Anesthesia and Perioperative Intensive Care

15

John R. Klinck

Abbreviations

ACLF	Acute-on-Chronic Liver Failure
BMI	Body Mass Index
CNS	Central Nervous System
CPET	Cardiopulmonary Exercise Testing
CPM	Central Pontine Myelinolysis
CT	Computed Tomography
EACA	Epsilon Aminocaproic Acid
ECG	Electrocardiogram
EF	Ejection Fraction
ESLD	End-stage Liver Disease
FEV_1	Forced Expiratory Volume (in 1 s)
FFP	Fresh Frozen Plasma
F_IO_2	Fraction Inspired Oxygen
FRC	Functional Residual Capacity
HAS	Human Albumin Solution
HPS	Hepatopulmonary Syndrome
ICP	Intracranial Pressure
ICT	Intracardiac Thrombosis
ICU	Intensive Care Unit
IHD	Ischemic Heart Disease
MELD	Model for End-stage Liver Disease
MRI	Magnetic Resonance Imaging
NASH	Non-alcoholic Steatohepatitis
NIPPV	Non-Invasive Positive Pressure Ventilation

J. R. Klinck (✉)
Division of Perioperative Care, Addenbrooke's Hospital, Cambridge, UK

P. Burra (ed.), *Textbook of Liver Transplantation*,
https://doi.org/10.1007/978-3-030-82930-8_15

PA	Pulmonary Artery
PAP	Pulmonary Artery Pressure
PEEP	Positive End-expiratory Pressure
PNF	Primary Non-function
POPH	Portopulmonary Hypertension
PT	Prothrombin Time
PTE	Pulmonary Thromboembolism
PVR	Pulmonary Vascular Resistance
QTc	Corrected QT-interval
RAAS	Renin-Angiotensin-Aldosterone System
ROTEM®	Rotational Thromboelastometry (device)
RV	Right Ventricle
SIRS	Systemic Inflammatory Response Syndrome
SNS	Sympathetic Nervous System
TEE	Transesophageal Echocardiography
TEG®	Thromboelastograph (device)
THAM	Tris-buffer
UNOS	United Network for Organ Sharing
VVBP	Venovenous Bypass
vWF	Von Willebrand Factor

Overview

- Liver transplantation is a technically complex, physiologically challenging vascular procedure. It has a high operative mortality, often associated with surgical hemorrhage and difficulties achieving adequate graft blood supply.
- In patients with acute liver failure or severe chronic liver disease, these technical challenges may be compounded by multi-organ dysfunction and limited physiological reserve.
- Specialist, liver-focused anesthetic and perioperative critical care is therefore essential, including pre-listing evaluation by an anesthesiologist experienced in liver transplantation.

Key Points

- Evaluation of perioperative mortality risk is needed to avoid futility and misuse of a graft. It often involves assessing the combined risks of age, co-morbidities, and potential surgical hazards. Estimated perioperative risk >30% is probably prohibitive since 5-year survival will fall below the widely accepted utility threshold of 50%.

- Advanced monitoring of the circulation and coagulation is critical in intraoperative management, including immediate access to transesophageal echocardiography, pulmonary artery catheterization, point-of-care biochemistry, and thromboelastography.
- The support of transfusion services and expert operating room technical personnel is vital, including individuals skilled in the management of red cell salvage, rapid infusion, venovenous bypass, and hemofiltration.
- The preservation of intravascular volume, cardiac output, and renal perfusion during a series of planned and unplanned surgical events is the central aim of transplant anesthesia. This requires optimal management of fluids, electrolytes, vasoactive infusions, and coagulation products, among other measures, as described in detail in this chapter.
- Transplant critical care involves the same goals, with added emphasis on weaning from mechanical ventilation, sedation and analgesia, infection surveillance and prevention, and early recognition of complications.

▶ **Tip** Several specialist societies provide excellent educational and networking resources for anesthesiologists and intensivists involved in liver transplantation. These include the International Liver Transplantation Society (ILTS), the Liver Intensive Care Group of Europe (LICAGE), and the Society for the Advancement of Transplant Anesthesia (SATA).

15.1 Introduction

The perioperative management of the liver transplant recipient presents a formidable challenge. Severe liver disease affects all organ systems, and candidates today are older and have more co-morbidities than ever before [1, 2]. The increasing use of organs from marginal or non-heart-beating donors aggravates these factors in a procedure routinely marked by cardiovascular instability, life-threatening hemorrhage, and major electrolyte, acid–base, and hemostatic disturbances. This chapter outlines key concepts in liver pathophysiology, evaluation of perioperative risk, and multidisciplinary management of the transplant recipient in the perioperative period.

15.2 Preoperative Evaluation

15.2.1 Pathophysiology of Liver Disease

End-stage liver disease presents with portal hypertension, impaired hepatic synthetic function, malnutrition, peripheral and pulmonary microvascular shunting, renal impairment, and encephalopathy in varying degrees. Life-threatening

complications are common, including variceal hemorrhage and sepsis from bacterial peritonitis or pneumonia, often accompanied by marked systemic inflammation and multi-organ decompensation. Common liver-related disorders and their perioperative management are summarized in Table 15.1.

Portal hypertension and hypoalbuminemia lead to ascites and hydrothorax. Some patients need regular paracentesis, thoracentesis, or intrapleural catheter drainage with infusions of albumin for relief of shortness of breath and abdominal discomfort. Varices are treated with sclerotherapy and propranolol, especially after bleeding. Transjugular intrahepatic portosystemic shunt insertion is sometimes used in refractory ascites or recurrent bleeding but may induce encephalopathy, liver decompensation, or fluid overload, potentially affecting candidacy for transplant.

Coagulation defects may be related to reduced concentrations of vitamin K-dependent clotting proteins, thrombocytopenia, impaired platelet function, and activated fibrinolysis. However, liver disease has complex effects on the balance between pro- and anti-hemostatic proteins, and reduced levels of protein C and antithrombin may compensate. Similarly, although platelet numbers are typically reduced, high levels of Factor VIII and von Willebrand Factor in cirrhosis appear to enhance platelet adhesion. Therefore, routine screening tests such as Prothrombin Time (PT) and platelet count may not predict bleeding [3]. Thrombin generation and thromboelastography are more reliable tests of the fluid phase of clotting and often demonstrate preserved coagulation in these patients.

The fibrinolytic system is also affected, as both pro- and antifibrinolytic factors may be decreased in cirrhosis. The net effect of these imbalances is unpredictable, and sensitivity of the coagulation system to factors promoting both bleeding and thrombosis is probably increased. Routine prophylactic administration of fresh frozen plasma (FFP), platelets, tranexamic acid, and other products before invasive procedures and transplant surgery is now disputed, and treatment may be better based on clinical findings, such as bleeding from puncture sites, an oozy operative field, or failure of shed blood to form clots.

Anemia is common, from impaired hematopoiesis, gastrointestinal bleeding, or hypersplenism. Varices should be treated and overt iron deficiency corrected, but transfusion is only carried out for active bleeding or in the presence of symptoms clearly attributable to low hemoglobin.

Hyponatremia may be caused by diuretic therapy, secondary hyperaldosteronism, and other, poorly understood renal abnormalities. It predicts worse outcomes, with or without transplant. Rapid increases in plasma sodium in the perioperative period, which are associated with high volumes of sodium-rich volume expanders, blood products, and sodium bicarbonate, carry a significant risk of central pontine myelinolysis (CPM) and long-term neurological disability [4]. In our center, patients with Na <122 mmol/L are suspended from the transplant waiting list to attempt correction, while patients with Na 123–125 mmol/L are considered on an individual basis according to the risks of major operative blood loss. Factors such as re-transplant, portal vein thrombosis, and extended criteria donor may favor deferral in the patient with a plasma sodium below this threshold.

Table 15.1 Pathophysiology of end-stage liver disease and perioperative management of the liver recipient[a]

System	Disorder	Perioperative management
Cardiovascular: cardiac function, systemic and splanchnic circulations	• Increased ejection fraction and cardiac output, often with impaired diastolic function and contractile response to increased afterload • Increased chamber sizes • Prolonged QTc • Cardiomyopathy (esp. alcohol, amyloid, Wilson's, hemochromatosis) • Increased splanchnic blood volume +/− flow • Reduced systemic blood volume +/− flow • Activation of compensatory responses (SNS, RAAS, endothelin) • Intrahepatic vasoconstriction aggravates portal hypertension and varices • Autonomic neuropathy (mild in cirrhosis, marked in amyloid)	• PA catheter and/or transesophageal echo • Balance preload + vasoconstrictors (vasopressin, terlipressin, or norepinephrine) • If renal or cardiac dysfunction consider caval preservation technique or venovenous bypass • Pacing wire if amyloid polyneuropathy
Cardiovascular: pulmonary circulation	• Portopulmonary Hypertension (POPH): PA mean > 25, PVR > 250 • Hepatopulmonary Syndrome (HPS): hypoxemia from pulmonary micro- or macrovascular shunting	• POPH: preop right heart catheter if Doppler PAsys >40 (to differentiate from high-flow state/overload); defer transplant and treat if PAmean >35 (and PVR raised) or RV impaired; intraoperative PA catheter +/− TEE essential if pulmonary hypertension suspected • HPS: bubble echo to exclude atrial shunt, chest CT to exclude other causes and treatable macrovascular lesion; increase F_IO_2; "lung-protective" ventilation (see below); Trendelenburg positioning; inhaled epoprostenol/nitric oxide; methylene blue; extracorporeal membrane oxygenation

(continued)

Table 15.1 (continued)

System	Disorder	Perioperative management
Respiratory	• Restrictive defect (ascites and/or hydrothorax) • Flow-related or anatomical intrapulmonary shunting (hepatopulmonary syndrome) • Non-cardiogenic pulmonary edema (fulminant hepatic failure) • Obstructive airways disease (esp. cystic fibrosis, alpha-1 antitrypsin deficiency) • Interstitial lung disease (primary biliary cirrhosis)	• $F_IO_2 \geq 0.5$, "lung-protective" ventilation (tidal volume 6–8 ml/kg, 4–6 cm PEEP, regular recruitment maneuvers) • Drain large effusion early intraop (beware re-expansion pulmonary edema, especially at reperfusion)
Renal	• Hepatorenal syndrome (pre-renal failure from neuroendocrine activation: splanchnic "steal") • Acute tubular necrosis from sepsis, hypovolemia • Tacrolimus/cyclosporine-related renal impairment • Renal tubular acidosis	• Preoperative renal replacement therapy if K+ > 5.5; stand-by otherwise • Maintain mean arterial pressure > 60–65: adequate volume plus norepinephrine, vasopressin, or terlipressin • Maintain hemoglobin > 9 g/dL (hematocrit >27) • Caval preservation technique or venovenous bypass
Electrolytes/ metabolic	• Hyponatremia • Hypomagnesemia • Hyperkalemia • Metabolic acidosis • Hypoglycemia in fulminant liver failure • Hyperglycemia and insulin resistance common after reperfusion	• Defer transplant if high surgical risk and Na < 122 • Treat hyperkalemia if preanhepatic > 5.0 or rapid anhepatic rise (insulin and/or salbutamol) • Wash bank blood using red cell salvage device if pre-existing renal failure or $K^+ > 5.0$ • $MgSO_4$ if any arrhythmia • Consider THAM, intraoperative hemodiafiltration if acidosis severe • Close monitoring and treatment of hypo/hyperglycemia

Table 15.1 (continued)

System	Disorder	Perioperative management
Hematological/ coagulation	• Anemia, thrombocytopenia, leucopenia (hypersplenism and marrow depression) • Impaired vitamin K absorption • Reduced liver synthesis of clotting factors • Hyperfibrinolysis • Reduced synthesis or clearance of anticoagulant factors (Proteins C & S, Antithrombin, FVIII, vWF) often preserves hemostasis and may cause pathologic thrombosis	• Consider prophylactic tranexamic acid or EACA if high bleeding risk and no prothrombotic history • Assess coagulation clinically before treatment (cannulation sites, surgical field) • Treat clinical coagulopathy according to thromboelastography and laboratory data (plasma, platelets, cryoprecipitate, factor concentrates, antifibrinolytic) • Maintain normothermia • If loss > 2 blood volumes consider massive transfusion protocol
Central nervous system	• Hepatic encephalopathy • Cerebral edema with intracranial hypertension	• Avoid/minimize benzodiazepines; • In fulminant liver failure with Grade III/IV encephalopathy consider ICP monitoring; maintain cerebral perfusion pressure > 60 mmHg (norepinephrine), +/− mannitol/ hypertonic saline/ thiopental to control ICP

[a]Adapted from Klinck and De Wolf, Chap. 22, Oxford Textbook of Transplant Anaesthesia and Critical Care (Eds Pretto et al., Oxford `University Press 2015), with permission

Preoperative hyperkalemia is uncommon but should be treated aggressively, since fatal intraoperative hyperkalemic arrest is still reported, usually associated with reperfusion of a steatotic or otherwise marginal graft. It may be caused by renal impairment, treatment with spironolactone, or blood transfusion. Preoperative values above 5.5 mmol/L should be treated with renal replacement therapy, usually hemofiltration, continued into the intraoperative phase if it does not fall to < 5.0 mmol/L.

Renal impairment and acute kidney injury develop easily because of underlying circulatory and hormonal disturbances. Overtreatment with diuretics is a common cause, and acute tubular necrosis may be seen in patients with fulminant hepatic failure or sepsis associated with spontaneous bacterial peritonitis or chest infection. Hepatorenal syndrome, mimicking pre-renal failure but occurring in the absence of clinical hypovolemia or intrinsic renal disease, is also common. This may respond to vasopressor treatment combined with volume loading and resolves after

transplantation. However, renal impairment is a strong predictor of both pre- and postoperative sepsis and mortality.

Cardiovascular dysfunction in liver failure is characterized by a disturbance of microcirculatory function causing arteriovenous shunting, increased cardiac output, and abnormal blood volume distribution, in proportion to the severity of the underlying hepatic disease [5]. Central blood volume is reduced, inducing increased sympathetic and hormonal vasoconstrictor activity. Despite this, splanchnic blood volume and flow are increased, a phenomenon known as *splanchnic steal* [6]. This may be related to increased intestinal nitric oxide production, gut translocation, or poor clearance of inflammatory cytokines or other vasoactive toxins. Subtle functional and structural changes occur in the heart, currently described as cirrhotic cardiomyopathy [7]. These include impaired responses to increased preload and afterload, and conduction abnormalities. Chamber enlargement, mild left ventricular hypertrophy, and diastolic dysfunction are common findings on resting echocardiography.

15.2.2 Cardiac Disease

Any evidence of significant cardiac disease must be taken seriously in view of the major insults imposed during and after surgery. Patients with alcoholic cirrhosis, amyloidosis, or Wilson's disease may have overt cardiomyopathy and should be carefully screened. Patients with a history of *symptomatic* ischemic heart disease (IHD) have much increased perioperative and long-term mortality risk, even with aggressive preoperative investigation and management [8]. They should be referred for cardiology review and considered for coronary angiography.

Significant triple vessel disease and/or global left ventricular dysfunction (ejection fraction [EF] < 50%) probably contraindicate transplant. Left ventricular impairment is associated with high mortality because of vulnerability to arrhythmias and right ventricular decompensation intraoperatively and stress-induced heart failure in the early post-transplant period, causing progressive graft failure from hepatic venous congestion [9, 10]. Among recipients with end-stage liver disease, even those with an ejection fraction of 50–60% or left ventricular hypertrophy on routine echocardiogram have poorer outcomes [10]. However, one large unit has recently reported that selected candidates for living donor liver transplant with reduced ejection fraction but a normal contractile response to dobutamine stress have shown acceptable post-transplant survival (Bhangui P, personal communication 2019).

The approach to patients with risk factors (age > 55, NASH, diabetes, hypertension, smoking, family history, obesity), but *no history or symptoms of* IHD, is more controversial. Many patients with end-stage liver disease are unable to exercise because of gross ascites or hydrothorax, lethargy, encephalopathy, or leg weakness. On this basis, many centers routinely pursue stress imaging (dobutamine stress echo or myocardial perfusion scan) and/or coronary angiography in these patients to identify and invasively treat "silent" obstructive disease [11–13]. However, several

arguments can be raised against this. No randomized study of screening procedures and outcomes has been done in this population, and current American Heart Association guidelines do not recognize "silent" disease as an indication for preoperative intervention [14]. A high-quality randomized trial of coronary interventions in major vascular surgery showed no survival benefit, nor have long-term, randomized studies in patients with stable, symptomatic coronary disease [15–17]. Moreover, studies suggesting good outcomes in liver recipients undergoing routine angiography and invasive coronary procedures are confounded by the inclusion of patients with silent disease, since the latter undoubtedly have better outcomes than those with a clinical history [18, 19].

Further arguments are that coronary obstruction is frequently associated with effective collateralization (normal fractional flow reserve on invasive angiography), and that higher MELD patients are already functionally stressed by a high resting cardiac output. Significant coronary supply–demand imbalance under these conditions might be expected to present with symptoms. Evidence in other settings suggests that epicardial coronary obstruction identified on angiography may be less relevant to longer term outcomes than either plaque burden or microvascular disease, which are not improved by revascularization.

There are also significant risks associated with invasive angiography. Although small series in this population describe few complications, angiogram-related deaths have been reported in several centers, as have poor outcomes after transplant [20]. In any case, perioperative and early (30-day) mortality from primary cardiac disease is relatively low in this population, even in centers such as ours, where routine stress testing and/or angiography are infrequently performed in patients without cardiac symptoms [8].

A key issue is the interpretation of non-invasive test findings. A negative stress test is reassuring but has been shown to be no more so than clinical risk scoring [21]. However, a positive test has a poor predictive value for obstructive epicardial disease (angiograms are often negative), suggesting that perfusion changes reflect microvascular dysfunction, not obstruction. Although transplant outcomes in recipients with "false positive" stress imaging have not been reported in large series, recent data suggest that any evidence of an inducible perfusion defect, even in the absence of obstructive coronary disease, is a powerful adverse predictor [22]. Thus, non-invasive testing may be useful in some very high-risk candidates in whom this finding might affect the decision to list, even without proceeding to angiography.

CT coronary angiography, calcium scoring, and magnetic resonance (MR) perfusion imaging are newer modalities used in many transplant centers. Cardiac MR is especially promising since it is non-invasive and has been shown in symptomatic patients to be as effective in the detection of functionally significant obstruction as invasive angiography with measurements of fractional flow reserve [23]. As in the case of conventional testing described above, however, there have been no randomized studies in liver transplant candidates. Although observational studies have reported increased cardiovascular risk associated with a raised calcium score or multiple obstructive lesions on CT, superiority over current tests or clinical risk scoring has not been demonstrated [24, 25].

Mild functional mitral, tricuspid, and aortic valvular regurgitation are frequently found on echocardiography but are usually attributable to the hyperdynamic state of end-stage liver disease and do not appear to predict adverse outcomes. However, valvular aortic stenosis is often seen in older patients referred for liver transplantation and remains an important cause of perioperative death in all major surgery. Although a Doppler-derived mean transvalvular gradient <20 mmHg is usually benign, a gradient >40 mmHg, valve area < 1 cm^2, or any left ventricular dysfunction are generally seen as prohibitive. The listing of candidates in the 20–40 mmHg range is a matter of clinical judgment, since gradients may be overestimated in the high cardiac output state of end-stage liver disease, and perioperative risk associated with non-transplant surgery in patients in this range is reported to be acceptable [26]. Trans-catheter valve replacement may be possible in selected patients [27]. It is important to note that a persistent mean aortic gradient >20 mmHg left untreated has recently been associated with high 5-year mortality (>50%), so careful follow-up after transplant is essential [28].

Cardiopulmonary exercise testing (CPET) is performed in some units to stratify perioperative risk, since key parameters such as peak oxygen consumption and anaerobic threshold have been shown to be associated with poor outcomes [29]. However, CPET thresholds do not quantify risk accurately enough to be a sole determinant in clinical decision-making in this setting. Low CPET values may contribute to a decision not to list, but in the absence of a marked threshold effect on mortality, and without data from randomized trials, clinical assessment remains the dominant factor in patient selection. CPET may have a role in pre-transplant exercise programs (pre-habilitation), but published data are still lacking.

15.2.3 Portopulmonary Hypertension

Pulmonary hypertension is seen in up to 20% of adult liver transplant candidates and usually easily identified by transthoracic echocardiography. In most cases, it is associated with pulmonary venous hypertension related to fluid overload or high cardiac output in the presence of diastolic dysfunction and responds to diuresis. True portopulmonary hypertension (POPH) occurs in < 4% of adult candidates and is pathologically indistinguishable from primary pulmonary hypertension. Peak echo-Doppler pulmonary artery pressure (PAP) > 40 should be investigated by pulmonary artery catheterization to measure mean PAP, pulmonary capillary wedge pressure, and pulmonary vascular resistance (PVR). Mean PAP > 35 with a high PVR (> 240) has a reported 50% perioperative mortality, approaching 100% if > 50 or if associated with right ventricular dysfunction. Candidates with raised PVR on cardiac catheterization should be referred to a specialist pulmonary hypertension unit. Although elevated PVR may sometimes be seen in the presence of pure diastolic dysfunction, effective treatments for “true” portopulmonary hypertension are available (sildenafil, bosentan, iloprost, macitentan) and appear to reduce perioperative risk. In most but not all of these patients, pulmonary hypertension resolves after transplant [30].

15.2.4 Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) is characterized by marked pulmonary shunting and orthostatic arterial desaturation (orthodeoxia) in the absence of intrinsic pulmonary disease. It is associated with portal hypertension and presents a spectrum of severity, affecting 10–32% of transplant candidates. The most common pathophysiological feature is the "perfusion-diffusion" defect of high flow through diffusely dilated pulmonary capillaries. Arteriovenous malformations identifiable on CT-pulmonary angiogram are an uncommon cause but may be amenable to therapeutic embolization. Contrast echocardiography is a sensitive screening tool and importantly excludes right-to-left shunt at atrial level. A preoperative $PaO_2 < 50$ mmHg or radiolabeled macroaggregated albumin uptake in brain >30% is associated with increased 90-day mortality, although this is not prohibitive. Nonetheless, oxygen dependency in a candidate over age > 60 with other major co-morbidity would contraindicate transplant in some units. Refractory intraoperative or postoperative hypoxemia occurs in 6–21% of recipients, treatment of which may require epoprostenol, nitric oxide, methylene blue, or extracorporeal membrane oxygenation, and weaning from mechanical ventilation may be prolonged [31]. These patients are more vulnerable to sepsis and other post-transplant complications.

15.2.5 Respiratory Disease and Smoking

Obstructive airways disease, usually related to smoking but occasionally to familial emphysema or alpha-1 antitrypsin deficiency, is seen in up to 18% of adults presenting for liver transplant [32]. Recurrent chest infections may be a feature, but history and clinical signs are often minimal. Flow-volume measurements show an obstructive pattern, often mixed with the restriction of vital capacity seen in ascites/hydrothorax. There are no data on its effect on liver transplant outcome, although forced expiratory volumes (FEV_1) below 40–50% (in the absence of pleural effusion or ascites), hypoxemia, or hypercapnia usually contraindicate transplant, especially in the presence of other co-morbidities or risk factors. These patients require careful evaluation, including optimization and prognostic scoring by a thoracic medicine specialist. Use of the BODE index may be useful because it may show that 5-year mortality from lung disease alone is greater than 50% [33].

Other causes of respiratory impairment include ascites and hydrothorax, poorly controlled asthma, aspiration, and pulmonary infection. Primary biliary cirrhosis is occasionally associated with interstitial lung disease, which causes disproportionate dyspnoea and a restrictive defect on pulmonary function testing. Idiopathic pulmonary fibrosis is a progressive condition and contraindicates transplant.

Smoking is common in this population and is associated with an increased risk of postoperative chest infection and sepsis, as well as with increased rates of late cardiovascular death and cancer, aggravated by long-term immunosuppression. Reports on an association with early postoperative graft loss from vascular thrombosis have been contradictory, and policies on preoperative smoking cessation vary widely.

Some units require abstinence before listing and enforce this with serum cotinine testing. Others only insist on cessation if the candidate is already marginal from other major co-morbidities. Many warn of the added risk but only require that the patient seek smoking cessation advice [34–36].

15.2.6 Sarcopenia and Obesity

Nutritional impairment is severe in up to 30% of patients, resulting from anorexia, malabsorption, impaired protein synthesis, and chronic catabolism. Nutritional reserve is further depleted by accelerated catabolism during infection and surgery. Poorer outcomes are seen in low-BMI patients, and most centers would not list at estimated dry BMI <16. BMIs above this value but with low measured nutritional indices (e.g., grip strength, triceps skin-fold thickness, mid-upper arm circumference < fifth percentile) are common but not regarded as contraindications to transplant. BMI <18.5 associated with other major co-morbidities would be regarded as potentially prohibitive [37]. Calorie, protein, and vitamin supplementation, using an enteric feeding catheter if necessary, are routinely pursued. Exercise (prehabilitation) regimes have been reported to improve sarcopenic indices, but benefit in terms of perioperative outcomes has not yet been established [38].
Morbid obesity (BMI >35) is increasingly common in patients presenting for liver transplantation. An association with increased perioperative complications and intensive care unit length-of-stay has long been recognized, but increased mortality has been reported only recently following analysis of the UNOS database [39, 40]. Previous studies may have been underpowered and confounded by the inaccuracy of BMI in this population, while the rising prevalence of NASH has increased the number of high-risk candidates. Patterns of obesity and associated sarcopenia vary widely. An abdominal or central pattern of obesity affects surgical access, perioperative respiratory parameters, and ventilator weaning much more than a pelvic or generalized distribution, although this has not been formally investigated. Marked abdominal obesity (BMI > 45) in the presence of other major co-morbidities, limited effort tolerance, or poor hand-grip strength would contraindicate transplant in many units. Although some centers have published good results with simultaneous liver transplant and sleeve gastrectomy, more experience is needed to confirm the risks and benefits of this approach [41].

15.2.7 Overview of Perioperative Risk

Age-related co-morbidities, in particular cardiovascular disease, chronic renal impairment, and metabolic syndrome associated with NASH, have increased in those considered for liver transplantation, as have surgical challenges such as re-transplantation, portal vein thrombosis, and aorto-celiac atherosclerosis. The effects of these on both perioperative and long-term survival are relevant, given the widely held consensus that 50% survival at 5 years fairly balances the needs of any individual patient against

those of others on the waiting list, thus optimizing utility and transplant benefit. Conditions carrying a prohibitive perioperative risk (30-day mortality estimated greater than 30%) have been outlined above but for most candidates with co-morbidities perioperative risk remains well below this level. In some, however, the combined effects of multiple acute and chronic conditions, including surgical hazards, may place them in the prohibitive range without an overt contraindication.

A recent analysis of the UNOS database has identified and weighted some of these factors to yield a useful, point-based perioperative mortality risk [42], while smaller observational studies have provided hazard ratios for many individual conditions. These studies provide an objective guide to overall risk, but the confidence limits of estimates are typically wide, and adding them together for a total combined risk is statistically unreliable. Therefore, decisions in patients' multiple co-morbidities are still largely based on the experience and clinical judgment of the multidisciplinary team. Assessments of nutritional and cardiorespiratory fitness, including frailty scoring, 6-min walk test, cardiac stress imaging, and cardiopulmonary exercise testing, when not part of routine testing, can generate additional hazard ratios that may be helpful in marginal cases.

15.3 Pre-transplant Intensive Care

15.3.1 The Chronic Liver Disease Patient in the Intensive Care Unit

Intensive care unit (ICU) admission in ESLD patients listed for or potentially treatable by liver transplantation is common. This may be precipitated by encephalopathy or circulatory failure from sepsis associated with bacterial peritonitis or pneumonia, by variceal hemorrhage, acute kidney injury, trauma, or a surgical procedure. Mortality is high, especially in those with an altered inflammatory response (SIRS), analogous to that seen in sepsis and now described as acute-on-chronic liver failure (ACLF). Outcome in this setting is clearly related to the number of extrahepatic systems affected, and mortality is 50% or higher when mechanical ventilation, renal replacement therapy, or vasopressors are needed. However, transplant in an ICU-dependent patient with decompensated ESLD or ACLF may not be contraindicated, and good results have been reported [43, 44]. Prospective studies to identify diagnostic and prognostic markers are ongoing, aiming to assess the potential for both reversibility and benefit from transplantation. A consensus on suitability for transplant in this setting awaits further experience.

Initial management of the septic patient in ICU includes prompt antimicrobial treatment; intubation and ventilation for airway protection with the onset of Grade 3 encephalopathy or frank hypoxemia; incremental volume loading with crystalloid or Human Albumin Solution to bring central venous pressure into the upper normal range (8–12 cm H_2O) and central venous oxygen saturation to >70%; and vasopressor infusion starting with norepinephrine, adding vasopressin or terlipressin if needed, to a target mean arterial pressure of 65 mmHg (75 mmHg in suspected acute kidney injury). Serial monitoring of serum lactate assesses the response to

these measures, and adrenocortical insufficiency should be excluded if hypotension is difficult to treat. Focused bedside transthoracic echocardiography is now widely used to assess cardiac filling and function, diagnose acute lung conditions and thromboembolism, and for safe placement of intravascular catheters.

In the intubated patient, airway care protocols and lung-protective ventilation have reduced the incidence of ventilator-acquired pneumonia and other complications of ventilation. Tidal volumes of 6–8 ml/kg and plateau airway pressures <30 mmHg are used, with ventilator rates adjusted to maintain minute volume. Inspired oxygen is adjusted to maintain oxygen saturation > 88%.

Treatment of hepatic encephalopathy focuses on the underlying cause and any aggravating factors, including infection, gastrointestinal bleeding, hypoglycemia, hyponatremia, and acidosis. Atypical or focal signs should prompt brain imaging, and lumbar puncture performed if CNS infection is suspected. Lactulose and rifaximin are proven pharmacological treatments, reducing gut urea production and absorption. Extracorporeal albumin dialysis, high-volume plasmapheresis, and the gut purgative polyethylene glycol have also improved encephalopathy in randomized trials, but benefit in terms of survival is still uncertain [45].

Hepatorenal failure and acute kidney injury are common and predict both high short-term mortality and later chronic kidney disease. Treatment is with albumin-based volume expansion and vasopressor to maintain mean arterial pressure > 75 mmHg. Both terlipressin and norepinephrine are effective. Renal replacement therapy is implemented early if needed for control of hyperkalemia, acidosis, or fluid overload. Continuous venovenous hemofiltration is favored over intermittent hemodialysis in most ICUs for better hemodynamic stability.

15.3.2 Acute Liver Failure

Special problems are encountered in patients with acute liver failure, who need urgent etiologic diagnosis and admission to ICU at the onset of Grade 3 encephalopathy. The aims of intensive care are to optimize hepatic oxygen delivery, preserving residual hepatocyte function and enabling regeneration, and to prevent and treat complications such as sepsis, cerebral edema, renal and cardiorespiratory failure, and hemorrhage.

Close monitoring of conscious level, cardiorespiratory parameters, and renal function is essential, along with frequent evaluation of metabolic and coagulation parameters, including blood glucose, sodium, lactate, INR, and platelet count. These patients usually have severe coagulopathy and may progress rapidly to multiorgan failure, including non-cardiogenic pulmonary edema, renal insufficiency, and vasoplegia, with or without sepsis.

Raised intracranial pressure is common and may rapidly progress to fatal brainstem compression if untreated. Intracranial pressure monitoring is sometimes used in this setting, although this can cause fatal intracranial hemorrhage and no consensus on the balance of risks has emerged. Non-invasive techniques for estimation of intracranial pressure using Doppler waveform analysis and ultrasound

measurements of optic nerve diameter are under investigation [46]. Paralysis, ventilation, and 20–30 degree head-up tilt are essential, using propofol sedation supplemented by mannitol or hypertonic saline and pentobarbital if needed. Mild hypothermia (34–36 °C) is advocated [47]. Norepinephrine remains the vasopressor of choice if needed for maintenance of a minimum cerebral perfusion pressure of >50 mmHg. Continuous venovenous hemofiltration may be needed to correct hyperkalemia and control metabolic acidosis.

Sepsis may be difficult to diagnose in this context as many of its clinical manifestations are mimicked in terminal hepatic decompensation. However, fever, hypotension, and dependence on vasopressors clearly suggest its presence, and the risks of proceeding with transplantation at this stage may be prohibitive.

There are no data to guide decisions on the appropriateness of transplanting the patient with fulminant hepatic failure who will not recover spontaneously but is likely to die or sustain permanent neurological injury if transplanted. The following criteria indicating futility have been suggested [48]:

- Severe intracranial hypertension (cerebral perfusion pressure < 40 mmHg for >2 h);
- Tonsillar herniation (fixed dilated pupils and CT evidence);
- Cardiorespiratory failure, with norepinephrine infusion > 1 mcg/kg/min, F_IO_2 > 0.60, PEEP > 12, mean PAP > 40;
- Bedbound >10 days.

15.4 Intraoperative Care

15.4.1 Immediate Preoperative Preparation

Full multisystem assessment should have been performed before listing, but all patients require careful review by the attending anesthesiologist when a cadaveric graft becomes available. Intercurrent conditions associated with prohibitive perioperative risk should be excluded, since cancellation of the transplant procedure or preparation of a backup recipient may be appropriate. These include untreated infection and sepsis (e.g., incipient bacterial peritonitis or bronchopneumonia), new-onset encephalopathy or focal neurological deficit, overt pulmonary edema requiring oxygen, hyperkalemia > 5.5 mmol/L, and severe hyponatremia. Recent deterioration in patients with known partial portomesenteric thrombosis requires repeat vascular imaging to determine operability. Timing of the last dose of anticoagulant treatment in these patients should be confirmed to guide testing and possible pro- or anticoagulant treatment in the operating room. Patients with known pulmonary hypertension should have a recent or new echocardiogram confirming normal right ventricular function. In living donation, both donor and recipient must be in optimal condition before transplant.

If unusual risks are identified, a discussion between the attending anesthesiologist, hepatologist, and surgeon is essential, to consider the balance of risks

associated with delay or cancellation of the procedure versus proceeding with the operation. Although cold ischemia times should be kept be as short as possible, cadaveric retrieval times and liver preservation techniques (especially machine perfusion) typically allow adequate time for assessment and intervention. Antibiotic prophylaxis may be given preoperatively and or intraoperatively according to local protocol.

Preoperative correction of abnormal measured coagulation indices (prothrombin time, fibrinogen concentration, platelet count) with fresh frozen plasma, fibrinogen, and platelets is no longer recommended unless the patient has obvious clinical signs of coagulopathy and/or bleeding [1, 49]. Ten units of blood are routinely cross-matched, and at least 20 additional group-specific units should be available if needed. Predictors of transfusion requirement include preoperative hemoglobin concentration, renal impairment, and previous transplant [50]. Fresh frozen plasma and platelets must be available whatever the preoperative coagulation values, because of the possibility of dilutional or fibrinolytic coagulopathy during surgery.

15.4.2 Anesthesia

General anesthesia involves careful preoxygenation and a rapid sequence induction with propofol. A nasogastric tube and urinary catheter are placed, followed by vascular cannulations and placement of a transesophageal echocardiography probe. Maintenance with fentanyl, remifentanil, or sufentanil given with air/oxygen/desflurane or isoflurane are common techniques. The choice of muscle relaxant is arbitrary, most units using atracurium or cis-atracurium. Short-acting agents are advocated as many patients can be extubated soon after the completion of surgery. Point of care blood gases, chemistry (sodium, potassium, glucose, lactate, ionized calcium, chloride), full blood count, and coagulation tests are performed at least hourly, more frequently during the peri-anhepatic period or during episodes of major blood loss.

15.4.3 Surgical Procedure

Major cardiovascular and biochemical changes are directly related to operative events. The first part of the operation is the dissection phase, during which the liver and its vessels are isolated from the surrounding tissues. Venous collaterals in the abdominal wall and mesentery may be extensive and can bleed heavily, especially in the presence of adhesions from previous peritonitis or upper abdominal surgery. This initial phase of the procedure varies in length (about 1 to 6 h), and the risk of major hemorrhage is greatest during the final stage, as the liver is dissected from the vena cava and other retro-hepatic structures.

Following mobilization of the liver, the bile duct and hepatic artery are divided, and clamps are placed on the portal vein and inferior vena cava. This begins the anhepatic phase. In the conventional (caval replacement) approach, the inferior vena

cava is clamped both at the level of the diaphragm and above the renal veins. The diseased liver is then removed along with the hepatic veins and retro-hepatic length of the vena cava. A widely used alternative, the "piggyback" or caval preservation technique, leaves the recipient vena cava intact. Although this avoids a full mobilization of the cava, it requires a challenging dissection of the plane between the liver and anterior wall of the cava. After this, the cava is side-clamped while the donor hepatic venous/caval confluence is anastomosed to it, preserving some caval blood flow during the anhepatic phase. The caval side clamp is then released before portal reperfusion. Lobar implants from living donors are done similarly, without resection of the recipient cava.

In the caval replacement operation, anastomoses of the suprahepatic cava, portal vein, and intrahepatic cava are performed, after which the new liver is flushed with colloid or crystalloid given through a cannula in the portal vein. This is to wash out storage perfusate and entrained air, which escape via the incomplete lower caval anastomosis. After flushing and completing the anastomoses, both caval clamps are released, followed by unclamping of the portal vein. Blood flow to the donor's liver is thereby restored, beginning the final or reperfusion phase of the operation.

Hepatic artery and biliary anastomoses follow, usually without hemodynamic implications unless there is side clamping of the aorta for an arterial conduit. A conduit (e.g., iliac artery graft) may be used to take flow directly from the aorta when an end-to-end hepatic arterial anastomosis appears inadequate. Biliary drainage may be completed by a donor–recipient end-to-end anastomosis or by a Roux-en-Y choledochojejunostomy, depending on the recipient's biliary anatomy.

Details of surgical technique vary between centers, particularly in the unclamping sequence of the vascular anastomoses, the use of venovenous bypass (see below) and of a temporary portocaval anastomosis to decompress the portal circulation during the anhepatic phase. Duration of surgery also varies widely, from four to more than 12 h depending on the patient and surgical technique.

15.4.4 Vascular Access

Large-bore intravenous access is vital, but techniques vary between centers. Two peripheral lines are dedicated to transfusion. A multi-lumen catheter and pulmonary artery catheter introducer can both be placed in the right internal jugular vein under ultrasound guidance. It is our longstanding practice to place two 5F cannulae alongside these in the right internal jugular vein. These may be used as reserve volume-infusion lines or re-wired to 10F size for use in the return limb of a venovenous bypass circuit (see below). Unless large-bore percutaneous access for venovenous bypass outflow is intended, the femoral route is avoided because the cava is clamped intraoperatively. These vessels may also be needed for surgical access for venovenous bypass. Subclavian cannulation has a higher risk of arterial hematoma and pneumothorax, and our unit is performed only under ultrasound and fluoroscopic guidance in an angiography suite.

15.4.5 Monitoring

Radial, brachial, or femoral arterial and central venous pressure monitoring are essential, while pulmonary artery flotation catheters are used routinely in many centers. Radial artery pressure monitoring may underestimate aortic pressure in hypotensive states, especially when vasopressors are used, and should be interpreted with caution. Pulmonary artery pressure and thermodilution cardiac output measurements help in the assessment and management of hypotension, which may arise unpredictably because of changes in venous return, altered systemic vascular resistance, and cardiac or embolic events. A pulmonary artery catheter is essential if pulmonary hypertension is present or suspected.

Cardiovascular monitoring is further enhanced by the use of transesophageal echocardiography, which gives continuous information on biventricular function and an immediate diagnosis of embolization of air or thrombus. The risks of this modality appear to be acceptable, and in many units this has replaced routine use of a pulmonary artery catheter [51, 52]. The major obstacle to wider use is the significant training requirement and capital cost in units without local cardiac anesthesia expertise.

Coagulation monitoring practices vary widely. In most centers, routine coagulation screening tests, including prothrombin time, partial thromboplastin time, fibrinogen, and platelet count are supplemented by thromboelastography (TEG® or ROTEM®). Despite poor agreement with conventional laboratory coagulation tests, thromboelastography provides a prompt global assessment of coagulation function, and targeted sample treatment also allows demonstration of heparin effect, fibrinogen effect, and platelet function. However, abnormal results in both conventional and viscoelastic testing are poorly correlated with visually apparent coagulopathy (an oozy surgical field and/or lack of visible clot), and their main value may be to indicate the appropriate treatment when coagulopathy is a clinical problem.

15.4.6 Blood Replacement and Fluid Management

Blood product use during liver transplantation has declined over the last 20 years, with a substantial proportion of recipients avoiding blood products altogether. Refinement in surgical techniques, better understanding of hemostasis, and improved anesthetic management have all contributed [49, 53, 54].

Since bleeding during liver transplantation is not usually caused by problems with the major anastomoses, but by dissection through myriad portosystemic collateral veins, fluid management, portal hyperemia, and blood loss may be linked. Compared to healthy controls, patients with cirrhosis and portal hypertension have splanchnic hypervolemia, which volume loading increases [1, 55, 56]. They also have smaller increases in cardiac output with infusion, so the larger volumes needed to improve systemic perfusion may have a disproportionate effect on portal venous pressure and flow. Aggressive administration of crystalloid and colloid may also have a more detrimental effect on clotting, since baseline factor levels are low.

Thus, the conventional approach of administering blood products pre-emptively and optimizing cardiac output by generous fluid loading has been challenged. Indeed, fluid restriction with vasopressor infusion during the dissection and anhepatic phases has been associated with very low blood product use [57]. On the other hand, volume restriction in the anesthetized patient requires liberal use of vasopressors and may risk systemic and renal hypoperfusion, although current data discount this risk. Substantial support for a conservative, incremental approach to dissection-phase fluid replacement based on these principles comes from randomized trials in the setting of variceal bleeding [58, 59].

Arterial pressure is maintained with boluses of 5% human albumin (HAS), synthetic colloid, or crystalloid, although use of low-dose vasopressors (norepinephrine, phenylephrine, or vasopressin) to counteract the sympatholytic and vasodilating effects of anesthetic agents is increasingly common. HAS is increasingly used in the long-term management of cirrhosis, with a recent multicenter ANSWER trial showing survival benefit [60]. It has no effects on coagulation apart from dilution but is costly. Modified fluid gelatin solutions are inexpensive and have been used perioperatively in high volumes in liver recipients in the United Kingdom and Europe for many years but are associated with a small risk of anaphylaxis.

When surgical bleeding occurs, many now accept a transfusion threshold of 70 g/dL of hemoglobin. Transfusion at a higher value (80–90 g/dL) may be prudent in the settings of renal impairment or clinical ischemic heart disease.

15.4.7 Management of Coagulopathy

New concepts in the interpretation of coagulation tests in liver disease, outlined above, should be considered in intraoperative management. However, true coagulopathy is often induced or aggravated perioperatively dilution, pathological fibrinolysis, effects of synthetic colloids, and release of heparinoids and inflammatory mediators from the graft. Prophylactic tranexamic acid, shown to reduce blood loss safely in traumatic coagulopathy, liver transplantation, and many other surgical procedures, is used selectively in many units.

Treatment of established coagulopathy is guided by monitoring (see below) [61]. In the presence of fibrinolysis or heparin effect, tranexamic acid or protamine can be given. Otherwise, platelets, fresh frozen plasma, and cryoprecipitate remain the mainstay of treatment, with frequent assessment of the surgical field to minimize the number of units given. Although data in liver recipients are limited, virally deactivated factor concentrates of fibrinogen and prothrombin appear safe and effective, and are increasingly used to treat established coagulopathy [1]. Normothermia and a pause in the procedure (after full reperfusion) to allow the liver to recover from surgical handling may also help.

Recombinant factor VIIa (eptacog alfa activated) has controlled intractable bleeding in patients with complex acquired coagulation defects, but two randomized trials have failed to show efficacy when the drug is given prophylactically.

Most centers use it only in consultation with a specialist in transfusion medicine after other measures have failed.

A growing number of case reports indicate that hypercoagulability and thromboembolism may cause serious or fatal complications during liver transplantation [50, 62]. The incidence of pulmonary thromboembolism (PTE) or intracardiac thrombus (ICT) formation has been estimated at 1–1.5%. Neither antifibrinolytics nor VVBP nor pulmonary artery catheterization has been firmly implicated. Hypercoagulability is demonstrable on thromboelastography and other tests in a significant number of liver recipients, particularly those with primary sclerosing cholangitis and hepatocellular carcinoma, but its importance as a cause of intraoperative thrombosis is unclear. Thromboembolism may occur at any stage of the procedure, and overall mortality is 68%. Aggressive therapy with thrombectomy or alteplase thrombolysis has been successful in some cases. TEE provides the clear benefit of immediate diagnosis [63].

Autotransfusion techniques are widely used and safe, but effects on coagulation and even on total use of bank blood are still unproven. Although not implicated in observational studies of tumor recurrence in liver resection, use of cell salvage is relatively contraindicated in patients with hepatic malignancy undergoing transplant, since malignant cells have been identified in processed blood even after filtration, and because liver recipients receive long-term immunosuppression. Enteric contamination of the peritoneum also contraindicates this technique.

15.4.8 Electrolyte and Acid–base Changes

The infusion of large volumes of blood products and reperfusion of the donor liver cause marked changes in plasma biochemistry. Plasma sodium is sub-normal in many recipients and tends to increase during surgery. Rises of more than 12 mmol per liter in 24 h have been associated with pontine myelinolysis and neurological injury. In susceptible patients, this may happen with smaller increases, and this condition has been reported to affect as many as 1.4% of liver recipients [4, 64]. Minimizing citrated blood products, avoiding sodium bicarbonate, and intraoperative use of hemofiltration with reduced-sodium replacement fluid may attenuate this increase and reduce risk [65].

Plasma potassium increases on reperfusion of the liver. Liver flush potassium values of over 100 mmol per liter and arterial plasma levels as high as 13 mmol per liter may be measured, and characteristic ECG changes are seen. Many anesthesiologists give 5–10 ml of calcium chloride at reperfusion to reduce the risk of hyperkalemia-induced ventricular tachycardia or fibrillation. In most patients, redistribution follows within seconds and a progressive decrease is subsequently seen. However, pre-existing renal failure, residual beta-blockade, and a relatively large, fatty, or ischemic donor liver may be associated with prolonged and life-threatening hyperkalemia.

Hyperkalemia may also complicate rapid transfusion, especially in the presence of renal impairment. Plasma potassium concentrations in stored blood increase with

storage time and are often >20 mmol per liter. Potassium concentration should be checked frequently when transfusion is rapid. In some centers, donor units are washed using cell salvage equipment whenever life-threatening hyperkalemia is anticipated. Values above 5.0 during the dissection or anhepatic phases should be treated aggressively with furosemide and glucose–insulin [66]. Nebulized or intravenous salbutamol and sodium bicarbonate should also be considered. As at reperfusion, any ECG changes associated with hyperkalemia should be treated with calcium chloride.

Trisodium citrate in transfused blood and plasma depresses ionized calcium, which should be maintained to preserve myocardial function. Calcium chloride is given if hypotension occurs in the presence of a depressed ionized calcium value. A less marked effect is seen in relation to magnesium concentrations, although supplementation in the absence of either arrhythmias or availability of rapid measurement is not routine.

Metabolic acidosis is usually absent or minimal at first, unless there is renal impairment. However, it increases during the operation, owing to many causes. Transfused blood introduces a substantial quantity of exogenous lactic acid into the circulation, while liver lactate and urea metabolism are impaired. Acid metabolites associated with venous stasis in the portal and lower body circulations, as well as those that accumulate in the new liver during storage, are released into the general circulation on reperfusion, causing a further increase in acidosis. A poorly functioning liver fails to metabolize lactate, and worsening lactic acidosis is a typical sign of graft failure.

Hyperchloremia related to high-chloride-containing fluids, especially 0.9% sodium chloride and blood products, may contribute to late acidosis. Intraoperative use of balanced electrolyte solutions and low sodium HAS (30% HAS) may mitigate this effect.

Acidosis is treated with modest hyperventilation. The place of sodium bicarbonate in the management of acidosis remains controversial. Evidence that global circulatory function is impaired by moderate metabolic acidosis is slight, while detrimental effects of bicarbonate therapy on oxygen delivery, intracellular pH, and plasma lactate have been described. Alternative buffers producing less or no carbon dioxide, including dichloroacetate and tris-buffer (THAM), may be of value but remain to be fully assessed.

If liver and cardiovascular functions are adequate after reperfusion, metabolic acidosis tends to clear. Potassium reuptake by the grafted liver can cause hypokalemia in the early postoperative period, requiring potassium chloride infusion.

15.4.9 Glucose Control

Blood glucose typically increases during the procedure because of administration of acid-citrate-dextrose blood and stress-related insulin resistance. Hypoglycemia, though seen preoperatively in patients with fulminant hepatic failure, is rarely observed intraoperatively even when normal hepatic glucose release is interrupted

during the anhepatic and early reperfusion phases. Glucose concentrations tend to rise during surgery, and conventional doses of insulin are often ineffective. Recent literature suggests an association between poor glucose control and adverse outcomes in the perioperative and critical care settings, but a clear causal relationship has not been established. However, hypoglycemia is a significant hazard when tight control is attempted, especially in the unconscious patient. Insulin infusions, ranging from 2 to 10 units per hour, have been advocated to moderate blood glucose values and prevent hyperkalemia. Blood glucose and electrolyte checks, at least hourly, are essential when this is done.

15.4.10 Cardiovascular Changes

Surgical bleeding presents the greatest threat, and the ability to replace blood rapidly has been emphasized. Cardiac filling may be impaired during the dissection phase by intermittent obstruction of venous return during surgical manipulation of the liver, or by direct compression of the diaphragmatic surface of the heart. Anesthetic agents and hypocalcemia will amplify these effects. Interpretation of filling pressures may be difficult during the dissection phase, since caval obstruction is variable and may coexist with true hypovolemia. Observation of the surgical field and communication with the surgeon are vital when there is uncertainty about the cause of reduced venous return. The responses to clamping of the inferior vena cava for hepatectomy and to unclamping when the grafted liver is reperfused depend on several factors. The most important of these is whether the cava is side-clamped for a piggyback implantation or cross-clamped for the conventional.

Cross-clamping of the cava at hepatectomy produces a marked (40–50%) decrease in central venous pressure and cardiac output. Systemic vascular resistance increases, but a decrease in blood pressure is expected. Provided cardiac filling pressures and contractility are maintained, frank hypotension (<80 mmHg systolic) is unusual. Although the need for venovenous bypass is usually predetermined by other factors (discussed below), when its use is not planned, many teams perform a trial clamping of the inferior vena cava to assess the patient's ability to maintain an adequate systemic blood pressure. Once the liver is removed, lower filling pressures are accepted as long as the arterial blood pressure is satisfactory. Overtransfusion at this stage, more likely when bypass is not used since higher filling pressures are needed to maintain cardiac output, may result in high filling pressures following unclamping. This may have adverse effects on right ventricular function, gas exchange, and hepatic blood flow.

When a piggyback technique or venovenous bypass is used, the decrease in cardiac output is usually less (20–30%). Arterial pressure is well maintained, although this may depend on the extent of caval clamping or flows through the bypass circuit. Nonetheless, a progressive decline in cardiac output occurs during the anhepatic phase, and both bypass and the piggyback techniques fall short of maintaining a normal circulatory state, reflected in worsening metabolic acidosis.

Reperfusion of the transplanted liver is usually associated with reduced heart rate, contractility, and peripheral vascular tone. Portal unclamping releases desaturated blood from the obstructed portal circulation, which mixes with cold, potassium-rich preservation fluid in the new liver and enters the systemic circulation. Slowing of the heart and hyperkalemia are common, and asystole, tachyarrhythmias, and ventricular fibrillation are sometimes seen. Blood pressure decreases in almost all patients, because of arteriolar vasodilatation and transient myocardial depression. These changes may be caused by inflammatory mediators from the ischemic liver, by peptides released during splanchnic stasis, or by reflex vasodilatation. In most patients, blood pressure and cardiac output are restored within minutes. In some, typically those with a marginal graft or pre-existing vasopressor dependency, recovery takes longer and sustained vasopressor support is needed. This has been described as the "post-reperfusion syndrome." In patients undergoing urgent re-transplantation for graft non-function or infarction, or in those with unrecognized sepsis, hypotension and acidosis after unclamping may be progressive and irreversible.

Transient pulmonary hypertension may be seen at reperfusion, as central blood volume increases. Pulmonary artery wedge pressure is raised, and the transpulmonary gradient is normal (mean PAP minus PCWP <15 mmHg). Pre-existing pulmonary hypertension is usually diagnosed by echocardiography at the time of referral but is occasionally found only on placement of the PA catheter for transplant. If it is true portopulmonary hypertension (PVR > 240, transpulmonary gradient >15 mmHg), the risks of proceeding need to be balanced against those of deferring transplant in favor of treatment. If severe (mean PAP >50 mmHg, or RV dysfunction), perioperative mortality approaches 100% and the operation should not proceed. If moderate (35–50 mmHg), a trial of treatment with prostacyclin and/or nitric oxide is advocated, ideally monitored by transesophageal echocardiography. It may be reasonable to proceed if right heart function is well maintained, especially if the patient responds to vasodilator therapy.

15.4.11 Veno-venous Bypass

Venovenous bypass is a pumped extracorporeal shunt taking blood from the femoral and (sometimes) portal vein to the axillary or internal jugular vein, intended to decompress the portal system and maintain venous return during the anhepatic phase. Heparin-bonded tubing and non-occlusive pumps allow its use without systemic heparinization. Use has declined as use of the piggyback technique has become more widespread, and because many centers have demonstrated good results without it. It is now used selectively in most liver transplant programs and in some units never.

Advocates of bypass cite physiological advantages during the final stages of dissection and during the anhepatic period, at least when the implantation technique involves full clamping of the cava. These include decompression of the portal, lower caval and renal venous systems, and maintenance of cardiac output, thus preserving splanchnic and renal blood flow. Hemodynamic stability and systemic acidosis are

improved, and control of surgical bleeding is easier since venous pressure in portosystemic collaterals is reduced. However, evidence that bypass improves results is lacking, and a comprehensive evaluation of its complications has yet to be published.

The most serious hazards of bypass are perforation of central vessels during insertion of large-bore percutaneous catheters and embolization of air or thrombus, all of which have caused fatalities. Body temperature decreases during bypass unless a heat exchanger is used, which may carry an added risk of thromboembolism. Local complications at access sites also occur, including nerve injury, hematoma, lymphocele, and infection. Most units now reserve the technique for patients most likely to gain from its use. Indications may include severe portal hypertension, renal or cardiac impairment, marked metabolic acidosis or vasopressor dependency, and hypotension on trial clamping of the cava.

15.4.12 Respiratory Complications and Hepatopulmonary Syndrome

Changes in respiratory function caused by liver disease have been described above. Further respiratory problems arising during surgery are not common. Rapid desaturation occurs easily after induction of anesthesia, even with preoxygenation, since functional residual capacity (FRC) is often reduced by ascites or hydrothorax. Pulmonary edema presents a more important hazard. Overtransfusion can occur because of the highly variable rate of blood loss. Plasma oncotic pressure is reduced, and some patients appear to have abnormal vascular permeability, especially after reperfusion and if graft function is poor. Intraoperative drainage of a large pleural effusion (hepatic hydrothorax) is routine but can cause re-expansion pulmonary edema, which may only present after reperfusion. Atelectasis, tension pneumothorax, and significant pulmonary embolism may occur intraoperatively but are rare. Major pneumothorax is easily diagnosed on transthoracic ultrasonography, while transesophageal echo is essential to rapid recognition of pulmonary embolism.

Patients with hepatopulmonary syndrome usually respond to increased inspired oxygen if needed, but persistent desaturation <85% on 100% inspired oxygen at a PEEP of 10 cm H_2O reflects severe shunting and should be aggressively managed. Trendelenburg positioning may be helpful, but persistent hypoxia should prompt treatment with inhaled prostacyclin or nitric oxide, or intravenous methylene blue. Evidence is limited but a useful treatment algorithm, including the use of extracorporeal membrane oxygenation in life-threatening circumstances, has been published (Fig. 15.1) [31].

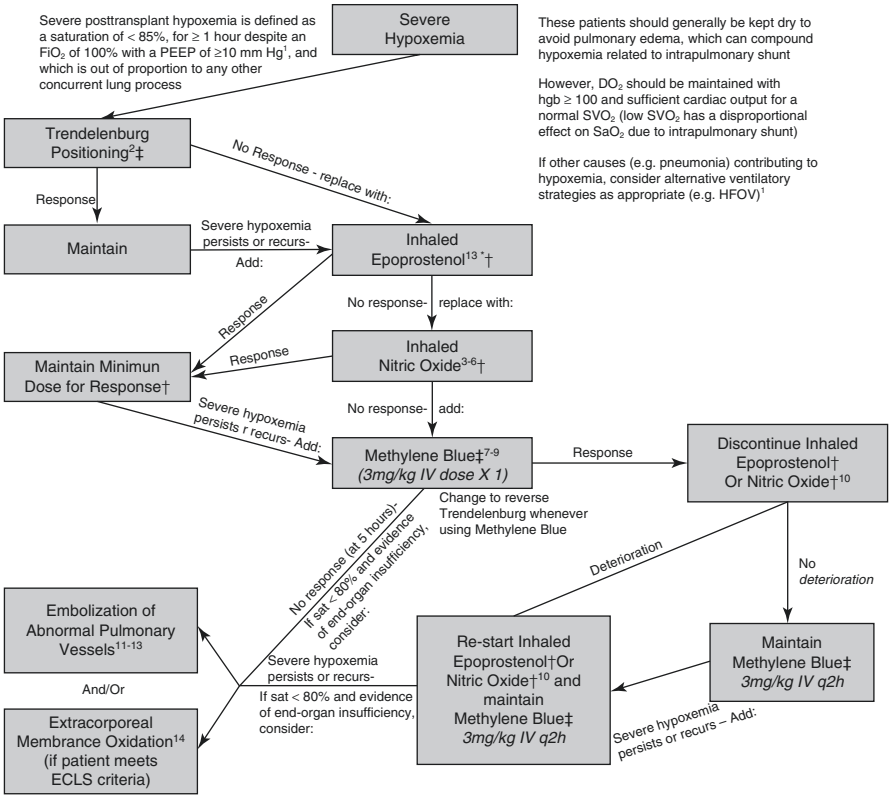

Fig. 15.1 Proposed management algorithm for severe post–liver transplant hypoxemia in patients with hepatopulmonary syndrome (Nayyar D, Man HSJ, Granton J, Lilly LB, Gupta S. Am J Transplant, Off J Am Soc Transplant Am Soc Transpl Surg. 2015 Apr;15(4):903–13)
Response is defined as a 20% improvement in PaO_2/F_IO_2 ratio (and deterioration a 20% drop in PaO_2/F_IO_2 ratio), as measured at 30 min for all other interventions, and at 5 h for methylene blue (MB) (MB response can be seen as early as 30 min, but peak effect is at 5 h). ‡If feeding in this position, ensure that patient has a post-pyloric feeding tube. *If ventilated with high-frequency oscillatory ventilation (HFOV), skip this step and go directly to inhaled nitric oxide. †In accordance with the modified University Health Network Inhaled Pulmonary Vasodilator Policy (see Supporting Information 1). ‡MB 3 mg/kg in 50–100 cc's normal saline IV over 15 min; change to reverse Trendelenburg for MB (if not possible, place supine). Hold MB after every three doses to assess ongoing need. Maximum recommended duration: 24–48 h (effects of larger cumulative doses unknown) 15, 16. Notes: hold any selective serotonin reuptake inhibitor (SSRI) and await appropriate washout if using MB (risk of serotonin toxicity) 17; MB can cause spuriously low pulse oximetry (verify oxygenation with ABG). Algorithm should be adapted in accordance with any available pre-operative testing results of Trendelenburg positioning, inhaled nitric oxide and/or IV MB, and any prior pulmonary angiography identifying embolizable pulmonary vessels. F_IO_2 denotes fraction of inspired oxygen; DO_2 denotes systemic oxygen delivery; SVO_2 denotes mixed venous oxygen saturation; HFOV denotes high frequency oscillatory ventilation

15.4.13 Renal Protection

Intraoperative changes in renal function are related to marked alterations in cardiac output and renal blood flow. Urine flow is diminished, and markers of renal injury are raised during caval clamping, when cardiac output is reduced and renal venous pressure acutely raised. This response may be attenuated when venovenous bypass or a piggyback implantation is used. Pre-existing renal impairment, prolonged hypotension, and high transfusion volumes are associated with a high risk of postoperative renal failure. No measures have yet been shown to prevent intraoperative renal injury, although a rationale for the use of low-dose vasopressors including vasopressin and norepinephrine exists, given the pathophysiology of the hepatorenal syndrome. However, concerns about the effects of these on perfusion of the newly implanted liver remain.

15.5 Post-transplant Intensive Care

Most liver recipients are transferred to an intensive care unit for postoperative care. Care involves a full multidisciplinary team including intensivists, hepatologists, transplant surgeons, radiologists, specialists in infectious disease, and others. The postoperative course is highly variable. In addition to respiratory and fluid management, frequent adjustment of immunosuppression, anticoagulation, and antimicrobials may be required. Much can be protocolized, and the formulation of treatment algorithms that are regularly reviewed and modified is essential to high-quality care.

Extubation in the operating room or within a few hours of admission to ICU is usually possible, but this depends on recipient co-morbidity, the complexity of the surgery, and especially on adequate initial graft function [67]. To be extubated, the patient must be awake, hemodynamically stable, and normothermic with good gas exchange and no bleeding or major acidosis. Postoperative pulmonary atelectasis and subsequent infection are common, and prevention depends on a routine respiratory care bundle, including 30-degree head-up tilt while ventilated (semi-sitting once extubated), with regular intratracheal saline and suctioning. Adequate analgesia, chest physiotherapy, and exercises to encourage deep breathing and coughing are also important. The use of modest positive end-expiratory pressure (PEEP) while ventilated, and non-invasive positive pressure ventilation (NIPPV) after extubation, which is sometimes needed in patients with chronic lung disease, hepatopulmonary syndrome, or post-transplant pulmonary edema, helps prevent atelectasis and does not appear to compromise hepatic venous flow [68].

Key graft-related early complications are primary non-function, hepatic artery thrombosis, and bleeding. Biliary leaks, rejection, and sepsis tend to occur after the first 5–7 days. Sepsis requires early recognition, aggressive antimicrobial management and resuscitation, and close observation, usually involving readmission to ICU.

Primary non-function (PNF) often presents in the operating room as coagulopathy, persistent hyperkalemia, acidosis, hyperlactatemia, hypotension, and oliguria. These worsen in the early postoperative period, accompanied by hypoglycemia, anuria, deteriorating gas exchange, and circulatory collapse. Urgent retransplantation may be lifesaving, but these patients deteriorate rapidly and it is important to recognize when re-transplant becomes futile. Close liaison between hepatologists, intensivists, anesthetists, and surgeons is required. Some groups perform total hepatectomy once a replacement organ has been identified, which may stabilize the patient, but clear indications and evidence are lacking.

Hepatic artery thrombosis is a life-threatening complication that must be identified early to avoid graft loss. Doppler ultrasound studies should be routine 12–24 after surgery and at least daily afterward to confirm hepatic arterial and portal venous flow. The absence of either should prompt urgent angiography and thrombectomy or revision. Vascular thrombosis may not be associated with immediate biochemical changes and is otherwise easily missed when early intervention could save the graft. Complex arterial or venous reconstructions may increase the likelihood of thrombosis, as may the postoperative use of vasopressors. Loss of arterial inflow, if not causing early graft infarction and sepsis, later leads to ischemic cholangitis, biliary leak, and strictures, and usually precipitates retransplantation. If urgent retransplantation is needed, immunosuppression is reduced and prophylactic antibacterial and antifungal agents are given.

Hemorrhage requiring re-exploration is now unusual, but even patients closed with a dry surgical field may bleed. Recognition and timely intervention are essential. Bleeding may not be revealed in abdominal drains and should be suspected in the setting of a rising heart rate, falling blood pressure, reduced skin temperature, and oliguria. A falling hemoglobin concentration confirms the diagnosis. Although an abnormal prothrombin time is not routinely corrected post-transplant, since it is useful as a marker of improving synthetic function, signs of active bleeding should prompt volume resuscitation and administration of fresh frozen plasma, platelets, and red cells as soon as possible. If hemodynamic stability is not achieved after initial resuscitation, the patient should be returned to the operating room immediately.

Although early biliary leak is uncommon, it can be detected by careful inspection of drain fluid for volume and especially color. The diagnosis is confirmed by measuring the concentration of bilirubin: if greater than that in the patient's serum, surgical exploration is usually required. Typically, the standard duct-to-duct anastomosis is converted to a Roux loop.

Non-cardiogenic pulmonary edema (Adult Respiratory Distress Syndrome) is an infrequent complication but occurs in the setting of massive transfusion, graft nonfunction or infarction, and fulminant sepsis or rejection. It is managed with mechanical ventilation with small tidal volumes, PEEP, and increased inspired oxygen sufficient to prevent systemic hypoxemia.

Acknowledgments The author gratefully acknowledges the following colleagues for their important contributions to earlier published work, which have helped shape this manuscript: Andrew Butler FRCS, Andre De Wolf MD, James Findlay MD, and Andrea De Gasperi MD.

References

1. Tovikkai C, Charman SC, Praseedom RK, Gimson AE, van der Meulen J. Time-varying impact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. BMJ Open. 2015;5(5):e006971.
2. Mousa OY, Nguyen JH, Ma Y, Rawal B, Musto KR, Dougherty MK, et al. Evolving role of liver transplantation in elderly recipients. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2019;25(9):1363–74.
3. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011;365(2):147–56.
4. Leise M, Cárdenas A. Hyponatremia in cirrhosis: implications for liver transplantation. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2018;24(11):1612–21.
5. Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut. 2008;57(2):268–78.
6. McAvoy NC, Semple S, Richards JMJ, Robson AJ, Patel D, Jardine AGM, et al. Differential visceral blood flow in the hyperdynamic circulation of patients with liver cirrhosis. Aliment Pharmacol Ther. 2016;43(9):947–54.
7. Izzy M, VanWagner LB, Lin G, Altieri M, Findlay JY, Oh JK, et al. Redefining cirrhotic cardiomyopathy for the modern era. Hepatology. 2020;71(1):334–45.
8. Konerman MA, Fritze D, Weinberg RL, Sonnenday CJ, Sharma P. Incidence of and risk assessment for adverse cardiovascular outcomes after liver transplantation: a systematic review. Transplantation. 2017;101(7):1645–57.
9. Josefsson A, Fu M, Allayhari P, Björnsson E, Castedal M, Olausson M, et al. Impact of peritransplant heart failure & left-ventricular diastolic dysfunction on outcomes following liver transplantation. Liver Int Off J Int Assoc Study Liver. 2012;32(8):1262–9.
10. Kwon H-M, Moon Y-J, Jung K-W, Park Y-S, Kim K-S, Jun I-G, et al. Appraisal of cardiac ejection fraction with liver disease severity: implication in post-liver transplantation mortality. Hepatology. 2019.
11. Raval Z, Harinstein ME, Skaro AI, Erdogan A, DeWolf AM, Shah SJ, et al. Cardiovascular risk assessment of the liver transplant candidate. J Am Coll Cardiol. 2011;58(3):223–31.
12. VanWagner LB, Harinstein ME, Runo JR, Darling C, Serper M, Hall S, et al. Multidisciplinary approach to cardiac and pulmonary vascular disease risk assessment in liver transplantation: an evaluation of the evidence and consensus recommendations. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. 2018;18(1):30–42.
13. Lentine KL, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation. 2012;126(5):617–63.
14. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Developed in collaboration with the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Vascular Medicine Endorsed by the Society of Hospital Medicine. J Nucl Cardiol Off Publ Am Soc Nucl Cardiol. 2015;22(1):162–215.
15. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med. 2004;351(27):2795–804.
16. Shaw LJ, Berman DS, Maron DJ, Mancini GBJ, Hayes SW, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation. 2008;117(10):1283–91.

17. Sedlis SP, Hartigan PM, Teo KK, Maron DJ, Spertus JA, Mancini GBJ, et al. Effect of PCI on Long-term survival in patients with stable ischemic heart disease. N Engl J Med. 2015;373(20):1937–46.
18. Wray C, Scovotti JC, Tobis J, Niemann CU, Planinsic R, Walia A, et al. Liver transplantation outcome in patients with angiographically proven coronary artery disease: a multi-institutional study. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. 2013;13(1):184–91.
19. Romero-Cristóbal M, Mombiela T, Caballero A, Clemente A, Fernández-Yunquera A, Diaz-Fontenla F, et al. Clinical Utility of a risk-adapted protocol for the evaluation of coronary artery disease in liver transplant recipients. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2019;25(8):1177–86.
20. Snipelisky DF, McRee C, Seeger K, Levy M, Shapiro BP. Coronary interventions before liver transplantation might not avert postoperative cardiovascular events. Tex Heart Inst J. 2015;42(5):438–42.
21. Bhutani S, Tobis J, Gevorgyan R, Sinha A, Suh W, Honda HM, et al. Accuracy of stress myocardial perfusion imaging to diagnose coronary artery disease in end stage liver disease patients. Am J Cardiol. 2013;111(7):1057–61.
22. Baibhav B, Mahabir CA, Xie F, Shostrom VK, McCashland TM, Porter TR. Predictive value of Dobutamine stress perfusion echocardiography in contemporary end-stage liver disease. J Am Heart Assoc. 2017;6(2)
23. Nagel E, Greenwood JP, McCann GP, Bettencourt N, Shah AM, Hussain ST, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. N Engl J Med. 2019;380(25):2418–28.
24. Kong Y-G, Kang J-W, Kim Y-K, Seo H, Lim T-H, Hwang S, et al. Preoperative coronary calcium score is predictive of early postoperative cardiovascular complications in liver transplant recipients. Br J Anaesth. 2015;114(3):437–43.
25. Sheth T, Chan M, Butler C, Chow B, Tandon V, Nagele P, et al. Prognostic capabilities of coronary computed tomographic angiography before non-cardiac surgery: prospective cohort study. BMJ. 2015;350:h1907.
26. Samarendra P, Mangione MP. Aortic stenosis and perioperative risk with noncardiac surgery. J Am Coll Cardiol. 2015;65(3):295–302.
27. Tirado-Conte G, Rodés-Cabau J, Rodríguez-Olivares R, Barbanti M, Lhermusier T, Amat-Santos I, et al. Clinical outcomes and prognosis markers of patients with liver disease undergoing transcatheter aortic valve replacement: a propensity score-matched analysis. Circ Cardiovasc Interv. 2018;11(3):e005727.
28. Strange G, Stewart S, Celermajer D, Prior D, Scalia GM, Marwick T, et al. Poor long-term survival in patients with moderate aortic stenosis. J Am Coll Cardiol. 2019.
29. Bernal W, Martin-Mateos R, Lipcsey M, Tallis C, Woodsford K, McPhail MJ, et al. Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2014;20(1):54–62.
30. Krowka MJ, Wiesner RH, Heimbach JK. Pulmonary contraindications, indications and MELD exceptions for liver transplantation: a contemporary view and look forward. J Hepatol. 2013;59(2):367–74.
31. Nayyar D, Man HSJ, Granton J, Lilly LB, Gupta S. Proposed management algorithm for severe hypoxemia after liver transplantation in the hepatopulmonary syndrome. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. 2015;15(4):903–13.
32. Rybak D, Fallon MB, Krowka MJ, Brown RS, Reinen J, Stadheim L, et al. Risk factors and impact of chronic obstructive pulmonary disease in candidates for liver transplantation. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2008;14(9):1357–65.
33. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350(10):1005–1012.

34. Fleetwood VA, Hertl M, Chan EY. Liver transplantation to the active smoker: transplant provider opinions and how they have changed: transplantation in smokers: a survey. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2015;19(12):2223–7.
35. Leithead JA, Ferguson JW, Hayes PC. Smoking-related morbidity and mortality following liver transplantation. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2008;14(8):1159–64.
36. Duerinckx N, Burkhalter H, Engberg SJ, Kirsch M, Klem M-L, Sereika SM, et al. Correlates and outcomes of posttransplant smoking in solid organ transplant recipients: a systematic literature review and meta-analysis. Transplantation. 2016;100(11):2252–63.
37. Lai JC. Defining the threshold for too sick for transplant. Curr Opin Organ Transplant. 2016;21(2):127–32.
38. Williams FR, Berzigotti A, Lord JM, Lai JC, Armstrong MJ. Review article: impact of exercise on physical frailty in patients with chronic liver disease. Aliment Pharmacol Ther; 2019.
39. Spengler EK, O'Leary JG, Te HS, Rogal S, Pillai AA, Al-Osaimi A, et al. Liver transplantation in the obese cirrhotic patient. Transplantation. 2017;101(10):2288–96.
40. Northup PG, Intagliata NM, Davis JPE, Argo CK, Pelletier SJ. Macrosteatotic allografts and obese recipients have nearly equal negative impact on liver transplant survival. Transplantation; 2019.
41. Diwan TS, Rice TC, Heimbach JK, Schauer DP. Liver transplantation and bariatric surgery: timing and outcomes. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2018;24(9):1280–7.
42. Molinari M, Ayloo S, Tsung A, Jorgensen D, Tevar A, Rahman SH, et al. Prediction of perioperative mortality of cadaveric liver transplant recipients during their evaluations. Transplantation. 2019;103(10):e297–307.
43. Karvellas CJ, Lescot T, Goldberg P, Sharpe MD, Ronco JJ, Renner EL, et al. Liver transplantation in the critically ill: a multicenter Canadian retrospective cohort study. Crit Care. 2013;17(1):R28.
44. Karvellas CJ, Garcia-Lopez E, Fernandez J, Saliba F, Sy E, Jalan R, et al. Dynamic prognostication in critically Ill cirrhotic patients with multiorgan failure in ICUs in Europe and North America: a multicenter analysis. Crit Care Med. 2018;46(11):1783–91.
45. MacDonald AJ, Karvellas CJ. Emerging role of extracorporeal support in acute and acute-on-chronic liver failure: recent developments. Semin Respir Crit Care Med. 2018;39(5):625–34.
46. Rajajee V, Williamson CA, Fontana RJ, Courey AJ, Patil PG. Noninvasive intracranial pressure assessment in acute liver failure. Neurocrit Care. 2018;29(2):280–90.
47. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369(26):2525–34.
48. Steadman RH, Van Rensburg A, Kramer DJ. Transplantation for acute liver failure: perioperative management. Curr Opin Organ Transplant. 2010;15(3):368–73.
49. Bezinover D, Dirkmann D, Findlay J, Guta C, Hartmann M, Nicolau-Raducu R, et al. Perioperative coagulation management in liver transplant recipients. Transplantation. 2018;102(4):578–92.
50. McCluskey SA, Karkouti K, Wijeysundera DN, Kakizawa K, Ghannam M, Hamdy A, et al. Derivation of a risk index for the prediction of massive blood transfusion in liver transplantation. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2006;12(11):1584–93.
51. Soong W, Sherwani SS, Ault ML, Baudo AM, Herborn JC, De Wolf AM. United States practice patterns in the use of transesophageal echocardiography during adult liver transplantation. J Cardiothorac Vasc Anesth. 2014;28(3):635–9.
52. Lu SY, Matsusaki T, Abuelkasem E, Sturdevant ML, Humar A, Hilmi IA, et al. Complications related to invasive hemodynamic monitors during adult liver transplantation. Clin Transplant. 2013;27(6):823–8.
53. Verbeek TA, Stine JG, Saner FH, Bezinover D. Hypercoagulability in end-stage liver disease: review of epidemiology, etiology, and management. Transplant Direct. 2018;4(11):e403.
54. Chow JH, Lee K, Abuelkasem E, Udekwu OR, Tanaka KA. Coagulation management during liver transplantation: use of fibrinogen concentrate, recombinant activated factor VII,

prothrombin complex concentrate, and antifibrinolytics. Semin Cardiothorac Vasc Anesth. 2018;22(2):164–73.
55. Kiszka-Kanowitz M, Henriksen JH, Møller S, Bendtsen F. Blood volume distribution in patients with cirrhosis: aspects of the dual-head gamma-camera technique. J Hepatol. 2001;35(5):605–12.
56. Møller S, Bendtsen F, Henriksen JH. Effect of volume expansion on systemic hemodynamics and central and arterial blood volume in cirrhosis. Gastroenterology. 1995;109(6):1917–25.
57. Carrier FM, Chassé M, Wang HT, Aslanian P, Iorio S, Bilodeau M, et al. Restrictive fluid management strategies and outcomes in liver transplantation: a systematic review. Can J Anaesth J Can Anesth; 2019.
58. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368(1):11–21.
59. Odutayo A, Desborough MJR, Trivella M, Stanley AJ, Dorée C, Collins GS, et al. Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of andomised controlled trials. Lancet Gastroenterol Hepatol. 2017;2(5):354–60.
60. Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet Lond Engl. 2018;391(10138):2417–29.
61. Hartmann M, Walde C, Dirkmann D, Saner FH. Safety of coagulation factor concentrates guided by ROTEM™-analyses in liver transplantation: results from 372 procedures. BMC Anesthesiol. 2019;19(1):97.
62. Fukazawa K, Pretto EA, Nishida S, Reyes JD, Gologorsky E. Factors associated with mortality within 24 h of liver transplantation: an updated analysis of 65,308 adult liver transplant recipients between 2002 and 2013. J Clin Anesth. 2018;44:35–40.
63. Dalia AA, Khan H, Flores AS. Intraoperative diagnosis of intracardiac thrombus during orthotopic liver transplantation with transesophageal echocardiography: a case series and literature review. Semin Cardiothorac Vasc Anesth. 2017;21(3):245–51.
64. Morard I, Gasche Y, Kneteman M, Toso C, Mentha A, Meeberg G, et al. Identifying risk factors for central pontine and extrapontine myelinolysis after liver transplantation: a case-control study. Neurocrit Care. 2014;20(2):287–95.
65. Lenk MR, Kaspar M. Sodium-reduced continuous venovenous hemodiafiltration (CVVHDF) for the prevention of central pontine myelinolysis (CPM) in hyponatremic patients scheduled for orthotopic liver transplantation. J Clin Anesth. 2012;24(5):407–11.
66. De Wolf A, Frenette L, Kang Y, Tang C. Insulin decreases the serum potassium concentration during the anhepatic stage of liver transplantation. Anesthesiology. 1993;78(4):677–82.
67. Mandell MS, Stoner TJ, Barnett R, Shaked A, Bellamy M, Biancofiore G, et al. A multicenter evaluation of safety of early extubation in liver transplant recipients. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2007;13(11):1557–63.
68. Saner FH, Pavlakovic G, Gu Y, Gensicke J, Paul A, Radtke A, et al. Effects of positive end-expiratory pressure on systemic haemodynamics, with special interest to central venous and common iliac venous pressure in liver transplanted patients. Eur J Anaesthesiol. 2006;23(9):766–71.