10 Liver transplantation

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Orthotopic liver transplantation (OLT) is the mainstay of treatment of end-stage liver disease in the USA and much of the world. The first transplantation with extended survival was performed by Thomas Starzl in 1967. The recipient was an 18-month-old girl with hepatocellular carcinoma. Additional historical landmarks include the development of cyclosporine as an effective and tolerated immunosuppressant agent, and a 1983 National Institutes of Health consensus conference which concluded that liver transplantation was no longer an experimental procedure, but a "therapeutic modality" for advanced liver disease. Over 6500 deceased and living donor liver transplant procedures are now performed in the USA annually.

One of the most far-reaching changes in liver transplantation in the past decade centered on the implementation of the model for end-stage liver disease (MELD) system for organ allocation in 2002. Before implementation of the MELD system, organs were allocated using a "status" system that relied on a combination of disease severity and recipient waiting time. The MELD system, using a score that incorporates serum bilirubin, serum creatinine and the international normalized ratio (INR), prioritizes patients for transplantation based on their calculated 90-day mortality rate without a liver transplant. The implementation of the MELD system, along with a steady growth in the number of deceased donor livers between 2000 and 2007, has led to shorter waiting lists, a shorter median time to transplantation, and reduced death rates for patients awaiting liver transplantation. Moreover, the transparent and quantitative nature of the MELD system allows an on-going rational and statistical evaluation of the efficacy of organ allocation. This has facilitated additional changes in the allocation system, including the "share 15 rule" (see below) and changes in priority accorded to patients with "MELD exceptions," including the exception allotted to the growing number of patients transplanted for hepatocellular carcinoma (HCC).

The 5-year patient survival rate after liver transplantation is currently about 73%, and the 5-year graft survival rate is 68%. However, major challenges remain in the care of liver transplant recipients before graft and patient survival rates can improve further. This chapter focuses on several of these obstacles, including optimization of patient and graft selection, management of recurrent underlying liver disease with a focus on hepatitis C, and the care of complications of long-term immunosuppressive therapy, including nephrotoxicity.

Patient and allograft outcomes

Patient and graft survival after liver transplantation have continued to improve over the last decade. From 1987 to 1997, the 1-year patient survival rate increased from 64% to 86% with the 10-year survival rate increasing from 42% to 60%. During the same time period, the graft survival rate at 1 year increased from 55% to 79% and the 10-year graft survival rate from 34% to 52%. In 2008, the 1-year patient and

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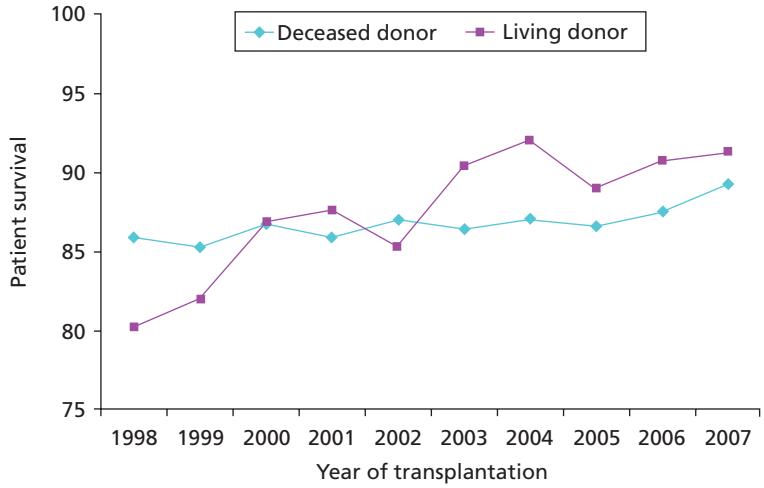

Figure 10.1 Changes in patient survival rates over time in liver transplantation in the USA.

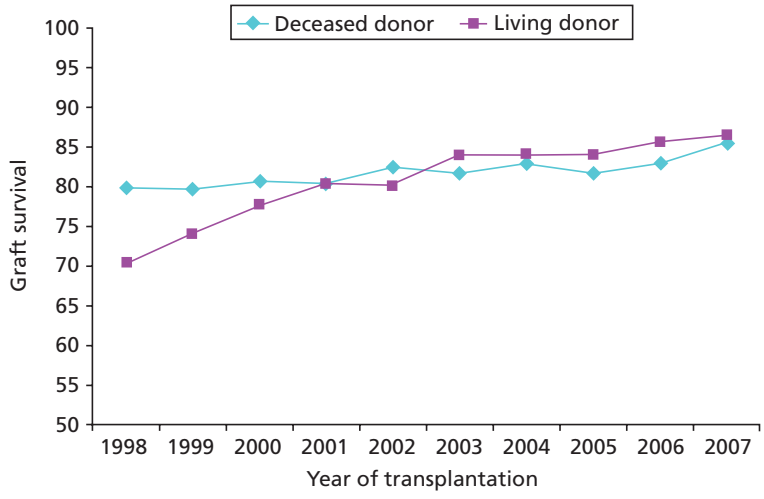

Figure 10.2 Changes in graft survival rates over time in liver transplantation in the USA.

graft survival rates nationally were 88% and 84%, respectively (Figures 10.1 and 10.2).

One of the biggest challenges facing patients awaiting liver transplantation is the increasing discrepancy between the number of transplantations performed yearly and the number of patients on the waiting list. In general, this has led to more ill patients receiving transplants while at the same time changing donor selection as transplant centers become more aggressive in attempting to match donor availability with recipient needs. Over the last 20 years, the number of new registrants on the waiting list has far exceeded transplantations performed and subsequently has resulted in increased wait-list mortality. From 2002 to 2008, the number of patients waiting for liver transplantation has remained high, approximately 16 000 each year. Over this time, approximately 6000 liver transplantations were performed annually in the USA with approximately 2000 deaths per year during the same time period (Figure 10.3).

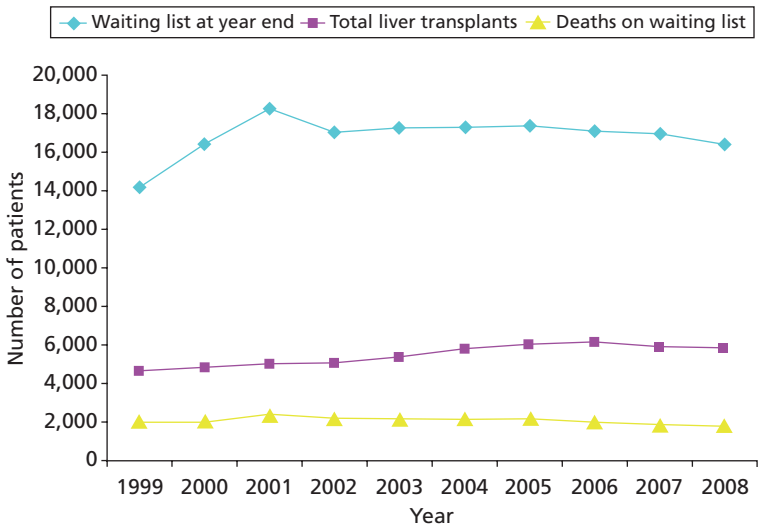

Figure 10.3 Changes in the size of the liver transplant waiting list, number of transplants performed, and deaths on the waiting list over time in the USA.

As noted above MELD was implemented in 2002 as a way to prioritize patients on the wait-list. MELD takes into account only severity of illness, and minimizes waiting time as a variable, and has been shown to effectively predict 3-month mortality from liver disease. Utilizing the MELD system for allocation of livers in the USA has resulted in a reduction in wait-list mortality by 15%, with the median wait time reduced from 656 days to approximately 300 days. Transplantation in patients with MELD scores ≤14 has been associated with higher mortality than for patients with the same MELD score who did not undergo transplantation. This finding led to the "share 15" policy which indicates that, if an organ is available and the highest MELD score of local patients is <15, the organ should be offered to a larger region first before it can be used locally. Several studies have shown that patients transplanted with MELD scores >25 have a lower survival than patients transplanted for lower MELD scores. However, the survival benefit remains high among patients with such scores. As a result, there is currently no MELD score for which removal from the list is mandated. It is important to note that MELD was designed to predict mortality risk from liver disease while waiting for liver transplantation and is less useful in predicting duration of survival *after* transplantation.

Key points 10.1 The MELD (model for end-stage liver disease) score

MELD calculators, requiring only an INR, serum creatinine, and serum bilirubin concentration, are widely available on the internet and on hand-held computers. The actual formula for calculating MELD is as follows:

$$\begin{aligned}\text{MELD score} = {} & 0.957 \times \log_e(\text{creatinine, mg/dL})^* \\ & + 0.378 \times \log_e(\text{bilirubin, mg/dL}) \\ & + 1.120 \times \log_e(\text{INR}) \\ & + 0.643\end{aligned}$$

Multiply the score by 10 and round to the nearest whole number. Laboratory values <1.0 are set to 1.0.

*The maximum serum creatinine considered within the MELD score equation is 4.0 mg/dL. For candidates on dialysis, defined as having two or more dialysis treatments within the prior week or 24 h of continuous venovenous hemodialysis (CVVH) within the prior week, the serum creatinine entered in the MELD equation is automatically entered as 4.0 mg/dL.

Liver re-transplantation is associated with relatively poor survival rates, as has been established by many investigators. Multiple prognostic factors have been evaluated, including interval to re-transplantation,

age, gender, and diagnosis of primary non-function (PNF) versus non-PNF. In addition, higher MELD scores have been shown to result in poorer survival after re-transplantation. Graft survival is significantly reduced in patients undergoing re-transplantation compared with first transplantation. For patients undergoing re-transplantation, 1-, 5- and 10-year graft survival rates are 69%, 54, and 38% which are significantly lower than those reported (84%, 69%, and 55%) for patients undergoing a first transplantation.

Deceased donor transplantation

Multiple factors contribute to outcomes after primary OLT. These can be classified as donor, recipient, operative, and postoperative factors.

Donor characteristics associated with poor post-OLT outcomes can be divided into relative and absolute factors. Many of the studies attempting to identify donor factors that contribute to poor post-transplant outcome have been performed at single centers, and the results have been variable and often contradictory. However, a compilation of multiple studies has identified 15 donor factors that may be associated with poor outcomes. These include donor age, gender, ethnicity, weight, ABO compatibility status, cause of brain death, length of hospital stay, pulmonary insufficiency, pressor use, steatosis, cardiac arrest, prolonged cold ischemia time, serum sodium level, and blood chemistry. Severe macrosteatosis (>60%) and cold ischemia time >30 h are absolute risk factors associated with poor post-transplant outcomes. Relative risk factors include moderate steatosis (defined as steatosis 30–60%), cold ischemia time >12 h, and donor age >50 years.

Recipient outcomes do vary by recipient age, gender, race, and diagnosis. In general, recipient characteristics have also been extensively investigated, including etiology of liver disease, age, coagulopathy, impaired renal function, ventilator status, hepatic function, and MELD score. Of all these factors, renal function before transplantation appears to be most closely associated with post-transplant outcomes. Ultimately, only a few absolute contraindications for liver transplantation exist., including extrahepatic malignancy, uncontrolled sepsis, and irreversible multisystem organ failure.

Operative and postoperative factors associated with post-transplant survival are often difficult to identify, because many of these factors have never been assessed in survival models. In terms of operative risk factors, warm ischemia time has been the most extensively evaluated in pretransplant models. Postoperatively, it has been extremely difficult to identify when urgent re-transplantation should occur. Although factors, such as bilirubin, prothrombin time, and creatinine, have been identified to help predict graft failure, the models generated may not be applicable for daily use and, currently, the decision to re-transplant relies on clinical assessment rather than mathematical models.

MELD is effective in predicting pretransplant mortality. Unfortunately, MELD scores have not been as helpful in predicting post-transplant outcomes. The transplant community has discussed the need for identifying the "upper limit" of utility, i.e., the need for identifying patients who have become too ill to benefit from transplantation. Thus far, criteria for determining when a patient should be removed from the list have not been established, and the decision remains with the transplant center. This is still a major difficulty with liver organ allocation, because the patients most in need of transplantation may not be the patients who will reap the most long-term survival and benefit.

Living donor transplantation

Adult to adult living donor transplantation (LDLT) began to grow in the 1990s as a possible solution to the widespread organ shortage. Previous work in Asia and Europe had established the utility of LDLT using the right hepatic lobe of a living donor for transplantation into adults with liver failure. Early on, from 1997 to 2001, the number of LDLTs being performed in the USA increased to a peak of over 400 in 2001. At that time, this represented about 8% of liver transplantations being performed in the USA. However, since that time, there has been a plateau and subsequent decrease in the number of adult LDLTs performed, partly due to concerns over donor morbidity and mortality (Figure 10.4).

Several factors suggest that outcomes from LDLT would be better than for deceased donor transplantation. These include decreased waiting time for the

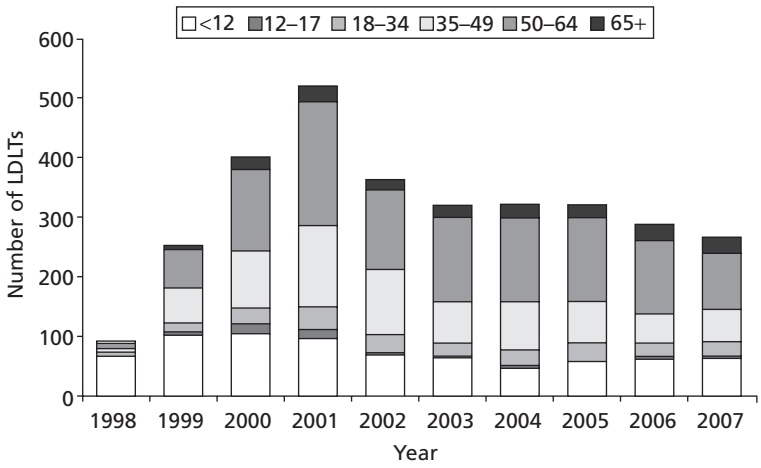

Figure 10.4 Number of living donor liver transplants (LDLTs) by recipient age, 1998–2007.

recipient, optimal evaluation of the donor organ before selection, and reduced cold ischemia time. In fact, both patient and graft survivals are improved in LDLT compared with deceased donor transplantation. The 1- and 3-year patient survival rates in LDLT are 91% and 82%, compared with 88% and 78% for deceased donor transplant recipients. The 1- and 3-year graft survival rates for LDLT are 86% and 76% compared with 84% and 73% for deceased donor liver transplantation. Overall, recipient outcomes have been shown to be comparable to those of deceased donor transplants. However, recipients of living donor livers are generally younger and have less severe liver disease.

Recipient selection and evaluation

There are several diagnostic indications for liver transplantation (Table 10.1). However, the need for transplantation is determined by weighing the natural history of the patient's liver disease against the likely outcome of transplantation. There are several basic questions that should be asked when evaluating patients referred for liver transplantation. First, is the liver disease severe enough to consider transplantation? In other words, is the patient at the point in the natural history of their disease at which no other alternate therapy is likely to improve their state of health other than transplantation? Second, is the patient an acceptable candidate? Are there recipient factors that would likely alter the expected outcome of transplantation, or are there factors that would interfere with the ability of the patient to benefit from transplantation? Finally, if patients appear to need a transplant and if they are found to be acceptable, are they willing and do they have the support to fully participate in the process?

With respect to the first question, the Childs–Turcotte–Pugh (CTP) score (Table 10.2) has been utilized to assess severity of cirrhosis, with minimal listing criteria considered a CTP score of ≥7 (Child's B cirrhosis). In these patients, the 1-year survival with a liver transplant would be expected to exceed the 1-year survival without a transplant. Obviously, other complications of cirrhosis, such as a diagnosis of HCC, hepatopulmonary syndrome, refractory ascites, or refractory encephalopathy, may make a candidate eligible for transplantation if the benefit outweighs the risk of surgery.

Case

A 43-year-old woman with autoimmune hepatitis is referred for possible liver transplantation. She has been taking prednisone for more than 1 year. On physical examination, she is alert and oriented and has no asterixis. She has a cushingoid appearance with centripetal obesity but no obvious ascites. An abdominal ultrasound scan does, however, show mild ascites. Laboratory evaluation shows a bilirubin of 1.4 mg/dL, albumin of 3.2 g/dL, and INR of 1.3. Based on her CPT score and her MELD score, you recommend that liver transplantation would likely not offer a survival advantage over medical therapy at this point in time. You also recommend close

Table 10.1 Indications for liver transplantation

Decompensated cirrhosis
Non-cholestatic
- Viral hepatitis B or C
- Alcohol
- Non-alcoholic steatohepatitis
- Autoimmune
- Drug induced
- Cryptogenic

Cholestatic
- Primary biliary cirrhosis
- Secondary biliary cirrhosis
- Sclerosing cholangitis
- Drug induced
- Sarcoidosis
- Cystic fibrosis
- Biliary atresia
- Alagille's syndrome
- Progressive familial intrahepatic cholestasis

Metabolic/Inherited
- α_1-Antitrypsin deficiency
- Wilson's disease
- Hereditary hemochromatosis
- Glycogen storage disease
- Tyrosinemia

Benign disorders
Polycystic liver disease
Budd–Chiari syndrome
Non-cirrhotic portal hypertension
Hemangioma (giant)

Malignant disorders
Hepatocellular carcinoma
Hepatoblastoma
Epithelioid hemangioendothelioma
Endocrine tumors

Other
Type 1 primary hyperoxaluria
Familial amyloidosis
Urea cycle or branched-chain amino acid disorders

Acute liver failure
Drugs
Toxins
Vascular
Immune
Metabolic (Wilson's disease)
Neonatal hemochromatosis

Acute graft loss
Primary non-function
Vascular
Humoral rejection

Late graft loss
Recurrent disease
Chronic rejection

Table 10.2 Child–Pugh classification of severity of liver disease

Parameter	Points		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
International normalized ratio	<1.7	1.7–2.3	>2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

follow-up with serial re-evaluations of the severity of her liver disease.

Medical evaluation

The answer to the second question involves the medical evaluation of the patient. Initial assessment should begin with a consultation with a hepatologist and a transplant surgeon as well as preliminary evaluation of financial coverage. Patients at this point may be deemed either too early or too ill for transplantation and no further evaluation may be necessary. However, in most patients it would be expected that further evaluation would be required to determine

suitability for transplantation. The general evaluation consists of several consultations as well as laboratory and diagnostic testing (Table 10.3). The hepatologist evaluates the patient for disease diagnosis and assesses severity and considers whether alternate treatments may be appropriate. The surgeon's assessment should consider the technical aspects of the operation as well as donor selection and postoperative issues. Consultation with the "psychosocial team" may include evaluation by a social worker, clinical psychologist, chemical dependency specialist, or a combination of these consultants. Social support, risk of recidivism, and determination of patient ability to understand and cooperate with recommendations should be evaluated. A financial counselor should meet with the patient and family to assist them in understanding coverage and any out-of-pocket expenses. Consultation with a dietician or other specialists would be warranted based on specific patient issues or medical needs. In particular, clearance by cardiology would be warranted in patients aged >40 or those with a past medical history that dictates concern.

Laboratory testing is used to assess disease etiology, the degree of hepatic dysfunction and other comorbidities. Further evaluation of abnormal findings may warrant consultation with specific specialists such as infectious disease or nephrology. Basic laboratory testing includes a complete blood count, biochemical profile, and coagulation profile, blood group and cross-match, thyroid-stimulating hormone, and lipid profile. Further evaluation may vary from center to center, but should also include serologic work-up for viral hepatitis, testing for autoimmune and metabolic liver disease, screening for HCC with α-fetoprotein, urinalysis, and determination of the glomerular filtration rate (GFR) and arterial blood gas, a toxicology screen, and appropriate screening for extrahepatic malignancy (i.e. breast cancer screening in women aged >40 years, colon cancer screening). A patient may undergo more extensive testing if comorbid medical conditions or some positive test during the evaluation reveals a potential contraindication for transplantation.

Imaging is used to define the portal vasculature and to exclude malignancy. In patients with documented hepatocellular cancer, additional imaging of the chest with computed tomography (CT) is mandatory before listing. Cardiovascular testing with an echocardiogram is important to screen for increased pulmonary pressures. If evidence of increased pulmonary pressures is suspected, right heart catheterization and evaluation by both cardiology and pulmonary medicine is warranted. Cardiovascular testing should include some form of stress testing with either a dobutamine stress echo or nuclear stress testing to screen for ischemic disease.

In addition to the medical evaluation for transplantation, a psychosocial assessment is mandatory. Almost half of potential candidates for liver transplantation have at least one psychiatric disorder. A thoughtful and thorough assessment of each patient's psychiatric status will aid in assessing suitability for liver transplantation as well as in making recommendations for further evaluation or treatment before listing.

Patients with a history of substance abuse need further evaluation by a chemical dependency specialist. A generalized requirement of 6 months of abstinence has been accepted by most transplant centers. In addition, active participation in treatment may be recommended and required. Patients must participate in their abstinence. Poor prognostic factors include multiple prior episodes of relapses with substance abuse, limited insight into the consequences of substance abuse, and refusal or inability to participate in recovery.

Finally, evaluation of support and finances is mandatory. Patients must have adequate insurance to undergo transplantation and the resources to maintain health after transplantation. Evaluation of prescription coverage, patient and family resources, family and friend support, and individual barriers to success must be investigated by the social worker and other team members.

Selection of candidates

There are several absolute and relative contraindications for liver transplantation (Table 10.4). Uncontrolled sepsis or infection, extrahepatic malignancy, active substance abuse, and significant cardiopulmonary disease are absolute contraindications. Advanced age is a relative contraindication for transplantation, and the age cut-off varies from center to center. Patients aged >70 years may have poorer post-transplant outcomes compared with younger patients. Prior substance abuse, especially a history of

Table 10.3 Evaluation of the liver transplant recipient

Consultations
Hepatology
Transplant surgery
Cardiology
Social work
Financial
(Psychiatry, chemical dependency, nutritional, gynecology, other as necessary)
Laboratory
Complete blood count
Complete chemistry
International normalized ratio
Lipid profile
Blood group
Viral serology: HBsAg, HBcAb, HBsAb, HCV antibody, HAV antibody, HIV antibody, CMV, EBV
TSH
VDRL
α-Fetoprotein
Urinalysis
Measurement of GFR (calculated or 24 hours)
Toxicology screen
Arterial blood gas
(CEA, CA 19-9, PSA)
Imaging
Chest radiograph
EKG
Echocardiogram with/without stress
Cardiovascular stress testing
Dual-phase CT or MRI
Other
Colonoscopy (age >50, family or personal history, primary sclerosing cholangitis)
Mammography (age >40 or family or personal history)
Dental
Pap and pelvic

CEA, carcinoembryonic antigen; CMV, cytomegalovirus; EBV, Epstein–Barr virus; GFR, glomerular filtration rate; HBcAb, hepatitis B core antibody; HAV, hepatitis A virus; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; PSA, prostate-specific antigen; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Reference Laboratory.

heavy alcohol use, may be a relative contraindication for transplantation. Data have shown that 20–50% of patients will consume some alcohol within the first 5 years after transplant, and 10–15% of those patients will have significant alcohol intake. Unfortunately, no reliable predictors exist to help determine which patients will be at highest risk of relapse after transplantation. Presence of significant pulmonary disease

Table 10.4 Absolute and relative contraindications to liver transplantation

Absolute
Severe uncontrolled sepsis
Extrahepatic malignancy
Active alcohol or substance abuse
Lack of adequate social support
Inability or unwillingness to comply with medical recommendations
Severe pulmonary hypertension
Severe cardiopulmonary disease
Relative
Advanced age
Hepatocellular carcinoma outside the Milan criteria
Previous history of malignancy
HIV
Intra-abdominal vascular thrombosis
Neuroendocrine malignancy

including pulmonary hypertension increases a patient's perioperative mortality and may become an absolute contraindication for transplantation due to anticipated worse post-transplant survivals. Finally, infection with HIV was once considered to be an absolute contraindication for liver transplantation. It is now felt to be a relative contraindication in the setting of well-controlled HIV disease because short-term outcomes appear to be reasonably good in these patients. Currently, only select centers in the USA have protocols for transplantation of HIV patients.

Once patients have completed their evaluation, they are reviewed individually by the multidisciplinary transplant team. The ideal candidate for listing is a patient with liver disease advanced to the point where the benefit of transplantation outweighs the risk (Child–Pugh score ≥7), in whom no obvious medical or social issues have been discovered that would interfere with a successful outcome. Once it is recommended that the patient undergo transplantation, if the patient and family agree, the patient is placed on the waiting list.

Table 10.5 American Association for the Study of Liver Disease guidelines for diagnosis and follow-up of varices

Screening esogastroduodenoscopy (EGD) for the diagnosis of esophageal and gastric varices when the diagnosis of cirrhosis is made
In patients with compensated cirrhosis and no varices on the initial EGD, repeat in 3 years
In patients with decompensated cirrhosis, EGD should be repeated annually
In patients with cirrhosis and small varices without prior bleeding but increased risk for hemorrhage (Child's B/C or red weal marks on varices); non-selective β blocker should be used for the prevention of first variceal hemorrhage
In patients with medium/large varices that have not bled but have high risk of hemorrhage (Child's B/C or red weal markings); non-selective β blockers or variceal ligation may be recommended for prevention of first variceal bleed

Management of patients listed for liver transplantation

The advent of MELD has changed the landscape of liver transplantation by allocating organs according to need rather than accumulated waiting time. The key for maintaining patients on the transplant list includes monitoring for complications of cirrhosis. Patients should be screened for HCC with an imaging study and α-fetoprotein every 6 months. Upper endoscopy should be performed to screen for varices. Both the treatment of varices and the timing of subsequent endoscopies depend on the presence and size of varices according to American Association for the Study of Liver Disease (AASLD) guidelines (Table 10.5). Yearly cardiac evaluation is mandated by most insurance carriers. In addition, other screening tests, such as mammograms and pap smears in women, should be updated.

Patients with cirrhosis related to hepatitis C may benefit from attempts to clear viremia, because such patients have better short- and long-term outcomes compared with patients with viremia. Unfortunately, most patients cannot tolerate therapy with pegylated interferon and ribavirin, and the presence of cirrhosis is associated with significantly decreased rates of a sustained virologic response (SVR). Thus, although

attempts can be made to treat a patient for hepatitis C while they are waiting for transplantation, most patients will not be able to tolerate treatment.

In patients with hepatitis B and cirrhosis, those with active viral replication should be placed on oral antiviral treatment. Oral nucleoside and nucleotide reverse transcriptase inhibitors, such as lamivudine, adefovir, telbivudine, entecavir, and tenofovir, may be used for viral suppression. Current guidelines from the AASLD recommend use of an antiviral agent in patients diagnosed with cirrhosis. Avoidance of resistance is mandatory in this population to prevent both further decompensation before and viral resistance after transplantation. Most transplant centers choose either entecavir or tenofovir because these drugs have very potent viral suppression in addition to minimal documented resistance.

The MELD scores should be updated regularly. On average, recalculation of scores occurs every 90 days. However, patients with higher scores as well as those with clinical deterioration should have MELD scores updated more frequently. The interval in patients who are critically ill is defined by the United Network for Organ Sharing (UNOS). Finally, deterioration of clinical status may compromise a patient's candidacy for transplantation. Presence of active infection, multisystem organ failure, or other significant changes in clinical status should prompt the transplant team to re-evaluate the patient's candidacy, potentially resulting in either delisting or a change to "hold" status.

Patients should be screened for and immunized against both hepatitis A and hepatitis B if not already immune. Patients should receive the pneumococcal vaccine, and be referred to infectious disease if childhood immunizations are not up to date.

Evaluation and selection of liver allograft donors

Major advances in the long-term success of liver transplantation have resulted in a broadening of the criteria used in the evaluation of potential liver allografts. A continued imbalance between the number of patients on the wait-list for liver transplant and the number of deceased donors highlights the need for optimizing the use of extended criteria donor (ECD), donation after cardiac death donor (DCD), and living donor liver allografts. Further advances in the technical aspects of the transplant procedure may continue, although more slowly than in the growth phase of liver transplantation. In contrast, donor management and the matching of donor allografts to appropriate recipients continue to evolve.

In selecting livers for transplantation, surgeons and hepatologists take a myriad of variables into account. Donor profiles include age, body mass index, social history including drug and alcohol use, medical and surgical history, liver function tests, serological testing, and, in some cases, pre-donation liver biopsies. These are balanced against the recipient's current medical condition, especially cardiac and renal function, history of a prior liver transplantation or other abdominal surgery, etiology of the liver disease, and known presence of HCC. A number of special considerations sometimes come in to play, e.g., although patients on the waiting list with the highest MELD scores are frequently the most sick, not all of them do well with livers from ECDs. Patients with fulminant hepatic failure often require urgent transplantation before the onset of brain-stem herniation or overwhelming sepsis. Some patients with well-compensated liver disease develop HCC and may require transplantation as a cure of their cancer rather than for criteria dictated by MELD.

Deceased organ donors

The vast majority of livers used in transplantation continue to come from deceased donors who have met brain death criteria. According to the Scientific Registry of Transplant Recipients, at the end of 2008 there were 16 450 patients wait-listed for liver transplant, with 6069 deceased donor transplantations and 249 living donor transplantations performed in 2008. Of the donors, 41.5% had a cerebrovascular accident and 16.4% trauma from a motor vehicle accident; 79.1% of all deceased donors were between the ages of 18 and 64.

In the past decade, the number of livers transplanted from DCDs, also known as non-heart beating donors (NHBDs), has increased dramatically, from 33 DCDs (0.9% of total donors) in 2000 to 277 DCDs (4.7% of total donors) used for 60 different programs in 2006. Graft survival of DCD liver allografts is inferior to survival from deceased donors meeting brain death criteria (Figure 10.5). In addition, biliary complications are more common with

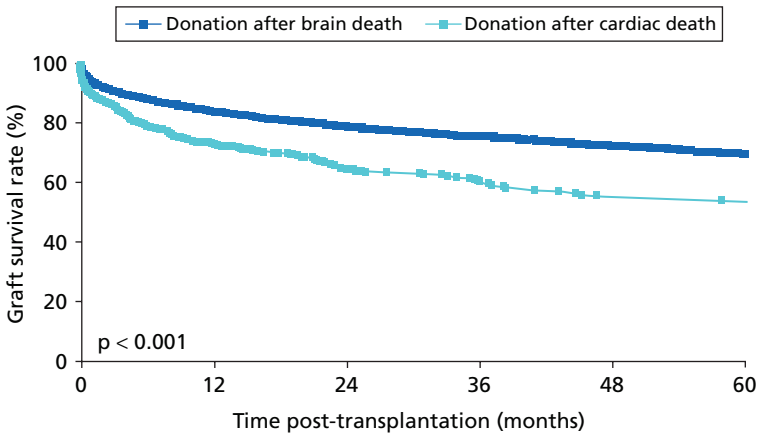

Figure 10.5 Adjusted graft survival for donor after cardiac death and brain dead donor liver transplants, 2001–2006.

DCD livers. Thus, specific criteria may be used in assessing the suitability DCD donors for liver transplantation (see "Donation after cardiac death").

Standard versus extended criteria donors

A "standard" or "reference donor" implies a very low risk of initial poor function or early allograft failure leading to death or requiring retransplantation. Additional factors such as transmissible disease, which do not directly affect the risk of graft failure, must also be considered in the definition of extended criteria. Factors that are not directly related to the donor, such as technical difficulties during the procedure, surgical complications, or disease recurrence, should not be included in the definition. An ideal allograft is different from an ideal donor. The ideal allograft category may be influenced by variables that are introduced after procurement, such as the prolonged cold ischemia time, or technical variants, such as those occurring with allograft reduction (e.g., split-liver allograft). These variables should not be included in the definition of the ECD because the aim is to assess risk before procurement.

In the past, a reference (or ideal) donor was defined according to the following criteria: age <40 years, trauma as the cause of death, donation after brain death, hemodynamic stability at the time of procurement, no steatosis or any other underlying chronic liver lesion, and no transmissible disease. An ECD, on the other hand, implies higher risk in comparison with a reference donor. The risk may be manifested as increased incidence of poor allograft function or allograft failure, or transmission of a donor-derived disease.

Key points 10.2 The characteristics of the ideal deceased donor for liver transplantation

Age <40 years

Trauma as the cause of death

Donation after brain death

Hemodynamic stability at the time of procurement

No steatosis or any other underlying chronic liver lesion

No transmissible disease

At the Paris Consensus Meeting on Extended Criteria Donors in Liver Transplantation (March 2007), broad recommendations were made with regard to donor type, donor history, and donor allograft quality in the evaluation of grafts to be used in liver transplantation. Specific distinction was made between factors that affect initial donor allograft function and factors independent of donor graft function (such as infectious disease or donor-derived malignancy). The conference highlighted the reality that donor allografts represent a continuum of risk that is impossible to separate into fixed categories,

but is better viewed as high or low probability of both initial function and long-term allograft survival. This probability index can then be weighed against the risk profiles, comorbidities, and expected mortality rates of potential recipients.

Further attempts at codifying an "extended criteria liver" include various objective criteria: age >55 years, aspartate transaminase (AST) >150 IU/L, serum bilirubin >2 mg/dL, serum sodium >150 mmol/L, high doses of any vasoactive pressor, period of cardiac arrest, intensive care unit (ICU) stay >5 days, and moderate or severe macrosteatosis. Various studies have concluded that the use of such ECD livers, when carefully selected for the appropriate recipient and implanted efficiently, is viable and safely expands the numbers of liver transplantations, thereby diminishing the number of deaths on the waiting list.

Older age donors

Advanced donor age was once considered a contraindication to liver donation because it was feared to increase the risk of poor graft function. In fact, the outcome of transplantation using older donors without any other risk factors has been shown to be similar to that of using younger donors. Accordingly, the UNOS data show that the upper age limit for liver donation has increased over the past decade. In 1996, 25% of all transplanted livers were from deceased donors aged >50 years. Ten years later, that percentage had increased to 34%.

Although advanced donor age is not by itself a contraindication, careful assessment must be made on a case-by-case basis. Older livers tend to be smaller and more fibrotic than younger livers, but these morphologic changes might not impair functional hepatic capacity. Possible explanations for the relatively good results with aged livers include great functional reserve, regenerative capacity, and dual blood supply, which far exceed the metabolic needs of the recipient. However, older donors in general have a higher incidence of severe atherosclerosis and fatty infiltration in the liver. In addition, the combination of older donor age and moderate-to-severe steatosis adversely impacts early allograft survival. Transmission of malignancy is another consideration with aged donors because of the higher incidence of unrecognized malignancies in elderly people. Advanced donor age may also be associated with early severe recurrent liver disease in patients with hepatitis C.

Hepatic steatosis

The prevalence of steatosis in liver donors ranges from 13% to 26%, with two histologic patterns of fatty infiltration typically observed: microvesicular steatosis, in which the cytoplasm contains diffuse small-droplet vacuolization, and macrovesicular steatosis, in which large vacuole deposits displace the nuclei. The outcome of transplantation is not affected by microsteatosis in the donor liver, regardless of the severity. In addition, grafts with mild macrosteatosis (<30%) can be used safely, because the outcomes of such liver allografts are similar to those of non-steatotic grafts. Donor livers with severe macrosteatosis (>60% of hepatocytes having large fat deposits within the cytoplasm) do have a significant risk of graft failure and are generally not used for transplantation. As a result of impaired hepatic microcirculation, steatotic livers have reduced tolerance for ischemia–reperfusion injury.

Key points 10.3 Impact of hepatic steatosis on selection of liver donors

Microvesicular steatosis (cytoplasm containing diffuse small droplet vacuolization):

- no contraindication to donation

Macrosteatosis (large vacuole deposits displacing nuclei):

- <30% of hepatocytes affected– usually acceptable for donation
- >60% of hepatocytes affected – usually not acceptable for donation

Prolonged ischemia

Prolonged ischemia remains one of the major causes of early graft dysfunction, with clear evidence that preservation times affect the incidence of PNF, as well as overall outcomes, in liver transplantation. Prolonged cold ischemic time, defined as the time from cross-clamping and perfusion with preservative solution in the donor operation to the time of reperfusion with blood in the liver recipient, increases the risk of PNF and is an independent risk factor for hepatic ischemia–reperfusion injury. The

vulnerability of individual grafts to cold ischemia varies, however. Total ischemic times of <12–16 h are well tolerated by donor livers without any other risk factors, but not by marginal grafts. In the modern era of liver preservation, the incidence of ischemia–reperfusion injury and PNF is low if recipients are transplanted with standard grafts. In extended criteria grafts, however, with such risk factors as steatosis, donor age >50 years, DCD source, or reduced size, it is essential that cold ischemia time be minimized.

Split-liver transplants

Surveys in western populations indicate that split-liver transplantation in adults is associated with significant increases (about 10%) in graft failure and recipient morbidity. Results are notably better in children. Even if split-liver allografts are procured from young donors with normal parenchyma and short cold ischemia times, they should be considered extended criteria grafts for the following reasons: .

- The graft volume is generally lower than the recipient's standard liver volume and may be insufficient to adequately meet the metabolic demand during the early postoperative course.
- There are higher technical requirements, and non-optimal positioning of the partial graft may result in compromised venous outflow.

As a result, biliary leakage, hepatic artery thrombosis, focal or global outflow obstruction, and poor early graft recovery are more frequent in comparison with whole organ transplantation.

Donation after cardiac death

In the past 10 years, a number of transplant programs have begun to use livers from DCDs, or non-heart-beating donors. DCDs can be divided into two categories: uncontrolled and controlled donation. In uncontrolled DCDs, death has occurred without life-support equipment in place. As a result of prolonged warm ischemia before cold perfusion, the organs suffer severe ischemic insult. Liver transplantation using uncontrolled DCDs has resulted in inferior outcomes. In an early study from Pittsburgh in 1995, three of six allografts from uncontrolled DCDs did not function and the 1-year graft survival rate was 17%. Otero et al. reported that the incidence of PNF was 25% in uncontrolled DCDs ($n = 20$), with graft and patient survival rates of 55% and 80%, respectively (see Further reading).

In contrast, in controlled DCDs, life support is carefully withdrawn in the operating room, when donor surgeons are available, resulting in minimal hypotension and warm ischemia. Under these circumstances, the outcomes of liver transplantation are acceptable. In an early report from Pittsburgh, although the 1-year graft and patient survival rate was 50%, there was no incidence of PNF. D'Alessandro et al. reported that the rate of PNF was 10.5% in controlled DCD donors (see Further reading). The 1-year graft survival rate in recipients from DCDs was lower than that from donation after brain death (53.8% vs 80.9%; $p = 0.007$) but there was no difference in patient survival. Abt et al. reported that controlled DCD livers had a higher incidence of intrahepatic ischemic-type biliary strictures compared with DBD livers (33.3% vs 9.5%; $p < 0.01$), but the two types of livers had similar graft and patient survival.

Nationwide data have confirmed inferior outcomes from DCD livers. UNOS data between 1993 and 2001 characterized 117 DCD grafts as controlled, 11 as uncontrolled, and 16 as unknown or not identified. When the controlled DCD and DBD livers were compared, the graft survival rate at 1 year was lower in controlled DCD (72.3% vs 80.4%; $p = 0.056$). DCD recipients had a higher incidence of PNF (11.8 vs 6.4%; $p = 0.008$) and re-transplantation (13.9% vs 8.3%; $p = 0.04$) compared with DBD recipients. However, patient survival was similar in both. Predictors of early graft failure within 60 days of transplantation were prolonged cold ischemia time and use of recipient life support at time of transplantation (e.g., pressors). Merion et al. examined a national cohort of DCD ($n = 472$) and DBD ($n = 23\,598$) liver transplantations between 2000 and 2004 using the Scientific Registry of Transplant Recipients (SRTR) database (see Further reading). There was no categorization of DCD donation such as controlled/uncontrolled status in their analysis. The adjusted relative risk of DCD graft failure was 85% higher than that for DBD grafts.

Mateo et al. reported the importance of risk evaluation to improve graft survival in a DCD setting using the UNOS database between 1996 and 2003. They identified six significant risk factors in recipients for graft loss: a history of a previous liver transplantation, being on life support, being hospitalized or in an ICU, having received dialysis, serum creatinine

value >2.0 mg/dL at time of transplantation, and age >60 years. Graft survival rates at 1 year (n = 367) were significantly inferior to those with DBD donors (80% and 72%; $p < 0.001$). However, low-risk recipients with low-risk DCD livers (warm ischemia time <30 min and cold ischemia time <10 h; n = 226) achieved graft survival rates at 1 and 3 years (81% and 67%) not significantly different from those of recipients with DBD livers (n = 33 111). In addition, increasing donor age was more highly predictive of poor outcomes in DCD, especially in recipients in poor preoperative condition.

Although there is, as yet, no consensus on the use of DCD livers, the preponderance of data suggests three things:

- DCD allografts from younger donors (<40 years) fare better over both the short and the long term.
- DCD livers must be used in technically efficient operations with resultant short ischemia times.
- DCD grafts should be used in recipients who tend to be younger and have fewer comorbidities, especially with regard to renal dysfunction.

As these general guidelines are used more frequently, it is possible that, although the use of DCDs may not expand significantly, outcomes will improve.

Living donors

Consideration of a living donor involves both medical and psychosocial evaluation. Donors are evaluated on the basis of suitability of the quality of organ to be donated as well as for the safety and risk to the donor. Evaluation of the donor begins with pre-clinical criteria, followed by extensive medical and psychosocial evaluation. If patients are deemed to be appropriate from both a medical and a psychosocial standpoint, further anatomical evaluation of the organ is performed to determine suitability for the intended recipient. The general format for evaluation of potential donors is outlined in Table 10.6.

The initial evaluation of the living donor begins once recipients have been determined to be suitable candidates for liver transplantation. Often, the public views living donation as a "get out of jail free" card. It is important for recipients and families to understand that, given the magnitude of risk to the potential donor, recipients are required to be deemed appropriate candidates first for transplantation, at which point various donation options can be considered. In general, given the risk of potential coercion, recipient and donor pairs are separated with respect to the hepatologist and transplant surgeon caring for them as well as the coordinator involved with the evaluation. In general, potential donors have to have basic medical suitability to include age ≥18 or ≤50, good medical health, and a blood type compatible with the recipient.

Once a potential donor is identified and the preclinical evaluation found to be suitable, the medical evaluation continues to identify potential health risk to the donor. The general medical evaluation is listed in Table 10.6. In addition to the general evaluation of medical health, potential donors are evaluated by the psychosocial team to determine psychiatric stability, financial and social support, and whether there is any evidence of potential coercion. During this process, patients are educated as to the risks and outcomes of donation. They are required to meet independently with a separate donor advocate who has knowledge of the transplant process but is not part of the transplant team caring for the patient or donor.

Finally, if it appears that there are no medical or psychosocial barriers to donation, the donor undergoes anatomic evaluation of the organ to ensure adequate volume for both the donor and recipient. Donor remnant volumes of at least 35% must be weighed against adequately sized donor grafts. A graft to recipient body weight ratio of ≥0.8% and graft weight as a percentage of standard liver mass of >40% result in improved outcomes for recipients.

Given the need for extensive evaluation of both the donor and the recipient in the setting of LDLT, it is estimated that only 15–28% of potential donors are ultimately found to be suitable for donation. In the adult-to-adult living donor liver transplantation registry, major reasons for disqualification included medical (28%), anatomical (19%), psychosocial (9%), graft (11%), and declining to donate (11%). In addition, 11% of recipients received a deceased donor graft before LDLT and an additional 7% died or were removed from the waiting list before surgery.

Surgical techniques and complications

Liver transplantations are performed in an orthotopic manner and consist of three phases: the hepatectomy

Table 10.6 Evaluation of living donors

Preclinical
Age ≥18 or ≤50 years
Identical or compatible ABO blood type with recipient
Absence of significant medical conditions
Medical
Evaluation by transplant coordinator with consent for evaluation
Evaluation by transplant hepatology
Laboratory evaluation:
Basic biochemistries and blood count
Screening tests for undiagnosed liver disease
Viral serologies: HCV antibody, HBsAg, HBcAb, HBsAb, CMV, EBV
Chest radiograph
EKG
Doppler ultrasonography of the liver
Echocardiogram
Psychosocial
Social work
Psychiatry
Independent donor advocate
Anatomic evaluation of donor organ
Abdominal MRI/CT with volumetric assessment
Liver biopsy (as clinically indicated)
Arteriogram (as clinically indicated)
Final evaluation
Transplant surgery (with consent for donation)
Evaluation by multidisciplinary team for review of information and discussion

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

phase, the anhepatic phase, and the post-perfusion or post-implantation phase. The liver is removed by one of two techniques: conventional (bicaval) (Figure 10.6a) or "piggyback" (caval preserving) (Figure 10.6b). The conventional technique may be done with or without use of venovenous bypass, depending on the recipient's hemodynamic stability and ability to tolerate temporary clamping of the inferior vena cava and the associated decrease in preload due to interruption of venous return to the heart.

Although most studies comparing the two techniques are retrospective, there is evidence that the piggyback method requires one less venous anastomosis and thus lends itself to shorter warm ischemia times. The method also facilitates re-transplantation (particularly important in patients with hepatitis C), and is associated with shorter anhepatic phases, less blood loss and blood product usage, and shorter postoperative ICU stays. On the other hand, it may be associated with higher incidence of venous outflow obstruction which may lead to ascites.

The four main anastomoses involved in liver transplantation are the aforementioned inferior vena cava anastomosis, portal vein anastomosis, hepatic artery anastomosis, and bile duct anastomosis. A brief review of the technical aspects of each of these steps follows, with discussion of the diagnosis and management of potential complications.

Biliary complications are the most common technical complications after liver transplantation, reported in between 6 and 34% of all liver transplant recipients. Their incidence varies with the type of liver allograft (whole vs partial, brain dead vs DCD). The two most common types of biliary reconstruction are choledochocholedochostomy (CC) (Figure 10.7a) and choledochojejunostomy (CJ), usually with a roux-en-Y loop (Figure 10.7b). More than 75% of adult full-size OLTs are performed as a CC. More common reasons for use of a CJ reconstruction are re-transplantation, living donor or split-liver transplantation, pediatric grafts, presence of ductal disease in the recipient, or significant donor-to-recipient duct discordance.

An acute elevation in alkaline phosphatase or bilirubin with relatively little change in transaminases should prompt a diagnostic work-up of a potential biliary stricture or sphincter of Oddi dysfunction (in the case of CC anastomoses), or, less commonly in

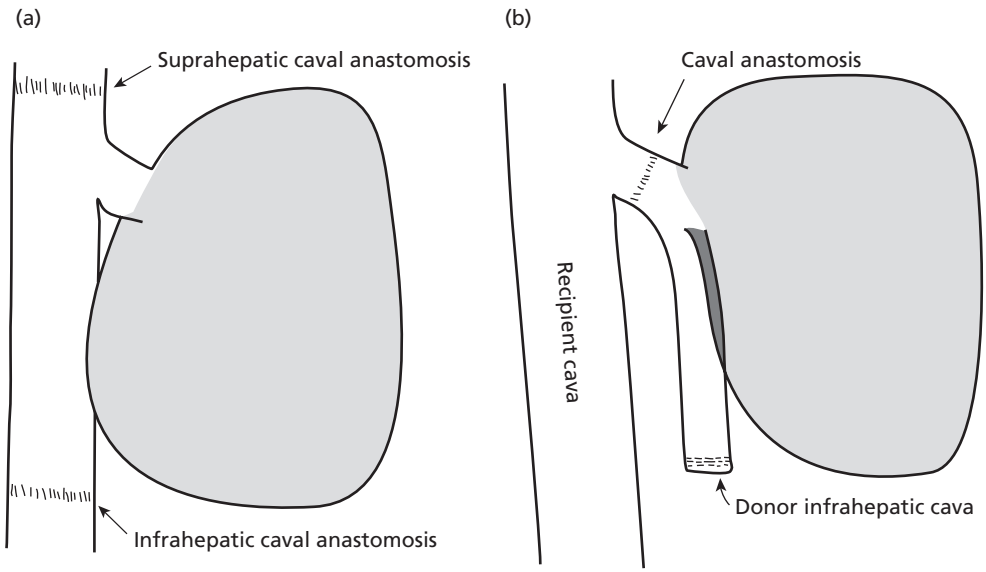

Figure 10.6 The bicaval (a) and piggyback (b) techniques used for orthotopic liver transplantation.

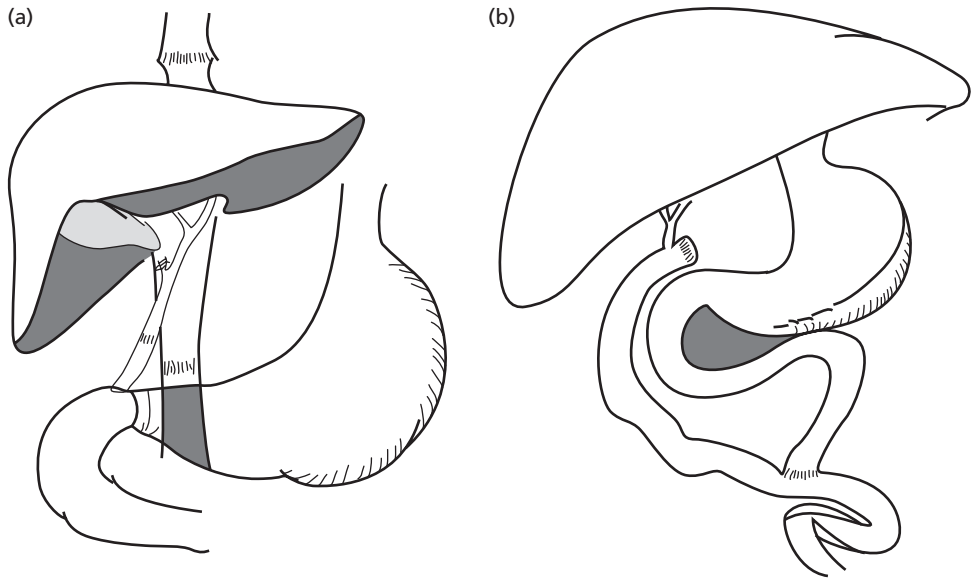

Figure 10.7 Two techniques for biliary reconstruction in liver transplantation: (a) the choledochocholedocostomy or "duct-to-duct" technique; (b) the choledochojejunostomy with roux-en-Y loop technique.

the CJ patient, ascending cholangitis. With no valve to limit reflux of enteric contents, some patients with roux-en-Y CJ post-OLT will have episodes of ascending cholangitis requiring admission for intravenous antibiotics followed by short-term outpatient oral treatment.

Patients with CC-type anastomoses may have T-tube stents, internal stents, or no stents placed. With the advent and experience of endoscopic retrograde cholangiopancreatography (ERCP), the relative risks of T-tubes and internal stents has caused a shift away from surgically placed stents, but with greater use of ERCP post-transplant for diagnosing and treating strictures. Patients with CJ may need evaluation of their biliary–enteric anastomosis with CT, magnetic resonance cholangiopancreatography (MRCP), or percutaneous transhepatic cholangiogram (PTC) post-transplantation, with the last affording the option of placing internal stents for dilation alone or internal–external stents for drainage.

Strictures in the post-transplant period may be anastomotic (usually due to technical issues, vascular insufficiency, or fibrotic healing), or non-anastomotic. Both types may be diagnosed and treated by ERCP or PTC, but non-anastomotic strictures with the presence of biliary casts or stones should prompt careful evaluation of the hepatic arterial supply. In some studies, approximately 50% of patients with non-anastomotic strictures also have hepatic artery stenosis or thrombosis.

Although most biliary complications are related to strictures or bile duct redundancy, leaks also occur in 2–10% of OLTs. Early leaks, defined as those occurring within a month post-transplantation, are usually technical in nature and should be managed with surgical exploration and conversion of a CC to a CJ anastomosis, or a redo of the initial CJ anastomosis. Leaks that occur over 1 month post-transplantation are usually related to ischemia or infection. Careful attention should be paid to the hepatic artery in these patients, while the leak is generally best managed with ERCP or PTC in concert with percutaneous drainage of potential abdominal abscesses or collections.

Hepatic artery thrombosis (HAT) is the most common vascular complication after OLT, and the most common technical complication requiring re-transplantation. Recent reviews document an HAT rate of 1.6–4% in adult recipients and 12–30% in children. Split-liver and living donor liver transplants, in addition to having a higher rate of biliary complications, have an increased incidence of HAT. Mortality rates for HAT range from 11% to 35% depending on the interval after OLT, symptoms on presentation, and mode of therapy.

Patients with HAT will develop acute or chronic symptoms, with the types of symptoms dependent on the time interval between OLT and development of HAT. Signs may range from fulminant hepatic necrosis in the early postoperative period to transaminitis, biliary strictures or abscesses, relapsing bacteremia, or recurrent fevers. Imaging studies, including hepatic duplex ultrasonography, CT angiography and, the gold standard, celiac angiography, have been used to diagnose HAT.

Patients with early HAT who are asymptomatic or mildly symptomatic are candidates for graft salvage with surgical exploration and arterial reconstruction, including the possible use of aortic jump grafting, preferably using an autogenous vein. Acute HAT within the first week post-transplantation is an absolute indication for relisting a patient as status 1 (i.e., the highest priority patient, taking precedence over all other patients listed regardless of MELD score). Patients in whom late HAT develops but who have biliary sepsis are also best served by r-transplantation.

Catheter-directed therapies, with angioplasty, stenting, and long-term use of either warfarin or antiplatelet agents, have also had some success in salvaging allografts when patients are discovered to have HAT by routine ultrasonography or CT. The goal of therapy is to prevent progression to complete occlusion as a result of the diminished blood flow, and consequently to avert associated ischemic biliary strictures and sepsis. The long-term results of such therapies are still under investigation.

Case

One year after an otherwise successful liver transplant performed for alcoholic cirrhosis, a 51-year-old man is admitted for evaluation of fever and abdominal pain. Abdominal CT scan reveals a large hepatic abscess that is drained percutaneously. Further imaging with Doppler ultrasonography reveals thrombosis of the hepatic artery. The patient completes 6 weeks of antibiotic therapy. Follow-up CT shows no residual abscess and the patient continues to be managed as an outpatient.

Other, rarer hepatic artery complications include pseudoaneurysm, which occurs in less than 1% of patients and is usually due to trauma or infectious processes. Treatment almost always requires urgent surgical reconstruction, although occasionally cases can be managed with interventional techniques.

Less common than either biliary or hepatic arterial technical complications are hepatic venous outflow or portal vein stenoses. Hepatic vein outflow obstruction, which occurs more commonly with the piggyback technique (2–10% incidence), may be corrected with catheter-guided venous stent placement with or without subsequent anticoagulation. Portal vein stenosis, reported in 1–2% of patients, may also be corrected with venous stenting, although surgical reconstruction should also be considered in such cases.

Immunosuppression

Immunosuppression after liver transplantation, as with all solid organ transplantation, is guided by the principle that the incidence of rejection is greatest soon after transplantation and declines with time. In contrast, complications associated with immunosuppressive medications accrue the longer a patient is "out" from the transplantation. Chronic rejection is an unusual cause of graft loss or death, but over half of liver transplant recipients will die from complications attributable to antirejection medications including cardiovascular disease, renal failure, infection, and malignancy. As a result, there is a general strategy of using multiple medications at high doses early on and fewer medications at lower doses later.

Traditionally, most liver transplant centers used a regimen of three medications early after transplant. These include the primary long-term immunosuppressant, typically either cyclosporine or tacrolimus, corticosteroids and an antimetabolite usually mycophenolate mofetil (MMF), mycophenolic acid (MPA), or azathioprine. The corticosteroids are administered at high doses intravenously in the days immediately proceeding transplantation and then tapered off typically within a few months to a year. The antimetabolite (MMF or MPA) may be discontinued 3–6 months after the corticosteroid and many patients are maintained on either a dual (with cyclosporine) or single agent (with tacrolimus) regimen depending on the calcineurin agent used.

Immunosuppression after liver transplantation is in evolution as efforts are made to avoid complications and side effects. There are several recent trends of note. There is a tendency to taper corticosteroids more rapidly than in the past to diminish the incidence of steroid side effects. Several new approaches are designed to reduce the burden of renal insufficiency which is associated with the use of cyclosporine or tacrolimus. Antibody-mediated "induction therapy" with antibodies that either deplete T cells or block the interluekin-2 receptor (IL-2RA) is being used with greater frequency to help minimize the use of steroids or to delay the introduction of cyclosporine or tacrolimus to preserve renal function. Typically MMF or MPA is also discontinued within a year of transplantation. However, there is evidence that, if MMF/MPA is continued, lower doses of tacrolimus and cyclosporine can be used with a resulting improvement in renal function. Finally, the newer agent, sirolimus, is being used in some patients in an effort to avoid renal dysfunction. Rapamycin can either be used instead of tacrolimus or cyclosporine or with lower doses of one of these agents.

Cyclosporine and tacrolimus

Both cyclosporine and tacrolimus suppress the immune system through the inhibition of calcineurin, a protein that drives production of cytokines such as IL-2 that drive T-cell activation. Collectively, the two drugs are called calcineurin inhibitors (CNIs) and they are the workhorses of solid organ transplantation. The vast majority of liver transplant recipients are maintained on one or the other indefinitely. Before the advent of cyclosporine, corticosteroids and azathioprine were used with a 1-year survival rate of 25–35%. Cyclosporine, a fungally derived peptide, was approved in 1983, resulting in markedly improved survival. It is lipophilic and requires enterohepatic circulation for absorption. This can be problematic in liver transplant recipients with biliary T-tubes or those with poor graft function. Generic formulations of cyclosporine have been available since 2000. Tacrolimus is a macrolide agent of bacterial origin that was approved for use in liver transplantation in

1994. The primary commercial form of tacrolimus is Prograf but generic forms were released in 2009.

Both tacrolimus and cyclosporine are oral agents taken every 12 hours though a modified formulation of tacrolimus that be given once daily is anticipated. Cyclosporine is available in 25 and 100 mg pills and tacrolimus in 0.5, 1, and 5 mg pills. The dosage is based on trough levels of the drugs and is highly individualized. Higher trough levels are sought initially after transplantation when the risk of rejection is high and lower levels are sought later when concerns about adverse effects start to predominate. Typical trough levels for cyclosporine are 200–300 ng/mL initially and 50–150 ng/mL long term. Typical trough levels for tacrolimus are 5–15 ng/mL with the higher end targeted early after transplantation.

CNIs have significant side effects and nephrotoxicity is their Achilles' heel. Renal insufficiency is a major cause of morbidity and mortality after liver transplantation. Other side effects common to both drugs are hyperkalemia, hypertension, and neurotoxicity, ranging from headaches and tremor to neuropathy and seizures. Cyclosporine is more commonly associated with hyperlipidemia, and gingival hyperplasia, whereas tacrolimus is more frequently associated with diabetes. There is significant debate over the merits of the two drugs. What is clear is that tacrolimus is now used in 89% of OLT patients in the USA at the time of initial discharge. Tacrolimus is associated with less rejection than cyclosporine and this may explain its appeal early on. Both drugs are comparable in their deleterious effects on renal function.

Antibody induction therapy

A strategy that has grown in popularity in the MELD era is the use of potent intravenous antibody preparations that deplete or inhibit T lymphocytes early after transplantation. These agents can be used to delay the introduction of calcineurin inhibitors (CNIs) to facilitate recovery of renal function or to minimize exposure to corticosteroids and lower the incidence of diabetes and osteoporosis. The most commonly used agents include rabbit antithymocyte globulin (Thymoglobulin), daclizumab (Zenapax), and basiliximab (Simulect). However, production of Zenapax has recently been halted. Thymoglobulin is a polyclonal antibody formulation made by immunizing rabbits with human T lymphocytes. Thymoglobulin binds multiple antigens on lymphocytes and leads to T-lymphocyte depletion. It is administered at a fixed dose for 7–14 days and fevers and chills can be seen in up to a third of patients.

Daclizumab and basiliximab are monoclonal antibodies that bind to CD25 or the IL-2R and inhibit T-cell activation. Basiliximab is typically given in two doses, at the time of transplantation and on day 4. Daclizumab has been used in two-, three- and five-dose regimens. Both agents are well tolerated with few specific side effects. OKT3 (Muromonab-CD3) is used less often now because of toxicity and the advent of newer agents, and alemtuzumab (Campath-1H) has not found widespread use in liver transplantation.

Induction therapy can be used to delay the introduction of CNIs for up to a week and it has a beneficial effect on renal function in this setting. In addition, induction therapy is a mainstay in steroid avoidance protocols. In some randomized studies, induction therapy is associated with a lower incidence of acute rejection and it is not clearly associated with an increased incidence of severe recurrent hepatitis C. The use of induction therapy is not as widespread in liver transplantation as it is with other organ transplantations but its use is growing in popularity especially in patients with renal insufficiency at the time of transplantation.

Corticosteroids

Corticosteroids are potent immunosuppressant drugs that inhibit T-lymphocyte, monocyte, and macrophage activity. Corticosteroids are administered at high doses intravenously in the days immediately preceding transplantation. Methylprednisolone may be given at doses of 500–1000 mg/day and then tapered to doses of 10–20 mg/day after 1–2 weeks. There is a tendency to taper corticosteroids more rapidly than in the past. Most centers eliminate corticosteroids within a year but many aim to do so within 3 months or sooner. This has been shown to result in less hypertension, diabetes, hyperlipidemia, and infection. There are several reports of effective induction antibody-based regimens that avoid steroids and these regimens are currently used in up to 20% of liver transplant recipients. Corticosteroids may be continued for longer durations at reduced doses in some patients with autoimmune liver diseases or recurrent rejection.

Antimetabolites

Antimetabolites are a group of drugs that interfere with purine nucleotide synthesis which leads to preferential inhibition of T and B lymphocytes. Azathioprine was a mainstay of immunosuppression early in organ transplantation but, in recent years, mycophenolate mofetil (MMF, CellCept) and enteric-coated mycophenolate sodium (MPA, Myfortic) are used more commonly in liver transplantation. Azathioprine can be associated with cholestatic hepatitis. MMF and MPA do not exhibit this toxicity and are more potent. Antimetabolites are not potent enough to be used as the primary immunosuppressive agent but are important as adjunct agents, especially in the first few months to a year after transplantation. MMF is typically given at 1–2 g daily in two divided doses and MPA is typically given at 720–1440 mg daily in two divided doses. Side effects are frequent and include marrow suppression and gastrointestinal side effects such as gastritis, nausea, diarrhea, and abdominal pain. These agents are typically discontinued by 1 year after liver transplantation. However, several reports suggest that they may be beneficial for longer periods by facilitating lower doses and levels of CNIs.

Sirolimus (mTOR inhibitors)

Sirolimus (Rapamune), similar to tacrolimus, is a macrolide. It is named after the Easter Island of Rapa Nui where it was discovered. Unlike tacrolimus, sirolimus is not a CNI but targets T cells through cell cycle inhibition via the mammalian target of rapamycin (mTOR) pathway. Sirolimus is a newer immunosuppressant agent that is touted as being potent enough to be used as a primary immunosuppressive agent but without the nephrotoxicity of CNIs. Sirolimus can therefore be considered as an alternative to a CNI or, in some instances, in combination with lower doses of one of the CNIs. Sirolimus has been associated with hepatic artery thrombosis and graft loss in new liver transplant recipients in some but not all trials. It has received a "black box warning" from the Food and Drug Administration, which suggests avoiding the drug in the first month after liver transplantation.

The combination of sirolimus and MMF has been compared with a CNI and MMF in a randomized study in patients 4–12 weeks post-liver transplantation. In patients randomized to receive sirolimus, there was a 22.1% increase in glomerular filtration rate from baseline to year 1 compared with a 6.2% increase in patients receiving the CNI, and this difference was significant. There was a higher incidence of rejection in the sirolimus arm. Based on randomized trials, there does not appear to be a clear benefit of converting patients to sirolimus in stable liver transplant recipients. A major drawback to this medication is its side -profile. Side effects include hyperlipidemia, cytopenias, poor wound healing, lymphoceles, and oral ulceration. There is also an association with an unusual but potentially fatal aseptic pneumonitis. Between 25% and 30% of liver transplant recipients who receive the drug are not able to tolerate it.

Drug interactions

Tacrolimus, cyclosporine, and sirolimus all have clear dose-related toxicity and relatively narrow therapeutic windows. As a result the knowledge of drug interactions is critical. Certain medications can affect CNI levels by inducing or inhibiting the cytochrome P450 (CYP) 3A4 pathway, as discussed extensively in Chapters 2 and 7. Allopurinol, by blocking xanthine oxidase, can increase levels of azathioprine to toxic levels. Non-steroidal anti-inflammatory medications can potentiate CNI-induced nephrotoxicity and spironolactone can increase CNI-induced hyperkalemia. Carvedilol has been shown to increase CNI levels by inhibiting the P-glycoprotein pathway. Grapefruit products can dramatically raise CNI levels.

Drugs that are felt to be well tolerated include amlodopine, nifedipine, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II AT_1-receptor blockers (ARBs), and β blockers (excluding carvedilol) for hypertension; oral hypoglycemics, metformin, sulfonylureas, and thiazolidinediones for diabetes mellitus; HMG-CoA reductase inhibitors for hyperlipidemia; and gabapentin and evetiracetam for seizures. Antibiotic agents including penicillins, cephalosporins, quinolones, and sulfonamides should not affect immunosuppressant levels. Narcotics are safe outside their addictive potential and antidepressants are typically well tolerated. Up to 4 g/day of acetaminophen can be given to liver transplant recipients with functioning grafts.

Table 10.7 Snover's criteria for diagnosis of acute cellular rejection

Presence of mixed portal infiltrate
Presence of bile duct injury
Presence of endothelial cell damage

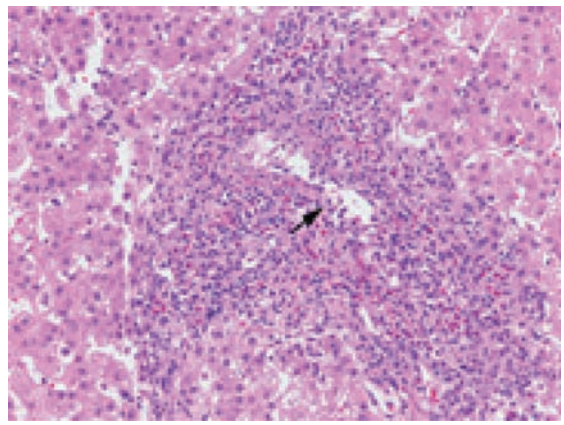

Figure 10.8 Acute cellular rejection in a liver allograft characterized by mixed portal infiltrate, bile duct damage, and endothelialitis, here consisting of a perivenular lymphocytic infiltrate.

Rejection in liver transplantation

Diagnosis

Acute cellular rejection (ACR) is the most common cause of early allograft dysfunction. The median time to ACR is 8 days with 48% of patients experiencing rejection by 6 weeks and 65% experiencing rejection by 1 year. Early rejection correlates with suboptimal immunosuppression, lower recipient age, prolonged ischemia time, and older donor age. In addition, females and those with autoimmune disorders show a higher frequency of ACR in some studies.

Patients may present with elevated transaminases or cholestasis. They may have fever, right upper quadrant pain, or leukocytosis. More commonly, with mild ACR, patients are asymptomatic. The use of biochemistries to distinguish ACR from other etiologies has not proven to be helpful. Currently, the only reliable way to diagnose either ACR or chronic rejection (CR) is with liver biopsy.

The histologic diagnosis of ACR is based on Snover's criteria (Table 10.7) which include: (1) mixed portal infiltrate, (2) bile duct inflammation and damage, and (3) endothelialitis of either the portal or terminal hepatic vein branches. The minimum criteria for a diagnosis of ACR are at least two of the above in addition to biochemical evidence of liver injury. Of these three findings, the most specific for a diagnosis of ACR is the presence of endothelialitis (see Figure 10.8).

Atypical presentations of ACR can include central perivenulitis and plasma cell rejection. Central perivenulitis can be a component of early ACR in association with characteristic portal tract changes. However, isolated perivenulitis has been described and may represent a more severe form of ACR that is less likely to respond to conventional immunosuppression. Differential diagnosis in these isolated cases includes ischemia–reperfusion injury, vascular ischemia, viral or autoimmune hepatitis, or drug toxicity (tacrolimus or azathioprine). Plasma cell ACR may also occur in the setting of recurrent hepatitis C and is a poor prognostic factor for patient and graft survival. Whether this represents a form of ACR or, alternatively, a new form of autoimmune hepatitis is unclear.

For both adults and children, rejection is uncommon more than 12 months post-transplantation. Late rejection more often correlates with reduction in immunosuppression, or poor compliance, which may be more common in adolescents. Late rejection may have histological features different from those seen in acute rejection, and include a predominantly mononuclear portal inflammatory infiltrate and less inflammation of the bile ducts or vascular endothelium. Both interface and lobular hepatitis may be present and, in these cases, it is important to rule out viral hepatitis as a potential cause. Increased immunosuppression and reinforcement of adherence to medications is paramount to prevent progression to chronic rejection.

CR occurs in 3–5% of patients undergoing liver transplantation. It is almost always preceded by one or more episodes of ACR. Additional risk factors for the development of CR include younger recipient age, primary diagnosis of immune disease, relatively lower baseline level of immunosuppression, and non-white recipient race. Features may include progressive duct injury with cholestasis, loss of hepatic synthetic function, or pruning of the intrahepatic arteries on angi-

ography. A less common form of CR targeting hepatocytes has also been described. Bile duct injury is not prominent and patients present with elevated transaminases as opposed to a more cholestatic picture. Diagnostic criteria developed by the Banff group include: (1) senescent changes with cytoplasmic eosinophilia, cell enlargement and multinucleation, uneven nuclear spacing, and loss of polarity affecting a majority of the bile ducts with or without bile duct loss; (2) convincing foam cell obliterative arteriopathy; or (3) bile duct loss affecting more than 50% of the portal tracts. A significant proportion of these patients will progress to cirrhosis and up to half will require re-transplantation. If diagnosed at an early stage and treated with additional immunosuppression, CR has been shown to be reversible in some patients.

Differentiating ACR from recurrent hepatitis C can be difficult. This is an important distinction because treatment of ACR with bolus steroids has been associated with more aggressive recurrence of hepatitis C virus (HCV). ACR and recurrent HCV often share common features and both may be present simultaneously. Bile duct injury may be seen in both ACR and recurrent HCV. Although ACR often occurs in the first month after, with HCV recurring later, significant overlap may exist, making diagnosis and treatment decisions difficult. Marked elevations of HCV RNA may be present with recurrence; however, viral loads cannot be used to distinguish the two. Other features that may suggest recurrent HCV over rejection include the presence of steatosis, predominance of lymphocytes within portal tracts, acidophilic bodies, and lack of endothelial cell damage.

Case

Two months after a liver transplantation performed for cirrhosis resulting from hepatitis C, a 39-year-old man has a liver biopsy for evaluation of a recent rise in serum alanine transaminase (ALT), AST, and alkaline phosphatase levels. The biopsy shows mixed portal inflammation with a predominance of lymphocytes. There is mild endothelialitis involving branches of portal venules. Mild steatosis is noted as well. The pathologic diagnosis is recurrent hepatitis C and possible mild acute rejection. As a result of concerns that additional immunosuppression might increase the replication of hepatitis C, no additional therapy is administered for rejection. The patient's liver function tests gradually stabilized.

Treatment

High-dose corticosteroids are usually the first-line therapy for ACR after liver transplantation. Treatment regimens vary between centers but generally include intravenous methylprednisolone from 500 mg to 1000 mg daily for up to 3 days. Tapering regimens of 1000 mg followed by a 6-day taper from 200 mg/day down to 20 mg/day is effective and may result in fewer complications than high-dose steroids for 3 consecutive days. Using one of these regimens, ACR is controlled in approximately 80% of cases.

Ten to twenty percent of patients will experience steroid-resistant ACR. Rescue therapies including rabbit ATG and OKT3 have been used to treat these episodes. Resolution of rejection is generally seen in 60–80% of patients treated. After treatment, further adjustments in baseline immunosuppression are required to prevent early recurrence. Consideration of increased baseline immunosuppression must be weighed against potential side effects and often varies from center to center.

Treatment of rejection in the setting of HCV requires careful consideration. The use of corticosteroid boluses and OKT3 clearly has a negative impact in HCV-infected individuals. Therefore, it is critical to clearly define significant rejection and minimize over-treatment in equivocal cases or in cases with overlap. Many centers do not aggressively treat mild rejection in the setting of HCV. Consideration of increasing baseline immunosuppression and avoiding bolus corticosteroids should be made. What is clear is that immunosuppression in patients with HCV needs to be individualized and careful consideration of biopsy findings with an experienced pathologist should be considered before any changes in medical therapy.

Recurrent disease

Hepatitis C

Hepatitis C currently accounts for most liver transplants performed at many large centers. It is the most common diagnosis for transplantation in the USA. Current estimates suggest that the overall prevalence of HCV antibodies in the USA is 1.8%. Statistics from the Centers for Disease Control (CDC) indicate that approximately 4 million Americans are infected with

HCV and, of these, an estimated 2.7 million have chronic HCV infection. Chronic liver disease from hepatitis C is the tenth leading cause of death among American adults and accounts for approximately 25 000 deaths each year, or 1% of all deaths in the USA. Once exposed, approximately 75% of patients remain chronically infected.

The NHANES III database shows that this cohort of patients chronically infected with HCV is aging. In the 1990s the 30- to 39-year-old group had the highest prevalence of HCV antibody, 3.9%, for an estimated 1.6 million HCV-infected individuals in this age group. Currently, people aged 40–59 years have the highest prevalence of HCV infection and, in this age group, the prevalence is highest in African–American individuals (6.1%). These aging individuals are at increasing risk of fibrosis and consequences of long-term infection such as HCC, decompensation, and liver transplantation. Computer projections have corroborated CDC predictions that mortality from HCV-related liver disease may increase two- to three-fold over the next 10–20 years.

In addition, HCV accounts for an estimated third of HCC cases in the USA and is currently the most common risk factor for HCC. HCC rarely occurs in the absence of cirrhosis or advanced fibrosis. The incidence of HCV-related HCC continues to rise in the USA and worldwide, in part because of the increasing numbers of people who have been chronically infected for decades, the presence of comorbid factors, and the longer survival of people with advanced liver disease due to improved management of complications. The increased risk of HCC places further burden on transplant centers as patients present for consideration.

Key points 10.4 Facts about hepatitis C in the USA

Most common cause of end-stage liver disease requiring liver transplantation

1.8% prevalence of antibodies to hepatitis C in the US population

Tenth leading cause of death among adult Americans with approximately 25 000 deaths annually

Currently the prevalence of hepatitis C is highest in patients between the ages of 40 and 59 years

The earliest studies of the outcome of OLT for HCV reported post-transplant patient and graft survival similar to those achieved after OLT for other chronic liver diseases. These were usually single-center reports limited by small numbers and relatively short periods of follow-up. Several large registry analyses have recently reported reduced graft and patient survivals in recipients with HCV. An analysis of the UNOS database shows that 3-year patient survival rate was 78% in HCV-positive liver transplant recipients versus 82% in HCV-negative patients. Likewise, 3- and 5-year graft survivals are significantly reduced in patients undergoing OLT with HCV compared with non-HCV-infected patients.

Later studies have shown that up to 40% of patients with recurrent HCV develop cirrhosis within 5 years, suggesting that HCV is becoming more aggressive in transplant recipients in recent years. Stronger immunosuppressive agents, rapid steroid withdrawal, and increasing donor age are possible explanations, although increased diagnosis due to more liberal use of diagnostic biopsies may also be important. Unlike non-HCV-infected patients in whom graft survival has consistently improved over time, patients with HCV have shown a worsening of graft survival rates over time, again suggesting that some change in practice may have negatively influenced HCV recurrence and/or progression.

The natural history of HCV progression is accelerated after transplantation. As noted above, up to 40% of patients develop cirrhosis within 5 years, compared with 30% after 20–30 years in the non-transplant setting. Once patients have cirrhosis, clinical decompensation is also accelerated: 60% exhibit decompensation 3 years after the diagnosis of cirrhosis in HCV transplant recipients compared with only 10% at 10 years in immunocompetent patients. Finally, once patients have evidence of decompensation, death is accelerated with less than 10% survival at 3 years versus 60% in immunocompetent patients.

HCV RNA levels decrease significantly after hepatectomy during the anhepatic phase. During the first 12–24 h after OLT, HCV RNA levels may fall further or plateau but then start to rise progressively, reaching levels 12 times pretransplant levels by months 1–4. The clinical spectrum of recurrence is highly variable. In 20–30% of patients, progression is not quickly apparent and liver injury remains mild or absent for the first few months. These patients may

eventually progress to chronic hepatitis or may remain with minimal injury over several years. A small percentage of patients will develop early, severe recurrence, termed "fibrosing cholestatic hepatitis." This is a severe form of liver injury with progression to cirrhosis and death within a few months of liver transplantation. Most patients will develop what appears to be an acute hepatitis early post-transplantation which develops into chronic hepatitis and progressive fibrosis over time. Currently 10% of patients will require re-transplantation for cirrhosis and HCV after OLT.

Several factors have been shown to be associated with accelerated fibrosis in patients with HCV undergoing OLT. In addition to factors related to immunosuppression, including steroid boluses as well as rapid *withdrawal* of steroids, other host, viral, and donor factors likely influence disease progression. The age of the donor has been found to be independently associated with disease severity, progression, and graft and patient survival. The increasing age of the donor population over time may be one of the most significant contributors to the increased severity of recurrent HCV disease in recent years. Several studies have shown that pretransplant HCV levels in the serum or in the explanted liver correlates with the severity of HCV recurrence, with a high pretransplant viral load being associated with increased mortality and graft loss. The number and severity of rejection episodes and treatment with steroid boluses are associated with increased severity of HCV recurrence and the development of cirrhosis. Interestingly, early and rapid steroid withdrawal has also been shown to be associated with increased development of fibrosis. By contrast, there is really no convincing evidence to date that choice of CNI influences outcome.

There are several strategies employed to decrease morbidity and mortality of recurrent HCV before and after OLT. Before transplantation, HCV is treated primarily to prevent fibrosis progression to cirrhosis. This would be the ideal time to treat most patients because treatment is reasonably tolerated and safe with sustained virologic response (SVR) rates in excess of 50%. Once a patient has developed cirrhosis, one might consider treatment either to prevent decompensation or to reduce HCV RNA levels in the liver before transplantation. Unfortunately, treatment in patients with advanced liver disease is poorly tolerated and associated with high rates of infection and low rates of response.

After transplantation, treatment can be either pre-emptive or delayed once disease is established. The advantage of pre-emptive therapy may be that HCV RNA levels are lower during the first 1–3 months after OLT; however, immunosuppression levels are the highest. In addition, numerous medications during this time period contribute to bone marrow suppression, making effective treatment challenging. Certainly the main goal in treating HCV after OLT is prevention of graft loss and improved graft and patient survival. Given that recurrence of HCV is almost 100% after OLT, treatment before transplantation should be considered in appropriate individuals.

It is well known that higher pretransplant HCV RNA correlates with increased mortality and graft loss. However, tolerability in patients with more advanced liver disease is poor, with a significant rate of serious adverse events and systemic infections. Several authors have reported on treatment of HCV in patients with advanced liver disease. Everson from the University of Colorado reported results on 124 patients with cirrhosis treated with interferon and ribavirin, with a mean Child's score of 7.4 and a MELD score of 11 (see Further reading). On treatment virologic response was 46% with SVR of 24%. Recurrent HCV infection was prevented in all patients achieving SVR. Overall, the data suggest that on treatment responses and SVR rates are generally lower than in patients with less advanced disease. In addition, dose reduction occurs in the majority of patients with very high rates of discontinuation as compared with patients with less advanced disease.

Many patients present for transplantation with decompensation and have limited or no opportunity for antiviral therapy before transplant. After OLT, viral eradication becomes the primary goal of therapy. Interferon-based therapies have been shown to eradicate virus both pre- and post-transplantation. Recently, Veldt from Mayo Clinic performed a cohort study evaluating the impact of treatment of HCV after OLT on graft survival. The incidence of graft failure was lower for patients treated within 6 months of recurrence compared with patients not treated within this time period (log rank $p = 0.002$). Time-dependent multivariate Cox's regression analysis showed that treatment of recurrent HCV infection was associated with a decreased risk of overall graft

failure (hazard ratio [HR] 0.34; confidence interval [CI] 0.15–0.77; $p = 0.009$) and a decreased risk of graft failure due to recurrent HCV (HR 0.24; CI 0.08–0.69; $p = 0.008$). In conclusion, although a cause and effect relationship cannot be established, treatment of recurrent HCV infection after liver transplantation is associated with a reduced risk of graft failure.

Several challenges with the use of interferon are seen after OLT, including poor tolerance, limited eligibility, and lower efficacy. After transplantation there is an initial decline in HCV RNA levels with a variable rate of increase over the first 2 weeks to peak values 3–4 months after OLT. A pre-emptive strategy initiates treatment within the first few weeks after OLT when HCV RNA values are lowest and histologic injury is minimal. Treatment in the early phase of infection may be easier than with established chronic disease. These benefits have only partially been seen with pre-emptive clinical studies. Rates of SVR have been variable ranging from 8% to 35%. Most studies used combination ischemia–reperfusion with studies using monotherapy having the lowest SVR. Dose reductions were required in a significant portion of patients. Although several early studies reported a trend toward reduced severity of recurrent HCV at the end of treatment in patents receiving pre-emptive therapy, compared with untreated controls, this strategy is applicable only to patients without significant post-transplant complications and whose clinical status is sufficiently stable to allow initiation of antiviral treatment within a few weeks of OLT. Other studies have evaluated the efficacy of treatment within the first 6 months after OLT. Tolerability appeared to be somewhat better than that seen in studies with earlier treatment with fewer patients requiring discontinuation.

Finally, there have been numerous studies evaluating treatment of established recurrent HCV infection after OLT. Most of these studies have been uncontrolled and retrospective with relatively small sample sizes. Two systematic reviews of the efficacy of interferon/pegylated interferon and ribavirin for 6–12 months have also been published. Wang included studies of both non-pegylated and pegylated interferon with ribavirin (P/R). A total of 38 studies published between 1980 and 2005 were included. The pooled estimate of SVR was 20% for interferon and ribavirin and 24% for P/R. End-of-treatment virologic response (EOTR) rates were 34% and 42% respectively, indicating close to a 50% relapse rate for most studies. A second systematic review from Berenguer focused on studies of P/R between 2003 and 2007: 611 patients were included with overall EOTR and SVR rates of 42.2% and 30.2%. The mean SVR was 28.7% in G1 patients. Baseline factors associated with SVR included non-1 genotype, low pretreatment HCV, absence of prior antiviral therapy, and endovascular repair (EVR). Failure to achieve a decline in HCVRNA during the first 3 months of treatment was highly predictive of non-SVR. Relapse occurred in a substantial number of patients 43% and 21% in the Wang and Berenguer reviews respectively (see Further reading).

Liver transplantation for viral hepatitis continues to increase. Recurrence of virus post-transplantation leads to increased morbidity and mortality. Management of liver recipients with HCV is post-transplant treatment of recurrent disease. New strategies are needed to improve outcomes based on patient selection and use of current antiviral treatment. Improved therapies are needed both pre and post transplantation to reduce the need for transplantation and improve outcomes following transplant.

Hepatitis B

Early in the history of liver transplantation, hepatitis B was considered a relative contraindication to transplantation. Patients frequently experienced reinfection of the graft with significantly decreased patient and graft survival rates. In the early 1990s, trials using hepatitis B immunoglobulin (HBIg) showed that recurrence of the disease could be prevented in a significant number of patients. Trials using HBIg showed that recurrence of disease could be prevented in up to 90% of patients with long-term intravenous administration. As a result, 5-year graft survival rates for patients transplanted with hepatitis B have improved from 53% to 76%, equivalent to survival rates of patients transplanted for other diseases.

Further studies, combining a nucleos(t)ide analogs with HBIg showed additional opportunities for the prevention of recurrent disease. The first agents used included lamivudine and adefovir, both of which showed added efficacy when combined with HBIg. In these studies, recurrent HBV occurred in only 4–8% of patients.

Concerns about cost and viral resistance led to further investigations with different regimens of HBIg administration and use of newer nucleos(t)ide analogues. With traditional intravenous administration of HBIg, yearly costs could approach US$100 000. Studies using intravenous HBIg in a modified regimen, including lower doses of HBIg administered intramuscularly, have proven to be both efficacious and cost-effective, reducing costs by approximately 50%.

Currently, there are five oral agents approved for the treatment of HBV. Several studies evaluating the efficacy of these agents in patients with end-stage liver disease have shown both improvement in Child–Pugh scores and resolution of clinical sequelae of liver failure, such as ascites. However, the emergence of viral resistance to some drugs such as lamivudine and adefovir poses a challenge in these patients. Once resistance occurs, decompensation can return and treatment after transplantation becomes more challenging. As a result, current practice suggests that oral agents associated with a very low risk of inducing viral resistance, such as entecavir or tenofovir, be considered in patients with cirrhosis or decompensated liver disease.

After transplantation, most centers continue patients on HBIg and a nucleos(t)ide agent indefinitely. Although the original trials used lamivudine in combination with HBIg, current practice is to combine an oral agent such as entecavir or tenofovir with less risk of inducing viral resistance. The surface antigen of HBV (HBsAg) should be measured regularly to monitor for recurrence of HBV. A positive HBsAg on two or more occasions documents recurrence. Once recurrence occurs, HBIg is no longer useful and should be discontinued. Patients should be managed with oral nucleos(t)ides, the choice depending on prior therapies and the possibility of viral resistance from prior treatment.

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) has been shown to recur in up to 50% of patients undergoing liver transplantation for that diagnosis. PBC usually recurs 3 years or more after OLT but has been reported to recur earlier in some patients and has not been identified as having significant impact on either quality of life or the need for re-transplantation.

Diagnosis of recurrent PBC is dependent on histologic features. Antimitochondrial antibody titers persist after transplantation and cannot be used as an indicator of disease recurrence. The gold standard for defining recurrent PBC are histologic features, including florid duct lesions with granulomatous cholangitis or destructive lymphocytic cholangitis within a dense portal infiltrate. Early or mild recurrence may limit the identification of these features. The diagnosis of recurrent PBC can be established in a patient with a history of PBC before transplantation, a persistent positive antimitochondrial antibody level, and three of the following five histologic features: (1) mononuclear inflammatory infiltrate, (2) lymphoid aggregate formation, (3) epithelioid granulomas, (4) lymphocytic cholangitis with biliary epithelial eosinophilia, and (5) the presence of ductular proliferation with portal and periportal fibrosis small bile duct loss, foamy hepatocytes, and lysosomal pigments with copper deposition in periportal hepatocytes.

Risk factors for recurrent PBC probably include a genetic predisposition. Associations between PBC and common genetic variants in HLA class II, IL12A, and IL-12 receptor β_2 loci have been demonstrated. Some authors have suggested that a smaller number of HLA-A, HLA-B, and HLA-DR mismatches between donor and recipient may be an independent risk factor for disease recurrence after OLT. Others have suggested that tacrolimus may be an independent risk factor for recurrence and that cyclosporine may be protective. A recently discovered association of betaretrovirus with PBC suggests that this virus may also play a role in recurrence; however, this has not been further elucidated.

Most studies have concluded that recurrent PBC is unlikely to affect long-term patient or graft survival. Few patients have been identified with organ dysfunction resulting from recurrence, and re-transplantation for recurrent PBC is rare.

Primary sclerosing cholangitis

The diagnosis of recurrent primary sclerosing cholangitis (PSC) includes a confirmed diagnosis of PSC before OLT, cholangiographic evidence of nonanastomotic biliary strictures with beading, or a liver biopsy revealing fibrous cholangitis and /or biliary–obliterative lesions of large bile ducts in the absence of other potential causes. Several entities can mimic

PSC in the post-transplant setting when there is injury of biliary epithelium resulting from a variety of insults. Biliary strictures may occur with severe recurrent acute rejection, chronic ductopenic rejection, ABO incompatibility, hepatic arterial thrombosis or stricture, and after use of a DCD donor.

Histologically, early stages of recurrent PSC are characterized by mild, non-specific pericholangitis or cholangitis. Portal inflammation may be present and small bile duct loss may be observed. Later features include cholestasis, intralobular foam cell clusters, and copper deposition. Fibro-obliterative lesions may be observed involving the medium and small bile ducts. Radiographically, a cholangiogram revealing non-anastomotic biliary strictures of the intra-/extrahepatic biliary tree with beading and irregularity, occurring more than 90 days post-transplantation is essential for the diagnosis.

Predictive factors for recurrent PSC may include the presence of specific HLA haplotypes; however, this has not been confirmed. Certain factors such as recipient age, male gender, donor–recipient gender mismatch, coexistence of inflammatory bowel disease, CMV infection, recurrent ACR, or steroid-resistant ACR all have been implicated in recurrence of PSC after OLT.

Recurrent PSC can affect graft survival; however, there are limited data with regard to specific treatment. Currently, use of corticosteroids or altered immunosuppression has not been shown to be beneficial in these patients. Ursodeoxycholic acid is often utilized; however, neither pre- nor post-transplant studies have demonstrated definite benefit. Re-transplantation for recurrent disease and graft loss has been described and should be considered in select patients.

Autoimmmune liver disease

Recurrence of autoimmune hepatitis (AIH) occurs in up to 27–42% of patients after OLT. Histologic features include lobular and interface necroinflammatory activity with a predominance of plasma cells. Serologic features may include positive autoantibodies in titers ≥1:40, but patients may have evidence of histologic recurrence in the absence of positive autoantibodies. The criteria for diagnosis should include a combination of biochemical changes, histological features, and corticosteroid dependency.

Studies have suggested that patients with HLA-DR3 may have increased risk of recurrence. In addition, patients with type I AIH (antinuclear antibody [ANA]/anti-SMA [smooth muscle antibody] positive) vs type II (anti-LKM positive) may have increased risk of recurrence as well. In most patients with suspected recurrence, biochemical and histological response occurs with increased immunosuppression. Severe recurrence has been documented and graft loss and need for re-transplantation reported. In addition, typical features of AIH have been reported in recipients transplanted for both PBC and PSC. This raises the issue of whether these cases represent new AIH or a recurrence of an overlap syndrome.

Transplantation for HCC

The incidence of HCC is 1–3 per 100 000 in the USA and Europe, nearly doubling in the past two decades. An estimated 8500–11 000 new cases of HCC occur each year in the USA. HCV-associated HCC is expected to further double in the next 20 years, and outcomes for patients with HCC and cirrhosis remain poor without liver transplantation, with expected 1-year survival often less than 1 year.

During the NIH consensus development conference in Washington DC in 1982, liver transplantation was accepted as a treatment modality for patients with end-stage liver disease (ESLD) and unresectable tumors of the liver. A quarter century later, OLT has become the standard of care for all forms of ESLD, including HCC. In providing complete oncologic resection and correcting the hepatic dysfunction in patients with cirrhosis and HCC, OLT is well suited to such patients. Although early experience with OLT for cancer resulted in poor patient survival and high recurrence rates, methods of patient selection have been refined, and results have improved dramatically.

The so-called Milan criteria were born as a result of a 1996 study by Mazzaferro and colleagues, which reviewed radiologic and histologic results of patients with ESLD and HCC who received liver transplants. They reported that, in patients with a solitary tumor ≤5 cm or no more than three tumors, each no larger than 3 cm, overall and recurrence-free survival rates after transplantation were 85% and 92%, respectively. Overall HCC recurrence was 8% at the 4-year follow-up. Patients who exceeded the criteria showed

an actuarial survival rate of 50%, only 59% of whom were recurrence free. The Milan criteria are currently the standard by which the UNOS and Medicare to guide selection of patients for cadaveric OLT in the USA, with some variation established by regional review boards.

Over the past decade, several studies have challenged the Milan criteria, reporting comparable outcomes after transplantation for more advanced stages of HCC. Yao and colleagues showed a 5-year survival rate of 70.2% in patients with HCC fulfilling so-called University of California, San Francisco (UCSF) criteria. These criteria, based on explant pathology, allowed inclusion of single tumors ≤6.5 cm, or a maximum of three tumors ≤4.5 cm, and a cumulative tumor size ≤8 cm.

The Barcelona Clinic Liver Center has developed a system for treatment of HCC with OLT, based on tumor stage, liver function, physical status, and cancer-related symptoms. Their emphasis is on drop-out rates and intention-to-treat analyses, and their expanded criteria include one tumor <7 cm, three tumors <5 cm each, or five tumors <3 cm each, or downstaging to conventional Milan criteria with pretransplant adjuvant therapies. Using this expanded approach, the Barcelona group has achieved 5-year post-transplant survival rate in excess of 50%, versus 20% for palliative treatment alone.

Studies that followed UCSF and the Barcelona group seemed to support their criteria, and such observations led to the description of the so-called "Metro Ticket Paradigm," formulated by Mazzaferro using a decision analysis model. The larger the tumor diameter and/or the higher the number of nodules, the higher the "price of the ticket" in terms of potentially higher HCC recurrence rates.

Pretransplant adjuvant therapy

Within the framework of persistent organ shortage and high wait-list drop-out rates due to HCC growth, pretransplant patient selection has become the determining factor in treating HCC in patients with ESLD, and pretransplant adjuvant therapies a routine component of this process. Controlling tumor growth during the wait-list time may have several advantages, including preventing drop-out, influencing HCC recurrence rates post-transplantation, and overall survival for this subgroup of patients.

Current strategies to control tumor growth focus mainly on surgical and radiologic interventions, as systemic chemotherapy has had little success thus far in treating HCC. Transarterial chemoembolization (TACE) and transarterial embolization (TAE) are frequently used in HCC patients who are not candidates for surgical resection, either because they are beyond Child's class A, they have bilobar tumors, or they have significant medical comorbidities. TACE in particular has been shown in some centers to allow for significantly longer disease-free survival post-OLT, but the effectiveness of TACE seems to depend in large part on tumor stage and the degree of tumor necrosis. Moreover, a French multicenter study by Decaens and colleagues demonstrated no overall effect from TACE on overall and disease-free survival. No controlled randomized trials comparing patients with HCC with or without TACE before liver transplantation are available to date. Further qualifying the use of TACE is the theory that incomplete TACE can invoke a neoangiogenic reaction and promote tumor growth through increased levels of vascular endothelial growth factor (VEGF) and β-fibroblast growth factor (β-FGF).

The other main modality for pretransplant adjuvant therapy is radiofrequency ablation (RFA), a relatively easy method of inducing coagulation necrosis in a tumor by heat generated by electrical current. It is a viable option for tumors up to 4 cm in size, and is sometimes used in combination with percutaneous ethanol injection (PEI) in larger tumors, under ultrasound or CT guidance. Recurrence rates after RFA differ depending on whether the success is assessed by radiologic methods or explant pathology, though tumor necrosis induced by RFA is uniformly higher than necrosis induced by TACE or TAE. Recurrence rates after transplantation in patients where RFA achieved complete or nearly complete tumor necrosis is very low, ranging from 0% to 6% in retrospective studies.

Although single treatment modalities are effective in slowing tumor progression in many patients with HCC, multimodality treatment may allow for increased rates of complete tumor necrosis, and thus better post-transplant recurrence-free survival. Several centers, most notably Yao and colleagues from UCSF, have shown in uncontrolled studies that multimodality approaches can offer a low drop-out rate during the waiting time, favorable survival figures, and a low

recurrence rate after transplantation. Also, Freeman showed similar results in a retrospective review of the Scientific Registry of Transplant Recipient (SRTR) data on liver transplantation in the USA from 1997 to 2006. He observed a significant survival advantage at 3 years post-transplantation of patients with HCC exemptions and local ablative therapies during the waiting time.

Case

A 48-year-old man with chronic liver disease due to hepatitis C is referred for possible liver transplantation. Imaging studies reveal three solid lesions in the liver parenchyma and biopsy confirms hepatocellular carcinoma. One of the tumors is 3 cm in diameter and the other two are each 4 cm in diameter. Radiofrequency ablation is performed on each tumor, successfully shrinking each tumor to <2 cm in diameter. Now satisfying the Milan criteria, the patient is subsequently wait-listed for liver transplantation.

Selection of patients with HCC for liver transplantation

Overall, series reporting use of expanded criteria for OLT in patients with HCC, with or without preoperative locoregional therapy of some sort, have uniformly achieved a 50% 5-year survival rate when the tumor burden is categorized based on explant pathology. Furthermore, series comparing pretransplant imaging and pathologic data generally show higher overall survival using the latter, particularly for tumors beyond the Milan criteria. Possible explanations include understaging of HCC by preoperative imaging, a lag period between last imaging and OLT during which tumor size and extent may progress, or variability in radiologists' interpretations of tumor size and number among regenerative nodules in cirrhotic livers.

In the largest, prospectively collected, single-institution study of HCC in OLT to date, from the University of California at Los Angeles (UCLA), factors that predicted poor survival included increased tumor number, presence of lymphovascular invasion, and poor tumor differentiation. These findings echo the results of prior series, and underscore the key principle that tumor biology, more than size or number, determines outcome after OLT for HCC. This has led several researchers to surmise that tumors that respond favorably by radiologic images to pretransplant therapy, be it TACE or RFA, possess a more favorable biologic profile. More study needs to be done to elucidate this theory, especially with regard to the best means of assessing tumor biology pretransplant, be it by serologic or radiologic testing.

Based on these findings, Duffy and colleagues from UCLA propose that preoperative tumor staging is best accomplished with CT or MRI within 6 months of the time of OLT, as well as liver biopsies to assess histologic grade and the absence or presence of lymphovascular invasion. As there are real concerns about liver biopsies in patients with cirrhosis and the risks of sampling error, bleeding, or risk of tumor dissemination, others have recommended using tumor biopsies only in cases of large tumors that approach ≥3 cm, or tumors that do not respond well to locoregional therapy.

Long-term complications of liver transplantation

The major sources of long-term morbidity and mortality after OLT, not related to graft loss, include malignancy, infections, and metabolic complications leading to renal insufficiency and cardiovascular events. Although there remains an appreciation that renal insufficiency and many of the metabolic complications associated with transplantation are associated with immunosuppressive medications, there is a growing awareness that many of these complications are related and are a manifestation of a liver transplantation-associated metabolic syndrome. Post-transplant metabolic syndrome (PTMS) includes the constellation of obesity, hypertension, diabetes, and hyperlipidemia mediated by underlying insulin resistance. PTMS can affect over half of liver transplant recipients compared with 27% of the adult US population overall. It is associated with increased morbidity from cardiovascular events after liver transplantation and potentially graft loss.

The influence of PTMS on outcomes after liver transplantation is further complicated by a complex interplay between metabolic complications, renal insufficiency and recurrent HCV after transplantation. A preponderance of evidence suggests that infection with HCV is a significant risk factor for the development of type 2 diabetes in both liver trans-

plant and non-transplant recipients infected with HCV. HCV has also been identified as an independent risk factor for renal insufficiency after liver transplantation. Conversely, type 2 diabetes and insulin resistance are associated with accelerated damage to the post-transplant liver from recurrent HCV.

As patients liver longer after liver transplantation and as so many transplantations are done in individuals with HCV or non-alcoholic fatty liver disease (NAFLD), PTMS will become an increasingly important target in efforts to improve liver transplantation outcomes.

Renal insufficiency

Renal insufficiency is a major source of morbidity and mortality after liver transplantation. In 2003, Ojo et al. published a seminal paper marrying the SRTR database with the Centers for Medicare and Medicaid Services (CMS) database to establish that liver transplant recipients had an 18.1% chance of chronic renal failure (GFR ≤29 mL/min per m^2) by 5 years after OLT. Traditionally, renal insufficiency after organ transplantation is felt to be largely mediated by nephrotoxicity from CNIs. However, the incidence of renal failure after liver transplantation exceeded rates for all other non-renal solid organ transplants with the exception of the intestine, despite the perception that the allogeneic liver is more tolerizing than other organs and requires less immunosuppression. This may result partially from the fact that HCV infection was a risk factor for post-transplant renal failure in the analysis and HCV is prevalent only in liver transplant recipients. Moreover, several reports clearly show that liver transplant recipients who require renal replacement therapy have markedly diminished survival. Finally, as pretransplant renal function is an important predictor of post-transplant renal function and as the MELD allocation system gives priority to patients with an elevated serum creatinine, there is concern that the burden of renal insufficiency after liver transplantation will only increase.

To date, there does not appear to be diminished outcomes in the MELD era, in part because survival for any given level of pretransplant renal insufficiency has improved. Although there has been a greater use of combined kidney–liver transplants in the MELD era, much of the improvement is likely due to newer immunosuppressive strategies. One intervention that has had a substantial effect on renal function and survival in patients with diminished renal function before liver transplantation is the use of antibody-based induction therapy with agents such as rabbit antithymoglobulin and IL-2R antagonists. These agents allow a delay in the initiation of CNIs and, as a result, may protect the kidneys in the delicate immediate post-transplant period before nephrotoxic CNIs are introduced. The use of induction therapy has grown significantly in liver transplant recipients when comparing the pre-MELD and MELD eras.

Another agent that has been used to preserve renal function after OLT is sirolimus. Sirolimus is one of a few agents potent enough to be used as a primary immunosuppressant that is not a CNI. Although sirolimus has a variety of adverse reaction and is not tolerated by up to a third of patients, it is not clearly nephrotoxic. In patients randomized to receive sirolimus, as opposed to a CNI, within 4–12 weeks of a liver transplantation, there was a 22.1% increase in GFR from baseline to year 1 compared with a 6.2% increase in patients receiving the CNI, and this difference was significant. There was a higher incidence of rejection in the sirolimus arm. There does not appear to be a clear benefit in randomized trials to sirolimus conversion in stable liver transplant recipients who are further out from liver transplantation.

In patients who develop renal insufficiency after liver transplantation aggressive efforts should be make to control factors associated with diminished renal function including hypertension and diabetes. In addition, nephrotoxic drugs should be avoided and an effort made to decrease CNI exposure. Multiple studies have also shown that OLT patients can experience benefit in renal function from succinct efforts to lower CNI levels often together with an antimetabolite such as MPA. As with sirolimus, these efforts have the most efficacy when initiated early.

Diabetes mellitus

Diabetes is frequent after liver transplantation and can occur in about a third of patients with insulin resistance in up to 45% of patients. Risk factors for post-transplant diabetes mellitus (PTDM) include corticosteroid and tacrolimus use, multiple courses of steroid-resistant rejection, infection with HCV, diabetes before transplantation, and obesity. The increase in NAFLD as an indication for transplantation has

the potential to increase the incidence of PTDM. The association between HCV and PTDM is especially compelling. In many HCV patients with PTDM, the onset of diabetes coincides with recurrence of allograft hepatitis and effective antiviral therapy can improve glycemic control. It should be noted that chronic liver disease and cirrhosis are diabetogenic and liver transplantation has the potential to cure diabetes. In one report of 618 OLT patients, 37 of 66 patients who had diabetes pretransplantation did not have diabetes afterwards. However, patients with type 1 diabetes pretransplantation typically maintain their need for insulin.

PTDM is associated with diminished outcomes and appropriate control of hyperglycemia is desirable. Patients may benefit from adjustments in immunosuppressive medications when possible. The use of more rapid steroid tapers and steroid-sparing protocols in recent years is associated with a decline in the incidence of PTDM. In addition, tacrolimus at higher levels is associated with diabetes and lowering or eliminating the medication can be helpful in some patients. Azathioprine and MPA derivatives are not associated with hyperglycemia. Management of PTDM is similar to management of diabetes in non-transplant patients in most other ways. All patients should be counseled on diet and lifestyle modifications with an emphasis on weight loss. Oral hypoglycemic drugs are typically well tolerated although patients receiving metformin and thiazolidinediones should be monitored for lactic acidosis and hepatotoxicity, respectively.

Hypertension

Hypertension is frequent after liver transplantation and can occur in between 40% and 70% of patients, with the incidence increasing over time. Patients with ESLD typically have low systemic vascular resistance and blood pressure as a manifestation of their cirrhosis but this reverses almost immediately after transplantation with the functioning of a non-cirrhotic allograft and the use of CNIs and corticosteroids. CNIs elicit a potent vasoconstriction of renal afferent arterioles with subsequent sodium reabsorption through activation of the renin–angiotensin system. As with diabetes and metabolic syndrome in general, the use of steroid minimization or elimination protocols has the potential to decrease the incidence of hypertension. Aggressive control of hypertension has the potential to diminish the impact of both renal insufficiency and cardiovascular complications after OLT.

The Ad Hoc Group on "Prevention of Post-Transplant Cardiovascular Disease" recommends maintaining the systolic blood pressure <140 mmHg and the diastolic <80 mmHg. Efforts can start with minimization of both corticosteroids and CNIs. As with non-transplant patients, OLT patients should pursue lifestyle modifications including weight loss, salt restriction, and avoidance of nicotine and caffeine. The ideal pharmacologic management of hypertension post-transplantation has not been defined but, in practice, calcium channel blockers (CCBs) have proven to be effective and well tolerated. They are potent vasodilators and have the ability to reverse the vasoconstriction induced by CNIs. Diltiazem, verapamil, and nicardipine all have the potential to raise CNI levels and amlodipine, nifidepine, and felodipine have emerged as popular choices because they do not. β Blockers are less effective than CCBs, but can be used, especially as adjunct agents. With the exception of carvedilol, they do not affect CNI levels; labetolol is an effective agent. Diuretics can be used especially in patients with fluid retention but have the potential to exacerbate hyperuricemia and azotemia. ACE inhibitors and ARBs have the potential to be very effective agents and to reduce the progression of diabetic nephropathy. In practice, they can exacerbate hyperkalemia, especially soon after transplantation, and they are often abandoned if the serum creatinine starts to rise.

Hyperlipidemia

Hyperlipidemia, defined as hypercholesterolemia and/or hypertriglyceridemia, is common after OLT and affects approximately 40% of transplant recipients. Potential risk factors include female sex, cholestatic liver disease, a pre-OLT cholesterol level >141 mg/dL, diabetes, and obesity. Immunosuppressant medications associated with hyperlipidemia include cyclosporine, corticosteroids, and sirolimus. Sirolimus is associated with unusually high levels of both cholesterol and triglycerides, and its use can be limited in some individuals on this basis. Treatment begins with minimization of exacerbating medications, and lifestyle and dietary modifications including weight loss,

exercise, and a diet less rich in refined sugars and low saturated fats. Patients may benefit from conversion of cyclosporine to tacrolimus. Oral contraceptives, β blockers and thiazide diuretics also have the potential to exacerbate hyperlipidemia. The HMG-CoA reductase or "statin" drugs are effective and typically well tolerated in OLT patients and do not interfere with CNI levels. Patients should be monitored for myositis and elevated transaminases but these complications are unusual. Fibric acids can be used but the incidence of myotoxicity rises significantly when a fibric acid is used with a statin. Bile acid sequestrants, orlistat, and ezitimibe can affect CNI levels. When necessary, all other medications should be given 1 hour before or 2 hours after these agents and CNI levels, especially cyclosporine, should be monitored.

Obesity

Few problems in the long-term management of liver transplant recipients are as challenging as obesity because there are few successful options. There has been a dramatic increase in obesity in patients undergoing liver transplantation. Before 1996, 17% of transplant recipients had a BMI >30 but, between 2001 and 2004, 32% of patients did so. In addition, 22% of non-obese patients will become obese within 2 years post-transplantation. Risk factors for obesity after OLT include greater recipient BMI, greater donor BMI, being married, and higher cumulative doses of prednisone.

It should be noted that it has been difficult to demonstrate that an elevated BMI is associated with worse survival after outcome. Numerous single center studies and an analysis of the 704 patients in the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) did not show an association between BMI and patient and graft survival. An analysis of the UNOS database showed diminished survival only in the "very severely obese" population with a BMI >40. Even here, most of the difference in survival occurred early and much of the difference was due to infectious complications. This may be a result, in part, to the fact that obese patients are screened for cardiac disease pretransplantation and no doubt exposed to the selection bias. The impact of obesity on survival did increase if patients had coexisting diabetes or coronary artery disease.

Few interventions have had success in treating obesity. Dietary interventions are no more successful in OLT patients than in the population at large, which is minimal. Few medical options are available. Orlistat has been shown to be safe in transplant recipients on tacrolimus although tacrolimus levels frequently had to be adjusted. The medication did not result in weight loss. Bariatic surgery with gastric banding either at the time of transplantation or subsequently has been described at the case report level.

Bone disease

Metabolic bone disease is common after liver transplantation. Cirrhosis itself is a risk factor for bone loss. Up to 25% of patients with cirrhosis will have bone density at the less than thee fractures threshold and the number is higher in patients with cholestatic liver disease. Other risk factors include a history of smoking or heavy alcohol use, low BMI, postmenopausal state, physical inactivity, and advanced age. Bone loss accelerates in the period right after transplantation as a result of immobilization and corticosteroid use and nadirs between 3 and 6 months post-transplantation. The risk of fracture is greatest during this period. Bone density increases after this period although no further improvement occurs after the end of the second year. Although a third of OLT patients have traditionally been left with bone density below the fracture threshold, this number has been clearly declining in recent years, in part because of steroid minimization and medical intervention.

There are few uniform recommendations for management of bone loss in transplant recipients. A dual energy X-ray absorptiometry (DXA) scan is the preferred modality to monitor bone loss and a baseline study at the time of transplant evaluation is useful followed by yearly studies initially. Patients should be mobilized and should avoid alcohol and nicotine. Corticosteroid use should be minimized and patients with renal insufficiency should be evaluated for renal osteodystrophy. All patients should receive 1500 mg calcium and 800 IU vitamin D daily, which is typically adequate to provide normal levels. Estrogen therapy can be considered in postmenopausal women and testosterone replacement in men with low testosterone. Prospective randomized studies with

bisphosphonates, oral alendronate, and intravenous pamidronate have shown significant improvements in bone density after OLT. Their effect on the incidence of fractures is still unclear.

Malignancy

In all series of late term mortality after liver transplantation, new malignancies are a major source of mortality. The immunosuppression associated with solid organ transplantation places patients at an increased risk of both lymphoproliferative and solid tumor malignancies. In addition, many OLT patients have engaged or continue to engage in the high-risk behaviors of nicotine and excess alcohol use. Finally viral infections including the Epstein–Barr virus (EBV), human papillomavirus (HPV) and herpesvirus are associated with malignancy post-transplantation. The incidence of new malignancy increases with the age of the patient and the time from transplantation with an incidence of up to 50% in patients many years from transplantation. Surveillance for malignancy is an integral aspect of the long-term care of these patients.

PTLD is a specific entity observed in all solid organ transplant recipients. It is most common in the first year after transplant but can occur at any time. It is classically a B-cell lymphoproliferative disorder associated with infection with the EBV which has the potential to immortalize B-cell clones. It occurs in 1–2% of adult liver transplant recipients but is more common in pediatric liver transplant recipients who may naive to EBV post-transplantation and who frequently require intense immunosuppression. There are more unusual forms of PTLD that are not B-cell derived, including a T-cell malignancy. PTLD can present in the liver, lymph nodes, and other solid organs such as the gut and bone. It is always a consideration in patients with unexplained fevers, night sweats, or weight loss. It can respond to significant reductions in immunosuppression and antiviral agents such as ganciclovir. Patients should be considered for surgical resection when applicable. In recent years, an anti-CD20 monoclonal antibody or rituximab has been used commonly in patients with B-cell PTLD and has shown considerable activity.

Liver transplant recipients are at increased risk for solid cancers with an incidence of 2.5 times that seen in age- and sex-matched non-transplant individuals. Malignancies are more common after the first year and the risk increases over time. The most common malignancy in OLT patients is cutaneous cancer of the skin and lip, with an incidence 31 times that seen in non-transplant patients. Squamous cell carcinoma predominates although basal cell carcinoma and melanoma can be seen. Risk factors for cutaneous cancer are similar to those for the population at large including age, sun exposure, and a history of skin cancer or actinic keratosis. Additional risk factors include the duration of immunosuppression and a history of HPV infection. Other solid malignancies with an increased risk in liver transplant recipients include kidney cancer (relative risk [RR] 3.1), pancreatic cancer (RR 3.9), oral cancer (RR 2.5), colon cancer (RR 2.6), and lung cancer (RR 1.4). The incidence of colon cancer may be related to an increased incidence of rectal cancer and to the transplantation of patients with colitis. There is no clear increased risk of breast, cervical, and genitourinary cancer.

Recommendations for OLT patients should generally follow the recommendations of the American Cancer Society. Patients with a history of colitis should undergo yearly colonoscopic examination with biopsies. All patients should avoid nicotine use, limit exposure to sun and ultraviolet light, and undergo yearly dermatologic screening. It should also be noted that patients with a history of colon, breast, bladder, or symptomatic renal cell cancer even 5 years pretransplantation have a >20% chance of recurrence after liver transplantation.

Immunizations

The hepatitis A and B vaccines and the pneumococcal vaccine should be given preferentially pretransplantation but may be administered safely post-transplantation. Patients should receive the yearly influenza immunization typically in the fall. Inactivated vaccines are considered safe whereas live attenuated vaccines are generally avoided. The inactivated and injected influenza vaccine is administered instead of the inhaled, live, attenuated form. Other live attenuated vaccines that are avoided include Bacille Calmette–Guérin (BCG), measles, mumps, oral polio, rubella, vaccinia, and varicella.

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