a donor BMI >25, and a BMI, which was significantly higher than the recipient BMI. Organs were then refused caused by the risk of an abdominal compartment syndrome or an insufficient abdominal closure caused by limited abdominal domain. Logistical difficulties, like time schedules incompatible with the limited susceptibility of the intestine to cold ischemia time (cIT: typically 6 h), were a major challenge in the early years and remain a significant problem as long as the awareness of ITX/MVTX remains low even among authorities responsible for organ procurement and allocation. Other medical reasons for refusing organ offers concerning the donor included increased liver enzymes or laboratory signs of pancreatitis, as well as evidence of the consumption of potentially toxic substances (Table 7).

Blood groups and anti-HLA antibodies

An additional reason for long waiting times was the incompatibility of blood groups. It is remarkable that in comparison to successful transplant-recipients, the patients who died on the waitlist were mainly type O (Table 8). In addition, MVTX-recipients with blood group O seemed to have

Table 6. Time on TPN, time spent on the waitlist, and the number of organ offers are listed for all transplanted patients, compared to patients, who either died on the waitlist or who were not yet waitlisted, because they were stable on total parenteral nutrition.

			Organ offers	
Patients	Time on TPN (months)	Time on waitlist (days)	Means	Medians
Received				
ITX (18)	38.2 ± 45.2	320.6 ± 253.2	8.0 ± 12.8	4 [1;53]
(m)MVTX (12)	55.0 ± 71.4	311.3 ± 196.8	7.0 ± 8.3	2 [1;24]
Died on WL				
MVTX (7)	15.3 ± 9.6	243.1 ± 115.8	5.7 ± 7.9	2 [0;19]
Stable on TPN	37.5 ± 45.5	NA	NA	NA
Students *t*-test	*P*-values			
ITX vs. (m)MVTX	0.4353	0.9154	0.8132	
ITX + vs. died on WL	0.2023	0.4484	0.6637	
(m)MVTX vs. died on WL	0.1663	0.4176	0.7418	

TPN, total parenteral nutrition; ITX, intestinal transplantation; mMVTX, modified multivisceral transplantation; MVTX, multivisceral transplantation; WL, waitlist; NA, not applicable.

Table 7. Reasons for organ refusal. Listed are absolute numbers of organ offers refused to the respective reasons, as well as the percentage in relation to the overall number of organ offers, received by our center.

Reason for refusal	Offers	Percentage
BMI	81	26.1
ICU (length of stay)	46	14.8
Donor age	31	10.0
NT-status	31	10.0
Abdominal trauma	24	7.7
Logistics	21	6.8
Medical reasons donor	18	5.8
Backup offer	14	4.5
Hypernatremia	14	4.5
Donor hypoxia	14	4.5
CMV missmatch	8	2.6
Malignancy	3	1.0
Positive cross-match	5	1.6

BMI, body mass index; ICU, intensive care unit; NT, not transplantable; CMV, cytomegalovirus.

longer waiting times than MVTX-recipients with blood group A ($P = 0.2727$). Concerning blood group O, MVTX-candidates, who died on the waitlist, seemed to have spent less time on the waitlist than MVTX-recipients ($P = 0.1997$).

Another challenge for a timely graft reception is the development of anti-HLA antibodies (HLAabs), which may cause severe antibody-mediated graft rejection in the early post-transplant course. Because of chronic hospitalization of ITX- and MVTX-candidates before transplantation, the risk for the development of cytotoxic antibodies is high. In fact, 29% (2/7) of the patients who died on the waitlist had shown HLAabs of class I and II compared with 10% (3/30) of the TX-recipients (data not shown). The presence of preformed HLAabs is no contraindication for ITX/MVTX as long as the pretransplant CDC cross-match is negative and the post-transplant HLA-monitoring is performed frequently. However, it may complicate the quest for an adequate organ offer.

Model of end-stage liver disease score

All patients who were listed for mMVTX or MVTX had a ET Combined Organ Status (CO-status) positioned directly below the high-urgency status (HU-status). In addition, MVTX-candidates were allocated according to model of end-stage liver disease (MELD). The average MELD score for MVTX-candidates who died on the waitlist was significantly lower than that of the MVTX-recipients (12.4 ± 5.4 vs. 21.4 ± 8.0; $P = 0.02$) (Table 9). This striking result highlights the fact that other reasons besides end-stage liver failure increase the morbidity and subsequently the risk of waitlist mortality for MVTX-candidates.

Discussion

We present data of a retrospective analysis of a single center experience specialized on intestinal rehabilitation and intestine transplantation. Although the results of our analysis are limited by its retrospective nature and small patient numbers, which impair the statistical assessment, our analysis clearly displayed a growing number of combined and multivisceral transplantations at our center and a high waitlist mortality for patients on the MVTX – waitlist associated with long waiting time as also reported in other countries [16]. Despite these limitations and a subsequent lack of statistically significant data, four important factors were highlighted that may additionally challenge this worrying condition: (i) delayed referral of patients to an intesti-

Table 8. Blood groups of patients, who were transplanted, died on the waitlist or were waitlisted by study end, respectively.

Patient status	A+	A−	B+	B−	0+	0−	0 total	AB	A total vs. O total *P*-value (Fisher's exact test)
ITX	13	–	–	–	4	1	5	–	0.9954
WT (days)	320.4 ± 263.3				296.5 ± 286.1	420.0	321.2 ± 253.9		
(m)MVTX	6	–	–	–	5	1	6	–	0.2727
WT (days)	246.3 ± 154.4				337.4 ± 229.9	570.0	376.2 ± 226.5		
Died on WL	–	1	1	–	5	–	5	–	Not applicable
WT (days)		386.0	137.0		227.2 ± 117.1		227.2 ± 117.1		
On WL for ITX	–	1	–	1	–	–	–	–	
On WL for MVTX	2	–	–	–	2	2	4	–	

Comparing blood group	0 total vs. all other blood groups	Statistical analysis
ITX vs. (m)MVTX	0.2663	Fisher's exact test
ITX vs. died on WL	0.0455	Chi-square test
	0.0752	Fisher's exact test
(m)MVTX vs. died on WL	0.6332	Fisher's exact test
Comparing WT	**Blood group 0**	**Statistical analysis**
ITX vs. (m)MVTX	0.7168	Mann–Whitney
ITX vs. died on WL	0.4824	Mann–Whitney
(m)MVTX vs. died on WL	0.1997	Mann–Whitney

WL, waitlist; WT, waiting time; ITX, intestinal transplantation; MVTX, multivisceral transplantation; mMVTX, modified multivisceral transplantation.

Table 9. MELD scores of MVTX-candidates, who died on the waitlist and MVTX-recipients in relation to their underlying disease and time on the waitlist.

Patient number	Underlying disease	Time on WL (days)	MELD score	Cause of death
MVTX-candidates, who died on the waitlist				
1	SBS after peritonitis	262	16	MOF/sepsis
2	Gardner's syndrome + infiltrating desmoid tumor	134	7	MOF/sepsis
3	Mesenterial infarction	386	9	MOF/sepsis
4	Mesenterial infarction	414	19	MOF/sepsis
5	SBS after radiotherapy	193	7	MOF/sepsis
6	SBS after peritonitis + Gardner's syndrome	133	19	MOF/sepsis
7	Mesenterial infarction	180	10	MOF/sepsis
Average		243.1 ± 115.8	12.4 ± 5.4	
MVTX-recipients				
1	Crohn's disease	378	25	
2	Mesenterial infarction	341	19	
3	Congenital volvulus	403	37	
4	Road accident	44	17	
5	Gardner's syndrome	323	22	
6	Mesenterial fibromatosis	210	32	
7	Crohn's disease	101	16	
8	SBS after peritonitis	395	10	
9	Crohn's disease	10	18	
10	SBS after peritonitis	570	18	
Average		311.3 ± 196.8	21.4 ± 8.0	
Student's *t*-test		*P*-values		
MVTX vs. died on WL		0.6650	0.0213	

MVTX, multivisceral transplantation; MOF, multiorgan failure; MELD, model of end-stage liver disease; SBS, short bowel syndrome.

nal transplant center, which is accompanied by extensive morbidity and multiple organ disease; (ii) an ultra-SBS without re-established enteral continuity; (iii) the allocation system for MVTX-candidates according to MELD; and (iv) the status of blood group O.

Pironi *et al.* have lately published their results from a large study of the ESPEN working group. They concluded that the risk of death is greater in the early years of TPN treatment. The cause of death in the early years was mainly related to the underlying disease, whereas it was TPN-related in the later years. Therefore, an early referral was concluded to be mandatory, especially for patients with TPN-associated liver failure [7]. Furthermore, an early referral of IF patients to a specialized center was recommended to provide the opportunity to embark on intestinal reconstruction strategies like the STEP and Bianchi procedures. These conclusions are similar to our results, where a delayed referral was often associated with an advanced state of disease and TPN-associated liver fibrosis, minimizing the chance of intestinal reconstruction but also of isolated ITX. The subsequent requirement for a combined transplantation entailed a risk of 24.1% for dying while on the waitlist. However, even though TPN-associated hepatopathy appears to be the trigger for an inferior outcome, it was not the reason for death on the waitlist in the present study.

The etiology of TPN-associated liver disease (PNALD) is multifactorial and not yet clearly understood. Potential factors that correlate with its occurrence include the duration of TPN [17], the length of the residual intestine, and the presence of the residual colon [18]. Patients with <50 cm of remaining intestine have a 50% risk of developing liver dysfunction [18], and patients who develop end-stage liver disease have a 2-year survival rate of essentially 0% [19]. Furthermore, the presence of the ileocecal valve is acknowledged to be essential for intestinal adaptation and weaning from TPN [20]. Certain data indicate, however, that the presence of this valve is less decisive if parameters such as survival are used as endpoints [21,22]. Interestingly, recently published data showed that the ileocecal valve was detrimental to survival in children listed for transplant [21]. Factors, such as hyperbilirubinemia (>2 mg/dl), splenomegaly, and biopsy-proven liver cirrhosis, are also associated with a risk of dying within 6 months while on the waitlist [23]. These data mainly originate from studies in a pediatric population. Compared to children, who are likely to develop serious PNALD rapidly, adults typically experience long-term TPN-related complications, such as venous access complications. The incidence of sepsis during TPN ranges between 1 and 4 infections per 1000 TPN-days and is even higher among hospitalized patients. One study assumed that approximately 4% of patients die due to infection [24]. These complications often do not reflect the real potential for lethal decompensation [11] and may lead to the delayed consideration of referral to centers with comprehensive expertise in IF management.

In the presented study, the remaining gut length rather than the presence of the ileocecal valve appeared to be associated with improved survival on the waitlist, especially for ITX-candidates. A bilirubin above 3 mg/dl did not influence survival to transplantation.However, compared to ITX-recipients, patients who died on the waitlist had a higher incidence of fibrosis by the time of evaluation, straining the consequences of a late referral. One study of adult TPN-patients reported a median time to death of 10.8 months after an initial increase in serum bilirubin [19]. Remarkably, liver fibrosis and liver insufficiency were never a reason for death on the waitlist in our study. In fact, the cause of death in all cases was MOF following sepsis. Furthermore, all the patients who died on the waitlist had an occlusion of the celiac axis resulting from arteriosclerosis, catheter infections, or large systemic thromboses. We conclude from our results that time on TPN and cholestatic hepatopathy itself were not detrimental to patient survival while on the waitlist.

According to the current allocation policy in ET and despite CO-status, the MELD score influences organ allocation to liver-intestine or MVTX-candidates, even though it clearly underestimates their mortality risk [11]. As the impending lack of vascular access and recurrent sepsis episodes are the main reasons for high waitlist mortality rather than liver failure [25], the severity of disease is not mirrored in the MELD score. MELD is generally agreed to be used for patients with increasing liver failure, but was never meant to describe organ failure in patients with underlying IF. These patients do not reach the same level of essential laboratory parameters (bilirubin, INR, creatinin) so that the identification of patients with a poor prognosis is more difficult. In 2004, UNOS agreed to add an estimated 10% mortality risk to the MELD score of MVTX-candidates. This was performed after published data demonstrated the competitive disadvantage for these patients as compared to LTX-candidates regarding their chances of graft reception before dying or becoming too sick to benefit from transplantation [22,25]. In 2006, an international working group elaborated strategies to reduce mortality and morbidity in patients with chronic IF [11] and amongst other issues concluded that MELD does not predict waitlist mortality in ILTX-candidates. Following these results, the allocation system in the UK assigned higher allocation scores to ILTX-candidates, which improved graft availability [26]. Despite these published data, no changes have been made in the allocation system of ET. In the presented study, MVTX-candidates who died while on the waitlist had a significantly lower MELD score than MVTX-recipients. Furthermore, time until death seemed shorter ($P = 0.4$) than

time to organ reception, suggesting that the rapid deterioration of these patients was attributable to factors unrelated to MELD-relevant parameters, particularly infectious complications. However, differences were not significant and the described phenomenon should be subject to further research in larger patient cohorts.

Unfortunately, there is still a lack of awareness for ITX/MVTX at many centers that report potential donors. Frequently, suitable organ offers are separated because the liver, as an integral part of the *en bloc* organ package, is preferentially allocated to patients with acute liver failure on HU-status, which negatively impacts MVTX-candidates. This is especially true for young donors, because the selected donor criteria for ITX/MVTX allow a donor age only up to 45 years. Particularly concerning the blood group O, this policy may explain the high waitlist mortality rate, because type O liver grafts were often used as universal donors for HU-listed candidates in liver failure. Another potential disadvantage for waitlisted patients is the presence of cytotoxic HLA-antibodies that have developed during former hospital stays and blood transfusions. The appearance of HLAabs has become a major concern for several MVTX-candidates, such that the likelihood of eligible organ offers continues to decrease because a negative cross-match is mandatory. Furthermore, transplant-candidates may not be transplantable at the moment they receive an organ offer because of infections or ICU-stays; the longer MVTX-candidates stay on the waitlist, the more likely they are to be placed on inactive status, and this must be taken into account when the absolute numbers of organ offers are evaluated.

To assign higher allocation scores to MVTX-candidates there is need for the identification of variables influencing their pretransplant mortality. National and international collaboration between intestinal rehabilitation centers and the establishment of registries may help to better understand the process of deterioration and TPN-associated organ dysfunction in this patient group. ET has recently performed a study in which decision tables were used as input for a rule engine and compared this system with the currently used kidney allocation system. The introduction of decision tables provided more flexibility and transparency from recommendation of a new allocation rule to its technical realization [27]. Furthermore, the competing aims of allocation should be well considered and balanced, and there must also be flexibility to allow for exceptions and to support innovation and development [28]. A new scoring system with 'user friendly' decision tables should help to inform on the referral criteria for patients with IF to specialized centers. A HU-status or an additional percentage of mortality risk to the calculated MELD score, including factors like lack of venous access and high infection risk would help to provide MVTX-candidates a fair chance to receive organs in timely manner.

Conclusion

Multivisceral transplantation candidates are at a high risk of dying while on the waitlist owing to long waiting times, selective donor criteria, and organ shortages. During the period of the presented retrospective study, an increasing number of patients were listed for MVTX, because of their advanced TPN-associated liver fibrosis and their need for a liver graft. Early referral to IF centers and the early identification of eligible patients for ITX may help prevent TPN-associated liver disease by optimizing TPN composition, which would thus prevent the need for combined organ transplantation. Furthermore, emphasis should be placed on the identification of patients who would benefit from intestinal reconstruction such that they could be weaned from TPN, retain gut length and continuity, and survive for a longer period while on the waitlist.

The current allocation policy in ET should be reconsidered to prioritize this patient subgroup by adding a HU-status for critically ill MVTX-candidates and by providing them equitable access to suitable organs in timely manner.

Authorship

UAG: provided clinical treatment, contributed to the acquisition and analysis of data, and involved in the preparation and writing of the manuscript. ARS: involved in the statistical analysis and in the manuscript review and proofreading. UFP: responsible for the Gastroenterological Clinic for Short Bowel Syndrome and Intestinal Failure Management, involved in the manuscript review/proofreading. DJ: responsible for the pain management and pretransplant follow-up of patients with intestinal failure, and involved in the manuscript review/proofreading. TD: responsible for diagnoses and radiological intervention in patients with intestinal failure, and involved in the manuscript review/proofreading. PN: head of the Department of General, Visceral and Transplantation surgery, and involved in the manuscript review/proofreading. AP: Director of the Organ Transplant Program, and responsible for the Program of Intestinal and Multivisceral Transplantation, as well as for the clinic for Intestinal Failure Management, provided clinical treatment, contributed to the acquisition and analysis of data, and involved in the manuscript writing/review/proofreading.

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