REVIEW ARTICLE

Irreversible Liver Failure: Treatment by Transplantation

Part 3 of a Series on Liver Cirrhosis

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SUMMARY

Background: Liver transplantation is the only established, causally directed treatment for irreversible chronic or acute liver failure.

Methods: This review is based on papers retrieved by a selective search in the PubMed database, the index of randomized controlled trials of the European Society of Organ Transplantation, and the Cochrane database, along with an analysis of data from the authors' own center.

Results: 1199 liver transplantations were performed in Germany in 2011. The most common indications were alcoholic cirrhosis (28%), cirrhosis of other causes (24%), and intrahepatic tumors (20%). Among recipients, the sex ratio was nearly 1:1 and the median age was just under 50. Across Europe, the 1-, 5-, and 10-year survival rates after liver transplantation were 82%, 71% and 61%. In our own center, the Charité in Berlin, the corresponding rates were 90.4%, 79.6% and 70.3%, based on an experience of 100 to 120 cases per year. The current rate of functioning transplants five years after liver transplantation is 52.6% in Germany and 66.2% internationally. Standard immunosuppression consists of a calcineurin inhibitor, tacrolimus or cyclosporine A, and steroids. Early complications include primary functional failure of the transplant, hemorrhage, thrombosis, acute rejection, and biliary complications. Over the long term, complications that can impair the outcome include chronic rejection, biliary strictures, cardiovascular and metabolic adverse effects, nephrotoxicity, neurotoxicity, and opportunistic infections and malignancies.

Conclusion: Liver transplantation is a successful and well-established form of treatment that is nonetheless endangered by a shortage of donor organs and other structural and organizational difficulties.

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Since T. E. Starzl carried out the first liver transplant in 1963, this procedure has developed from an experimental treatment to a normal therapeutic option for the treatment of irreversible chronic or acute liver failure. Liver transplants may use organs donated after brain death (DBD) or right and left lobes from living donors. DBD liver transplantation may be carried out using the whole of the liver or only a part (split-liver transplantation). Advances in immunosuppression, organ conservation, and donor conditioning—that is, organ-protective treatment of a brain-dead patients in the intensive care unit—together with increasing experience of surgical and perioperative management have allowed 1-year patient survival rates of over 90% if recipients are carefully chosen (authors' data, see *Figure*).

Further advances in patient and organ survival are limited in Germany by the increasing relative shortage of organs. There have been 1792 new additions to the waiting list in the past year, while only 1199 liver transplantations have been performed. That numbers of liver transplantations have doubled in the past 15 years is due to increasing acceptance of 'extended-criteria donors' (1). With improved success rates in the past 20 years, however, the annual number of patients on the waiting list in the Eurotransplant area rose between 1999 and 2006 from 593 to 2319. In 2006, waiting list mortality was 21% (2, 3). Later in the article, we will discuss in brief the problems and challenges for transplantation medicine in Germany associated with these developments.

Because waiting list mortality was unacceptably high compared to figures from other countries, and because medical urgency was inadequately represented, the so-called Model for Endstage Liver Disease (MELD) system was introduced to regulate organ donation in Germany and the Eurotransplant countries on 16 December 2006. This system is based on the determination of bilirubin, creatinine, and INR. These three values, when plugged into the formula $[10 \times (0.957 \ln(\text{serum creatinine}) + 0.378 \ln(\text{total bilirubin}) + 1.12 \ln(\text{INR}) + 0.643)]$, produce a value between 6 and 40. Ideally, the patient with the highest score on the list should receive the available organ. Originally established to assess 3-month mortality in cirrhosis patients after TIPS (transjugular intrahepatic portosystemic

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FIGURE

Patient survival after liver transplantation 1988 to 2010.

Data from the European Liver Transplant Registry (ELTR) and authors' own data, showing a 1-year survival rate of about 90%, a 5-year survival rate in the whole patient population of almost 80%, and a 10-year survival rate of 71%

shunt) placement (MELD 40: 3-month mortality 100%), the MELD system took over from its predecessor, the European Liver Allocation System (ELAS), which carried out allocation on the basis of time on the waiting list and Child-Turcotte-Pugh score (4). The main objective of changing the system was to allocate liver transplants in an objective and patient-orientated manner according to medical urgency, as indicated by a calculable score, ignoring the waiting time. Because it prioritizes the most severely ill patients on the waiting list, this allocation method is known as the sickest-first policy. The MELD principle of allocation reduced waiting list mortality in the Eurotransplant countries from 21.0% in 2006 to 17.9% in 2007 (3). In addition to determining medical urgency as described, a growing web of exception regulations has been added with the intention of better classifying patients (a “learning allocation system”), the severity of whose disease is not adequately taken into account in organ allocation by the MELD system (5). A liver transplant should be considered in all cases of advanced liver disease with irreversible cirrhotic damage to the liver parenchyma. Other established indications for liver transplantation are acute liver failure, certain malignant tumors, and inherited metabolic disorders of the liver (*Box 1*).

Liver cirrhosis

Alcohol-related liver cirrhosis

At 28% of all cases, alcohol-related liver cirrhosis is the most common indication for liver transplantation in Germany. According to the transplantation guidelines of the German Medical Association (Bundesärztekammer), patients do not go on the waiting list until they have been abstinent from alcohol for at least 6 months (5). Although, despite careful interdisciplinary evaluation of patients' willingness and chances of lasting abstinence, between 10% and 25% of patients relapse after transplantation (6, 7 e1), the prognosis is very good, with 1- and 5-year patient survival rates of 95% and 88% respectively (e2).

Viral hepatitis

In hepatitis B virus (HBV)-induced cirrhosis, liver transplantation is simultaneously treatment for the cirrhosis and the means of eliminating the focus of infection. Around 5% to 10% of all transplantations are performed because of chronic or acute HBV infection (8). With the use of potent virostatics (including lamivudine and entecavir) in combination with hepatitis B immunoglobulin, a reinfection rate after transplantation of around 6% may be expected (9, 10). The 1-year survival rates are around 90% to 100% (e3). About 5% of HBV-infected patients are co-infected with the hepatitis D virus (e4). The hepatitis D reinfection rate is determined by the HBV reinfection rate.

Liver transplantation owing to hepatitis C virus infection occurs despite the availability of pegylated interferons and ribavirin. This is because these drugs have little effect on the genotype frequently encountered in Europe, genotype 1b, with reinfection rates of

BOX 1

Metabolic disorders that may be indicators for liver transplantation*

- Alpha1-antitrypsin deficiency
- Wilson disease
- Cystic fibrosis
- Hereditary tyrosinemia
- Glycogenosis types I, III, IV
- Transthyretin amyloidosis
- Disorders of bile acid synthesis
- Progressive familial intrahepatic cholestasis
- Mitochondriopathies
- Erythropoietic protoporphyria
- Primary hyperoxaluria
- Urea cycle disorders
- Familial hypercholesterolemia
- Organic acidopathies
- Crigler-Najjar syndrome
- Protein C deficiency
- Factor VII deficiency
- Refsum syndrome
- Hereditary tyrosinemia
- Galactosemia

*Modified from (e22)

TABLE 1

Indication criteria for liver transplantation in patients with acute liver failure of various causes*

Criteria	Indications
King's College criteria	Prothrombin time >100 sec (= Quick <7% or INR >6.7) or at least three of the following: – Unfavorable etiology (cryptogenic hepatitis, halothane hepatitis, drug toxicity) – Icterus more than 7 days before encephalopathy – Age <10 years or >40 years – Prothrombin time >50 sec (= Quick <15% or INR >4) – Serum bilirubin >300 µmol/L (>17.5 mg/dL)
Special criteria for paracetamol toxicity	Arterial pH <7.3 or all three of the following: – Prothrombin time >100 sec (= Quick <7% or INR >6.7) – Creatinine >300 mmol/L (>4 mg/dL) – Encephalopathy grade 3 or 4
Clichy criteria (in recipients with viral hepatitis)	Encephalopathy grade 3 or 4 and – Factor V <20% in recipients <30 years or – Factor V <30% in recipients >30 years

* Modified from (e31)

95% to 100% (11). Around one fifth of patients develop cirrhosis again, and the adverse effects of interferon therapy, which can be severe, limit the possibilities of therapeutic success (11, 12).

The current trend in donor age has particular implications for liver transplantation in patients with HCV infection, because a donor age above 40 years is an independent risk factor for:

- Patient survival (13)
- The progression of fibrosis if HCV reinfection occurs.

Autoimmune hepatitis

Conservative treatment of autoimmune hepatitis results in high remission rates under immunosuppressive treatment.

Liver transplantation is also the therapeutic option in patients with treatment-refractory disease or advanced cirrhosis at the time of diagnosis. In up to 38% of cases, recurrence of disease is to be expected in the transplant, although the long-term prognosis is still good, with 5-year survival rates of 70% to 75% (15).

Cholestatic liver disease

Primary sclerosing cholangitis (PSC), which has a progressive relapsing course, leads to destruction of the intra- and extrahepatic bile ducts. In almost 80% of cases, PSC is associated with ulcerative colitis (16). The lifetime risk of development of cholangiocellular carcinoma lies between 7% and 15% (16). If cirrhosis occurs, and medical and endoscopic therapies fail, this represents an appropriate indication for transplantation (16). Since March 2012, such patients have been assigned the same status as patients with hepatocellular carcinoma, since the severity of illness is inadequately reflected in the MELD system.

Primary biliary cirrhosis (PBC) is characterized by progressive destruction of the lesser bile ducts. Patients with clinically manifest cirrhosis should be considered for liver transplantation. Although disease recurs in 15% to 20% of patients (17), both indications are associated with a very good long-term prognosis (1-year survival around 90%, 5-year survival about 85%) (18). Much more rarely, secondary sclerosing cholangitis is an indication for transplantation (e5).

Metabolic/hereditary disease

Hereditary diseases are the reason for liver transplantation in less than 5% of cases. The underlying genetic defects are multifarious. Among diseases causing chronic damage to the liver, or where the defect is located in the liver, are:

- Wilson disease
- Hemochromatosis
- Alpha₁-antitrypsin deficiency
- Urea cycle disorders
- Storage diseases.

Another example is polycystic degeneration of the liver as a manifestation of autosomal dominant polycystic kidney disease (ADPKD) or, more rarely, as isolated polycystic liver disease (e6). *Box 1* gives an overview of common metabolic disorders that represent indications for liver transplantation.

Malignant tumors

Hepatocellular carcinoma

Liver transplantation is the treatment of choice in early-stage hepatocellular carcinoma (HCC). By following the so-called Milan criteria when listing patients and throughout the waiting period (tumor size ≤ 5 cm or a maximum of three tumors ≤ 3 cm; extrahepatic metastases and macrovascular invasion excluded), the

BOX 2

Malignant tumors for which under certain conditions liver transplantation is indicated*

- Hepatocellular carcinoma
- Cholangiocellular carcinoma
- Multifocal adenoma
- Liver metastases of neuroendocrine carcinomas
- Hepatoblastoma
- Epithelioid hemangioendothelioma

*Modified from (e7–e10)

TABLE 2

Most common main diagnoses (ICD) in new registrants registered for liver transplantation in 2011*

Indications for liver transplantation	n
Alcoholic liver disease (K70)	502
Fibrosis and cirrhosis of liver (K74)	422
Malignant neoplasm of liver and intrahepatic bile ducts (C22)	353
Hepatic failure, not elsewhere classified (K72)	153
Congenital malformations of gallbladder, bile ducts and liver (Q44)	113
Other diseases of biliary tract (K83)	104
Other metabolic disorders (E88)	32
Other diseases of liver (K76)	32
Disorders of mineral metabolism (E83)	27
Other venous embolism and thrombosis (I82)	14
Total	1752

* In total, 18 main diagnoses among 1792 cases; source: German Organ Transplantation Foundation (DSO) 2011, www.dso.de (1)

TABLE 3

Age distribution of transplant recipients in 2011 in Germany (liver transplantations without combined transplantation and transplants from living donors)

Age	n
0–15 years	73
16–55 years	520
56–64 years	377
65 + years	118
Total	1088

* Eurotransplant Annual Report 2011, (e23)

probability of recurrence will be kept appropriately low (19). For diagnosis, AFP > 400 ng/mL and positive imaging or evidence of tumor on two different imaging techniques is sufficient (5). In future, recent findings in tumor biology will become more important (20). Because tumor progression is independent of laboratory values, HCC patients are assigned a match MELD of 22, corresponding to a 3-month mortality rate of 15%. Every 3 month there is an increase of 10% in the assigned MELD score, so that within 1 year of going on the list, patients have a realistic option of transplantation. So long as the Milan criteria are fulfilled, 5-year survival rates of 70% to 75% may be expected after transplantation (21, 22).

For other, more rare malignant tumors (*Box 2*), liver transplantation is indicated only in selected cases or in the setting of clinical trials.

Acute liver failure

Estimates of the number of cases of acute liver failure in Germany range from 200 to 500 per year (23). Acute liver failure is potentially reversible, so clinical scoring systems have been established for prognosis and for the selection of patients who probably need a liver transplant (*Table 1*). Among the causes of fulminant acute liver failure, top of the list are acute paracetamol toxicity (16%) and acute HBV infection (13%) (e11). Patients with acute liver failure are registered on the waiting list as ‘high urgency’ according to the allocation rules and are given priority. Survival rates at 1 and 5 years after transplantation are 79% and 72% respectively (24).

Current state of the art and outcomes of liver transplantation in Germany

Since the first liver transplantation in Germany in 1969, more than 19 000 livers have been transplanted (25). At 1199, the number of liver transplantations in 2011 was slightly lower than the 1283 carried out in the previous year—the peak year so far (25). There were 1792 new registrations on the waiting list for liver transplantation. The three main diagnoses for registration for liver transplantation in 2011 were:

- Alcohol-related liver disease, 28% (K 70; n = 502)
- Fibrosis and cirrhosis of the liver, 24% (K74; assumes various causes; n = 422)
- Malignant neoplasms of liver and bile ducts, 20% (C22; n = 353) (*Table 2*).

In 5.9% of liver transplantations, the transplant organs came from living donors (25).

The age distribution of transplant recipients is shown in *Table 3*. Typical complications after liver transplantation are listed in *Table 4*. If these appear during the long-term course when the patient is under care as an outpatient, they should be treated in close collaboration with the transplantation center; in case of doubt, treatment should be carried out at the latter.

Even today, patients who have received a liver transplant require lifelong immunosuppression to avoid acute or chronic rejection or damage to the transplant.

Despite medical therapy, acute rejection occurs in 20% to 60% of cases during the first year following transplantation (26, 27). Risk factors are viral or autoimmune underlying diseases, long ischemic times, and young patient age (27). Confirmation of a suspected diagnosis is by biopsy. Standard treatment is to give a steroid bolus, e.g., methylprednisolone 500 mg, over 3 to 5 days (28). HCV-positive patients should first have their immunosuppression increased or another drug added (28). A large number of prospective, randomized studies (RCTs) have investigated various immunosuppressive strategies. An overview of these is offered by the RCT register of the European Society of Organ Transplantation (29). Standard immunosuppression uses one of the calcineurin inhibitors (CNIs) tacrolimus or ciclosporin, together with steroids. Studies have shown an advantage for the CNI tacrolimus in terms of patient survival (30, 31).

More recent studies tested either the efficacy of newer combination immunosuppressants (mycophenolate derivatives, mTOR inhibitors), induction immuno-

suppressants (anti-IL-2 receptor monoclonal antibodies [IL2R-mAb], T-cell-depleting antibodies [32, e12]), or strategies to reduce the most common adverse effects of CNIs and steroids, which include nephrotoxicity (CNIs), cardiovascular and metabolic adverse effects (CNIs and steroids), malignant tumor development (CNIs), or an increase in the rate of HCV replication (steroids [e13, e14]) (28).

Attempts to reduce immunosuppression-mediated adverse effects consist of reducing the dose and total burden of CNIs by combining them with other immunosuppressants immediately after transplantation (induction therapeutics; delayed initiation of CNIs; low-dose CNI regime) or later on (combination with azathioprine, mycophenolic acid derivatives, mTOR inhibitors), and in reducing the steroid burden (very short immunosuppressant regime or none at all). A meta-analysis showed an advantage for the use of IL2R-mAb in terms of reduced CNI use, improved renal function, and a low incidence of diabetes for the same immunosuppressant potency (33). Meta-analyses and

TABLE 4

This compilation gives an overview of selected complications after liver transplantation. Complications are divided according to their typical manifestation into early and late complications (27, 28, e24–e30)

Early complications (1st 6 months)	
Type of complication	Significance/incidence
Primary non-function	Incidence approx. 5–10%
Hepatic artery/portal vein thrombosis	Incidence approx. 3% (adults) – 8% (children)
Acute cellular rejection	Incidence approx. 20–60% within 1 year
Bile duct complications – Bile leaks – Bile duct stenoses – Papilla dysfunction	Incidence approx. 10–15%
Impaired renal function (acute kidney damage: doubling of serum creatinine, oliguria, anuria)	Incidence approx. 30–60%
Infections – Viral (suspected herpes group viral infection) – Bacterial – Mycotic	– Incidence of CMV infection: approx. 30–40% – Incidence of CMV disease: approx. 10–20% – Cumulative incidence of invasive mycotic infections after 1 year approx. 8%
Late complications (from 6 months on)	
Type of complication	Significance/incidence
Disease recurrence	– HBV – Recurrence rate approx. 5–10%, – HCV – Recurrence rate 100% with accelerated course in 30–40%, – HCC – Recurrence rate approx. 20–25% after 5 years
Chronic renal insufficiency (GFR <30 mL/min, need for dialysis, kidney transplant)	Cumulative 5-year incidence approx. 24%
De novo diabetes mellitus	Incidence up to 26%
Obesity	Incidence up to 50% after liver transplant
Cardiovascular complications	Cause of death after liver transplant in approx. 10%
Ischemic-type biliary lesions (ITBL) – Chronic, non-ischemic bile duct damage, usually with multiple strictures	Incidence up to 20%
Development of malignancy	Risk double that of normal population; cause of death after liver transplantation in approx. 22% of patients

CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; GFR, glomerular filtration rate

meta-regression analyses of more than 18 RCTs showed an advantage for steroid-free immunosuppression with respect to metabolic complications (diabetes, cholesterol levels), the course of HCV reinfection and transplantation fibrosis, and the incidence of opportunistic infections (e.g., cytomegalovirus infection), while patient and organ survival rates remained similar. If the steroids were replaced by another immunosuppressant (e.g., IL2R-mAb, mycophenolic acid derivative), the rejection rate also remained stable (34, 35). In meta-analyses, owing to their antiproliferative properties, the mTOR (mammalian target of rapamycin) inhibitors sirolimus and everolimus showed advantages in respect of tumor relapse after liver transplantation in patients with HCC (e15), and represent a possible second line of therapy in CNI-related neuro- or nephrotoxicity (e16–e18). Studies aimed at reducing or completely eliminating immunosuppressive treatment in selected patients are showing promising early results (e19–e21).

ELTR data show average 1-, 5-, and 10-year survival rates of 82%, 71%, and 61% respectively (36). The 5-year function rate after liver transplantation in Germany is 52.6% versus 66.2% internationally (25). Our own data from the liver transplantation program at Berlin Charité, audited in September 2012 and confirmed as working in accordance with the German Medical Association guidelines, show 1-, 5-, and 10-year survival of 90.4%, 79.6%, and 70.3% respectively in the overall patient population since 1989 (Figure). However, in our center too, since the MELD score was introduced in 2006, the 1-year prognosis for patient survival has dropped to about 83%. In 2009, in Germany as a whole, a MELD-score-dependent survival of 78.6% to 84.5% was documented for a lab MELD score between 10 and 30 (37). The sickest patient groups, with lab MELD scores higher than 30, showed a survival of 52.6%, but represented about 60% of the whole patient population (37). According to data for 2010 from the German AQUA-Institut (which car-

ries out research in quality assurance in healthcare), hospital mortality in the whole of Germany in 2010 was 16.8% , with a rising tendency compared to the previous year; the 1-year survival rates for 2009 and 2010 were 76.5% and 77.0% (38).

Problems and challenges

In our opinion, although the reasons for falling organ and patient survival rates after liver transplantation are no doubt multifactorial, the most important ones are the increasing scarcity of organs donated post mortem, the increasing use of so-called “extended-criteria organs” (i.e., those from donors of advanced age, with long periods in intensive care, and/or with parenchymal fatty degeneration over 40%) to compensate for this scarcity (37), and the increase in very sick recipients who can only be given poorer-quality donor organs, with reducing prospects of success.

The disproportionately large number of waiting list patients in Germany (37), which correlates with the low prioritization of transplantation success versus the primacy of urgency in the allocation process, reinforces the problem. Since 2006, waiting list mortality has reduced, but the 3-month patient survival rate has dropped from 90% to 80% (38). At the same time, there exists no transparent, center-specific analysis and presentation of data on quality (39). A transplantation register, such as would enable quality assurance, does not exist in Germany at present. The transplantation centers are compared primarily on the basis of quantitative performance indicators. Added to this is the economic incentive to increase profits by carrying out a larger number of liver transplantations. We are of the opinion that, compared to other countries, Germany has too high a density of transplantation centers, with overlapping catchment areas. This leads to strong competition in terms of numbers of transplantations, which in the case of the individual patient can result in false incentivization, with the result that patients who are too ill receive transplants despite the improbability of success, borderline-quality donor livers are accepted, or actual misconduct occurs.

Conclusion

Liver transplantation is the only causative treatment for terminal acute and chronic liver failure. A high success rate has led to its becoming a routine procedure. Further improvement of transplantation success rates will be limited by the lack of availability of suitable organs and by defects of structure and process.

Conflict of interest statement

Dr. Pascher has received reimbursement of conference fees, travel and accommodation costs, and fees for the preparation of medical training events from Astellas, Novartis, Roche, and Genzyme. He has also received fees from Astellas, Novartis, and Roche for a research project initiated by himself.

Dr. Nebrig declares that no conflict of interest exists.

Professor Neuhaus has received reimbursement of conference fees, travel and accommodation costs, and fees for the preparation of medical training events, fees for carrying out commissioned clinical studies, and funding for a research project initiated by himself, from Astellas, Novartis, and Roche.

KEY MESSAGES

- Liver transplantation is the only causative treatment for irreversible acute or chronic liver failure.
- Liver transplantation should be considered in all cases of acute liver failure and advanced liver disease with irreversible damage to the parenchyma (cirrhosis).
- Standard immunosuppressive treatment consists of a calcineurin inhibitor (CNI) (tacrolimus or ciclosporin) and steroids, which may be combined with other drugs according to need.
- Liver transplantation in Germany has been faced with a drop in survival rates and rising retransplantation rates.
- Liver transplantation in Germany faces challenges due to increasing scarcity of organ donors, an increase in the number of “extended-criteria” donated organs, and prioritization in allocation according to medical urgency, resulting in rising numbers of very sick potential recipients.

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REVIEW ARTICLE

Irreversible Liver Failure: Treatment by Transplantation

Part 3 of a Series on Liver Cirrhosis

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