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Anesthesia for liver transplant surgery

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> Ironically... liver replacement, which was once considered the most formidable of the whole organ transplantation procedures and the least likely to be practical, has become the flagship of new principles that are applicable to recipients of all whole organs....
>
> —Thomas Starzl, 1996

Liver replacement represents the sole definitive treatment for end-stage liver disease. Medical treatment does little to improve survival; when life-threatening complications of liver failure such as encephalopathy, gastrointestinal bleeding, or uremia develop, the 5-year survival rate is < 50% [1]. Acute variceal bleeding is a particularly ominous prognostic sign, with a hospital mortality rate similar to that of myocardial infarction. The 3-year survival is < 30%, despite endoscopic and pharmacologic advances [2].

The dismal prognosis in end-stage liver disease led to the search for improved therapy, including hepatic replacement through whole-organ transplantation. In 1963, shortly after the effectiveness of azathioprine and prednisone was established for renal transplantation, Starzl performed the first human liver transplant [3]. The recipient, a 3-year-old child with biliary atresia, died in the operating room from massive hemorrhage caused by venous collaterals and uncontrollable coagulopathy. In 1967, Starzl successfully transplanted a liver into an 18-month-old infant suffering from hepatocellular carcinoma. With the development of cyclosporine in 1979, survival after liver transplantation improved significantly to a 1-year survival rate of over 70%. With the intro-

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duction of tacrolimus in 1989, the incidence of adverse drug events related to immunosuppression decreased [4]. Presently, the use of murine monoclonal antibodies directed against CD3 receptors or the interleukin-2 receptor delays time to the first rejection and decreases the incidence of steroid-resistant rejection [5]. Over the last decade, continued improvements in surgical technique, the management of coagulopathy, the prevention of biliary complications, and the treatment of infections have contributed significantly to decreasing morbidity and mortality.

Indications for liver transplantation

End-stage liver disease is the fourth leading cause of death in the United States for individuals aged 45–54 years; it is surpassed only by cancer, heart disease, and unintentional injury. Among all age groups, liver disease accounted for over 27,000 deaths in 2001, making it the 12th leading cause of death [6]. Liver transplantation is the second most common transplant surgery, accounting for 21% of all organ transplants. Although the number of transplants has been relatively stable at 5000 per year, the number of patients waiting for transplantation continues to grow, increasing ninefold over the last decade [7]. The primary diagnoses for cadaveric liver recipients and their percentages of total cadaveric liver transplants for a 5-year period (1997–2001) are non-cholestatic disease (61%), cholestatic liver disease (11%), acute hepatic necrosis (9%), biliary atresia (4%), metabolic disease (3.9%), and malignant neoplasms (3%). Other diagnoses account for the remaining 7% of transplants.

The category of non-cholestatic disease includes chronic hepatitis C (21% of total transplants between 1987–1998, which is presently the leading indication for transplantation in the United States), alcoholic liver disease (17%), alcoholic liver disease and hepatitis C (4.4%), chronic hepatitis B (5.5%), cryptogenic cirrhosis (11%), and autoimmune hepatitis (5%) [8–10]. Absolute contraindications to transplantation include extrahepatic malignancy, cholangiocarcinoma, active untreated sepsis, advanced cardiopulmonary disease, active alcoholism or substance abuse, and anatomic abnormalities precluding transplantation. With recent reports [11,12] of successful transplantation in recipients with positive HIV serology, this condition is no longer an absolute contraindication. Living donor transplants increased markedly in 1999 and by 2001 comprised 11% of total liver transplants. Although adult-to-pediatric living donor transplantation has been performed for over a decade, most of the increase cited above is the result of the introduction of adult-to-adult living donor transplantation. Recipients of living donor organs, compared with cadaveric graft recipients, have a higher frequency of cholestatic liver disease (18% versus 10%) and biliary atresia (9% versus 3%) and a lower incidence of non-cholestatic disease (53% versus 60%) [7]. Management considerations for living donors are discussed elsewhere in this issue.

Pathophysiology of liver failure

Patients with end-stage liver disease have secondary dysfunction of virtually all other organ systems, and anesthetic management must include protection of other organs damaged by liver failure.

Central nervous system

Up to 80% of patients with acute liver failure develop cerebral edema and increased intracranial pressure [13]. The cerebral symptoms of chronic liver failure are not believed to be associated with cerebral edema, but increased intracranial pressure can occur [14,15]. These reports support the belief that the encephalopathy found in chronic liver disease may have a common underlying pathophysiology with the cerebral edema of acute liver failure, with only the rate and magnitude of change accounting for the clinically observed differences [16]. Further supporting this belief, a number of similarities exist in both acute and chronic encephalopathy. The failure of hepatic clearance leads to an accumulation of toxins, such as ammonia and manganese, and to alterations in endogenous transmitters and messengers, including γ-aminobutyric acid (GABA), glutamate, and nitric oxide. The enzymes of the urea cycle are absent in the brain. The resulting accumulation of glutamine, an osmotic compound, targets the glial astrocytes and results in cerebral edema in acute liver failure. Glutamine also accumulates in chronic liver disease; however, compensatory changes probably account for the absence of cerebral edema [17]. Other reports [18] have shown through magnetic resonance spectroscopy that counter-regulatory mechanisms are not always sufficient to prevent glial swelling, the cellular equivalent of low-grade cerebral edema. Recently, the blood breakdown products hemin and protoporphyrin IX have been suggested as possible endogenous benzodiazepines contributing to hepatic encephalopathy because they are potent activators of GABA receptors [19].

Cardiovascular system

Up to 70% of patients with end-stage liver disease develop a hyperdynamic state characterized by increased cardiac output and arteriolar vasodilatation [20]. Vasoactive substances bypassing normal hepatic metabolism are most likely responsible. A recent study [21] in cirrhotic animals suggests that cannabinoids may contribute significantly to the hemodynamic alterations characteristic of end-stage liver disease. The clinical improvement seen after total hepatectomy in patients with acute liver failure suggests that toxic substances released from necrotic liver may be involved. Nitric oxide and guanosine 3′,5′-cyclic monophosphate (cGMP) have been implicated as mediators [22]. Cardiomyopathy has been associated with alcoholic cirrhosis and hemochromatosis. Rhythm disturbances may result from electrolyte or acid–base abnormalities. As the criteria for transplantation have expanded, upper age limits for recipients have

been liberalized, making preoperative evaluation for ischemic heart disease more important. Atherosclerotic coronary artery disease is at least as common in patients with cirrhosis as in patients without liver disease [23]. Dobutamine stress echo (DSE) is the preferred preoperative screening study because it assesses the adequacy of myocardial oxygen supply, valvular function, and the presence of intrapulmonary shunting or portopulmonary hypertension [24]. This test has a 92–97% negative predictive value. A negative DSE predicts a good prognosis during orthotopic liver transplantation (OLT), that is, a low likelihood of perioperative cardiac events [25,26]. The presence of coronary artery disease is associated with high mortality and morbidity (50% and 81%, respectively) during OLT, making DSE screening a routine preoperative test for adult transplant candidates in most centers [27].

Pulmonary system

The pulmonary complications associated with liver disease include restrictive lung disease, intrapulmonary shunts, ventilation–perfusion (V/Q) abnormalities, and pulmonary hypertension. Restrictive disease results from ascites or pleural effusions and frequently responds to fluid removal, at least transiently. Hypoxemia occurring in the absence of ascites or intrinsic lung disease is referred to as hepatopulmonary syndrome (HPS). Vasodilation of unclear etiology is associated with the syndrome. A contrast (bubble) echocardiogram may define the cause of room air hypoxemia. In the case of cardiac shunts, microbubbles are seen almost immediately in the left atrium after venous injection of contrast. In the presence of intrapulmonary shunting, microbubbles appear three or more beats after injection, whereas with V/Q defects the bubbles are absorbed in the lungs [28]. Although HPS resolves after transplantation, the persistence of hypoxemia with 100% oxygen administration contraindicates transplantation in patients with this syndrome [29]. In eight patients with HPS who underwent transplantation at the author's center, preoperative oxygen dependency resolved in all patients over a range of 2 to 9 months [30].

Approximately 2% of patients with chronic liver disease have portopulmonary hypertension (PPH). PPH is defined as a mean pulmonary artery pressure > 25 mm Hg or pulmonary vascular resistance > 120 dyne $\cdot$ s $\cdot$ cm^{-5} in the presence of a normal pulmonary capillary wedge pressure. Mild (mean pulmonary artery pressure [PAP], 25–35 mm Hg) or moderate (mean PAP, 35–45 mm Hg) pulmonary hypertension does not contraindicate transplantation, particularly when the pulmonary arterial pressures are responsive to a pharmacologic trial of vasodilators [31]. The outcome of transplantation in patients with severe PPH is poor [32]. When mean PAP is > 35 mm Hg and PVR is > 250 dyne $\cdot$ s $\cdot$ cm^{-5}, OLT is associated with increased perioperative mortality caused by right heart failure or hepatic failure [33]; however, successful transplantation has been performed in patients with severe pulmonary hypertension who have undergone long-term vasodilator treatment with epoprostenol that resulted in a decrease in pulmonary artery pressure [34,35].

Renal system

Preoperatively, it is important to identify patients with advanced renal disease who need combined liver-kidney transplants and to treat any preexisting acid–base abnormalities and plasma volume defects. If left untreated, less advanced renal disease might worsen in the perioperative period [36]. The hepatorenal syndrome (HRS), a functional cause of renal failure, is common in patients end stage liver disease. Diagnosing this syndrome requires the absence of primary renal disease, proteinuria, hypovolemia, or hemodynamic causes of renal hypoperfusion. A urinary sodium level < 10 mEq/L or a fractional excretion of sodium < 1% is typical. The renin-angiotensin-aldosterone system is stimulated, and as the liver disease progresses, an increase in antidiuretic hormone results in an impairment of free water excretion and dilutional hyponatremia. In advanced stages of cirrhosis, intense renal vasoconstriction decreases glomerular filtration rate (GFR), resulting in HRS [37]. Endothelin may be responsible for afferent arteriolar constriction, whereas increased nitric oxide levels decrease the efferent arteriolar tone, further decreasing GFR [38]. Paradoxically, the current treatment of HRS is to administer vasoconstrictors to reverse splanchnic vasodilatation. Terlipressin, a vasopressin analog, has been shown to decrease serum creatinine, increase mean arterial pressure, and reverse the stimulation of renin [39,40]. Nephrotoxic antibiotics and contrast used for diagnostic studies should be avoided if possible. Cyclosporine adversely affects renal function postoperatively, typically decreasing the GFR by 30% to 50%. Some centers withhold cyclosporine for the first 48 to 72 hours postoperatively to allow functional renal impairment to improve.

Gastrointestinal system

Esophageal varices, portal hypertension, and ascites are common. Sclerotherapy or portosystemic shunts may be required. Gastric emptying is delayed, and drug metabolism is affected (see "Drug metabolism" below). In cirrhotic patients undergoing nontransplant surgery, the preoperative treatment of ascites (diuretics, paracentesis, and albumin administration) decreases the mortality rate. This strongly suggests that the preoperative condition of liver transplant candidates should be optimized before portosystemic shunt procedures or nontransplant surgery [41].

Hematologic and coagulation system

Anemia commonly occurs as a result of chronic disease, malnutrition, or bleeding, is common. Coagulation defects result from multiple causes including quantitative and qualitative platelet defects, decreased synthesis of clotting factors and their inhibitors, vitamin K deficiency, synthesis of abnormal clotting

factors, decreased clearance of activated factors, hyperfibrinolysis, and disseminated intravascular coagulation (DIC) [42].

Splenic sequestration of platelets decreases the number of circulating platelets and is the main cause of thrombocytopenia. Low levels of thrombopoietin, a liver-produced cytokine responsible for platelet formation, may also play a role [43,44]. Sepsis (bone marrow suppression) or DIC (consumption) also may lead to low platelet counts. Although a functional defect of platelet aggregation has been described, its clinical significance is unclear [45,46]. All clotting factors except von Willebrand factor are synthesized in the liver. As a result, liver failure patients have low levels of all factors except fibrinogen, an acute phase reactant, and factor VIII. Decreasing levels of fibrinogen and factor VIII suggest the presence of primary fibrinolysis or DIC. Prolonged prothrombin time (PT) correlates with the severity of liver disease and is one of the variables commonly used as a prognostic indication of perioperative risk (Table 1) [47]. Ongoing fibrinolysis may occur, caused by low levels of antiplasmin and inadequate clearance of tissue plasminogen activator. Whether the fibrinolysis is primary or caused by the activation of clotting (low-grade DIC) is controversial [48]. Using specialized assays, including thrombin-antithrombin and plasmin-α2-antiplasmin complexes [49], a condition termed accelerated intravascular coagulation and fibrinolysis has been identified in 30% of patients with end-stage liver disease; yet, the clinical diagnosis of DIC hinges on a triggering event (eg, surgery, sepsis, or shock) and compatible laboratory findings (worsening PT, partial thromboplastin time, and platelet counts). The use of antifibrinolytics, common during OLT, is contraindicated in patients with DIC.

Drug metabolism

End-stage liver disease patients tend to be sensitive to drugs, although they may be resistant to some drugs (eg, pancuronium), a condition caused by increased binding to globulin. The action of many drugs (eg, opioids, lidocaine,

Table 1
Pugh's modification of the Child-Turcotte classification

	<Points scored>		
Variable	<1>	<2>	<3>
Encephalopathy	None	1–2	3–4
Ascites	Absent	Slight	Moderate
Prothrombin time (sec prolonged)	<4	4–6	>6
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dL) for cholestatic disease	<2	2–3	>3
	<4	4–10	>10

Child-Pugh class A, 5–6; class B, 7–9, class C, 10–15.
Adapted from Weisner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001; 7(7):567–80 (p. 568).

propranolol) are prolonged because of an increased volume of distribution or decreased metabolism. Most opioids undergo oxidation in the liver. Morphine, which undergoes glucuronidation, is an exception. Oxidation of opioids is decreased in end-stage liver disease, whereas glucuronidation is less affected. The metabolism of fentanyl, however, is largely unaffected by liver disease [50]. The disposition of remifentanil, which undergoes ester hydrolysis, is independent of the liver.

Patient selection

In January 2004, there were over 17,000 candidates awaiting liver transplantation, with 10% of these prospective recipients dying annually [7]. This reality, caused by a growing number of indications for liver transplantation and a nonexpanding cadaveric donor pool, highlighted the need for an improved graft allocation system. In 1998, the Department of Health and Human Services issued the ''Final Rule'' [51], defining the principles of organ allocation: the effect of candidate waiting times should be minimized in favor of allocation based on medical urgency, whereas futile transplantations should be avoided to promote the efficient use of scarce donor organs. Pugh's modification of the Child-Turcotte (CTP) classification [52] (see Table 1), which has been in use as an assessment of disease severity since minimal listing criteria were first defined in 1998, was originally developed to assess operative risk in end-stage liver disease patients undergoing portosystemic shunt surgery. Based on the CTP classification system, the United Network of Organ Sharing (UNOS) allocation policy defined three categories of disease severity. When this score was applied to liver allocation, limitations were apparent, notably the lack of distinction between mildly and severely abnormal laboratory values (for example, all bilirubin levels over 3 were treated similarly), the subjective nature of the assessment for encephalopathy and ascites, and the limited discrimination afforded by only three UNOS disease severity categories (with the need for waiting time to serve as a tiebreaker within each of the three categories) [51]. These shortcomings led to the development of survival models for organ allocation [53].

The model for end-stage liver disease (MELD) and pediatric end-stage liver disease (PELD) models were adopted in February 2002 to allocate organs based on medical urgency and to decrease the number of waiting list patient deaths [51,54,55]. The MELD score is based on three laboratory results: bilirubin, creatinine, and the international normalized ratio (INR). These tests have been shown to be predictive of 3-month waiting list mortality (Fig. 1). Initial validation of the MELD score indicates that it is at least as good as the CTP score, using more objective, readily available variables [51]. There are known limitations to the MELD score, such as the effect of body mass on the serum creatinine (a significant contributor to the final score, which may put nutritionally wasted candidates at a disadvantage), the scoring for candidates with hepatocellular

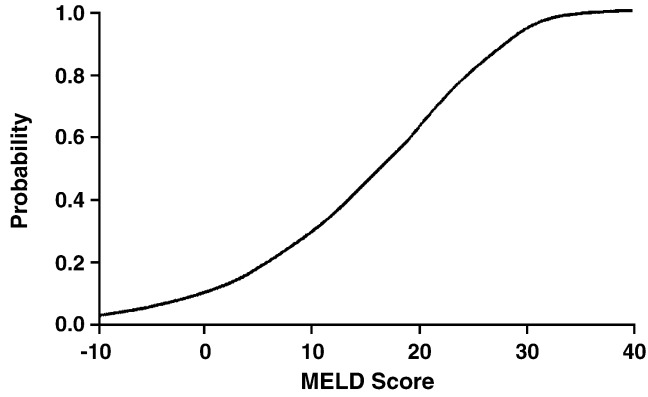

Fig. 1. Relationship between MELD score and 3-month mortality in patients with cirrhotic liver disease. (*From* Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7(7):567–80 (p. 578); with permission.)

cancer, and the effect of waiting time. However, scoring exceptions for these issues and other conditions that are unaccounted for, such as hepatopulmonary syndrome, should allow these populations to compete fairly for donor grafts. It remains to be seen whether deaths while awaiting transplantation will decrease or whether the MELD score will predict outcomes after liver transplantation. In 2002 there was an 11% decrease in the number of waiting list deaths, the first such decrease. The institution of the MELD system is one possible explanation, whereas improved pretransplant care may also play a role [7].

Anesthetic management for liver transplantation

Anesthetic preparation and induction

Anesthesia typically begins with a rapid sequence induction which is necessitated by the emergent nature of the surgery, preoperative administration of oral immunosuppressants and bowel decontamination antibiotics, and the presence of ascites. An arterial catheter is placed either before induction or shortly thereafter. Large-bore intravenous access is obtained. At UCLA, two 9 French introducers are placed centrally. Sites designated for venovenous bypass are avoided. A pulmonary artery catheter is commonly used in adult patients. Transesophageal echocardiography (TEE) is a technique that is increasingly being used during the procedure. Some liver transplant sites avoid pulmonary artery catheter insertion when TEE is used, although the pulmonary artery catheter may be necessary when continuous intraoperative monitoring of pulmonary artery pressures is desired or for postoperative hemodynamic and

fluid management in the intensive care unit (ICU). A rapid infusion system capable of high transfusion flow rates (500–1500 mL/min) is typically used. Such systems incorporate a reservoir, pump, filters, heat exchanger, and safety features designed to avoid and monitor for the presence of blood or air embolism, hypothermia, and line occlusion.

The effects of the anesthetic technique on patient outcome are unknown. At the author's center, a balanced anesthetic is used. This typically consists of a volatile agent in low to moderate concentrations (0.5–1.0 minimum alveolar concentration [MAC]) to ensure unconsciousness, while an opioid, usually fentanyl, is chosen to blunt the sympathetic response to stimulation and to provide a smooth transition to the postoperative period. In recipients with fulminant hepatic failure and cerebral edema, volatile agents are avoided or used cautiously in low concentrations with intracranial pressure monitoring (see ''Special situations'' below). In either case, periods of hypotension during the surgery may require temporary discontinuation of the volatile agent. Midazolam, with minimal hemodynamic effects, may be useful for its amnesiac effects during these hypotensive periods.

Historically, the volatile agent of choice has been isoflurane, which preserves splanchnic blood flow better than other volatile drugs [56]. Recent work [57] in healthy humans has confirmed the vasodilator effects of isoflurane on the hepatic circulation, compared with the vasoconstrictor effects of halothane. This beneficial effect on hepatic oxygen supply may be advantageous to the newly reperfused graft. The effects of desflurane on hepatic blood flow have been evaluated with conflicting results. In animals, desflurane decreased total hepatic blood flow in a dose-dependent fashion at concentrations up to 1.0 MAC [58]; however, in a human study [56] that excluded patients with liver disease, liver blood flow was slightly greater with desflurane than isoflurane, although this effect was not significant. Another study [59] compared the effects of sevoflurane and desflurane on hepatic blood flow and hepatocellular integrity in elderly patients. Both agents resulted in decreases in gastric mucosal pH and increases in cytosolic liver enzymes. The authors conclude that hepatocyte function is well preserved (lidocaine metabolism to monoethylglycinexylidide was unaffected by either agent), but disturbances of hepatocellular integrity and gastric tonometry suggest that splanchnic perfusion and oxygen delivery to the liver are decreased. Whether the increased metabolism of sevoflurane (100 times that of desflurane) is detrimental to the liver is unknown, but it seems unlikely that the metabolites of sevoflurane cause liver damage [60]. Compound A, a breakdown product of sevoflurane found to be nephrotoxic in animals, has not been shown to cause renal toxicities in humans, even during low-flow sevoflurane administration [61].

Cisatracurium may be the preferred neuromuscular blocking agent in patients undergoing liver transplantation because of its organ-independent elimination and diminished histamine release [62]. In patients with end-stage liver disease, the volume of distribution of cisatracurium is greater than that in healthy control patients. Hepatic clearance is also increased in patients with liver disease; this results in similar elimination half times and similar duration of action (time to

25% recovery). Other reports have suggested the use of rocuronium during liver transplantation because the duration of the neuromuscular block appears to be a useful predictor of primary allograft function. All patients whose recovery time was > 150 minutes experienced primary graft dysfunction [63].

Preanhepatic stage

The preanhepatic stage begins with surgical incision and ends with cross-clamping of the portal vein, the suprahepatic inferior vena cava, the infrahepatic inferior vena cava, and the hepatic artery. This phase involves dissection and mobilization of the liver and identification of the porta hepatis. With abdominal incision and drainage of ascites, hypovolemia typically occurs. Hypovolemia should be treated in an anticipatory fashion with colloid-containing fluid to minimize changes in preload. In the presence of preexisting coagulopathy, fresh frozen plasma is indicated soon after incision, although some authors have challenged the need for fresh frozen plasma during OLT [64]. Thromboelastography or standard laboratory tests (prothrombin time, fibrinogen and platelet count) are used to guide the correction of coagulopathy [65]. Other authors disagree with the premise that coagulation monitoring is associated with blood product transfusion requirements during OLT [66]. Considerable institutional variation exists in transfusion practices for OLT. These differences in transfusion requirements are not accounted for by variations in blood loss during the procedure [67].

Fibrinolysis is unusual during the preanhepatic phase of the surgery, so cryoprecipitate administration is typically unnecessary. Hyponatremia should not be corrected rapidly. A perioperative rise of 21–32 mEq/L in the serum sodium level was associated with central pontine myelinolysis in one report, whereas an increase of < 16 mEq/L was not [68]. Citrate intoxication, ionized hypocalcemia resulting from the infusion of citrate-rich blood products in the absence of hepatic function, is avoided by the administration of calcium chloride. Ionized hypomagnesemia also results from citrate infusion, but values of ionized magnesium gradually return to normal after graft reperfusion [69]. The clinical significance of this remains speculative, but cardiovascular function may be affected. Aggressive treatment of hypokalemia is best avoided, particularly in preparation for reperfusion and the associated increase in serum potassium. Supplemental glucose is usually not required except in pediatric patients or those with severe disease, such as fulminant hepatic failure. The maintenance of urine output is desirable; however, the use of low-dose dopamine for this reason is unproven [70]. Hypothermia should be avoided. The use of heated venovenous bypass during the anhepatic phase permits core temperature control. Bleeding during this phase of surgery is related to the degree of preexisting coagulopathy, the presence and severity of portal hypertension, and the duration and complexity of the surgical procedure [71,72]. The presence and severity of adhesions from previous abdominal surgery may add significantly to the complexity of the surgical dissection.

Intraoperative management: anhepatic stage

The anhepatic stage begins with the occlusion of vascular inflow to the liver and ends with graft reperfusion. Cross-clamping of the suprahepatic and infrahepatic vena cava (IVC) decreases venous return by as much as 50%. Venovenous bypass (VVB), which diverts inferior vena cava and portal venous flow to the axillary vein, attenuates the decrease in preload, improves renal perfusion pressure, lessens splanchnic congestion, and delays the development of metabolic acidosis [73]. The use of VVB is not without risk. Air embolism, thromboembolism, and inadvertent decannulation may be fatal or result in significant morbidity [74]. VVB is not uniformly used at all centers [75,76]. The use of the ''piggyback'' technique, with inferior vena caval preservation, decreases the need for VVB [77]. Hepatectomy is followed by hemostasis and vascular anastomoses of the supra- and infrahepatic IVC and the portal vein.

Despite the absence of hepatic clotting factor production during the anhepatic stage, blood loss is usually limited by vascular clamping of the inflow vessels to the liver. However, fibrinolysis may begin during this stage, caused by an absence of liver-produced plasminogen activator inhibitor, which results in the unopposed action of tissue plasminogen activator. The use of antifibrinolytics varies among centers (see below).

Intraoperative management: neohepatic stage

Reperfusion of the new liver through the portal vein begins the neohepatic stage. Reperfusion is associated with abrupt increases in potassium and hydrogen ion concentrations, an increase in preload, and a decrease in systemic vascular resistance and blood pressure. Hypothermia, monitored through a centrally placed catheter, is a marker for the presence of graft outflow into the central circulation. Life-threatening hyperkalemia, clinically detectable by changes in the EKG, requires prompt treatment. Calcium chloride and sodium bicarbonate are the drugs of choice for the acute treatment of hyperkalemia. If time permits, albuterol and insulin are also effective. Intraoperative dialysis should be considered early in the procedure for oliguric patients with elevated potassium levels.

The hallmark of the postreperfusion syndrome (PRS) is systemic hypotension and pulmonary hypertension occurring within the first 5 minutes after reperfusion of the graft. Approximately one in three patients undergoing OLT have profound hypotension after reperfusion. The cause is uncertain, but a number of factors, such as hyperkalemia, acidosis, hypothermia, emboli (air or thrombotic), and vasoactive substances, have been implicated [78]. A retrospective study [79] of 321 patients identified suboptimal grafts (higher degree of steatosis) and graft cold ischemia time as risk factors. All cases of PRS, defined as mean blood pressure < 60 mm Hg, occurred in suboptimal donors with graft cold ischemia times greater than 6 hours. In this study, suboptimal donors were defined by age older than 50, history of cardiac arrest, hypotension, need for high-dose inotropic

drugs, ICU stay longer than 5 days, or elevated liver fat content. In this study, the postreperfusion K+ level was higher (at 1 and 5 min), and the postreperfusion temperature was lower (at 1 min) in the PRS group.

Hepatic arterial anastomosis and biliary reconstruction are generally performed after venous reperfusion, although in pediatric patients the arterial anastomosis may be completed before reperfusion. Signs of graft function that may be observed in the operating room include decreased calcium requirements, improvement in acidosis, increased urine output, a rise in core temperature, and bile output from the graft.

Antifibrinolytics

Fibrinolysis is most severe after reperfusion and is caused by abrupt increases in tissue plasminogen activator from graft endothelial cell release. Antifibrinolytic drugs and cryoprecipitate may be required. In studies carried out before 1997, the benefits of antifibrindytic drugs for OLT, typically defined as a decrease in blood loss or transfusion requirements, were not present in prospective, randomized, blinded studies [80]. Nearly all of these studies evaluated aprotinin. In contrast, tranexamic acid and ε-aminocaproic acid have not been extensively studied. In 2001, a randomized, blinded study from the Mayo Clinic [81] showed a decrease in erythrocyte requirements (median of 5 units versus 7 units) with aprotinin compared with placebo. The European Multicenter Study of Aprotinin in Liver Transplant (EMSALT) [82] also showed a decrease in red blood cell usage with both high dose (2×10^6 kallikrein inhibiting units [KIU] loading dose followed by 1×10^6 KIU/h) and regular dose (2×10^6 KIU loading dose followed by 0.5×10^6 KIU/h) of aprotinin compared with placebo (red blood cell requirements of 1500 mL versus 1750 mL versus 2450 mL, respectively). The authors report no difference in the prevalence of thromboembolic events in the aprotinin groups compared with control group. It was noted that the three patients who developed hepatic artery thromboses occurred in the control group. These three events may have been related to surgical technical issues, whereas the thrombotic events in the aprotinin group (pulmonary emboli, right coronary occlusion) were not. It is unclear whether antifibrinolytic drugs increase the risk of thrombotic events [83,84]. Fibrinolysis is an unpredictable event, and the risks of treatment are unknown.

Postoperative complications

Postoperative bleeding, biliary drainage leaks, and vascular thromboses (hepatic artery or portal vein) may require exploratory surgery in the early posttransplantation period. Primary graft nonfunction or graft necrosis secondary to vascular thrombosis typically necessitate retransplantation. After the immediate postoperative period, infection is the primary cause of death. Immunosup-

pressive medications, used to prevent rejection, are largely responsible for this risk; and they also make the transplant recipient more susceptible to malignancy.

Special situations

Retransplantation

In the last five years, the retransplantation rate has averaged approximately 10% [85]. Early retransplantation, within days of the first transplant, is required in the presence of primary nonfunction of the graft or in the event of surgically uncorrectable portal vein thrombosis. Early retransplantation is usually not technically demanding because the necessary dissection planes are already present. The medical management, however, can be challenging because these patients frequently manifest all the signs of fulminant hepatic failure. On the other hand, patients with chronic rejection who require retransplantation years after the initial surgery, although typically ambulatory before the redo procedure, present technical challenges caused by extensive adhesions and the potential for massive hemorrhage. Graft survival rates after retransplantation are 20% lower than graft survival rates after primary transplantation [85].

Pediatric transplantation

The percentage of liver transplants in recipients under 18 years of age decreased from 15% in 1992 to 10% in 2000 [7]. This decrease is largely the result of the increase in adult patients who underwent transplantation for hepatitis C. Biliary atresia is the most common primary diagnosis in pediatric liver transplant recipients, whereas metabolic liver disease represents the second largest group [86]. Patients with biliary atresia typically have undergone previous abdominal surgery (Kasai procedure, portoenterostomy for biliary drainage), which complicates transplant surgery. Bleeding may not be severe in these patients because synthetic function is usually preserved. The increased risk of hepatic artery thrombosis in children compared with adults leads to less vigorous correction of any clotting defects. Fresh frozen plasma is used judiciously, and antifibrinolytic drugs are avoided. At the author's center, an INR of 1.5–1.8 at the conclusion of surgery is considered ideal. Venovenous bypass is not used in pediatric recipients. Children tolerate vena caval clamping better than adults, and less hemodynamic changes are seen. Reperfusion is also less likely to result in hemodynamic changes or rhythm disturbances. Maintaining target hemocrit values and avoiding fluctuations in the hematocrit can be difficult, particularly when volume replacement solutions without red blood cells are administered. Similarly, maintaining normothermia in children requires considerable effort, particularly during the anhepatic phase when the graft, in an orthotopic position while anastomoses

are performed, is packed in ice. The use of forced air warming blankets and heated fluid warmers are mandatory but typically insufficient to maintain normothermia. Once reperfusion has occurred, peritoneal irrigation with warmed saline is useful in correcting hypothermia. Rapid infusion devices typically used in adult transplantation are unnecessary in pediatric recipients.

Fulminant hepatic failure

Fulminant hepatic failure is an uncommon entity, and most physicians have little or no experience with it. The lack of experience coupled with the potential for rapid progression to coma, can lead to unnecessary morbidity secondary to delays in diagnosis and treatment [87]. Initial treatment focuses on frequent assessment of mental status, monitoring of liver enzymes and coagulation status, and confirmation of the diagnosis. During initial medical management when consideration for possible liver transplantation begins, it is important to avoid sedatives, which can obscure neurologic changes. The combination of coagulopathy and altered mental status is ominous, particularly when associated with a decrease of previously elevated liver enzyme values [16]. Once the patient progresses to grade III (stupor) or IV (coma) encephalopathy, airway management is indicated because aspiration pneumonia may preclude liver transplantation. Increases in intracranial pressure should be minimized during tracheal intubation. In patients in stage III or IV coma, intracranial pressure monitoring should be considered (see below). Fresh frozen plasma and platelet concentrates are indicated before ICP monitor placement when the INR is > 1.5 or the platelet count is < 50,000 or in the presence of clinically significant microvascular bleeding. The cerebral perfusion pressure should be maintained above 50 mm Hg [88]. Administration of diuretics, elevation of the patient's head 10 to 20° degrees, maintenance of arterial pressure, and treatment of agitation are important in maintaining cerebral perfusion pressure. Lactulose, the standard treatment for chronic encephalopathy, has not been shown to be beneficial for acute encephalopathy and may worsen underlying acidosis by causing bicarbonate loss [87]. *N*-acetylcysteine, originally identified as beneficial in acetaminophen overdoses because of its ability to replenish hepatic glutathione stores, has also been shown to have antioxidant properties and beneficial hemodynamic effects in fulminant hepatic failure of other causes [89].

The prognosis for spontaneous recovery in patients with fulminant hepatic failure depends on the patient's age, the underlying cause, and the severity of liver injury [90]. The prognostic criteria for acute liver failure at King's College Hospital distinguish acetaminophen overdose from other causes of acute liver failure. For the acetaminophen group, survival was related to values for arterial pH, peak prothrombin time, and serum creatinine. A pH level lower than 7.30, PT > 100 seconds and creatinine level > 300 μmol/L (3.4 mg/dL) indicated a poor prognosis. In the non-acetaminophen group (viral hepatitis and drug reactions), a poor prognosis was associated with the underlying diagnosis (non-A, non-B

hepatitis or drug reactions), age < 11 and > 40, duration of jaundice before the onset of encephalopathy of more than 7 days, bilirubin > 300 μmol/L (18 mg/dL) and PT > 50 seconds. These findings, known as the King's College criteria, have been used as guidelines for selection of fulminant hepatic failure patients for OLT, by identifying patients with little chance of spontaneous recovery as early as possible. Other authors, in attempts to validate the King's College criteria, have commented on the high positive predictive value (88%); however, that a lack of fulfillment of the poor prognosis criteria does not predict survival [91,92].

In the King's College experience, recovery is least likely to occur in patients with hepatitis B (39% survival with medical or ICU management), is intermediate in patients with acetaminophen-induced liver failure (53% survival with ICU management), and is most likely in patients with hepatitis A (67% survival with ICU management) [90]. In another, more recent study performed in 17 tertiary care centers in the United States, the incidence and spontaneous recovery rate associated with the various causes of fulminant hepatic failure were evaluated [93]. Acetaminophen overdose, hepatitis A viral infection, shock, liver, and pregnancy-related liver failure were associated with a short-term survival of more than 50% without liver transplantation. Acute liver failure related to drugs other than acetaminophen, hepatitis B, autoimmune hepatitis, Wilson's disease, Budd-Chiari syndrome, or cancer experienced short-term transplant-free survivals of < 25%. In these 17 US centers, acetaminophen overdose was the most common cause of acute liver failure (39% of 308 patients) followed by drug reactions (13% of cases) and hepatitis A and B (12% of cases).

Intracranial pressure monitoring

The intraoperative management of fulminant hepatic failure may benefit from intracranial pressure monitoring, although controlled studies of outcome based on this modality have not been done [94,95]. Insertion of an intracranial pressure monitor should not occur without correction of the INR to < 1.5. Avoidance of anesthetics associated with increases in intracranial pressure is warranted in patients with grade III and IV encephalopathy. If the management options mentioned earlier (elevation of the head of the bed, diuresis, treatment for agitation, tight regulation of arterial pressure) are ineffective, barbiturate coma should be instituted.

Besides OLT, fulminant hepatic failure has been treated with artificial liver systems, primarily as a temporizing measure while awaiting an OLT donor. A number of different hepatic support systems have been used including detoxification devices incorporating albumin dialysis [96,97] or charcoal hemoperfusion [98], and cell-based systems using either porcine [99,100] or human hepatocytes [101]. Uncontrolled clinical studies using these systems have reported reductions in serum ammonia and, in some cases, decreases in intracranial pressure [96,99]. These devices seem best suited to serve as a bridge to transplantation. Heterotopic or auxiliary liver transplantation and xenotransplantation have been investigated and are described elsewhere in this issue.

Anesthesia after liver transplantation for non-transplant surgery

Liver transplant recipients with functioning grafts typically metabolize drugs in a normal fashion, but graft function must be assessed rather than assumed. The prothrombin time (or INR) is an excellent marker of synthetic function. In patients with grafts that function less than optimally, correction of clotting abnormalities (with vitamin K or fresh frozen plasma), management of ascites (with diuretics, albumin administration, or paracentesis) and avoidance of encephalopathy (with lactulose administration and careful use of sedatives) may improve outcome. Such treatment for cirrhotic patients undergoing surgery is associated with improved outcomes [41].

Careful adherence to sterile technique is required to prevent infectious complications in this immunosuppressed population. A stress dose of corticosteroids is required for patients on chronic supplementation. Renal function should be assessed and managed carefully because cyclosporine is associated with renal impairment. Hypertension is also a common finding in patients managed on the calcineurin inhibitor class of immunosuppressants, particularly cyclosporine. Drugs known to decrease hepatic blood flow, such as propranolol, should be avoided. Regional anesthesia is an option in patients with acceptable clotting status.

Outcomes

Patient survival for deceased donor liver transplant recipients, as reported in the 2003 Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) annual report was 86% at 1 year, 78% at 3 years, and 72% at 5 years after transplantation [7]. Five-year patient survival after liver transplantation is similar to 5-year survival after heart transplantation (72%), greater than 5-year survival after intestine (47%) or lung (45%) transplantation, and lower than the 5-year survival after kidney transplantation (deceased donor, 80%; living donor, 90%) (Fig. 2). Patient survival varies with recipient age; 5-year survival was 84% for recipients aged 6–10 and 62% for recipients > 65 years of age. Patients going to transplantation from an ICU showed 10% lower 3- and 5-year survival compared with patients admitted from home. Patients on life support also fared less well, with approximately 10% lower survival than patients not on life support. Survival also varied based on the cause of the liver disease (Fig. 3). Five-year patient survival was worst for hepatic malignancy (59%), intermediate for acute hepatic necrosis and non-cholestatic liver disease (~70%), and best with metabolic liver disease, biliary atresia, and cholestatic liver disease (~80%). These differences are attributed to the likelihood of disease recurrence and the recipient age differences for these diagnoses. Graft survival after deceased donor liver transplant was 81% at 1 year, 72% at 3 years, and 64% at 5 years after transplantation. Interestingly, the transplant center volume did not affect patient survival. Patients who underwent repeat trans-

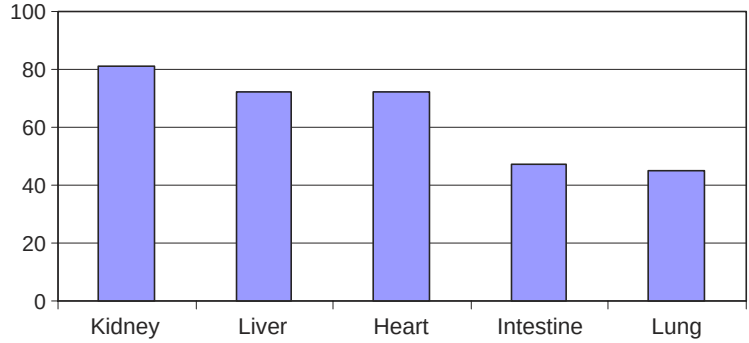

Fig. 2. Five-year patient survival by organ (deceased donors). Annual Report of the US Scientific Registry of Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data 1992–2002. *From:* http://www.optn.org/data/annualReport.asp; with permission. Accessed: February 16, 2004.

plantation showed a 20% lower graft survival rate than patients who underwent primary transplantation.

Future challenges

Expanding indications for transplantation, the optimal timing of surgery, and the most appropriate use of scarce donor organs remain important challenges for the future [102]. Solutions to the organ shortage, including increased use of marginal and split grafts, living-related donation, xenotransplantation, and stem

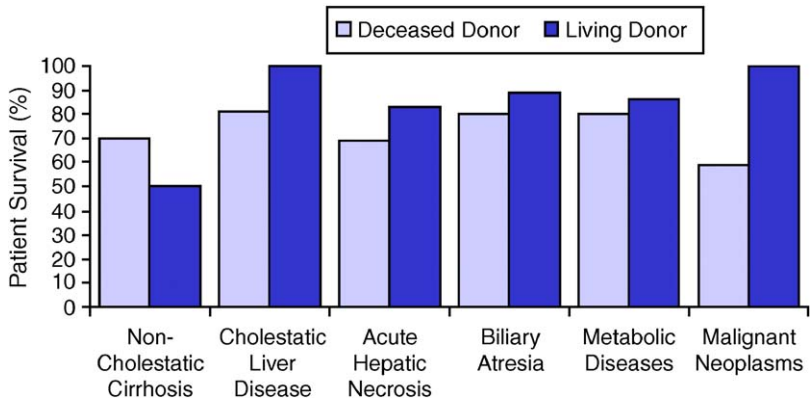

Fig. 3. Five-year unadjusted patient survival among liver transplant recipients, by diagnosis. Cohorts are for transplants performed during 1996–1997 for 5-year survival. 2003 Annual Report of the US Scientific Registry of Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data 1992–2002. *From:* http://www.optn.org/data/annualReport.asp; with permission. Accessed: February 16, 2004.

cell-derived organs, offer hope for the future. Xenotransplantation and stem cell-derived organs are discussed in other articles of this issue.

Reduced size and split-liver transplantation

Reduced size liver transplantation was first reported in 1984 [103]. This procedure has been used to provide left lateral segment (segments 2 and 3) and left lobe (segments 2, 3, and 4) grafts for pediatric recipients (Fig. 4). The extended right lobe (segments 4–8) is then discarded. Although this technique does not increase the supply of donor organs, it does increase the supply of organs for pediatric recipients [104]. Another advantage is the increased size of the adult donor's hepatic artery, which has been reported to result in a decreased incidence of hepatic artery complications [105].

Split liver transplantation was first reported in 1988 [106]. With this technique, the left graft is used for a pediatric recipient, and the right graft is placed into an adult recipient. Although the use of a single donor for two recipients has clear advantages, early results with this technique were not equivalent to those achieved with the use of whole-organ grafts. As experience accrued, however, outcomes reported from selected centers showed improvement. In some case series [104], survival, particularly for left lateral segment recipients, is nearly similar to that of whole-graft recipients. Survival for right lobe recipients remains controversial, but for right lobe recipients in urgent need of transplantation, survival is inferior to whole-graft recipients [107]. The splitting technique is

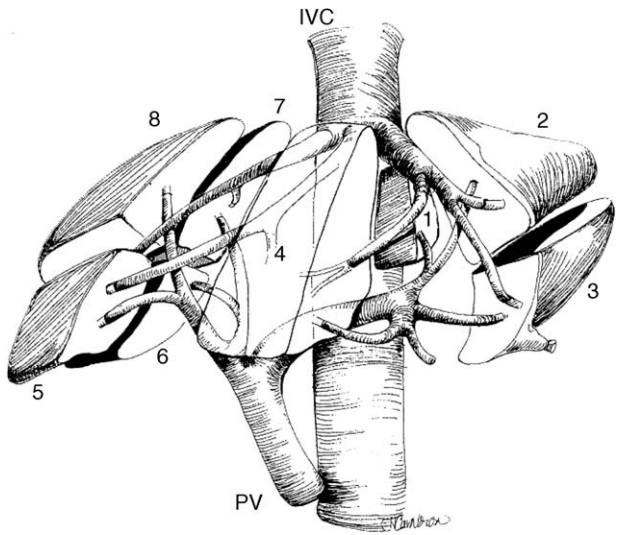

Fig. 4. Segmental anatomy of liver. Segment 1: caudate liver. Segments 2 through 4: left lobe. Segments 5 through 8: right lobe. Split liver grafts usually comprise segments 2 and 3 and segments 4 through 8. (*From* Busuttil RW, Goss JA. Split liver transplantation. Ann Surg 1999; 229(3):313–21 (p. 313); with permission.)

associated with unique complications. The incidence of biliary complications (15%–40%) and the need for reoperation caused by bleeding (20%) is higher than in whole-graft recipients [108,109]. These complications are reduced (to ≤3% for biliary complications and for reoperation) by the use of in situ, as opposed to ex vivo, splitting techniques [104]. In situ splitting, however, has logistical drawbacks both for the donor hospital, where this technique may prolong procurement by up to 2 hours, and for the other organ procurements teams, who may be reluctant to assent to the additional time for the procedure. Additionally, split grafts do not tolerate prolonged cold ischemia times, which limits the allowable transport times for these grafts. As a result of logistical drawbacks and variable patient outcomes, split-liver transplantation has been infrequently applied [107].

Living donor transplantation, including adult-to-adult transplantation

The fivefold increase in living donor transplantation since 1998 is one of the most significant recent developments in liver transplantation. Although adult-to-pediatric living donor transplantation has been performed for over a decade, most of this increase is caused by the introduction of adult-to-adult living donor liver transplantation (LDLT). In this procedure, the larger right lobe is harvested (segments 4–8), making the donor surgery more extensive than adult donor to pediatric recipient liver transplantation. The growth of this procedure is clearly related to the disparity in supply and demand and the success of pediatric recipients of LDLT [110]. The advantages of living donor transplantation include the ability to perform the transplant operation as a scheduled procedure, which allows optimal recipient preparation, shortened waiting time for the recipient, shortened graft cold ischemia time, and an increased pool of available donors [111]. Disadvantages of LDLT include standard surgical risks to the donor (bleeding, infection, anesthetic complications), risks related to the possibility of inadequate hepatic function and the possibility of biliary complications (primarily bile leaks and infectious complications), the risks of blood transfusions, and any risks as yet undefined related to major hepatic resection. Recipient risks include those related to the smaller transplanted liver mass and the fact that complications, such as the higher incidence of postoperative bile leaks, are different from those seen in whole-organ recipients.

A small-for-size syndrome (SFSS) has been described after split-liver transplantation. The clinical manifestations are the appearance of cholestasis, coagulopathy, portal hypertension, ascites, and, in severe cases, gastrointestinal bleeding at the end of the first week after transplantation [112]. The required graft-to-recipient body weight ratio is 0.8% to achieve graft and patient survival of 90% [113]. Recipients with portal hypertension, however, seem to require larger or better functioning grafts to avoid the SFSS. A graft-to-body weight of 1.5% has been suggested as ideal [112]. The dramatic growth of LDLT (and adult LDLT in particular) has occurred despite important questions related to a lack of standardized recipient outcomes and donor complication rates [110,114].

Several well-publicized donor deaths have focused more scrutiny on living donor transplantation and have resulted in state-mandated guidelines. As of 2002, nine deaths had been reported worldwide among partial-liver donors [115,116]. These events are believed to be responsible for a 30% decline in the number of living donor liver transplants in 2002, the first such decline since 1998. In 2001, living donor transplants represented 10% of the total number of liver transplants, whereas in 2002 living donor transplants comprised 7% of the total transplants.

Summary

Liver transplantation offers patients with liver disease an optimal chance for long-term survival because medical therapy, particularly after the complications of end-stage liver disease such as variceal bleeding, encephalopathy, and renal failure occur, is associated with a poor prognosis. The success of liver transplantation has led to a rapidly expanding waiting list of potential recipients. The long waiting list along with a nonexpanding pool of cadaveric liver donors have led to a shortage of grafts and prolonged waiting times. Novel solutions using segmental liver grafts, including those from living donors, have seen rapid growth in the last 5 years, until 2002 when the number of living donor liver transplants decreased for the first time because of reports of donor morbidity and mortality. These reports underscore the physiologic trespasses associated with extensive hepatic surgery. Undoubtedly, further refinement of techniques designed to improve the supply of scarce donor organs will remain an area of focus for the future.

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