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section 15 Gastroenterological disorders 3100 Other approaches to further improve prognostic criteria include sequential assessment of liver volumes by CT. This is a new tool to assess liver collapse and thus infer hepatocellular reserve, although it does not provide a measure of functionality. One study found that a liver volume of less than 1000 ml was associated with a pre- dicted mortality of 97%. Other attempts to improve on conventional scoring systems include the ALFSG (US Acute Liver Failure Study Group) index, utilizing a combination of clinical end-points and the biomarker of apoptosis M30. This was found to better predict outcomes of patients with ALF than the King's College criteria or MELD, but requires further validation. Future directions While much progress has been made in the last few years in char- acterizing the clinical phenotype and prognosis of ACLF, the underlying pathological mechanisms remain incompletely under- stood. It is evident from clinical studies that a dysregulated SIRS is a central driver of pathogenesis. Precipitating events may be initiators of ACLF but do not determine outcome. It is therefore likely that individual host susceptibility to injury (via PAMP/ DAMP signalling pathways in particular) and regenerative poten- tial accounts for the observed heterogeneity in clinical outcome. A clearer understanding of these underlying mechanisms will inform targeted immunotherapy. The goal of therapy in ACLF and ALF is to prevent or at least reverse organ failure and thus improve outcome. Organ failure occurs when organ injury overwhelms regenerative re- sponse. Unlike chronic decompensated disease in which regen- erative capacity has been exhausted, there may be potential for reversibility of organ dysfunction in patients with ACLF and ALF. Therapeutic interventions are likely to focus on abroga- tion of SIRS to diminish organ injury and either promotion of hepatocellular regeneration or bridging therapies with liver sup- port devices. Biomarkers to inform hepatocellular regenerative potential, extracorporeal support systems, and the use of growth factors to promote hepatocellular regeneration remain unmet clin- ical needs. Finally, further work is required to determine optimal criteria for early identification of patients requiring transplant- ation for ACLF. FURTHER READING Acute-on-chronic liver failure Arroyo V, et al. (2015). Acute-on-chronic liver failure: a new syn- drome that will re-classify cirrhosis. J Hepatol, 62 Suppl 1, S131–43. Gustot T, et al. (2015). Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology, 62, 243–52. Jalan R, et al. (2014). Development

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15.22.6 Liver transplantation 3101 Introduction Liver replacement has been an option for the management of a broad range of liver diseases in adults for about three decades. Improved immunosuppression strategies are credited with the tran- sition from a 20-year period of experimentation to a clinically based service with acceptable outcomes. The number of liver transplants performed globally on an annual basis is around 30 000, with early success rates well over 90%. Liver transplantation in the West is largely based on cadaveric donation with the constraints imposed by the limited availability of organs. By contrast, in the East most liver transplantation activity is by means of living donation and continues to increase. Indications The indications for liver transplantation are usually categorized under acute liver failure, end-stage

chronic liver disease, malignancy (mostly hepatocellular carcinoma), and metabolic disease. There is overlap between the latter three categories, exemplified by patients with cirrhosis complicated by hepatocellular carcinoma, and by end-stage liver disease caused by a metabolic condition that is also cured by liver transplantation, e.g. Wilson's disease. Acute liver failure Acute liver failure accounts for 4 to 6% of transplantation activity. These patients are given the highest level of priority in most alloca- tion systems and typically receive grafts within days of being placed on a waiting list. A range of prognostic models are in use that at- tempt to identify patients who would benefit from a transplant early in the course of the disease. These are generally considered to be accurate in predicting death, but perform less well in identifying all patients at risk of death. The most influential determinants of out- come are aetiology, age, rate of progression from onset of jaundice to encephalopathy, coagulation parameters, serum bilirubin, and serum creatinine. Young patients with a defined aetiology and rapidly progressive disease (hyperacute liver failure) often survive without emergency liver transplantation. By contrast, older patients with subacute liver failure have a very high mortality without trans- plantation. As the disease progresses, adverse clinical events, such as cerebral oedema or cardiovascular instability, may indicate the poor prognosis and determine the need for transplantation, albeit with a narrower window of opportunity. Cirrhosis All aetiologies of cirrhosis are potentially suitable for liver trans- plantation, but alcohol, nonalcohol-related fatty liver disease, and hepatitis C account for most cases. The indications for liver trans- plantation in end-stage liver disease were initially developed on an aetiology-specific basis that reflected advanced disease or severe impairment of quality of life, albeit with some common themes. However, the need for liver transplantation is increasingly being informed by generic prognostic formulae that predict short-term survival, with the Model for End-Stage Liver Disease (MELD) being the prototype. MELD is calculated using serum bilirubin, serum creatinine, and INR, although another version includes serum so- dium (MELD-Na), which is similar to the United Kingdom Model for End-Stage Liver Disease (UKELD). A MELD score of 16 or a UKELD score of 49 are considered to be the thresholds above which patients would benefit from a liver transplant. Some patients with cirrhosis but with scores below these thresholds have specific clin- ical complications that may also be effectively managed by liver transplantation (Table 15.22.6.1). Hepatocellular carcinoma Hepatocellular carcinoma arising in a cirrhotic liver accounts for most patients undergoing liver transplantation. The tumour may be the specific indication for liver transplantation in patients with compensated cirrhosis or a secondary indication in patients with Table 15.22.6.1 Variant syndromes that may indicate a need for liver transplantation Cirrhosis present Diuretic resistant ascites Not suitable for transjugular intrahepatic portosystemic shunt Chronic hepatic encephalopathy Failure of all therapy including rifaximin Hepatopulmonary syndrome Arterial Po2 <7.8, A–a gradient >20 mmHg Intractable pruritus Failure of all other therapies Recurrent cholangitis Failure of medical, surgical, and endoscopic options No cirrhosis Familial amyloidosis Transthyretin gene mutation in absence of debilitating cardiac disease Primary hyperlipidaemia Familial hypercholesterolaemia or low-density lipoprotein receptor abnormalities Primary hyperoxaluria Simultaneous or sequential renal transplant Crigler–Najjar syndrome Auxiliary graft an option Polycystic liver disease Alone or in combination with kidney transplant Tumours Neuroendocrine metastases Primary resected and bulk <50% liver volume Epithelioid haemangioendothelioma Absence of extrahepatic disease Adenomatosis or haemangiomas Extensive disease with hepatomegaly

 end-stage disease. An important difference between these two groups is the inability of the latter group to tolerate strategies aimed at controlling

disease progression, essentially bridging patients through to transplantation. The selection is based on patterns of tumour bulk, as determined by size and number of lesions, α-fetoprotein levels, evidence of tu- mour biology, and absence of alternative treatments with curative potential. The Milan criteria are the most widely used but also the most restrictive of the selection models, setting upper limits of 5 cm in diameter for a single nodule or 3 cm if two or three nodules are present. There is some evidence indicating that more extensive tumour bulk that responds well to therapy, such as transarterial chemoembolization, may be suitable for liver transplantation, a con- cept described as ‘downstaging’. A quarter of patients listed for liver transplantation have disease progression that results in deselection. Small, solitary tumours that are suitable for resection or ablative therapy are no longer being prioritized for liver transplantation. Hepatocellular carcinoma arising in noncirrhotic livers is rarely suitable for liver transplantation, unless it is of the fibrolamellar variant that is seen in young adults. Epithelioid haemangioendothelioma is another tumour seen in young adults that may benefit from transplant- ation. Cholangiocarcinoma is, in general, a contraindication to liver transplantation, although acceptable outcomes have been achieved in highly selected patients receiving aggressive pretransplantation therapies. Metastatic disease from neuroendocrine tumours may be suitable for transplantation, as may some patients with benign disease (Table 15.22.6.1). Patient selection and organ allocation Patients with indications for liver transplantation are assessed for suitability based on the absence of contraindications and likelihood of surviving the operation. The number of specific contraindications to transplantation is now relatively small (Box 15.22.6.1). Potential candidates are more likely to be declined on the basis of a pattern of coexisting comorbidities, particularly frailty, limited cardiopul- monary reserve under stress, and pre-existing conditions such as malignant disease with unfavourable prognoses. The decision with respect to the suitability of an individual patient is usually made by an extensive multidisciplinary team. Alcohol consumption A commitment to abstaining from alcohol is consistently expected in patients being considered for transplantation with alcohol-related liver disease, but there are inconsistencies between transplanting centres with respect to the detail of that commitment. Risk factors associated with a return to harmful alcohol consumption are out- lined in Box 15.22.6.2 and these broadly influence selection policy in individual programmes. The need for a significant duration of so- briety prior to listing for transplantation is the most contentious. Recent favourable reports relating to liver transplantation in the context of acute alcoholic hepatitis argues against the universal re- quirement for established sobriety. Policy is also variable with re- spect to the use of recreational drugs and range from zero tolerance to exclusion of patients actively injecting the drugs. Other factors Blood group compatibility and size are the main logistical param- eters considered in matching donors and recipients. The quality of the graft is also a consideration as so-called extended criteria donors may not be considered suitable for all potential recipients. Donation after cardiac death is one example, but other characteris- tics have been described to quantify the donor-associated risk. HLA matching is not normally required. The allocation of organs to specific patients is now usually deter- mined by systems that assess need or benefit. MELD and its iterations are the most widely used. Some allocation systems direct allocation to a specific patient based strictly on the MELD score, but others direct the organ to a specific transplant programme with some flexi- bility as to who receives the graft. Patients with hepatocellular car- cinoma or exceptional indications have their MELD score adjusted with time in order to get access to an organ. Transplantation options and operations Most liver transplantations using cadaveric organs implant the en- tire liver. Organs harvested after brain death are associated with the best outcomes, but organs from donors with controlled car- diac death are being increasingly used as an

alternative when need outstrips supply or waiting times are protracted. Living donation results in one lobe of the liver being available for implantation. Cadaveric organs may be split into right and left lobes, typically Box 15.22.6.1 Specific conditions that usually contraindicate liver transplantation • Complete occlusion of portomesenteric venous system • Severe pulmonary hypertension unresponsive to therapy • AIDS-defining illness not responding to therapy • Hepatocellular carcinoma with vascular invasion or extrahepatic disease • Current alcohol abuse in absence of commitment to positive care plan • Current intravenous drug use Box 15.22.6.2 Risk factors associated with return to alcohol consumption • Abstinence from alcohol for less than 6 monthsa,b • Family history of alcoholisma • Poor social supporta • Absence of spouse or partner in lifeb • Personality disorder • Anxiety or depressionb • Age under 40 years • Age over 50 yearsb • Females • Failed rehabilitation • Return to alcohol consumption after related illness • Cigarette smoking • Other substance abuse a Factors identified in a meta-analysis. b Coexisting factors associated with escalation of risk.

15.22.6 Liver transplantation 3103 for transplantation into an adult and a child, respectively. Auxiliary transplantation involves replacing one lobe of the liver, leaving the other in situ, and is performed in acute liver failure and some meta- bolic abnormalities. Domino transplantation occurs when a liver with a metabolic defect is transplanted into another patient (e.g. familial amyloid polyneuropathy). Surgical procedure The transplantation operation has three phases—hepatectomy, anhepatic, and reperfusion. Vascularized adhesions in the context of portal hypertension are a risk for haemorrhage during the dis- section phase. The severity of the portal hypertension can be miti- gated by the use of venovenous bypass. The anhepatic phase may be associated with deterioration in coagulation capabilities or lac- tate accumulation, but in acute liver failure can lead to stabilization of neurological and cardiovascular complications. Reperfusion of the implanted liver may be associated with severe haemodynamic compromise. Reperfusion syndrome is defined as a fall in mean ar- terial pressure of more than 30% from baseline, occurring within 5 min of reperfusion and lasting for at least 60 s. This may lead to life-threatening ventricular hypokinesia or refractory arrhythmias. The transplant involves four sets of anastomoses that are relevant to the management of the transplant recipients because each is po- tentially a site of technical complications. The arterial anastomosis is typically end to end, but arterial conduits to the aorta can be used if the anatomy is not favourable. The portal vein anastomosis is also end to end but requires some patency in the portomesenteric venous system. The intrahepatic cava may be removed with the liver and the cava replaced with two anastomoses. The alternative approach dis- sects the liver away from the cava and anastomoses the hepatic veins individually, the so-called piggy-back technique. In most patients undergoing primary liver transplantation, the donor and recipient bile ducts are anastomosed directly. However, when the bile duct is diseased, as in patients with primary sclerosing cholangitis, the donor duct is directly linked to a loop of bowel or Roux loop. Multiorgan transplantation Liver transplantation can be performed in combination with a range of other organs in the initial transplant intervention. The commonest scenario is the combination of liver and kidney, either because of in- trinsic renal disease or failing renal function consequent to the liver disease. The allocation systems that favour the sickest patients have seen the greatest increase in the use of liver–kidney combinations, as exemplified by the introduction of MELD in the United States of America in 2002. Up to 10% of liver transplants for end-stage liver disease undergo simultaneous renal grafting. Renal transplantation is indicated if patients have been receiving dialysis for 6 to 8 weeks prior to transplantation, or if a kidney biopsy shows more than 30% glomerulosclerosis or interstitial fibrosis. Nevertheless, some of these patients recover

native renal function after successful liver transplantation. Heart, lung, and pancreas transplantations have been performed with liver transplantations. The indications may be interlinked, for example, pulmonary hypertension in patients with end-stage liver disease. Alternatively, one of the organs may facilitate the transplantation of a second organ, for example, lung and liver grafting in patients with cystic fibrosis. The liver may be included in a combination of intestinal organs transplanted en bloc including stomach, small intestine, and pancreas. Transplant rejection and immunosuppression Graft rejection Prevention of rejection of a transplanted organ is essential. Modern immunosuppressive strategies have dramatically reduced the con- tribution of rejection to graft failure. Acute cellular rejection during the first few weeks occurs in as few as 10 to 25% of patients and presents a limited threat to graft survival as steroid-resistant rejec- tion rates are in the order of 5% of patients requiring treatment, and many of these respond to antibody therapy. Later episodes of acute cellular rejection occurring spontaneously or in the context of nonadherence with immunosuppression can be more resistant to therapy including the range of antibodies available. Chronic rejection of the graft now occurs in less than 2% of pa- tients, having previously caused graft failure in about one in six pa- tients within a year of transplantation. By contrast, the liver used to be considered almost immune to antibody-mediated rejection but this is now recognized as a cause of graft failure in about 2% of pa- tients. The presence of class II donor-specific antibodies points to the diagnosis of antibody-mediated rejection if the other diagnostic requirements are fulfilled. Plasma cell hepatitis, previously known as de novo autoimmune hepatitis, is increasingly being considered to be within the spectrum of graft rejection. The histological features of these entities are outlined in Table 15.22.6.2. Immunosuppression Immunological stability is typically achieved with a regimen based on a calcineurin inhibitor combined with other agents determined by the need for potency or avoidance of toxicity. Tacrolimus is the most commonly used calcineurin inhibitor. Prednisolone is used exten- sively during the first 3 months after liver transplantation but often withdrawn thereafter unless the indication for transplantation was Table 15.22.6.2 Histological features suggestive of immune-mediated liver injury Acute cellular rejection Portal tract infiltration rich in lymphocytes and often containing eosinophils Bile duct injury Endothelialitis Chronic rejection Ductopenia in >50% of portal tracts Foamy cell arteriopathy (if appropriate-sized artery captured in biopsy) Antibody-mediated rejection Centrilobular hepatocyte swelling Microvascular injury Bile duct proliferation Single cell necrosis Hepatic canalicular cholestasis Positive C4d staining at sites of injury Plasma cell hepatitis Portal tract infiltrate containing plasma cells Interface hepatitis

 an autoimmune disease. A third agent (e.g. azathioprine, everolimus, or mycophenolate) can be used from the outset or introduced when the need for another drug is demonstrated by problematic patterns of rejection or the need to reduce dosing of the calcineurin inhibitor because of related toxicity. A range of antibodies are used as part of the induction immunosuppression regimen or in the treatment of steroid-resistant rejection. Antibodies directed against interleukin- 2 receptors are most frequently used in the former role, and against lymphocytes or thymocytes in the latter. Complications of the transplantation episode Primary nonfunction of the transplanted liver is the earliest com- plication encountered, with an incidence up to around 5%. Risk factors may be identifiable, as with donation after cardiac death, but it can occur unexpectedly. The management is emergency retransplantation. Early graft dysfunction is a less discrete entity with evidence of suboptimal function from the outset (Box 15.22.6.3). This occurs in up to 23% of patients and has serious implications with a 7-fold increase in graft failure and an 11-fold increase in the risk of death during the immediate post-

transplantation period. Chronologically, the earliest threats to grafts that have established function are hepatic artery thrombosis and acute cellular rejection. Hepatic artery thrombosis occurs in 3% of patients, is poorly tol- erated, and is another indication for emergency retransplantation unless very prompt detection and revascularization is feasible. Ultrasonic assessment of vascular patency is an integral part of the investigation of any deterioration of graft function during the first 2 weeks. The development of acute cellular rejection is suggested by an increase in liver enzymes 5 to 10 days postoperatively, but the diagnosis should be confirmed and severity staged by liver biopsy. Milder episodes are either not treated or managed by an increase in the dose of tacrolimus, but more severe patterns are initially treated with high-dose steroids. Renal dysfunction is one of the most significant complications during this period. This may be impaired prior to transplantation or deteriorate afterwards for a range of reasons, including preventable factors such as hypovolaemia, drug toxicity, and interactions. Renal replacement therapy is required in 10 to 15% of patients. Impaired glycaemic control is the other frequently occurring metabolic abnormality in the early phase, both as a new diagnosis and in the sizeable cohort of patients with diabetes prior to trans- plantation. Tight glycaemic control is recommended to prevent de- hydration and bacterial infections. Significant volumes of fluid may also be lost from the abdominal cavity, particularly in patients with severe ascites prior to the transplantation, and these should be ap- propriate replaced. Bacterial infections are common with the usual sites being wound, abdominal cavity, lungs, and urinary tract. Management is directed by local antibiotic policy. Systemic fungal infection is more fre- quently encountered in patients transplanted for acute liver failure and in sicker patients with combinations of prolonged need for in- tensive care, renal failure, and cholestasis. Herpes simplex infection of the lips and mouth is common during the first week but is easily diagnosed and treated. The risk of developing cytomegalovirus (CMV) infection is determined by donor and recipient serological status and prophylaxis is instituted when a seronegative patients receives an organ from a donor with past exposure to CMV. Regular surveillance for CMV viremia is widely practised in patients with lower risk profiles. Technical complications Biliary complications Biliary complications occur in up to 20% of patients. The earliest risk relates to a leak at the site of the anastomosis with an incidence of 8%. This may be due to a technical issue or related to ischaemia. Initial management is with placement of a biliary stent endoscopic- ally when the anastomosis is duct to duct, or percutaneously when a Roux loop has been fashioned. Surgical correction is required in a few patients. The commonest of the complications (13%) is a stric- ture at the anastomotic site, when stent placement is again the initial intervention after balloon dilatation. Surgical revision of the biliary anastomosis is considered if a number of cycles of dilatation and stenting fail to establish satisfactory bile drainage. Nonanastomotic strictures of the biliary tract are more challenging to manage. This pattern of diffuse changes may be a sequel to hepatic artery throm- bosis but is also seen in organs donated after cardiac death. It is re- ferred to as ischaemic cholangiopathy, and retransplantation of the liver may be indicated when the symptoms of cholestasis and recur- rent infection cannot be managed medically. Vascular complications Late hepatic artery thrombosis occurs in 6% of patients but may be less devastating than the pattern of graft injury seen in the first weeks after transplantation. Biliary strictures and intrahepatic ab- scesses are the main presentations, but occlusion of the artery can be associated with good graft function in the long term if effective revascularization has occurred through the development of collat- eral vessels. The need for retransplantation is determined by the pattern of complications that develop rather than the diagnosis of arterial thrombosis per se. Hepatic artery stenosis may be detected on ultrasonography and can be amenable to balloon dilatation when considered to be haemodynamically significant. Portal vein stenosis is less likely to require

intervention unless it is considered to be the cause of portal hypertension. Thrombosis of the portal vein is present in 8% of patients with cirrhosis under- going liver transplantation and recurs in 13%. Pre-existing complete thrombosis of the portal vein increases 30-day mortality to 11%. New thrombotic occlusion of the portal vein may be associated with identifiable and modifiable risk factors such as an underlying pro- coagulant disorders as well as diseases associated with thrombophilia (e.g. primary sclerosing cholangitis and HIV/AIDS). Box 15.22.6.3 Parameters indicative of early graft dysfunction Any one of the following: • Bilirubin greater than 180 µmol/litre or 10 mg/dl at 7 days after transplantation • INR greater than 1.5 at 7 days after transplantation • Aspartate aminotransferase or alanine aminotransferase greater than 2000 IU/litre within 7 days of transplantation

15.22.6 Liver transplantation 3105 Venous outflow obstruction occurs more frequently when the cava is spared and the hepatic veins are anastomosed individu- ally. This may be transient if swelling of the graft leads to torsion of the hepatic veins. Dilatation of stenosis or stent insertion may be required if venous outflow obstruction is confirmed by venous pressure measurements and histology demonstrating features of congestion. Long-term management Immunosuppression Immunosuppression requirements decrease 6 months and longer after liver transplantation and this allows a cautious and progres- sive reduction in the number of drugs used and in drug doses. Most patients are on monotherapy with tacrolimus or dual therapy using tacrolimus and a second agent at 2 years after transplantation. The target blood level of tacrolimus is also reduced by about 50% at this time. The reduction in immunosuppression requires stable graft function and the specifics of the changes often reflect the pattern of side effects or complications encountered in individual patients. A few patients will develop operational tolerance and retain good graft function despite withdrawal of immunosuppression, but these patients cannot be confidently identified in advance of the with- drawal of immunosuppression. Investigation and management of late graft dysfunction Liver function tests are monitored at regular but increasing inter- vals after liver transplantation. The development of an abnormal profile requires immediate investigation that reflects the likely balance of immune-mediated injury, technical complications, and possibility of recurrent disease. Patient characteristics and the interval since the transplant will influence the direction of the investigations. Acute cellular rejection is the most pressing diagnosis to estab- lish and a more likely explanation of abnormal liver function tests in younger patients within a few years of transplantation. This re- flects the higher rate of nonadherence to the immunosuppression regimen in these patients. Autoimmune hepatitis typically recurs in the second or third year and may be precipitated by a programmed reduction in steroid therapy. The related entity of plasma cell hepa- titis in patients without a pre-existing diagnosis of autoimmune hepatitis is suggested by the detection of appropriate autoantibodies and elevated IgG levels. The possibility of recurrent disease should be considered in patients with hepatitis B and C. Hepatitis E is being increasingly recognized as a cause of chronic hepatitis in recipients of organ transplants, and 70% of patients respond to treatment with ribavirin. A pattern of cholestatic liver function tests should start with con- sideration of biliary strictures. Unlike the native liver, ultrasound examination is not a reliable screen for duct dilatation and mag- netic resonance cholangiography is required when the ultrasound examination does not identify an abnormality. When duct dilata- tion extends down to the ampulla, the possibility of intraluminal material should be excluded before considering a diagnosis of sphincter of Oddi dysfunction, which is relatively common after liver transplantation. Mild increases in cholestatic enzymes some years after liver transplantation for primary biliary cholangitis can reasonably be ascribed to recurrence of the disease and trigger treat- ment with

ursodeoxycholic acid. Fertility Reproductive capability improves rapidly after liver transplantation. Nonterminated pregnancies resulted in spontaneous abortion in 17%, stillbirth in 1%, and live births in 82% of episodes. The risk of pre-eclampsia is significantly higher than in the general popula- tion at around 20%. Preterm birth rates are in the order of 40% and caesarean section more likely than in the general population. With the exception of avoiding mTOR (mechanistic target of rapamycin) inhibitors and mycophenolate, routine alterations in immunosup- pression therapy are not required during pregnancy. Long-term complications of liver transplantation Renal and cardiovascular disease The impetus to reduce immunosuppression is, in part, due to the contribution of the immunosuppressive drugs to the high incidence of renal and cardiovascular disease in liver transplant recipients. The incidence of end-stage renal disease has been as high as 25% 10 years after transplantation. Calcineurin inhibitor dosing is ad- justed when there is evidence of deteriorating renal function until the glomerular filtration rate stabilizes on a lower dose or the drug is discontinued in the most severe cases. Aggressive management of hypertension and diabetes mellitus are also important in preserving renal function. The metabolic syndrome develops in up to 50% of patients and there is a high prevalence of systemic hypertension, diabetes mellitus, dyslipidaemia, and obesity. New-onset diabetes mellitus develops in up to 25% and new-onset obesity in around 20% of patients within the first 2 years after transplantation. The presence of the metabolic syndrome is associated with a fourfold higher risk of having a car- diovascular event. Withdrawal of corticosteroid therapy is generally indicated in these patients. The targets and strategies for the man- agement of these morbidities are similar to the general population. Disease recurrence Recurrence of the original disease is possible for many diseases managed by liver transplantation and is a major determinant of outcome (Table 15.22.6.3). Reinfection with hepatitis B or hepa- titis C was associated with significant mortality and need for retransplantation. In the case of hepatitis B, prevention of reinfec- tion using long-term immunoglobulin coupled with oral antiviral agents has almost eliminated graft injury as a consequence of recur- rence of this virus. Recurrent infection is still seen in a few patients who are nonadherent with therapy or who develop drug resistance and in patients developing recurrence of related hepatocellular carcinoma. Recurrence of hepatitis C was universal and more problem- atic, with approximately one-third of patients developing acceler- ated graft injury with cirrhosis or graft failure within 1 to 5 years of transplantation. Early indications are that the direct-acting antiviral drugs will have a dramatic impact on this pattern of

 disease recurrence. Firstly, more patients have cleared the virus before transplantation and seem to have little risk for recurrence. Secondly, the antiviral drugs seem to be as effective in the post- transplantation setting as in the general population. Tolerability also seems to be comparable unless there is potential for drug– drug interactions. It is anticipated that the direct antiviral agents will have a significant impact on long-term survival and reduce the requirement for retransplantation. The spectrum of fatty liver disease recurs both in the presence and absence of alcohol. Steatosis can be severe and established within a year of transplantation. The history of resumption of alcohol con- sumption may be suppressed. A resumption of alcohol consumption occurs in up to 50% of patients and about 15% do so in a hazardous manner with the implication of reduced survival 10 years after trans- plantation. The implications of recurrence of nonalcohol-related disease on graft function and survival are less clear cut as a consider- able proportion of mortality is attributable to the associated diseases rather than graft failure. All of the autoimmune diseases have the potential to recur, but with a range of consequences. The most benign pattern is seen in primary biliary cholangitis, where although the

diagnosis is fre- quently confirmed by liver biopsy, few cases progress to liver failure during the first two decades after transplantation. The consequences of recurrence of primary sclerosing cholangitis are potentially more serious, with some patients progressing to graft failure as quickly as 5 years after transplantation. The diagnosis requires a combin- ation of compatible liver histology and classical changes of random strictures on cholangiography with exclusion of alternative explan- ations relating to ischaemic injuries acquired during harvesting of the organ or complications with the hepatic artery. The risk of developing primary sclerosing cholangitis recurrence is increased twofold in patients with ulcerative colitis who have an intact colon. Autoimmune hepatitis recurrence is usually detected when in- creased serum transaminases are detected on routine follow-up. The diagnosis requires a liver biopsy and most cases respond well to an increase in the corticosteroid component of the immunosuppres- sion regimen. Hepatocellular carcinoma recurs in 15% of patients selected using the most conservative approach known as the Milan cri- teria. No effective strategies have been identified to reduce the incidence of disease with adjuvant therapy in patients identified as high risk, or to modify the progression of tumour once it has recurred. Post-transplantation lymphoproliferative disease Post-transplantation lymphoproliferative disease is an important consideration in liver transplant recipients who are unwell because it can occur any time after transplantation and has many modes of presentation. The link to Epstein–Barr virus has become less sig- nificant, with the exception of younger patients. Screening with lactate dehydrogenase levels and positron emission tomography scans in suspicious cases has simplified the diagnostic pathway. Reducing the intensity of immunosuppression remains an initial response, but most cases now require additional therapy. Anti- CD20 monoclonal antibodies and conventional chemotherapy are the strategies most commonly used. The mortality rate is in the order of 40%. Outcomes Mortality The overall survival rates after liver transplantation are now very good, with 1-year survival rates over 95% for elective liver trans- plantation and around 85% for emergency transplantation being reported by individual centres. MELD scores at the time of trans- plantation correlate poorly with outcome and a clear relationship with mortality is only apparent at scores of 35 or above. Patients with chronic liver disease who are in intensive care environments at the time of transplantation have inferior 1-year survival rates of around 60%. Hospitalized patients who are older and have associ- ated comorbidities or renal dysfunction also have increased post- transplantation mortality. Registry data from Europe and the United States of America indicate 5-year graft survival rates in the order of 75 to 80%. The survival rates differ significantly by aetiology of the original liver disease, reflecting a combination of impact of recurrence and the pattern of comorbidities linked to each disease. Among pa- tients with chronic liver disease, the best 5-year survival rates are seen with primary biliary cholangitis, primary sclerosing cholan- gitis, and nonalcohol-related disease; intermediate outcomes in alcohol-related disease; and the highest mortality is associated Table 15.22.6.3 Disease recurrence after liver transplantation Cause of liver disease Incidence of disease recurrence (%) Diagnosis Management Consequence Alcohol 15–50 Compatible histology in context of alcohol consumption Abstain from alcohol Increased mortality at 5–10 years Nonalcoholic fatty liver disease (NAFLD) Compatible histology Tight control of weight, elements of metabolic syndrome Hepatitis B 5 Hepatitis B virus DNA positive Antiviral drugs Limited impact Hepatitis C 100 Liver histology Antiviral drugs Increased mortality at 5 years Primary biliary cholangitis 40 Liver histology Ursodeoxycholic acid Limited impact but occasional retransplant Primary sclerosing cholangitis 15–40 Cholangiography and liver histology No specific therapy May require retransplantation Autoimmune hepatitis 40% Liver histology Corticosteroids Limited impact

15.22.6 Liver transplantation 3107 with hepatitis C virus and hepatocellular carcinoma. The survival rates are poorer for retransplants and decrease progressively with the number of transplantations performed in individual patients. The 5-year survival rates for the third or subsequent transplant- ation falls to less than the 50% threshold commonly used as an indicator of utility. Extended survival is being increasingly documented in popula- tions of liver transplant recipients. Patients who were 55 years of age or older at the time of transplantation have been shown to have the potential of a normal life expectancy measured over a 20-year period. Younger patients continue to lose life years when compared to the general population. Premature mortality is mainly associ- ated with malignant disease, infection, and renal or cardiovascular disease. Late deaths from infection are caused by pneumonia or sepsis- related multiorgan failure as opposed to opportunistic infections. Renal and cardiovascular diseases contribute to about 40% of pre- mature death, particularly beyond the first decade after transplant- ation. Data at 20 to 25 years after transplantation indicate that mortality increases when the glomerular filtration rate falls to less than 60 ml/min but increases exponentially below a threshold of 30 ml/min. The fourfold risk of cardiovascular disease identified in pa- tients with the metabolic syndrome also reflects in higher mortality at this time, especially in men. Morbidity Lymphoproliferative disease (20-fold increase), skin malignancy (30-fold increase), and selected tumours with pre-existing as- sociated risk profiles dominate the malignant category. Patients with alcohol-related disease have a marked increase in malig- nancies of the lung and upper gastrointestinal tract. Patients with primary sclerosing cholangitis and ulcerative colitis are at increased risk of colon cancer and should have enhanced sur- veillance at yearly intervals. However, there is no evidence of a generalized increased risk of common cancers such as breast, prostate, and colon. Quality of life studies before and after liver transplantation docu- ment a dramatic improvement in quality of life in patients with chronic liver disease, but they also demonstrate a shortfall in some domains relating to physical and emotional well-being. There is also evidence of underperformance of those still in education and those of working age, with only 40 to 45% returning to work after the transplant. FURTHER READING Ashwani S, et al. (2013). Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. Transplantation, 95, 755–80. Deshpande NA, et al. (2012). Pregnancy outcomes of liver transplant recipients: a systematic review and meta-analysis. Liver Transplant, 18, 621–9. Kim WR, et al. (2019). OPTN/SRTR 2103 annual data report: liver. Am J Transplant, 19 Suppl 2, S184–283. Lucey MR, et al. (2013). Long-term management of the successful liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl, 19, 3–26. Madhwal S, et al. (2012). Is liver transplantation a risk factor for car- diovascular disease? A meta-analysis of observational studies. Liver Transplant, 18, 1140–6. McCaughan GW, Vajdic CM (2013). De novo malignant disease after liver transplantation? Risk and surveillance strategies. Liver Transplant, 19, S62–7. Nadim MK, et al. (2012). Simultaneous liver-kidney transplantation summit: current state and future directions. Am J Transplant, 12, 2901–8. Neuberger J, et al. (2008). Selection of patients for liver transplantation and allocation of donated livers in the UK. Gut, 57, 252–7. O'Grady JG (2014). Timing and benefit of liver transplantation in acute liver failure. J Hepatol, 60, 663–70. Ojo AO, et al. (2003). Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med, 349, 931–40. Rodriguez-Castro K, et al. (2012). Management of nonneoplastic portal vein thrombosis in the setting of liver transplantation: a sys- tematic review. Transplantation, 94, 1145–53. Schoening WN, et al. (2013). Twenty-year longitudinal follow-up after orthotopic liver transplantation: a single-center experience of 313 consecutive cases. Am J Transpl, 13, 2384–94. Seehofer D, et al. (2013). Biliary complications after liver transplant- ation: old problems and new challenges. Am J Transplant, 13, 253–65. Singal AK, et al. (2019). Simultaneous liver kidney transplantation. Transpl

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