Overview of the Indications and Contraindications for Liver Transplantation

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Liver transplantation is the only definitive treatment option for patients with irrevocable acute or chronic liver failure. In the last four decades, liver transplantation has developed from an experimental approach with a very high mortality to an almost routine procedure with good short- and long-term survival rates. Here, we present an up-to-date overview of the indications and contraindications for liver transplantation. It is shown how the evaluation of a candidate and finally listing for transplantation has to be performed in a multidisciplinary setting. Meticulous listing, timing, and organ allocation are the crucial factors to achieve an optimal outcome for the individual patient on the one hand, and reasonably using the limited deceased donor pool on the other hand. Living-donor liver transplantation is demanding but necessarily increasing. Because patients after liver transplantation need lifelong aftercare, it is important for primary care clinicians to understand the basic medical problems and risks.

Despite significant improvements in the medical management of the complications of liver cirrhosis including hepatocellular carcinoma, liver transplantation (LTx) remains the only definitive treatment option for patients with end-stage liver disease. Significantly improved graft and patient survival rates have been observed over time and, in the last 15 years, are relatively stable, with an overall survival rate of 85% in the first year and ~75% at 5 yr (Kim et al. 2013). However, ~10% of patients listed for LTx die on the waiting list (Kim et al. 2006), and many potential candidates are not listed because of the shortage of deceased donor organs (Fig. 1). Other patients are not candidates because of comorbidities, psychosocial issues, and medical issues like hepatocellular carcinoma exceeding a designated size. Acute liver failure is less common but has an excellent outcome if the patient is transplanted promptly.

HISTORY

The pioneer of human orthotopic liver transplantation, Thomas E. Starzl, learned about experimental auxiliary liver transplant models in dogs while attending a lecture by C. Stuart Welch in 1957 (Starzl 2012). After discussing and refining these canine models, Starzl was the first to attempt an orthotopic liver transplant into a 3-yr-old human recipient suffering from biliary atresia in 1963 (Starzl et al. 1963). The patient did not survive the operation. After several equally unsuccessful attempts, Starzl...
succeeded in performing an orthotopic liver transplant into a patient diagnosed with hepatoblastoma in 1967 (Starzl et al. 1968). This patient survived for 18 mo before dying from metastatic disease. During the following years, major breakthroughs such as the expansion of the organ donor pool by introduction of the brain-dead criteria in 1968 (Shapiro 1968), refined surgical technique, and, last but not least, introduction of new immunosuppressive medication such as cyclosporine in 1979 (Starzl et al. 1981a,b) led to a significant increase in liver transplantation. In 1983, the NIH declared that liver transplantation was a valid therapy for end-stage liver disease (National Institutes of Health 1984), and, a few years subsequently, the United Network for Organ Sharing (UNOS) was founded (United States Congress 1984). Already in 1967, the Eurotransplant (ET) International Foundation was founded in Leiden, The Netherlands. In 1988, Rudolf Pichlmayr was the first to perform a split-liver transplantation, offering one liver to two recipients (Pichlmayr et al. 1988). In 1988 and 1989, living-donor liver donation was successfully introduced in the adult-to-pediatric and adult-to-adult settings (Fig. 2) (Broelsch et al. 1990). As of today, approximately 6200 and 1700 liver transplants are performed each year within the UNOS and ET networks, respectively.

**INDICATIONS FOR LIVER TRANSPLANTATION**

Indications for liver transplantation are manifold and can be classified into end-stage liver disease, acute liver failure, and certain benign and malignant liver tumors. An overview is given in Table 1. Liver transplantation should be considered for any patient in whom anticipated overall survival exceeds life expectancy of the underlying disease or where a significant increase in quality of life can be achieved. Within the UNOS and ET networks, liver cirrhosis caused by chronic viral hepatitis and alcohol abuse is the major cause for end-stage liver disease, accounting for ~70% of liver transplants (Zakhari 2013).

Liver transplantation for malignant disease is a medical and ethical challenge with regard to long-term oncological outcome under immunosuppressive therapy and allocation justice because of organ shortage. Childhood hepatoblastoma (Meyers et al. 2012), epitheloid hemangiendothelioma (Grossman and Millis 2010), and limited hepatocellular carcinoma (HCC) (Dhir et al. 2012; Lim et al. 2012), within the Milan criteria (one lesion ≤5 cm, or two to three lesions each ≤3 cm, no extrahepatic lesion and no vascular invasion), are standard indications for liver transplantation. Patients diagnosed with HCC—often presenting in good clinical condition—therefore receive additional MELD (model of end-stage liver disease) points according to HCC tumor size and waiting time to enable transplantation before the tumor exceeds the Milan criteria (Earl and Chapman 2013). Surgical resection and therapeutic interventions to control HCC progress during the waiting period as well as liver transplantation for patients exceeding the Milan criteria are a
Living-donor liver transplantation may here offer a treatment option for selected HCC patients to minimize waiting time or enable liver transplantation in tumors exceeding the Milan criteria (Grant et al. 2013). In contrast, patients diagnosed with intrahepatic cholangiocellular adenocarcinoma (CCA) have shown poor long-term overall survival after liver transplantation and are not transplant candidates (Ali et al. 2011). However, recent clinical trials by the Mayo Clinic evaluating a multimodality treatment concept for CCA combining neoadjuvant radiochemotherapy and liver transplantation have established CCA as an indication for liver transplantation in selected patients with unresectable hilar CCA or CCA arising in patients with primary sclerosing cholangitis (Rosen et al. 2010; Darwish Murad et al. 2012). Clinical trials evaluating liver transplantation for selected patients with neuroendocrine hepatic metastases have shown long-term graft and patient survival comparable with patients transplanted for HCC (Gedaly et al. 2011). In individual cases, patients with neuroendocrine liver metastases thus are eligible for liver transplantation. Extrahepatic malignancies as well as hepatic metastases from non-neuroendocrine tumors so far remain absolute contraindications for liver transplantation. However, a recent Norwegian pilot study evaluating liver transplantation for unresectable colorectal liver metastases showed that overall survival exceeds by far the reported outcome for chemotherapy, is comparable with overall survival after liver resection for resectable colorectal liver metastases, and is comparable with overall survival after repeat liver transplantation for nonmalignant diseases (Hagness et al. 2013). Thus, ongoing improvements in multimodality cancer therapy may in the future widen indications for liver transplantation in malignant disease.

**CONTRAINDICATIONS FOR LIVER TRANSPLANTATION**

Absolute and relative contraindications for liver transplantation are shown in Table 2. Abstinence from alcohol and drug abuse for a minimum of

### Table 1. Indications for liver transplantation

**Acute liver failure**
- Hepatitis A/B
- Intoxication (e.g., acetaminophen, death cap)
- Wilson's disease
- Budd–Chiari syndrome

**Chronic liver failure: Noncholestatic cirrhosis**
- Hepatitis B/C
- Autoimmune hepatitis
- Alcohol-induced cirrhosis

**Chronic liver failure: Cholestatic cirrhosis**
- Primary biliary cirrhosis (PBC)
- Primary sclerosing cholangitis (PSC)
- Secondary biliary cirrhosis

**Chronic liver failure: Metabolic**
- Wilson's disease
- Hemochromatosis
- α-1 Antitrypsin deficiency
- Amyloidosis
- Cystic fibrosis
- Tyrosinemia

**Chronic liver failure: Vascular**
- Budd–Chiari syndrome

**Other indications**
- Primary oxalosis
- Gycogen storage diseases
- Hyperlipidemia
- Polycystic liver disease

**Malignant disease**
- Hepatocellular carcinoma (HCC, within Milan criteria)
- Fibrolamellar carcinoma (FLC)
- Hepatoblastoma
- Epitheloid hemangioendothelioma
- Cholangiocellular adenocarcinoma
- Neuroendocrine liver metastases

**Benign liver tumors**
- Adenomatosis

**Liver transplantation in pediatric patients**
- Biliary atresia
- Byler's disease
- Alagille's syndrome
- Neonatal hepatitis/neonatal viral hepatitis
- Autoimmune hepatitis
- Hepatoblastoma
6 mo is required in the UNOS, ET, and other transplant programs. This mandatory duration of abstinence is a matter of debate because the 6-mo threshold has shown to be insufficient for predicting long-term graft and patient survival (Rice and Lucey 2013). Although uncontrolled systemic infections, which exclude patient survival under immunosuppression, and AIDS-defining symptoms in HIV patients are absolute contraindications, the possibility of performing a liver transplantation in patients diagnosed with infections such as HBV and HIV and controllable local infections must be assessed for each individual patient (Grossi 2003; Tavio et al. 2011; Campsen et al. 2013). Further absolute contraindications for liver transplantation are life-limiting medical conditions such as advanced cardiovascular, pulmonary, or neurologic disorders; intrahepatic CCA; hepatic metastases other than neuroendocrine metastases in selected patients; and extrapleural malignancy (see also Lakkis and Lechler 2013).

Patients diagnosed with HCC exceeding the Milan criteria can still be candidates for liver transplantation, depending on local or national allocation guidelines (Yao 2008; Grant et al. 2013). Further absolute contraindications for liver transplantation are life-limiting medical conditions such as advanced cardiovascular, pulmonary, or neurologic disorders; intrahepatic CCA; hepatic metastases other than neuroendocrine metastases in selected patients; and extrapleural malignancy (see also Lakkis and Lechler 2013).

From a transplant-physician viewpoint, patients should be referred for consideration for liver transplantation as early as possible. Referral does not automatically mean listing of the patient, but allows thorough assessment of candidacy for transplant before listing. If the interdisciplinary decision is made that the patient is eventually a candidate for listing, an extensive patient evaluation is performed (Table 3).

After exclusion of absolute contraindications and discussion of relative contraindications, several medical, psychosocial, and ethical questions have to be answered:

- Can the patient survive the operation and postoperative period?
- What gain of lifetime and what quality of life will the patient have after transplantation?
- Will the patient be compliant regarding the medical regimen?
- In patients with alcoholic liver disease and/or a history of drug abuse, besides being abstinent for at least 6 mo, what is the chance of the patient staying abstinent lifelong?
- Psychosocial issues: Do psychological disorders or lack of social support compromise long-term outcome?
- Is living donation an option?

Some comorbidities are discovered only at the evaluation process but can also be corrected before transplantation. As the transplant patient age has increased throughout the years, cardiovascular disease is common and has to be treated before listing. An increasing number of patients in Western countries suffer from morbid obesity and have to be critically evaluated concerning perioperative risk and probable need of weight loss with or without bariatric surgery. Up to one-third of patients with cirrhosis develop diabetes. These patients require good metabolic control before listing because the re-

### Table 2. Contraindications for liver transplantation

<table>
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<tr>
<th>Absolute contraindication</th>
<th>Relative contraindications</th>
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<tr>
<td>Active alcohol abuse</td>
<td>Psychosocial conditions</td>
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<tr>
<td>Uncontrolled systemic infections</td>
<td>Advanced age</td>
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<tr>
<td>Uncontrolled extrahepatic malignancy</td>
<td>Severe hepatopulmonary or severe hepatorenal syndrome</td>
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<td>Uncontrolled/limiting medical conditions</td>
<td>Severe obesity/ malnutrition</td>
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EVALUATION
Acquired immunosuppression itself increases the risk of and probably worsens preexisting diabetes mellitus (Prokai et al. 2012).

Portopulmonary hypertension and hepatopulmonary syndrome may be reversed by liver transplantation. However, uncontrolled portopulmonary hypertension during the transplantation procedure may cause severe anesthesia problems and severe damage to the graft due to elevated central venous pressure.

Hepatorenal syndrome may also be reversed after transplantation, but a simultaneous listing for liver and kidney may be considered if persistence of chronic kidney disease is suspected (Angeli and Gines 2012). Because the results of a simultaneous liver and kidney transplantation are critical (Papafragkakis et al. 2010), with an increased loss of kidneys in the Eurotransplant area, the following solution was found. Patients listed simultaneously for liver and kidney can be first transplanted with a liver alone and receive extra points on the kidney waiting list. If they are still in need of a kidney transplant (clearance, 15 mL/min) 90–360 d after liver transplantation, they have the chance to receive a kidney transplant within 3 mo. Thus, loss of kidneys during simultaneous transplantation, early death with a functioning kidney graft, and unnecessary kidney transplantations should be prevented. This approach has to be evaluated during the next years.

The listing criteria by the UNOS state that LTx candidates can be listed for kidney transplantation too if they have a documented stage 4–5 chronic kidney disease, acute kidney injury with a glomerular filtration rate lower than 25 mL/min continuously for 6 wk, or a metabolic disease such as hyperoxaluria.

Patients with HCC who are eligible for an exceptional MELD (eMELD) have to be evaluated concerning the specificity of the lesion and the size and number of tumors and vascular infiltration in the liver. Furthermore, extrahepatic spread has to be excluded. For that purpose, imaging with MRI and CT and—for specificity of the typical arterial hyperperfusion in the HCC lesion—contrast enhanced ultrasound (CEUS) is recommended. Thus, it can be evaluated if the patient fits, for example, in the Mi-

### Table 3. Evaluation for liver transplantation

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<th>General assessments</th>
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<td>Previous medical/surgical history</td>
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<td>Physical examination</td>
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<tr>
<td>Vaccinations: Hepatitis A/B, tetanus, diphtheria, polio</td>
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<tr>
<td>Psychosocial assessment by psychiatrist</td>
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<td>Assessment by hepatologist</td>
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<td>Consult with transplant surgeon</td>
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<th>Blood tests</th>
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<tr>
<td>ABO and Rh blood group, full blood count, electrolytes, BUN, creatinine, creatinine-clearance, coagulation (INR, APTT, factor II, factor V), liver function tests, glucose, ferritin, transferrine, protein electrophoresis, thyroid hormones, tumor marker (AFP, CA19-9, CEA, CA125 in females; PSA in males), isotypes of antibodies (IgA, IgG, IgM, ANA, AMA)</td>
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<td>Urinalysis and microscopy</td>
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<th>Microbiology/virology</th>
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<tr>
<td>Hepatitis serology (Hepatitis A/B/C/D), CMV IgG/IgM, EBV IgG/IgM, VZV IgG/IgM, HIV, tuberculosis</td>
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<th>Screening for infections/tumors</th>
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<td>Maxillofacial/dental examination</td>
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<td>ENT examination</td>
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<td>Dermatological examination</td>
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<td>Gynecology/urology examination</td>
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<td>Gastroscopy</td>
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<td>Coloscopy in patients at risk or &gt;40 yr</td>
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<th>Preparation for surgery</th>
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<tr>
<td>Pulmonary function test and blood gas analysis</td>
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<td>EKG and echocardiography</td>
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<td>Cardiac catheterization in patients at risk or &gt;65 yr</td>
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<td>Assessment by transplant anesthetist</td>
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<th>Radiologic assessment</th>
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<td>X ray of paranasal sinuses</td>
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<td>Thoracic and abdominal three-phase angio-CT scan</td>
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<td>Mammography in female patients at risk or &gt;40 yr</td>
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<td>Duplex-sonography of the liver</td>
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<th>Final assessment</th>
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<td>Interdisciplinary review by transplant board</td>
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<tr>
<td>(hepatologist, transplant surgeon, transplant anesthetist, psychiatrist)</td>
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lan criteria or the UNOS criteria for listing with exceptional MELD. These patients should be also evaluated concerning bridging strategies until the expected time of transplantation. Here interventional radiologists and oncological liver surgeons should be included.

LISTING AND TIMING AND ALLOCATION OF LTX

Listing

After extensive evaluation, the final listing of the patient is an interdisciplinary process. In the liver transplantation board, transplant surgeons, transplant hepatologists, anesthesiologists, radiologists, transplant coordinators, and psychiatrists should be included. All participate in the decision of listing the patient formally for transplantation (Dawwas and Gimson 2009).

Timing and Allocation

Timing is crucial for the success of liver transplantation. On the one hand, best results are achieved if the patient is not decompensated and still in a good general condition. On the other hand, the decompensated and sickest patients are the ones who most urgently need transplantation—but have the worst outcome. Owing to organ shortage, different allocation solutions are in use but are currently intensively discussed. A model for the sickest-first policy, MELD, was implemented in the allocation in the UNOS area in 2002 and in the Eurotransplant area in 2007. It consists of serum creatinine, international normalized ratio (INR), and bilirubin (patient-based allocation). The MELD calculator can be found, for example, on the following website (www.mayoclinic.org/meld/mayomodel6.htm). The MELD was originally developed to predict 3-mo survival after transjugular intrahepatic portosystemic shunt replacement (Malinchoc et al. 2000; Said et al. 2004). Since implementation of the MELD system, waiting list mortality has declined. However, patients with very high laboratory MELD scores (>35) are normally ICU-bound, on dialysis, and often require vaso-pressor support and artificial ventilation. If these patients are transplanted and not temporarily delisted until recovery, the 1-yr mortality is very high. Studies are ongoing to assess whether the addition of parameters that are associated with poor patient outcome (serum sodium, renal failure, and serum albumin) will improve the predictive ability of MELD (Biggins et al. 2005; Kim et al. 2008).

“Center-based allocation” is in use especially in countries with few transplant programs, for example, in Australia, the United Kingdom, and Austria. Moreover, it is used parallel to the MELD system for extended criteria donors and for recipients who are stable but not well represented in the MELD system. The advantage of center-based allocation is that the physicians can match the organ to the patient, which results in a relatively good outcome although extended criteria organs are used.

“High-urgency allocation” is generally only possible in case of acute liver failure (see above) or for retransplantation.

DECEASED-DONOR LIVER TRANSPLANTATION (DDLT)

The deceased-donor pool is limited. Thus, in the last decade, different strategies have been implemented to increase the pool of deceased liver donation and transplantation. Donation after brain death is widely accepted and well established. Donation after cardiac death (DCD) is well established, for example, in the UNOS area, but still controversial in Europe. The results after DCD transplantation are not as good compared with donation after brain death; however, it seems to be a feasible source to increase the donor pool. In addition, older donors are increasingly accepted, because in some countries the majority of donors are >50 yr. Absolute contraindications for deceased organ donation are cancer and uncontrolled infections (e.g., hepatitis). Cardiac arrest, hypotension, high sodium, and liver steatosis are not absolute contraindications. Macroscopic evaluation of the liver at time of retrieval (before and after perfusion with cold storage solution) is very important to assess organ quality. Frozen sections may not always be available at the donation site and are
not optimal to evaluate the degree of steatosis. Extension of the donor pool by use of marginal grafts may result in higher complication rates such as early graft failure, biliary complications (ischemic type biliary lesions), and need for retransplantation (Busuttil and Tanaka 2003).

Another technique to increase the donor pool is split-liver transplantation. Optimal grafts can be split into an extended right lobe for an adult recipient and a left lateral lobe for a pediatric recipient (Fig. 3). Also, so-called full splits (right and full left lobe for two adult recipients) are used in some cases (Gundlach et al. 2000). These techniques—if used in experienced centers—do have good long-term results but are often limited by logistic and thus ischemic time problems if the split is allocated to two different centers.

**LIVING-DONOR LIVER TRANSPLANTATION (LDLT)**

Living-donor liver transplantation (LDLT) is an established method with increasing numbers worldwide. In Asian countries, close to 90% of liver transplantations are from living donors because of social and religious factors. In western countries and especially in the UNOS area, some recent donor deaths led to a decline in LDLT numbers. The advantage of LDLT is the use of an optimal healthy donor, minimal ischemic time, elective surgery, and timing of transplantation owing to the recipient’s need and medical stability and not to deceased organ availability. A further advantage of LDLT is the possibility of ABO-incompatible transplantation (Song et al. 2013). However, living donation is not without risk for the healthy donor, and LDLT is surgically more demanding than whole-organ transplantation. The remaining liver in the donor regenerates within 3 mo to 90% of its original volume. The donor has a risk of a 30% morbidity and a mortality risk of up to 0.8% (Ghobrial et al. 2008). Especially, the bile duct system has to be evaluated intraoperatively by cholangiogram, and aberrant bile ducts have to be taken care of meticulously (Jeon et al. 2013). In addition, the venous outflow in the recipient is crucial, and

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**Figure 3.** Anatomy of the liver with liver segments (seg). (A) Left lateral splitting or living donation of seg II/III for a pediatric recipient. (B) Living donation of the right lobe (seg V, VI, VII, VIII) for an adult recipient.
branches of the middle vein may have to be re-
constructed. Moreover, in adult LDLT, small-
for-size syndrome is sometimes a problem.
Thus, a precise imaging evaluation with three-
phase CT angiography and volume measure-
ment of the future liver remnant of the donor
as well as of the graft size have to be performed
and calculated with the patient body weight. For
all LDLT, careful selection and extensive evalua-
tion of the donor are very important (Table 4)
(Berg et al. 2007). All ethical, legal, and insur-
ance aspects have to be cleared with the author-
ities and well documented. Altogether, a risk
adjustment for the donor and the recipient has
to be performed multidisciplinarily. The risk of
the recipient must equal or exceed the risk of the
donor (Thuluvath and Yoo 2004).

LIVER TRANSPLANTATION—TECHNIQUES

The transplant operation itself has been signifi-
cantly standardized and optimized during the
last two decades. Nowadays liver transplanta-
tion in a stable donor with a standard donor
organ is a routine operation and may be per-
formed without any blood transfusion and only
few plasma replacements. However, the stan-
dards developed for liver transplantation after
deceased donation are different based on surgi-
cal training.

First, the native liver has to be explanted via
right angular incision. Here, two different meth-
ods are used: replacement of the inferior vena
cava (IVC) or so-called piggyback, in which the
inferior vena cava is preserved. The clamping of
the IVC needed for resection can decrease blood
pressure and can cause cardiac problems diffi-
cult to manage for the anesthetist. Moreover,
renal insufficiency may be a problem because
of clamping of the IVC causing reduced perfu-
sion of the kidneys. Recently, in a Cochrane data-
base analysis, the piggyback technique versus
standard technique was reviewed, and they
found two randomized trials with a total of
106 patients (Gurusamy et al. 2011b). Warm is-
chemic time was shorter in the piggyback meth-
od because only one caval anastomosis had to be
performed. However, the proportion of patients
who developed chest complications was signifi-
cantly higher with the piggyback method. There
was no significant difference in postoperative
defath, primary graft nonfunction, complica-
tions related to the blood vessels, kidney failure,
blood transfusion requirements, or ICU stay or
hospital stay between the two groups. In our
institution, we prefer replacement of the IVC
because we see a substantial shortening of oper-
ation time.

To reduce the effects of clamping, the IVC
and also the portal vein—which may cause mes-
enterial congestion—veno-venous bypass was
once widely used and has now developed a re-
vival in some centers. There are different tech-
niques described for the bypass: open or percu-
taneous, heparin-coated or no heparin-coated.
This was reviewed as well in a Cochrane database
analysis, and no difference regarding renal fail-
ure or blood transfusions was found between the
groups in two randomized trials (Gurusamy
et al. 2011a). The operating time was signifi-
cantly shorter in the percutaneous bypass group.
To aim at a short operating time, we perform no
veno-venous bypass at all at our center.

Another point of discussion is the technique of
flushing and reperfusion for liver transplanta-
tion. Marginal organs are prone to ischemic
time biliary lesions (ITBL) due to reduced flow
in the pericanalicular arteries of the bile ducts.
Here some studies hint that the way and se-
quence of reperfusion influence the rate of ITBL (Heidenhain et al. 2006; Farid et al. 2011). The Cochrane database analysis searched for comparisons that included initial hepatic artery flush versus initial portal vein flush or simultaneous flushing and different types of blood venting or use of perfusion fluid (Gurusamy et al. 2012). There was no significant difference in mortality, graft survival, or severe morbidity rates in any of the comparisons.

Bile duct reconstruction can be performed with a duct-to-duct or duct-to-small-bowel anastomosis. Duct-to-small-bowel is recommended for patients with PSC. Placing a T-tube or not in the bile duct remains controversial (Gastaca et al. 2013). The bile duct system and the common bile duct remain the Achilles heel of transplantation, because they are most sensitive to early ischemic injury already during cold storage. We developed a histological bile duct risk score that predicts biliary complications and may help decision making in LTx (Brunner et al. 2013).

**POSTTRANSPLANT CARE**

Lifelong aftercare is crucial for long-term graft and patient survival after liver transplantation. During the early postoperative phase, daily blood tests are necessary for surveillance of liver function, coagulation, electrolytes, and target blood levels of immunosuppressive drugs. Factor VII, being produced by the liver and having a half-life of 6 h, is an excellent parameter to assess liver function on a daily basis. Prophylactic antibiotic therapy is given for 3 d perioperatively. Prophylactic treatment for CMV and PCP infections should be given according to the donor/recipient risk profile (Lautenschlager 2009). Regular duplex-sonography is performed to assess liver perfusion.

Daily immunosuppressive therapy is mandatory to prevent organ rejection. Especially in the early posttransplant phase, immunosuppressive therapy consists of complex combinations of various drugs and needs to be adapted for each patient individually. Components are antilymphocyte antibodies, steroids, calcineurin inhibitors, and inhibitors of B- and T-cell proliferation (Scherer et al. 2007). Standard immunosuppressive combination regimens are basiliximab, MMF, cyclosporine, and prednisolone or basiliximab, MMF, sirolimus/everolimus, and prednisolone (Farkas et al. 2009).

The chimeric monoclonal T-cell IL-2-receptor antibody basiliximab is given on d 0 and 4 after liver transplant for induction therapy. Mycophenolate mofetil (MMF), a reversible inhibitor of inosine monophosphate dehydrogenase in purine synthesis, reduces proliferation of B and T cells (Schlitt et al. 2013). Calcineurin inhibitors such as cyclosporine inhibit T-cell production and excretion of IL-2. mTor inhibitors such as sirolimus and everolimus also inhibit the proliferation of B and T cells. However, in contrast to calcineurin inhibitors, mTor inhibitors show no renal toxicity (Schnitzbauer et al. 2010). The main side effects are bone marrow toxicity, inhibition of wound healing, and reduction of liver function. On the other hand, mTor inhibitors lower cancer risk in selected patients and therefore are recommended especially for patients transplanted for malignant disease (Law 2005). Steroids inhibit T-cell activation and block IL-1 and IL-2 synthesis. Steroids are the backbone of all immunosuppressive regimens and are given already before reperfusion of the transplanted organ intraoperatively. In the early postoperative phase, steroids are given in high doses but should be gradually reduced. In many patients, steroids can be tapered 6 mo after transplantation (Shapiro 2004), and long-term immunosuppressive therapy often can consist of monotherapy. Because immunosuppressive drugs can interact with many other medications and dietary components, target levels must be checked lifelong on a regular basis, and interactions must be considered when new medications must be introduced.

Although patients must be closely monitored by their transplant center in the early postoperative phase, long-term lifelong aftercare can also, at least in part, be conducted by general practitioners and primary care hospitals. The main focuses of aftercare must be screening for complications and side effects of immunosuppressive therapy, recognition and treatment of acute or chronic graft rejection, recognition
and treatment of biliary complications, malignant disease, and recurrence of the primary liver disease. Details are shown in Table 2. Especially, prevention, recognition, and treatment of infections including opportunistic infections are crucial for long-term patient survival because patients under immunosuppressive therapy often do not show typical clinical symptoms or leukocytosis. Infections can worsen rapidly to septic conditions, and infections present the leading cause of mortality after liver transplantation (Fishman and Rubin 1998; Torbenson et al. 1998).

For prevention of malignant disease, patients must be advised to use high sun-protection-factor sunscreen and to quit cigarette smoking. Furthermore, preventive screening examinations should be performed on a frequent basis (see Table 5) (Watt et al. 2009; Chak and Saab 2010). In patients transplanted for hepatitis B/C, PBC, PSC, autoimmune hepatitis, and hemochromatosis, screening for disease recurrence must be performed. Administration of hepatitis B immune globulin during transplant surgery and at regular intervals, in combination with antiviral therapy, can prevent HBC recurrence (Cholongitas et al. 2011). In contrast, treatment with pegylated interferone monotherapy or combined with ribavirin, owing to liver toxicity, is not started until HCV recurrence is proven (Gurusamy et al. 2010). Patients transplanted for alcoholic liver disease must stay sober after liver transplantation, and also patients transplanted for other indications should cease alcohol consumption.

### FUTURE PERSPECTIVES OF LIVER TRANSPLANTATION

The scarcity of deceased donor organs will remain one of the main problems for patients on the waiting list for liver transplantation. In addition, patients with end-stage liver disease are affected who cannot enter the waiting list at all because of strict allocation rules made to counterbalance the lack of organs. Extension of the deceased donor pool is essential but will reach a limit. Living-donation liver transplantation, which is standard procedure in Asian countries, will have to increase also in Western countries to cover the need for lifesaving organs.

Future immunosuppressive strategies in liver transplantation have to imply three main goals:

- Reduction of side effects like renal insufficiency,
- reduction of cancer recurrence of hepatocellular carcinoma and de novo cancer after transplantation, and
- finally, and optimally, induction of tolerance.

For that purpose, mTOR inhibitors are very interesting because they block the central pathway for vital aspects of tumor development, including angiogenesis and cell growth. mTOR inhibitors have anticancer activities, which may prove critical in the fight against high cancer recurrence and de novo cancer. They furthermore provide the capacity to interfere

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**Table 5. Overview of posttransplant aftercare**

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<th>General assessments</th>
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<td>Physical examination</td>
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<td>Dental examination</td>
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<td>Vaccinations: influenza, pneumonia, hepatitis A/B; live virus vaccinations should be avoided.</td>
</tr>
</tbody>
</table>

**Screening for nonmalignant disease and immunosuppressant side effects**

- Hypertension
- Renal dysfunction
- Diabetes
- Cardiovascular disease
- Infection/opportunistic infection

**Screening for malignant disease**

- Annual skin cancer screening
- Annual gynecology and mammography screening in women
- Annual urologic and PSA screening in men
- Colonoscopy at regular intervals (depending on risk factor)
- Annual abdominal and pelvic ultrasound
- In some centers: Annual chest + abdominal CT/MRI

**Screening for recurrence of primary liver disease**

- Hepatitis B/C, PBC, PSC, autoimmune hepatitis, hemochromatosis, malignancy
Liver Transplantation

with fibrotic processes that often accompany transplant rejection and to influence the preferential development of immunological tolerance. Studies are ongoing that try to induce tolerance by either stem cell therapy (Dahlke et al. 2009; Dillmann et al. 2012) or by transfusion of regulating cells in the setting of living donation (www.onestudy.org).

REFERENCES


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