# 53
# Postoperative Care of the Liver-Transplant Patient

Philip A. Berry, Hector Vilca Melendez, and Julia A. Wendon

## Introduction

Liver transplantation (LT) is performed to improve life expectancy and quality of life in patients with advanced chronic liver disease (CLD), and to save life in the context of acute liver failure (ALF). These two groups of patients differ significantly in terms of mean age, prior comorbidity, and degree of extra-hepatic organ dysfunction, requiring substantially different approaches to supportive care. Common aspects of care are those directed at the transplanted organ itself, with regard to monitoring and recognition of early dysfunction, initiation of immunosuppression, and management of surgical complications. Close liaison with the multidisciplinary team, which will include the intensivist, transplant surgeon, transplant hepatologist, anesthesiologist, and radiologist, is required.

## Preoperative Physiological Profiles and Approaches to Optimization

### Chronic Liver Disease

With an increasing imbalance between organ demand and supply, waiting times before surgery have become extended and complications of cirrhosis more challenging. Cardiorespiratory dysfunction in the form of portopulmonary hypertension, right ventricular dysfunction, alcoholic cardiomyopathy, coincident coronary vascular disease, and hepatopulmonary syndrome may create anesthetic and early postoperative problems. Preoperative hyponatremia due to secondary hyperaldosteronism and/or diuretic therapy may be associated with postoperative neurological and infectious complications, and may preclude surgery if too severe (e.g., <125/L).[1,2] Although these complications should have been recognized, delineated, and optimized during work-up for LT, abnormalities can evolve in the time between assessment and surgery. Pulmonary hypertension, for instance, can develop in as little as 5 months.[3]

### Acute Liver Failure

The life-threatening sequelae of ALF are refractory vasodilatory shock and intracranial hypertension (ICH) with tentorial herniation. Lactic acidosis, acute renal failure, coagulopathy (including disseminated intravascular coagulation), and sepsis also represent particular problems. Preoperative optimization will usually require invasive cardiovascular monitoring, fluid resuscitation, vasopressor support, continuous renal replacement therapy (RRT), platelet/coagulation support, cerebral monitoring in grade 3 or 4 coma, and in some cases, intracranial pressure monitoring. The decision to commence intracranial pressure monitoring will be taken on an individual basis depending on the degree of clinical suspicion that raised intracranial pressure (ICP) is present or evolving. Factors favoring this decision are young age, markedly raised arterial ammonia (>150 mmol/L), neurological signs such as clonus, pupillary hyporesponsiveness, or dilatation, and the combination of hypertension and bradycardia. A recent analysis of 58 patients in whom intracranial monitoring was undertaken reported radiological evidence of intracranial bleeding in 10%. In two cases, bleeding was felt to have contributed to the patients' deaths.[4] Measures to reduce the risk of raised ICP, and to treat it once suspected, are summarized in Table 53.1. ICH remains a critical issue in the early posttransplant period and may be particularly relevant if immediate graft function is suboptimal.

TABLE 53.1. Management of patients at risk of intracranial hypertension.

- Sedation: propofol, which reduces metabolic demands in the brain and may reduce ICP, is the favored agent (50–150 mg/h), co-administered with opiate
- Posture: positioning the head in the midline, with the angle of the body 20° from horizontal
- Normocapnia [$pCO_2$ 4.5–5 kPa]
- Body temperature: normothermia
- Avoidance of stimulation

If pupillary abnormalities (progressive dilation, or dilation with sluggish reaction to light) or other neurological signs evolve, or intracranial pressure exceeds 25 mmHg, and tentorial herniation appears imminent, specific measures can be employed:

- Mannitol: 0.5 g/kg boluses may be administered and repeated, but serum osmolarity should be monitored so that 320 mosm/L is not exceeded. To prevent fluid overload a 500 mL diuresis (or negative balance if being hemofiltered) should be obtained
- Hypernatremia: serum sodium in the range 145–155 mmol/L has been shown to have a beneficial effect on ICP. This target can be achieved with continuous central infusion of 3.0% sodium chloride (NaCl), with regular monitoring. A slow bolus of 20 mL 3.0% NaCl may also be administered for possible surges in ICP
- Hypothermia: a core temperature of 32–33°C, achieved with active cooling, can bring about prolonged reductions in ICP if raised pressure persists despite the above management strategies
- Indomethacin: 25 mg IV bolus
- Hyperventilation: short-term reductions in ICP are seen secondary to induced hypocapnia; however, this strategy is most appropriate if cerebral hyperemia is indicated by high jugular bulb saturations



FIG. 53.1. Major vessels and anastomoses utilized on conventional liver transplantation.
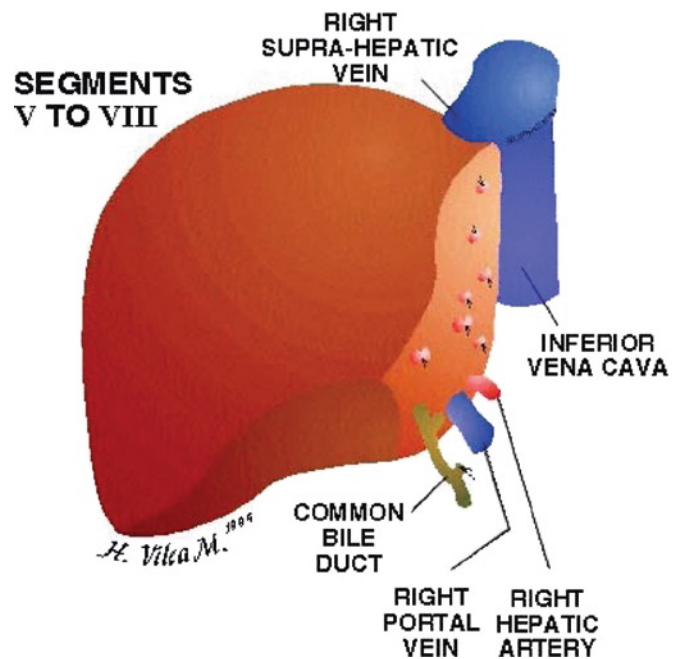


FIG. 53.2. Right liver segments used in "split" liver transplantation.

## Overview of Surgical Techniques

The method of organ implantation may have significant consequences in terms of posttransplant care. The conventional method involves removal of the native liver together with a short section of the inferior vena cava (IVC) above and below the organ, followed by implantation of the equivalent anatomy ("caval interposition") from the donor (Fig. 53.1). The "piggyback" method, in which a cuff of the donor's IVC with the donor liver draining into it through the three hepatic veins is piggybacked onto the recipient's IVC, avoids cross clamping and transection of the recipient's IVC. "Split liver" grafts are used when it is felt that the donor organ is of sufficient size to provide liver tissue to two patients. The lobe is implanted conventionally; however, a cut surface remains that may bleed or leak bile (Fig. 53.2). Another technique, employed in ALF when it is projected that the insult to the native liver will abate and regeneration occur effectively (e.g., acetaminophen toxicity), is to implant a whole or partial graft as an "auxiliary" adjacent to the native liver. Ongoing necrosis of the native liver with release of cytokines and toxins can promote an ongoing inflammatory response. If a straightforward "duct-to-duct" biliary anastomosis is not possible (for instance in patients with primary sclerosing cholangitis [PSC], or those receiving auxiliary transplants), a hepaticojejunostomy and Roux-en-Y jejunal loop may be formed.
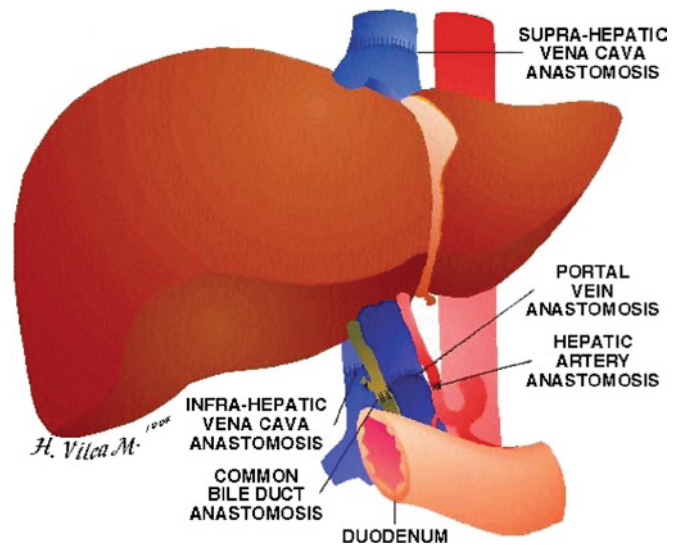
This intestinal anastomosis requires rest from feeding for up to 5 days postoperatively. In the case of a donor–recipient mismatch in bile duct diameter, or if the anastomosis is difficult, a T-tube may be inserted at the site of the anastomosis, its stem draining bile into a drain through the abdominal wall. Complex or suboptimal arterial anatomy may lead the surgeon to improvise arterial conduits from donor blood vessels (e.g., iliac), and knowledge of this will permit appropriate vascular investigations postoperatively.

# Physiological Challenges During Surgery

Conventional LT involves several major physiological challenges beyond those usually associated with major abdominal surgery. These are encompassed in the three phases of LT, namely, hepatectomy, anhepatic phase, and reperfusion. During these phases the portal vein and IVC will be clamped, with consequent reduction in venous return to the heart, and de-clamped following implantation, which is associated with further cardiovascular disturbance due to recovery of pre-load and release of vasoactive substances from the donor organ. Additionally, there will be variable blood loss in the context of coagulopathy with the potential for major transfusion. The proximity of the liver and its venous drainage to the right atrium can lead to surgical interventions and complications above the diaphragm. Major hemodynamic variations are associated with poor outcome.[5]

The decision to employ veno-venous bypass is weighed by pros (reduction in hemodynamic disturbances during portal and caval clamping) and cons (extended operation time, extended anhepatic period, cannulation site complications), the patient's functional status, and the proposed implantation technique. The piggyback technique, in avoiding caval interruption, obviates the need for veno-venous bypass.

# Immediate Postoperative Care

Electively transplanted CLD patients returning from the operating theater (OT) may be entirely stable, without the requirement of cardiovascular support, high inspired oxygen fraction or ventilatory support, renal support, or specific neurological therapy. If graft function proves satisfactory and there are no early surgical complications, such patients can be rapidly weaned from sedation and ventilation, extubated, and discharged to the general ward within 48 h. Management of the ALF and complicated CLD liver transplant patient will be divided into systems.

## Cardiovascular

Hypotension requiring vasopressor support (e.g., norepinephrine) during surgery, typically following reperfusion of the graft, will in many cases prove transient. More severe degrees of cardiovascular instability require investigation into the possibility of previously unrecognized cardiac dysfunction, or the evolution of a new ischemic event. In the previously cirrhotic patient, right heart dysfunction in the context of pulmonary artery hypertension may need to be excluded (Fig. 53.3a, b). This requires pulmonary artery catheter insertion, which can provide pulmonary artery pressure (PAP), right ventricular end diastolic volume index (RVEDVI), and calculated right ventricular stroke work index (RVSWI). Pulmonary hypertension can be separated from right heart dysfunction by calculation of the trans-pulmonary gradient.

Mild (>25 mmHg) and severe (>35 mmHg) elevations in mean PAP in the absence of intrinsic pulmonary disease are likely to represent portopulmonary hypertension. Preoperative treatment with pulmonary artery vasodilators, such as intravenous prostaglandin E2 (epoprostenol), have achieved sufficient reductions in PAP to allow surgery[6]; however, published series in postoperative management are lacking. Nebulized or intravenous epoprostenol, the phosphodiesterase inhibitor
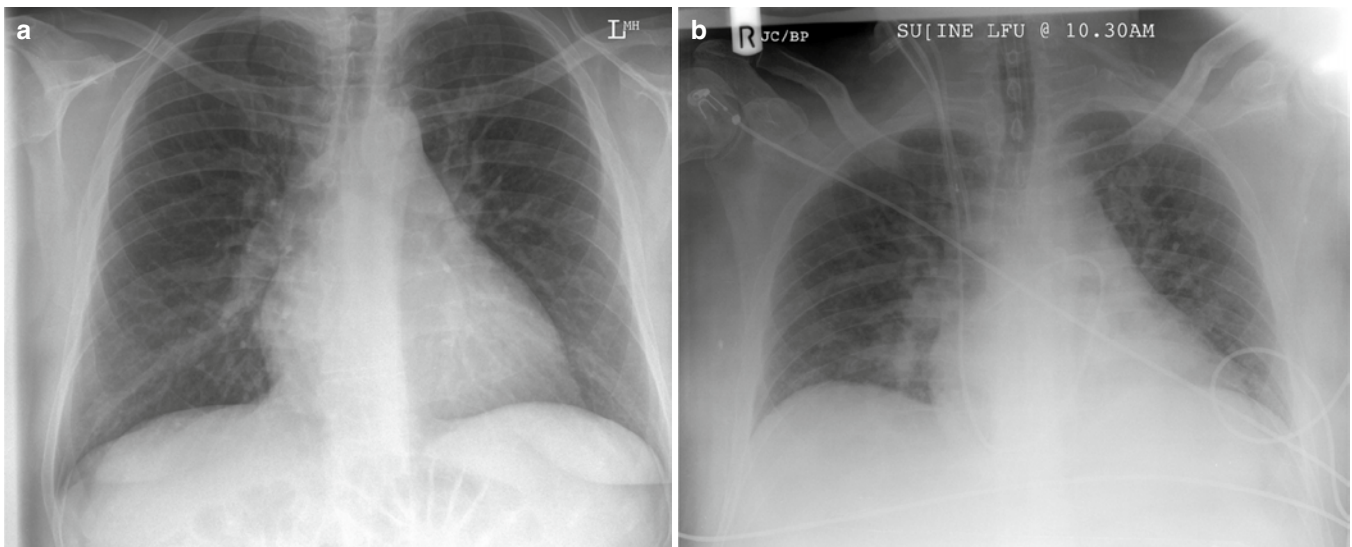


FIG. 53.3. (**a**) Pre-orthotopic liver transplantation (OLT) chest X-ray reported as normal in a man with end stage cirrhosis. There is pulmonary artery enlargement, indicating probable porto-pulmonary hypertension. (**b**) By 48 h post-OLT the patient was hypoxic and vasopressor- and inotrope-dependent. Pulmonary artery pressures via the Swan–Ganz catheter were 74/29 mmHg, and despite aggressive treatment with nebulized prostacyclin, bosentan, and sildenafil he succumbed due to cardiac failure 8 days later.

sildenafil, and the endothelin receptor antagonist bosentan have been used in this context.

Acute elevations in PAP and exacerbations in right ventriculo-arterial uncoupling occur during reperfusion. A hemodynamic study in patients with pulmonary artery (PA) hypertension demonstrated that although systolic ventricular function increased in response to the sudden change in pre-load, as per the Frank–Starling mechanism, afterload failed to decrease.[7] Use of dobutamine in this scenario demonstrated further increases in RVSWI and reductions in pulmonary afterload, with improved overall pulmonary hemodynamics.[8] Nevertheless, severe right ventricular dysfunction is associated with a poor prognosis.

Although most patients demonstrate high cardiac output with low peripheral resistance, global cardiac dysfunction is not uncommon in ALF, whether as a consequence of severe acidosis, or, in the case of acetaminophen, a direct toxic effect on the myocardium. Dobutamine is usually adequate in increasing cardiac output (CO); however, in more severe cases milrinone and levosimendan have been used. Evidence to support use of specific inotropes is lacking. Assessment of adrenal function by short Synacthen test and empirical hydrocortisone therapy is also indicated in the context of vasopressor or inotropic support, extrapolating from studies in acute hepatic dysfunction.[9]

Air embolism is a well-recognized complication of LT surgery. Air pockets within the donor portal venous anatomy may be mobilized during reperfusion,[10] air may enter during preparatory dissection of vessels within the recipient, and veno-venous bypass may itself result in this complication.[11] However, clinically significant volumes of air are unusual, and cardiovascular compromise will usually become apparent in the operating room (OR).

## Respiratory

High inspired oxygen fraction on return from the OR may be a manifestation of cardiac (i.e., pulmonary hypertension and RV impairment – see above) or primary respiratory dysfunction. Examination of the respiratory system and chest radiograph may reveal pneumothorax, lobar collapse, or pulmonary interstitial edema. Accumulation of alveolar fluid may be due to volume overload, especially if a previously anuric but hemofiltered patient has undergone prolonged surgery without renal replacement. However, transfusion-related acute lung injury (TRALI) should be considered if blood products have been administered. Re-expansion pulmonary edema may also occur following intraoperative drainage of longstanding hepatic hydrothorax. Acute lung injury (ALI) progressing to acute respiratory distress syndrome (ARDS) is a complication of ALF, and may progress during and after LT. In patients with chronic liver disease, ALI/ARDS can also occur without any other identifiable precipitant, although this is unusual (Fig. 53.4). Covert respiratory tract sepsis, present prior to transplant, may progress in some patients. Pulmonary
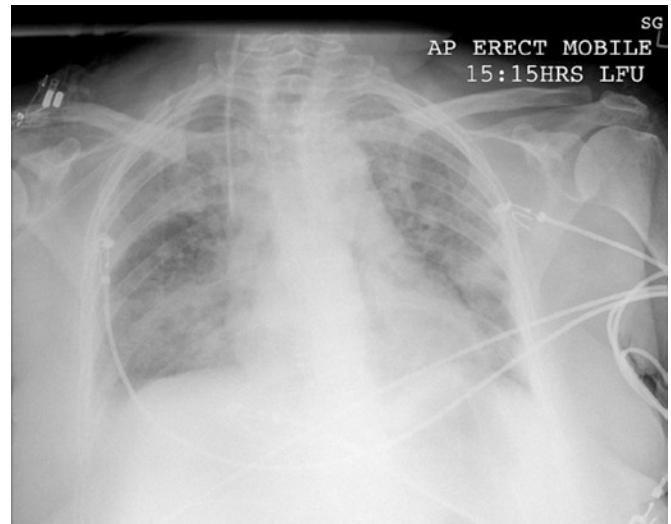


FIG. 53.4. Bilateral opacification 48 h after an uncomplicated elective OLT for primary biliary cirrhosis. ARDS developed and the patient died from respiratory failure despite excellent graft function.

infiltrates are common, seen in up to 44% of post-LT cases. In one study, pneumonia accounted for 38% of cases, pulmonary edema for 40%, and ARDS for 8%. Organisms isolated included methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Serratia marcescens*, and *Pneumocystis carinii*.[12]

There are no specifically favored ventilatory strategies post-LT; however, there are theoretical disadvantages in terms of liver blood flow with high positive end-expiratory pressure (PEEP).[13] This may limit venous return and lead to parenchymal congestion.[14] A recent human study found no impairment in systemic hemodynamics with short-term end-expiratory pressures up to 10 cmH$_2$O.[15]

## Renal

RRT will often have been commenced prior to transplant in many ALF cases, and should be continued postoperatively. CLD patients with impaired creatinine clearance are at risk of further reductions in renal function in the context of cardiovascular instability and volume depletion, and 12% of all CLD may develop ARF after surgery,[16] the vast majority (>90%) of whom will regain function. Early RRT is favored if there appears to be a deteriorating trend in excretory function or sustained oligoanuria despite volume repletion and optimum perfusion pressure. Intraoperative administration of mannitol does not appear to preserve renal function.[17] Reno-protective immunosuppression strategies may be appropriate in cases of significantly impaired preoperative renal function, and these are discussed below.

## Gastrointestinal

All patients should receive ulcer prophylaxis; this will normally be accomplished initially with proton pump inhibitors.

Enteral feeding can usually be commenced unless a new hepaticojejunostomy has been fashioned, or there are other surgical contraindications. If edema of intra-abdominal contents has developed, or a relatively large graft has been implanted in proportion to the size of the abdominal cavity (e.g., in small, female patients), primary closure of the abdomen may not be possible. In these cases the patient will be returned to the intensive care unit (ICU) with a dressing over the laparotomy. Closure will take place within 2–10 days according to the surgical assessment, and feeding is likely to be unaffected. Intra-abdominal pressure (IAP) should be monitored several times per day in all patients. Increased IAP (>25 mmHg) may occur in more than 30% of patients, and is associated with development of renal failure, prolonged ventilatory weaning, and death.[18] Further laparotomy may be considered if IAP rises, with formation of decompressive laparotomy.

Pancreatitis occasionally complicates ALF, and is a relative contraindication to urgent transplantation due to the high associated postoperative mortality. Clinical suspicion may be aroused during assessment by abdominal distension, raised IAP,[19] peritonism, and raised serum amylase. However, the systemic inflammatory response is common in both ALF and pancreatitis, and typical signs may be masked by sedation/paralysis.

## Neurological

Fluctuations in cerebral perfusion pressure have been well reported during the first 10 h after surgery, putting the patient with ALF at risk for ICH in the immediate postoperative period.[20] Continued "fulminant care" is usually required while satisfactory graft function and the absence of suspicious neurological features are confirmed. If an intracranial pressure system has been inserted and raised pressures are detected, deep sedation strategies are required (and other pharmacological interventions if necessary) until the graft begins to exert a beneficial effect. Neurological dysfunction and risk of maintained surges of ICP will normally have reduced by 48 h. Focal signs in the context of acute or chronic liver failure should be aggressively investigated. The fear of complicating intracranial hemorrhage in the context of coagulopathy and/or thrombocytopenia and reduced level of consciousness may prompt consideration for computerized tomography (CT) scanning. Porto-systemic/hepatic encephalopathy in CLD patients can cause a multitude of signs, including asymmetrical clonus, hyper-reflexia, dysconjugate gaze, and pupillary dilatation. However, these are rarely seen in the post-transplant period. Subclinical seizures may occur in ALF,[21] and high index of suspicion should be maintained. CT may be indicated to exclude development of a focal lesion acting as an epileptiform focus. Other neurological complications in the early post-transplant period include central pontine myelinolysis (CPM) and paradoxical air embolism.[22] CPM, which typically occurs in cirrhotic patients who enter surgery with hyponatremia, results in quadriplegia and brain stem signs, and requires magnetic resonance imaging (MRI) to confirm the diagnosis.

## Hematological

Patients often receive large volumes of platelets, fresh frozen plasma (FFP), and cryoprecipitate during surgery; and problems with hemostasis in the surgical field will mandate further transfusion on return to the ICU. However, coagulation indices represent a sensitive and early marker of graft function, so it is preferable to withhold further plasma, in the absence of bleeding, in order to gauge synthetic function in the first early period (see assessment of graft function). Full coagulation assessment with laboratory parameters and thromboelastography should be undertaken regularly in those with evidence of bleeding. The administration of FFP and cryoprecipitate should be discussed with the surgical team.

## Antimicrobial Prophylaxis

Bacterial infection post-LT is common, with gram-negative organisms predominating in recent years.[23] Bacteremia may be present in up to 21% of donors, and this may result in transmission.[24] Piperacillin–tazobactam (Tazocin®) was shown to be more effective in preventing infection than ciprofloxacin and amoxicillin in a randomized controlled trial (RCT) involving 217 LT cases.[25] Invasive fungal infection (candidiasis, cryptococcosis, or aspergillosis most frequently) complicates 4–11% of LT patients,[26,27] the median time to diagnosis being 17 days post-LT.[28] Interventions to reduce the risk of oral candidiasis are normally undertaken. Fluconazole interacts with tacrolimus and increases serum levels, so close monitoring of tacrolimus levels is required if fluconazole is started or the dose increased. A recent randomized trial demonstrated a marked reduction in the incidence of infection post-LT (to 3%) with the introduction of a lactic acid bacteria and fiber enteral supplement.[29]

ALF is a profoundly immunosuppressing condition, bacterial infection being identified in 60% of cases in one large study.[30] Fungal sepsis (usually candida species) has been reported in more than 30%.[31] The respiratory tract was identified as the source of sepsis in approximately 50%. Broad antibacterial and antifungal microbial prophylaxis would normally be commenced at the time of listing in the case of ALF, and continued as clinically and microbiologically indicated in the post-transplant period (e.g., piperacillin–tazobactam 4.5 g IV t.d.s., fluconazole 200 mg IV o.d.). Patients whose clinical course is complicated by bowel perforation, or in whom infected bile collections have developed (e.g., ischemic cholangiopathy complicating hepatic artery thrombosis), will need antifungal coverage (e.g., amphotericin 1 mg – 3 mg/kg daily).

## Graft Failure and Dysfunction

The major ischemic/anoxic insult suffered by a graft during removal and transportation results in a degree of hepatocellular dysfunction. A large number of mediators, including

reactive oxygen intermediates, are released resulting in a final pathway of neutrophil-mediated hepatic injury.[32] The reported incidence of clinically apparent graft dysfunction is up to 7%. Although donor factors such as advanced age, cardiovascular compromise prior to harvesting, raised body mass index, significant hepatic steatosis, and cold ischemia time are associated with reduced or delayed function, predicting graft dysfunction on an individual basis is very difficult.[33] A recent multivariate analysis indentified steatosis and non-cranioencephalic trauma as the only predictive factors.[34]

## Clinical Picture

Definitions of primary graft non-function (PNF) and primary graft dysfunction (PGD) have been published (Table 53.2); however, in practice a combination of factors including extrahepatic organ dysfunction will lead clinicians to suspect that the transplanted liver is not functioning well. The patient transplanted electively for CLD or urgently for ALF with a non-functioning graft will resemble a patient with ALF; worsening lactic acidosis, coagulopathy, and tendency to hypoglycemia will be observed. Cardiovascular instability and renal failure may ensue. Although worsening encephalopathy will not be detected in the sedated patient, ICH will not improve. Bile production will be absent, but cannot be assessed unless a T-tube is in situ. PNF requires early recognition as the only recourse is to re-list and offer a further transplant.

PGD manifests the same features but to a lesser degree. Extra-hepatic organ function can remain stable, but lactate may rise, measures of coagulation may appear to deteriorate

TABLE 53.2. Definitions of primary graft dysfunction and failure.

| Ploeg et al. | |
|---|---|
| *Primary dysfunction* | |
| AST >2,000 U/L | Day 2–7 |
| Prothrombin time >16 s | |
| *Primary non-function* | |
| Death or re-transplantation | Day 1–7 |
| Gonzales et al. | |
| Cumulative score | 7–9: severe graft dysfunction |
| | 5 or 6: moderate graft dysfunction |
| | 3 or 4: good graft function |
| Parameter | Assigned value |
| ALT (U/L) | |
| <1,000 | 1 |
| 1,000–2,500 | 2 |
| >2,500 | 3 |
| Bile output (mL/24 h) | |
| >100 | 1 |
| 40–100 | 2    First 72 h |
| <40 | 3 |
| Prothrombin activity (%) | |
| >60 | 1 |
| >60 while receiving FFP | 2 |
| <60 destpite receiving FFP | 3 |

rather than improve, and level of consciousness may remain subnormal even if the patient was lucid (in the case of CLD) before anesthesia.

A rarer explanation for apparent poor graft function is "small-for-size syndrome" (SFSS), in which the mass of hepatocytes is unable to cope with the excretory, metabolic, and synthetic demands of the body. This becomes apparent later than PGD, at day 4–5. SFSS has become more common as the splitting of donor organs and the use of living-related segments has become established.[35] Radiological studies have suggested that a graft-to-recipient body weight ratio of ≥0.8% is required to avoid the syndrome. The patient will display features of liver insufficiency, in particular progressive cholestasis, ascites formation, and coagulopathy.[36] Graft dysfunction may also be caused or exacerbated by right heart failure or high vasopressor therapy.

## Management of PGD

In the absence of PNF (for which the patient will require re-transplantation), or of hepatic artery thrombosis (HAT), therapy is directed at reducing the oxidative stress associated with ischemia/reperfusion, and improving microvascular perfusion. Infusion of prostaglandin E2 (epoprostenol), a potent vasodilator, has been shown in two RCTs to improve morbidity; however, the incidence of PNF/PGD was not altered.[37,38] Numerous case studies and uncontrolled series have described reversal of PGD with its use, and it is commonly utilized in this situation. The evidence base for *N*-acetylcysteine infusion is less well established. Benefits attributed to its anti-oxidative properties have been described.[39,40] It can be infused at 150 mg/kg per day.

## Immunosuppression

Immunosuppressive strategies will vary according to the policy at individual centers, and a full review of current combinations is beyond the scope of this chapter. Problems with immunosuppression in the ICU relate to toxicity and opportunistic infection.

Tacrolimus-based immunosuppression was shown to have advantages over cyclosporin A in 1994[41] in terms of cellular rejection, and is the most common agent currently utilized. It is neurotoxic at high serum concentrations, and is an important cause of seizures in the early post-LT period; high trough levels will usually be found. It is nephrotoxic, and if the risk of postoperative renal failure appears significant caution is required. "Renal-sparing" induction agents may be used, allowing some delay before institution of calcineurin inhibitors. These include the humanized monoclonal IL-2 receptor blocking antibody daclizumab, antithymocyte globulin (ATG), and monoclonal anti-T-cell antibody (muromonab-CD3, or OKT3). Risks of ATG and OKT3 are an increased incidence of opportunistic infections (discussed below) and development of lymphoma. Drug interactions with tacrolimus are common, and are summarized in Table 53.3.

TABLE 53.3. Selected interaction with calcineurin inhibitors tacrolimus and cyclosporin A.

| Increasing blood concentrations | Decreasing blood concentrations |
|---|---|
| *Antifungal agents* | *Anticonvulsants* |
| Fluconazole | Carbamazepine |
| Itraconazole | Phenytoin |
| Ketoconazole | Phenobarbital |
| *Macrolide antibiotics* | *Antibiotics* |
| Clarithromycin | Rifampin |
| Erythromycin | Rifabutin |
| Azithromycin | |
| *Calcium channel blockers* | *Others* |
| Diltiazem | Terbinafine |
| Verapamil | |
| Nifedipine | |
| *Prokinetic agents* | |
| Cisapride | |
| Metoclopramide | |
| *Others* | |
| Amiodarone | |
| Cimetidine | |
| Omeprazole | |

## Rejection

Acute cellular rejection (ACR) occurs in approximately 30% of recipients around 5–10 days post-LT. It is signified by acute elevations in transaminases and frequently fever. However, sepsis and ischemic insults (during episodes of shock) may also result in mild to moderate transaminase elevations, and differentiating these causes can be challenging. Pulsed methylprednisolone, the standard treatment of ACR, may represent a further challenge to the already immunosuppressed, possibly septic, ventilated patient. Liver biopsy, to confirm or exclude acute cellular rejection, is relatively contraindicated in patients in renal failure, because of the risk of bleeding. Management of early rises in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) requires detailed discussion with the multidisciplinary team (MDT), although a pragmatic approach may require empirical steroid therapy with broad spectrum antimicrobial coverage. Transjugular liver biopsy may also be considered, as the risk of hemorrhage is reduced. Steroid-resistant rejection will require specialized interventions, for example, the induction agents discussed above.

## Other Early Graft-Related Considerations

The etiology of liver failure may mandate particular measures. ALF secondary to hepatitis B virus (HBV) is usually associated with complete viral clearance; however, passive anti-viral prophylaxis with pooled hepatitis B immunoglobulin is administered to bind free virus and reduce the risk of early graft viral infection. Regular serum hepatitis B surface antibody and HBV DNA levels are required to direct further dosing and antiviral therapy. Patients with cirrhosis secondary to HBV will have been taking effective antiviral agents, and viral replication at the time of LT should be undetectable. Nevertheless, passive immunization is essential. ALF secondary to other viral hepatitides such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), or herpes simplex virus (HSV) will require specific antiviral coverage. Formal anticoagulation in veno-occlusive conditions such as Budd–Chiari syndrome will be indicated, and the timing of this requires close liaison with the surgical team, bearing in mind the risks of early bleeding.

## Further Monitoring of the Graft

### Laboratory Tests

Liver function tests should be performed on a daily basis. Transaminases will be raised during the first postoperative day; however, levels should fall exponentially thereafter. AST or ALT that does not fall according to this pattern is compatible with dysfunction. Coagulation indices should be monitored every 8–12 h during the first day, then daily. Development of a cholestatic profile is not uncommon, and may represent delayed function of the biliary transport mechanisms within the hepatocytes. A more sinister cause of cholestasis, in the patients transplanted for hepatitis B or C, is fibrosing cholestatic hepatitis (FCH), a rapidly progressive, destructive manifestation of early viral reinfection.

### Imaging

An ultrasound should be performed routinely on the first and fifth days to ensure continued patency of the hepatic artery (HA), hepatic vein (HV), and portal vein (PV). If flow is not seen in the HA, CT angiography is usually required to delineate the vasculature. Should hepatic artery thrombosis (HAT) be confirmed (Fig. 53.5a, b), the usual approach is re-transplantation; however, interventional radiology may have a role in reperfusion (e.g., balloon dilatation, stenting, or regional thrombolysis) with reported success of 50–88%.[42,43] Reported inaccuracy of ultrasound scan (USS) in detecting HAT is 10%, and strong clinical suspicion (large elevations in AST/ALT, synthetic dysfunction) should prompt CT, MRI, or invasive angiography. Infarction of the graft without visible HA obstruction ("non-thrombotic infarction") can occur, resulting in graft failure.

Although lack of biliary dilatation on USS would suggest that mechanical obstruction to bile flow is not present, intrahepatic bile ducts in transplanted livers do not tend to distend. If early obstruction to bile flow is suspected, a functional investigation (such as a hydroxy iminodiacetic acid [HIDA] scan) may be required to demonstrate bile production and adequate flow through the biliary tree. In some centers this investigation is routine during the first 3 days.[44] Fibrosis and contraction of tissue at the biliary anastomosis may cause stricturing of the bile duct, although the incidence of this complication is now low (<5%) and should not become apparent in the early postoperative period. Bile leaks are of greater
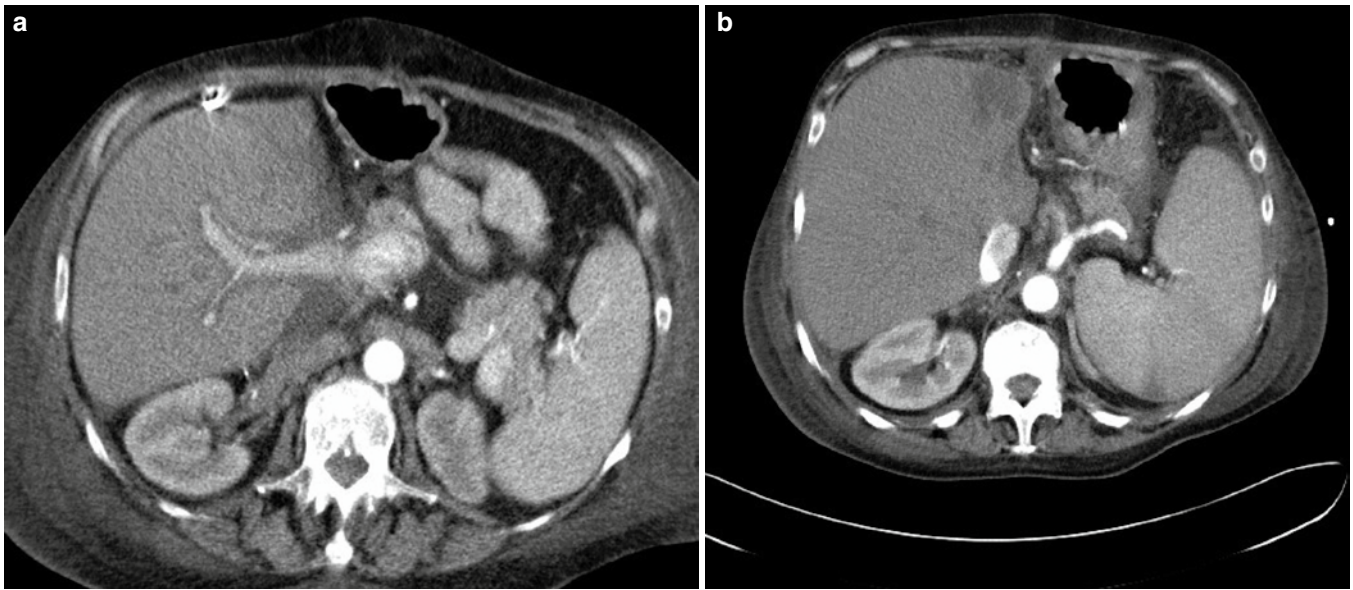
FIG. 53.5. (**a**) Arterial phase contrast enhanced CT scan of a right lobe split-liver graft demonstrating normal arterial and portal vein perfusion. (**b**) A further arterial phase contrast-enhanced scan of the same graft demonstrating proximal occlusion of the hepatic artery and an area of necrosis at the anterior right margin. The patient required re-transplantation.

immediate concern, their incidence being between 1% and 10%. Identification of an enlarging collection beneath the liver or near the porta will require diagnostic aspiration and drainage if a collection of bile is seen (biloma). Extended antibacterial and antifungal prophylaxis will be required, and formal surgical revision undertaken. Any biliary structuring or leaking should result in interrogation of the arterial supply to ensure patency.

## Postoperative Bleeding

Ten to fifteen percent of LT patients will need further laparotomy to investigate and manage abdominal hemorrhage. Sources of bleeding include injuries sustained to the donor liver during harvesting (lacerations to liver surface, untied small vessels around the gall bladder bed, or accessory veins draining into the vena cava), failure of hemostasis during removal of the diseased native liver, and failure to seal major vascular anastomoses.

Major bleeding may be signified by appearance of fresh blood in drains, although poor positioning of the drains and blockage during the initial period of hemostasis may result in retention of blood within the peritoneal cavity. Preexisting ascites and further ascites production post-LT may dilute the blood in the drains. Laparotomy may be indicated if there is hemodynamic instability or if transfusion requirement exceeds 4–6 U of blood/packed cells over a 24-h period; close consultation with the surgical team is required.

Late rupture of vascular anastomoses, with catastrophic bleeding, can occur in the context of postoperative intra-abdominal sepsis.

## Days 1–7

### Ventilatory Weaning and Decision to Perform Tracheostomy

In CLD patients, extubation can normally be achieved within 12–24 h of LT in the absence of important surgical or adverse cardiorespiratory complications. In ALF a longer recovery time is to be anticipated, although rapid global improvement, the absence of critical illness myopathy, and resolution of encephalopathy allow early extubation within the first week. Percutaneous or surgical tracheostomy will be required if prolonged ventilatory support is required. Significant graft dysfunction is independently associated with requirement for ongoing ventilation.[45] Complete diaphragmatic paralysis was found in 10 of 48 LT patients in one study, paralysis of the right diaphragm affecting another 11, with an associated prolongation in ventilation.[46]

### Sepsis

Sepsis and septic shock are difficult to confirm in ALF due to its highly inflammatory and vasodilatory nature; however, progressive cardiovascular deterioration in the absence of primary cardiac dysfunction may represent uncontrolled infection. Vascular catheter-related infection is common, and old lines (>7 days) should be changed. Chest X-ray changes due to ALI are common in ALF and may not represent infection; however, tracheal aspirates and broncho-alveolar lavage will be useful in excluding resistant organisms not treated by first-line agents. Intra-abdominal sources of sepsis may include infected hematomas, collections related to

pancreatitis, and, rarely, intestinal ischemia seen in ALF or in association with severely raised IAP. CT scanning and/or laparotomy may be required.

## The First Month

Specific complications encountered in the ICU after the first week include opportunistic infections and bone marrow dysfunction.

### Early Opportunistic Infection

Opportunistic infections encountered during the first month include disseminated herpes simplex 1 or 2 and cytomegalovirus reactivation. HSV is a cause of early graft dysfunction, and usually requires detection by polymerase chain reaction (PCR) to prove the diagnosis. Patients without prior exposure (anti-CMV IgG negative pre-LT) who receive livers from CMV-exposed donors are at risk of primary CMV infection, and previously exposed patients may suffer reactivation. Blood should be sent for CMV DNA measurement on a weekly basis while in the ICU, and treatment with an antiviral agent (ganciclovir, valganciclovir) commenced if DNA is detected. CMV viremia may present with fever, a hepatitic LFT profile, deteriorating respiratory function with CXR infiltrates, or diarrhea.

### Bone Marrow Dysfunction

Falling platelet, white blood cell, and hemoglobin counts are commonly seen in post-LT patients in the ICU. Thrombocytopenia may be heparin induced (HIT, type 1 and 2) requiring specific hematological investigation. Generalized bone marrow suppression is a well-established side effect of ganciclovir and valganciclovir. An important and possibly underrecognized cause of bone marrow dysfunction is acquired hemophagocytic lymphohistiocytosis (HLH), or reactive macrophage syndrome. Unregulated macrophage stimulation in the context of viral infection and/or immunosuppression results in auto-ingestion of cell lines, typically accompanied by the following clinical and laboratory features: fever, serous effusions and ascites, hepatosplenomegaly, skin rashes, hyperferritinemia, and hypertriglyceridemia. Diagnosis requires bone marrow examination; and treatment, although without a firm evidence base, comprises intravenous immunoglobulin and antiviral agents.

## Outcomes

Despite counseling during assessment for LT, relatives of patients transplanted for cirrhosis may be surprised if the transplant operation does not appear to bring about rapid improvement in physical condition. Although liver function may be good, failure of other organs and systems in the postoperative period may result in prolonged ICU stays, survival

from which cannot be guaranteed. A change of emphasis from liver disease to multiple organ dysfunction, with an attendant shift in expectation, must be achieved.

In ALF, where the time scale from diagnosis to surgery is far shorter and emotionally challenging to relatives, it is usual for the condition's severity and poor prognosis to have been emphasized before surgery. Perioperative and 3-month mortality rates are higher than in elective transplants, and multiple organ dysfunction, being a part of the ALF syndrome, will be anticipated.

Outcome studies in transplant patients have been shown that the requirement of mechanical ventilation, duration of mechanical ventilation, requirement for dialysis, development of pulmonary infiltrates, and ICU-related infections during the ICU stay are significantly associated with mortality. However, no discrepancy in postdischarge quality of life was found when survivors (82% in this study) were compared to those who did not require ICU. This observation may bring some comfort to relatives who fear that the patient, especially following tracheostomy and with evident global muscular weakness, will be wheelchair bound and dependent.[47]

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