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Anaesthesia for Liver Transplant

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ANAESTHESIA FOR LIVER TRANSPLANT

INTRODUCTION

Liver transplant surgery is a fairly uncommon procedure in our country, with centres existing only in Cape Town and Johannesburg which undertake this operation. Although uncommon, in our setting, it must be remembered that liver replacement is the sole life saving procedure for patients with end stage liver disease and acute liver failure(when all treatment options have been exhausted). The most commonly used technique is orthotopic transplantation, in which the native liver is removed and the donor organ is placed in the same anatomic location as the original liver.

The first liver transplant was undertaken in 1963 by Dr Thomas Starzl. The patient a 3 year old child with biliary atresia, died in the operating room from massive haemorrhage caused by venous collaterals and uncontrollable coagulopathy. The first successful liver transplant took place in 1967 and since then with continued improvements in organ preservation,surgical technique, the advent of better immunosuppressive agents, the management of coagulopathy, and the treatment of infections, it has resulted in a great expansion of this procedure to over 120 centres worldwide and more than 6000 transplants a year.

Survival after adult liver transplantation by diagnosis*

SURVIVAL (%)			
Diagnosis	**1-year**	**4-year**	**7-year**
Primary sclerosing cholangitis	91	84	78
Primary biliary cirrhosis	89	84	79
Autoimmune hepatitis	86	81	78
Chronic hepatitis C	86	75	67
Alcoholic liver disease	85	76	63
Cryptogenic cirrhosis	84	76	67
Chronic hepatitis B	83	71	63
Malignancy	72	43	34

** UNOS database 1987–1998; n ¼ 24,900 patients. Data from Seaberg EC, Belle SH, Beringer KC, et al. Liver transplantation in the United States from 1987–1998: updated results from the Pitt-UNOS liver transplant registry. In: Cecka JM, Terasaki PI, editors. Clinical transplants 1998. Los Angeles (CA): UCLA Tissue Typing*

The two major goals of liver transplantation are to prolong survival and to improve quality of life. Data from the United Network for Organ Sharing (UNOS) on 24,900 adult patients undergoing liver transplantation from October 1987 to September 1998 showed that 1-year, 4-year, and 10-year patient survival rates were 85%, 76%, and 61%, respectively, confirming that liver transplantation results in prolongation of life. Roberts and colleagues showed that the 1-year survival improved over time from 74.8% in 1990 to 86.2% in 1996. The best survival has been shown to occur among patients who undergo liver transplantation for chronic cholestatic liver diseases, including primary biliary cirrhosis and primary sclerosing cholangitis; the worst survival occurred in patients who underwent transplantation for hepatic malignancy.

INDICATIONS AND CONTRAINDICATIONS FOR LIVER TRANSPLANT [1]

Indications for Liver Transplantation
Acute liver failure
Acute hepatitis A
Acute hepatitis B
Drug/toxin hepatotoxicity
Cirrhosis from chronic liver diseases
Chronic hepatitis B virus and chronic hepatitis C virus infection
Alcoholic liver disease
Autoimmune hepatitis
Cryptogenic liver disease
Primary biliary cirrhosis and primary sclerosing cholangitis
Secondary biliary cirrhosis
Metabolic Disorders
Alpha-1 antitrypsin deficiency
Hereditary hemochromatosis
Wilson's disease
Glycogen-storage disorders
Type 1 hyperoxaluria
Familial homozygous hypercholesterolemia
Malignancy
Primary hepatic cancer: hepatocellular carcinoma and cholangiocarcinoma
Metastatic: carcinoid tumors and islet cell tumors
Miscellaneous
Polycystic liver disease
Budd-Chiari syndrome

Data from Yu AS, Keeffe EB. Liver transplantation. In: Zakim D, Boyer TD, editors.Hepatology: a textbook of liver disease. 4th ed. Philadelphia: Elsevier; 2003. p. 1617–56

Contraindications to Liver Transplantation

Absolute contraindications

Brain death
Extrahepatic malignancy
Active uncontrolled infection
Active alcoholism and substance abuse
AIDS
Severe cardiopulmonary disease
Uncontrolled sepsis
Inability to comply with medical regimen
Lack of psychosocial support
Anatomic abnormalities precluding liver transplantation
Compensated cirrhosis without complications
(Child-Turcotte-Pugh score, 5–6)

Relative contraindications

Cholangiocarcinoma
Portal vein thrombosis
Psychologic instability

Data from Yu AS, Keeffe EB. Liver transplantation. In: Zakim D, Boyer TD,editors. Hepatology: a textbook of liver disease. 4th edition. Philadelphia

The initial results of patients with HIV infection undergoing liver transplant was poor. Most patients died within a few years after transplantation from overwhelming infections. Now with the widespread use of HAART therapy, both the natural history of HIV infection and the outcome after transplantation have improved dramatically.

Recent results show that short-term survival after transplantation in patients with HIV infection, that are well controlled with HAART, is comparable with that seen in HIV-negative recipients. However a number of significant drug interactions have been reported between antiretroviral drugs and the immunosuppressive agents used after liver transplantation. Latest avenues in transplant surgery regarding HIV include the transplant of organs from HIV positive donors, to recipients who are already HIV positive. However the presence of AIDS is a contraindication to transplantation, because post transplant immunosuppression accelerates the course of AIDS.

Assessment of the patient's lifestyle, psychologic stability (including his or her perception of disability), and extent of family support require interaction with psychiatric and social work support services, especially those with alcoholic liver disease. The ability to abstain from alcohol after transplantation is predicted by the ability to abstain before transplantation

for at least 6 months, relatively stable employment history, and a family and friend support structure.

Tests to Exclude Contraindications

Infectious disorders : HIV, syphilis, EBV, cytomegalovirus, toxoplasmosis
Malignancy : Colonoscopy in primary sclerosing cholangitis (ulcerative colitis) ERCP in primary sclerosing cholangitis (cholangiocarcinoma)
In HCC: bone scan, lung CT (metastatic work-up) Screening (colon, breast, cervical, prostate cancer)
Cardiopulmonary status : Chest radiograph, electrocardiogram, two-dimensional-echocardiogram (routine) Thallium stress test, coronary angiography (patients at risk)Pulmonary function tests
Abbreviations: CT, computerized tomography; EBV, Epstein-Barr virus; ERCP, endoscopic retrograde cholangiopancreatography; HCC, hepatocellular carcinoma

SCORING SYSTEMS RELATED TO LIVER TRANSPLANT [29,30,31]

The continuing shortage of liver donors unfortunately results in some patients dying while on the waiting list. Thus, criteria for organ allocation are needed to establish a justice system and to improve utility—that is, to maximize better outcomes. The United Network for Organ Sharing (UNOS) has revised allocation and distribution policies on the basis of the ethical principles of justice for the individual patients vs. optimal use of the limited number of available organs. The Model for End stage Liver Disease (MELD) score was adopted in 2002 for determining disease severity, in order to allocate donor organs to the sickest patients first, rather than to those who had been on the waiting list longest. Previous to this organs were allocated to patients based on the Childs-Turcotte-Pugh (CTP) score.

Childs-Turcotte-Pugh score **Characteristic**	**1 Point**	**2 Points**	**3 Points**
Ascites	None	Controlled	Refractory
Encephalopathy	Absent	Grade 1-2	Grade 3-4
Albumin (mg/dL)	>35	28–35	<28
Bilirubin (mg/dL)	<2	2–3	>3
INR	<1.7	1.7–2.3	>2.3

CTP class A: 5–6 total points
CTP class B: 7–9 total points
CTP class C: 10–15 total points

The Child-Turcotte-Pugh (CTP) scoring system, is the most widely used system to grade the severity of liver disease. For listing purposes, a patient must have at least 7 points (ie, be at least a Child class B), according to the minimal listing criteria consensus initially developed when the CTP score was the basis for organ allocation.

The use of CTP, particularly for prioritizing potential liver transplant recipients, has revealed several drawbacks. Firstly, 2 of the variables, ascites and encephalopathy, are subjective because they are assessed by physical examination alone; and second, when other methods are used (ultrasonography, psychometric testing, EEG), a different degree of severity is diagnosed. In addition, the "ceiling" and "floor" effect in terms of the limits set to the laboratory parameters of bilirubin, albumin, and prothrombin time in the grades A, B, and C and changes of serum bilirubin concentrations with therapy (e.g., with ursodeoxycholic acid) do not allow assessment using a continuous scale of severity. Moreover, the absence of an assessment of renal function, which is a well-established prognostic marker in cirrhosis, is another limitation of the CTP score.

Due to its limitation and other factors such as, increasing number of deaths while on liver transplant waiting lists and reports suggesting that waiting time correlates poorly with death while on the waiting list, a consensus opinion emerged that a revised allocation scheme was needed, hence the MELD score.

MELD Score Formula

MELD score = (0.957 X $\log_e$[serum creatinine(mg/dL)] + 0.378 X $\log_e$[total serum bilirubin(mg/dL)] + 1.120 X $\log_e$[INR]) X 10

- Minimum for all values is 1.
- Maximum value for creatinine is 4.

The MELD score is based on 3 biochemical variables, (1) serum bilirubin, (2) serum creatinine, and (3) international normalized ratio, and has been shown in retrospective and prospective studies to be predictive of 3-month mortality in patients with chronic liver disease. However, the MELD score is not without limitations. It is known that serum creatinine is also influenced by gender, age, ethnicity, and muscle mass, which may lead to discrimination against women, white, or malnourished patients with cirrhosis if creatinine is considered as a surrogate of renal function. Moreover, INR was designed to standardize the anticoagulation effect of warfarin and may not reflect the severity of liver disease. Trotter et al have shown in 2 studies that different assays to measure INR lead to significantly different MELD

scores between transplant centres. In 2006 a review article from a liver transplant unit in the UK concluded the following:

"MELD has been useful in stimulating a resurgence of interest in assessing prognosis in cirrhosis, but this review demonstrates it is imperfect and not necessarily better than the CTP score. Its merit is the inclusion of a criterion relating to renal function. It deserves to be explored with less of the fervor conferred to new dogma, as well as explored by combining donor characteristics. It seems implausible that any system, which needs to combine justice and utility in organ allocation, would not include donor variables that have been shown to be important. MELDD—with an added D for donor—is prime priority for evaluation."

Pediatric End-Stage Liver Disease (PELD) scoring system incorporates the following criteria Albumin:

Total bilirubin
INR
Growth failure
Age (<1 y) (Scores for candidates listed for liver transplantation before the candidate's first birthday continue to include the value assigned for age (<1 y) until the candidate reaches 24 months of age.)

PELD score for each candidate is based on the following calculation:
PELD score = 0.436 (age [<1 y]) – 0.687 x Log_e (albumin g/dL) + 0.480 x Log_e (total bilirubin mg/dL) + 1.857 x Log_e (INR) + 0.667 (growth failure [<-2 SD present]).
Laboratory values <1.0 are set to 1.0 for the purposes of the PELD score calculation. Growth failure is calculated based on age and gender using the current CDC growth chart.

PREOPERATIVE EVALUATION AND COMPLICATIONS

The evaluation of patients for liver transplant is normally undertaken by a multidisciplinary team. Patients would normally have undergone numerous examinations and rigorous testing before being evaluated by an anaesthetist. A complete preop evaluation (including special investigations) and assessment of fitness for anaesthesia may need to be done emergently in those patients with acute hepatic failure or acute deterioration of end stage liver disease. When transplant is non emergent preoperative assessment may follow at a more leisurely pace. However due to long

waiting times for organs, it is imperative that patients be reassessed prior to the operation with regards to contra indications to the procedure and the development of new complications since the last assessment.

Patients with end-stage liver disease have secondary dysfunction of virtually all other organ systems, and anaesthetic management must include protection of other organs damaged by liver failure. In the preop assessment patients should be evaluated for the presence of liver failure and the complications of end stage liver disease, which include the following:

Pulmonary System[2,3,5,10,19]

Assessment of the patient`s pulmonary system should include review of a recent chest radiograph, lung function tests and ABG. Pulmonary complications associated with liver disease include:

a) Restrictive Lung Disease
This frequently results from ascites or pleural effusion and management involves removal of this fluid. Also pulmonary oedema may result from overzealous intravenous fluid administration.

b) Intrapulmonary shunts
Consists of the entity of Hepatopulmonary syndrome (HPS) which occurs in the setting of portal hypertension.

HPS is made up of the triad of acute or chronic liver disease, hypoxaemia, and right to left shunt due to intrapulmonary vasodilation and is found in 5% to 32% of cirrhotic patients followed at transplant centers.

Various circulating vasoactive substances have been proposed as possible causative agents of the vasodilation: glucagon, vasoactive intestinal peptide, prostacyclin and nitric oxide. Clues to the presence of HPS include platypnea(increased dyspnea in an upright posture) and orthodeoxia (oxygen desaturation in an upright posture).

Preoperative evaluation of patients suspected of having HPS should include arterial blood PO_2 determination, transthoracic contrast echocardiography, arterial oxygen response to 100% oxygen administration, and quantification of intrapulmonary shunting using a macroaggregated albumin (MAA) scan. Patients with severe hypoxia have increased perioperative mortality.

Preoperative PaO2 of 50 mmHg or less alone or in combination with a MAA shunt fraction of 20% or more are the strongest predictors of postoperative mortality.

c) Pulmonary Hypertension
Portopulmonary hypertension(POPH) is best defined as pulmonary artery hypertension (PAH) associated with portal hypertension, whether or not that portal hypertension is secondary to underlying liver disease. The diagnosis of POPH is defined as a mean pulmonary artery pressure >25 mm Hg or pulmonary vascular resistance > 120 dyne.s.cm^{-5} in the presence of a normal pulmonary capillary wedge pressure.

The pathogenesis of POPH is not fully understood. However it is known that the development of POPH appears to be independent of the cause of the portal hypertension.It is thought that a few vascular abnormalities combine to cause the vascular obstruction that leads to the increase in PVR seen in POPH: an imbalance of vasomediators(increase in endothelin-1, prostaglandin F2a, thromboxane B2, angiotensin 1 and a decrease in prostacyclin) thereby leading to vasoconstriction, endothelial damage leading to remodeling, with associated proliferation of endothelium and smooth muscle, and in situ microthrombosis.

Distinction between Hepatopulmonary Syndrome (HPS) and Portopulmonary Hypertension (PPHTN)		
	HPS	**PPHTN**
Symptomatology	Progressive dyspnea	Progressive dyspnea Chest pain Syncope
Clinical examination	Cyanosis Finger clubbing Spider angiomas	No cyanosis RV heave Pronounced P2 component
ECG findings	None	RBBB Rightward axis RV hypertrophy
Arterial blood gas levels	Moderate-to-severe hypoxemia	No/mild hypoxemia
CEE	Always positive; left atrial opacification For>3–6 cardiac cycles after right atrial opacification	Usually negative; however, positive for <3 cardiac cycles (if atrial septal defect or patent foramen ovale exists)
Pulmonary haemodynamics	Normal/low PVR	Elevated PVR Normal mPAOP
Pulmonary angiography	Normal/''spongy'' appearance (type I) Discrete arteriovenous communications (type II)	Large main pulmonary arteries Distal arterial pruning
OLT	Even indicated in severe stages	Only indicated in mild-to-moderate stages
^{99m}TcMAA shunting index	>6%	<6%

Abbreviations: CEE, contrast-enhanced echocardiography; mPAOP, mean pulmonary artery occlusion pressure; OLT, orthotopic liver transplantation; PVR, pulmonary vascular resistance; RBBB, right bundle-branch block; RV,right ventricle; 99mTcMAA, technetium-99m-labeled macroaggregated albumin.
Reprinted from Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB. Pulmonary hepatic-vascular disorders(PHD). Eur Respir J 2004;24(5):873.

Renal System[4,6,8,10,12]

Renal dysfunction is a dreaded complication in patients with cirrhosis. Advanced liver disease is associated with increased levels of endogenous vasodilators, which lead to peripheral vasodilatation, a chronic hyperdynamic circulation, and low blood pressure.Among the clinical consequences of a hyperdynamic circulation is activation of the sympathetic nervous system and renin–angiotensin–aldosterone axis. Elevated levels of renal vasodilatory prostaglandins attempt to compensate for the vasoconstrictive influence of angiotensin, and when this fails, hepatorenal syndrome(HRS) develops.

Diagnosing HRS requires the absence of primary renal disease, proteinuria, nephrotoxins, hypovolemia, or hemodynamic causes of renal hypoperfusion. A urinary sodium level <10 mEq/L or a fractional excretion of sodium <1% ,with a creatinine level of more than 1.5 mg/dL, a urine volume of less than 500 mL/day is required for diagnosis.

Two types of hepatorenal syndrome can be distinguished:

- Type 1 develops rapidly over a period of weeks and is associated with a high mortality. However renal function may recover spontaneously once the liver function improves or the patient receives a liver transplant. Type 1 is more commonly seen in acute liver failure, alcoholic hepatitis or acute decompensation of chronic liver disease.
- Type 2 follows a less acute course and is seen mostly in patients who develop a resistance to diuretic therapy.

CNS[1,3,4,7]

Hepatic encephalopathy is a life-threatening complication of endstage liver disease. Causes include accumulation of toxins such as ammonia, GABA agonists and other neuroactivesubstances. Cerebral metabolism and the blood-brain barrier may also be abnormal in these patients.
Tracheal intubation and mechanical ventilation should be instituted in patients with grade III and IV encephalopathy. Patients with grade IV encephalopathy may develop cytotoxic and vasogenic cerebral oedema with associated increase in intracranial pressure (ICP), a major cause of morbidity and mortality in patients. In such patients, intracranial pressure monitoring and first line therapy with mannitol should be instated. If refractory to mannitol, the following may be considered in the following order based upon ease and safety of administration, and efficacy based upon the available literature 1)hypertonic saline, 2)induced moderate

hypothermia 3)barbiturate coma 4)indomethacin (causes vasoconstriction with decrease in ICP and increase in CPP in selected patients).

ICP monitoring may be useful not only in guiding therapy preoperatively, but also in signalling the presence of moderate to severe cerebral oedema which may preclude livertransplantation.

Classification of Hepatic Encephalopathy

Grade 0	Normal
Grade I	Altered spatial orientation, sleep patterns and affect
Grade II	Drowsy but arousable, slurred speech, confusion, asterixis
Grade III	Stuporous, responsive only to painful stimuli
Grade IV	Unresponsive, with decorticate or decerebrate posturing

Gastrointestinal System[3,4]

Portal pressure increases because of increased hepatic vascular resistance and increased portal venous inflow. The anatomic site of the increased intrahepatic vascular resistance varies according to the etiology of the cirrhosis. Once a critical level of portal hypertension is reached (hepatic venous pressure gradient of 10–12 mm Hg, defined as the pressure gradient between the portal vein and the hepatic vein), portosystemic collaterals form to decompress the portal system. Portal hypertension is sustained by the development of increased portal venous inflow from a generalized hyperdynamic circulation in both acute and chronic liver failure.

Problems related to Portal Hypertension

a) Oesophageal Varices.
b) Hypersplenism – the associated thrombocytopaenia may predispose to life threatening bleeding, especially in the presence of coagulopathy and oesophageal and/or gastric varices.
c) Ascites – also caused due to hypoalbuminaemia.
d) Spontaneous Bacterial Peritonitis (SBP)- manifests in patients with cirrhosis who have ascites with an unexplained clinical deterioration, with or without the classic signs of peritonitis, and is associated with a high mortality rate. Secondary peritonitis, such as that due to a perforated viscus, should always be excluded prior to instituting therapy.
   Paracentesis findings that are diagnostic include an absolute neutrophil count in the ascitic fluid of > 250/µL and positive results from peritoneal fluid cultures. Antibiotic therapy, directed mostly toward gram-negative enteric organisms, should be started early.

Cardiovascular System[3,5,9,10]

Patients with end-stage liver disease develop a hyperdynamic circulation characterized by increased cardiac output and arteriolar vasodilatation. This condition has been attributed to sympathetic nervous system overactivity, inadequate clearance of vasoactive substances (bypassing the liver and decreased hepatic function), arteriovenous(A-V) shunting and relative hypoxia in peripheral tissues.
Circulating vasodilators which are thought to be involved include glucagon, vasoactive intestinal peptide, nitric oxide and guanosine 3’5’-cyclic monophosphate (cGMP).
Cardiomyopathy may be present and cardiac output may actually be diminished. Right ventricular dysfunction may occur secondary to portopulmonary hypertension. A preoperative ECG and echo is useful in identifying ventricular dysfunction, valvular pathology, pulmonary hypertension and hyperkinesis.

Another important consideration in adults undergoing transplant is the preoperative evaluation for ischaemic heart disease. A study by WD Carey et al in 1995 showed that atherosclerotic coronary artery disease is at least as common in patients with cirrhosis as in patients without liver disease.[9] Dobutamine stress echo (DSE) has been shown to be the preferred preoperative screening study because it assesses the adequacy of myocardial oxygen supply, valvular function, and the presence of intrapulmonary shunting or portopulmonary hypertension. This test has a 92–97% negative predictive value. A negative DSE predicts a good prognosis during orthotopic liver transplantation (OLT), that is, a low likelihood of perioperative cardiac events. The presence of coronary artery disease is associated with high mortality and morbidity during OLT, making DSE screening a routine preoperative test for adult transplant candidates in most centres.

Haematological System[5,8]

a) Thrombocytopenia due to portal hypertension-induced splenic sequestration and alcohol or sepsis induced bone marrow suppression is common. DIC (consumption) also may lead to low platelet counts.
b) Anaemia- normally occurs as a result of chronic disease, malnutrition, or bleeding.

Hepatic Synthetic Function[3,4,6,18]

Plasma concentrations of albumin, plasma cholinesterase and coagulation proteins are decreased in patients with liver disease(decreased synthesis

and dilutional effect from increased volume of distribution and blood volume).

a) Haemostatic abnormalities in patients with liver disease [3]
In patients with liver disease, impaired haemostasis reflects decreased production of clotting factors because of hepatic synthetic dysfunction and, in some cirrhotics, depletion of vitamin K stores(clotting factors II, VII, IX and X) due to malnutrition or decreased intestinal absorption. Increased fibrinolytic activity with laboratory features of mild disseminated intravascular coagulation are also frequent in patients with cirrhosis. Pre-operative coagulation abnormalities seem to be poorly correlated with intraoperative bleeding, their systematic correction before surgery is questionable. In fulminant hepatic failure, coagulation disorders are normally profound and the decision to correct coagulation factors is debatable. In patients with end stage chronic liver disease, no special preoperative coagulation management is necessary in the absence of bleeding.Severe deficiencies in antithrombin III as well as the anticoagulant proteins C and S occur, which may result in life-threatening intravascular thromboses.

Haemostatic abnormalities in patients with liver disease

- Hypocoagulability and coagulation activation Impaired synthesis of coagulation factors (except factor VIII, Von Willebrand Factor)
  Hypofibrinogenaemia occurs in the terminal stages of liver failure
  Impaired synthesis of coagulation inhibitors
  Synthesis of abnormal clotting proteins(dysfibrinogenaemia)
  Insufficient clearance of activated and degraded clotting products
  Vitamin K deficiency
- Enhanced fibrinolytic activity
  Increased levels of circulating t-PA activity(impaired hepatic clearance, secondary to coagulation activation, induced by portal hypertension)
  Diminished synthesis of fibrinolysis inhibitors(alpha 2 antiplasmin, PAI-1)
- Quantitative and qualitative platelet defects
  Increased splenic pooling
  Accelerated immune mediated platelet destruction
  Thrombin dependent platelet consumption
  Defective bone marrow destruction
  Disturbed platelet vessel wall interaction

b) Albumin
Hypoalbuminaemia contributes to low serum oncotic pressure which predisposes to intravascular hypovolaemia, interstitial oedema, ascites and pleural effusions. Drug protein binding is also affected.

c) Pseudocholinesterase
Plasma cholinesterase concentrations are lower due to decreased production, however this enzyme is normally produced in relative excess such that even patients with severe hepatic dysfunction have only mild prolongation of neuromuscular blockade after the administration of suxamethonium.

d) Metabolic dysfunction
Glucose metabolism - Diminished hepatic glycogen stores as well as impaired gluconeogenesis in patients with liver disease may result in severe hypoglycaemia. Hence high dose IV glucose infusions must be continued during patient transport as well as intraoperatively, and blood glucose concentrations should be measured frequently during surgery.
Ammonia - is produced by deamination of amino acids and other organic amines and is converted to urea by the liver. The blood urea nitrogen level may therefore be low in patients with endstage liver disease, whereas the ammonia concentration may be markedly elevated. Ammonia itself is neurotoxic and its accumulation in the blood is associated with hepatic encephalopathy.

Hepatic Blood Flow and Hepatic Drug Metabolism[3]

Drug elimination half-life is a function of clearance and volume of distribution. Endstage liver disease results in diminished hepatic drug clearance due to reduced hepatic blood flow and hepatic extraction ratio. Clearance of drugs with a high hepatic extraction ratio is diminished when hepatic blood flow is compromised. Such drugs include opioids, propranolol and isoproterenol. Drugs with a low hepatic extraction ratio will have decreased clearance when hepatic enzyme activity is diminished and are relatively less affected by changes in hepatic blood flow. Such drugs include barbiturates and phenytoin.

Hepatic Clearance of Commonly Used Drugs[3]

Group	Description	Kinetic effects	Examples
1	Drugs with high hepatic extraction rates	Decreased clearance 2° to decreased blood flow	Midazolam Morphine Labetolol
2	Drugs with low hepatic extraction rates	Decreased clearance 2° to decreased enzyme activity	Thiopentone Theophylline
3	Drugs sensitive to both decreased hepatic blood flow and decreased enzyme activity	Decreased clearance	Alfentanil Pethidine
4	Drugs sensitive to decreased protein binding and decreased enzyme activity	Decreased clearance	Phenytoin Lorazepam Diazepam

INTRAOPERATIVE MANAGEMENT [3,4,5,6,10,11]

Preoperative Preparation

- Organisation of an anaesthesia team that is experienced and prepared to handle the transplant and any other subsequent operation, at a short notice, is vital.
- An efficient Blood Bank service is a pivotal part of the transplant programme. Not only are they involved with the acquisition and provision of safe blood and blood components, but also in the laboratory testing of donor and recipient. Blood bank services should have sufficient packed cells/whole blood/platelets/cryoprecipitate and FFP`s in stock. Some centres recommend up to 24 units of each be available per transplant case with a minimum of 2-10 units immediately available in theatre.
- Lab services should be immediately available for blood sampling of ABG`s and coagulation studies including platelet count, TEG, PT, APTT, etc.
- Preparation of the operating theatre which includes the following:

Warm room to 21-26 °C (Paediatric cases)
Fluid warming devices
Airway humidifier
Forced air warming device (e.g. Bair Hugger)
Rapid fluid infusion systems, including pressurised devices
Availability of blood and blood components in OT
Blood salvaging devices eg cell saver
Antibiotics prepared
Drugs: epinephrine, atropine, calcium, dextrose, insulin, lignocaine
Transoesophageal echocardiography/cardiac output monitoring
Transducers for invasive haemodynamic monitoring(CVP/A-line)

Almost all liver transplants are done in an orthotopic fashion, where the native liver is removed and the new liver is placed in the same anatomic location. The large majority of liver transplants use the entire liver from a non-living donor for the transplant, particularly for adult recipients. Organ preservation with the University of Wisconsin (UW) solution in the late 1980s was a major advance. It allowed a longer cold ischaemia time which extrapolated to the ability to procure the donor organ from distances greater than could previously be achieved. It reduced the urgency of the recipient hepatectomy and engraftment and permitted the development of a number of innovative surgical strategies.

A major advance in paediatric liver transplantation was the development of reduced size liver transplantation, in which a portion of an adult liver is used for an infant or small child. Further developments in this area included split liver transplantation, in which one liver is used for transplants for two recipients, and living donor liver transplantation (LDLT), in which a portion of a healthy person's liver is removed and used as the allograft.

When there is a possibility that the afflicted liver may recover, a heterotopic transplantation is performed. The donor liver is placed in a different site, but it still has to the same connections. It is usually attached near the original liver, and if the original liver recovers, the donor will undergo atrophy or vice versa.

Induction of Anaesthesia[3,5,6,10,14]

The patient should only be transported to the operating theatre once the donor organ has been harvested and deemed suitable for transplantation. Standard monitoring equipment should be applied and peripheral venous access secured for induction. Invasive haemodynamic monitoring maybe applied before or after induction, depending on the cardiovascular status of the patient.

Issues to bare in mind at induction include:

- An increased risk of pulmonary aspiration. This is due to delayed gastric emptying, increased intra abdominal pressure from ascites and the emergent nature of the operation. Therefore, cricoid pressure should be applied in all cases during induction of anaesthesia and endotracheal tube ETT placement. In the absence of specific contraindications this may be achieved using succinylcholine (1-2 mg/kg). As pointed out earlier these patients have decreased levels of pseudocholinesterase leading to a prolongation in the duration of action of suxamethonium.
- All ETT should be placed orally. Nasotracheal intubation is contraindicated as it may cause bleeding, especially in the presence of coagulopathy and/or thrombocytopaenia. In addition, patients may require mechanical ventilation for a prolonged period following surgery and the use of immunosuppressive agents in patients with nasal tubes increases the risk of sinus infections.
- Appropriate tracheal tube size and positioning are especially important in infants and children undergoing LT. Placement of an uncuffed tracheal tube of insufficient diameter may result in inadequate alveolar ventilation, especially as chest compliance may be diminished during and after surgery. Chest compliance is reduced by upper abdominal retraction, tissue oedema of the lung parenchyma and chest wall, and placement of a large liver graft. The tube should be positioned at least 2 cm proximal to the carina in order to prevent accidental entry of the tip into the right mainstem bronchus. This may occur due to cephalad displacement of the carina associated with upper abdominal retraction or placement of a liver graft which is large relative to the patient's abdominal cavity.
- The effects of intravenous induction agents. Alterations in hepatic drug metabolising capacity in patients with liver disease will influence the rate of elimination but not the duration of action after a single IV injection.

  Thiopentone - The clearance of thiopentone maybe increased in patients with mild to moderate alcoholic cirrhosis(secondary to increased free fraction and enzyme induction) or decreased in patients with advanced cirrhosis(secondary to decreased hepatic oxidative capacity).

  Etomidate – is hydrolysed in the liver and the volume of distribution is large, leading to a long elimination half life.

  Ketamine- is highly extracted by the liver and not significantly bound to albumin leading to a variable clearance depending on the degree of synthetic liver function.

  Propofol -is an excellent choice in patients with liver disease, because it retains a short half-life even in patients with decompensated cirrhosis. Metabolites of propofol have been identified in the urine, after a single intravenous injection during the anhepatic phase of OLT, in keeping with the belief that propofol undergoes extra hepatic metabolism.
- Once induction is complete and the patient put on to maintenance anaesthetic agents, invasive monitoring lines maybe inserted. In some institutions this includes use of a pulmonary artery catheter(PAC), other institutions have moved away from PAC and use transoesophageal echocardiography(TOE) or other cardiac output monitoring devices. No studies to date are available to evaluate the outcome in patients undergoing OLT relating to the perioperative use of a PAC, and would be unlikely to be adequately powered given the number of procedures being undertaken. Nevertheless, the general lack of overall benefit in critically ill patients, does not form an encouraging picture for PAC efficacy in OLT.

  TOE provides real time monitoring of ventricular filling and contractile function. This information may guide the administration of i.v. fluids as well as inotropic drugs. In addition, intracardiac air or microthrombi may be observed during dissection or hepatic reperfusion. Pulmonary embolism of air or microthrombi may cause acute elevation of right ventricular and right atrial pressures.
- ICP monitoring may be indicated in patients with fulminant hepatic failure and severe encephalopathy and is initiated in the intensive care unit to determine the need for and assess response to such therapies as hyperventilation, osmotic diuresis and barbiturate administration. Persistence of increased ICP and reduced cerebral perfusion pressures despite such therapies may preclude LT, particularly because ICP has been shown to increase following reperfusion of the liver graft.
- Also 2-3 large bore peripheral and central IV access should be obtained. Sites designated for venovenous bypass are avoided. A rapid infusion system capable of high transfusion flow rates (500–1500 mL/min) is typically used. Such systems incorporate a reservoir, pump, filters, heat exchanger, and safety features designed to avoid and monitor for the presence of blood or air embolism, hypothermia, and line occlusion.

Comparison of the Pulmonary Artery Catheter against Transoesophageal Echocardiography[14]

	PAC	TOE
Accuracy	Good. Traditionally considered gold standard. Possibly inaccurate immediately after caval clamping and reperfusion	Good, but requires training and time to estimate left ventricular filling pressures and cardiac output numerically. "Global" visual assessment and very rapid
Precision	Good	Good, but relies on good view acquisition
Rapid response time/ Continuous data	PA pressure reading continuous andrapidly updated.Cardiac outputcalculation slow (intermittent thermodilution) and not continuous. (Continuous CO PAC equipment available)	Real time views continuously updated.Computer driven algorithms permit rapid calculation of pressure gradients and cardiac output. Dynamic appearance of cardiac structures instantaneous
"Real Time" updating	Poor	Excellent
Reproducibility	Good	Good
Maximal information	Limited to numerical measurement and calculated parameters Wedge pressure used to imply LVEDP can be misleading Pressure potentially a poor surrogate for filling or wall tension	No direct pressure measurements, but able to directly visualise structural as well as dynamic abnormalities. Filling represented visually and calculations possible to derive volume, cardiac output and other parameters Pulmonary artery pressure difficult to assess in absence of tricuspid regurgitation
Risk to patient	Risks associated with venous cannulation, catheter flotation and wedging of PAC.	Low risk. Relatively non-invasive.
Cost	Monitors integrated into standard monitoring equipment. Moderate unit cost of PAC	High set up cost, low unit cost. (cleaning of probe and protective sheath)

MAINTENANCE OF ANAESTHESIA [3,5,6,8,10,12,13]

A balanced anaesthetic is used which typically consists of a volatile agent in low to moderate concentrations (0.5–1.0 minimum alveolar concentration [MAC]) to ensure unconsciousness, while an opioid, usually fentanyl, is chosen to blunt the sympathetic response to stimulation and a benzodiazepine for its amnestic properties.

An important factor during surgery is maintenance of blood flow to the liver, which is especially crucial once the new allograft has been transplanted, hence the volatile agent of choice is very important. Historically, the volatile agent of choice has been isoflurane, which preserves splanchnic blood flow better than other volatile drugs. A study[13] in healthy humans has confirmed the vasodilator effects of isoflurane on the hepatic circulation, compared with the vasoconstrictor effects of halothane. This beneficial effect on hepatic oxygen supply may be advantageous to the newly reperfused graft. The effects of desflurane on hepatic blood flow have been evaluated with conflicting results. Nitrous oxide should be avoided, in order to minimize gaseous distension of the bowel as well as to avoid its effect on expansion of venous air emboli which may occur during the procedure.

Additional factors that may contribute to decreased hepatic blood flow intraoperatively include hypotension, hemorrhage, and vasoactive drugs. Intermittent positive pressure ventilation mechanically decreases hepatic blood flow. In addition, traction on the abdominal viscera may cause reflex dilatation of splanchnic capacitance vessels and thereby lower hepatic blood flow.

Opiods such as morphine and pethidine have a prolonged half-life and increased bioavailability, whereas fentanyl, sufentanil and remifentanil clearance is unaffected. Benzodiazepines are often used to supplement the anaesthetic. Midazolam, with its minimal hemodynamic effects, may be useful for its amnesiac effects during periods of hypotension. However slower metabolism of midazolam can lead to accumulation and prolonged clinical effects.

The neuromuscular blocking agents vecuronium and rocuronium are degraded by the hepatic system exclusively. Atracurium and cisatracurium are metabolized independent of the liver and are therefore preferred in patients with liver disease. In patients with end-stage liver disease, the volume of distribution of cisatracurium is greater than that in healthy control patients. Hepatic clearance is also increased in patients with liver disease;

this results in similar elimination half times and similar duration of action (time to 25% recovery). Other reports have suggested the use of rocuronium during liver transplantation because the duration of the neuromuscular block appears to be a useful predictor of primary allograft function. All patients whose recovery time was > 150 minutes experienced primary graft dysfunction.[5]

Plasma cholinesterase levels are decreased in severe liver disease, possibly resulting in the observed prolonged duration of mivacurium.

The transplant operation can be conceptualized as consisting of three phases:

1. hepatectomy (liver removal, pre-anhepatic) phase,
2. anhepatic (no liver) phase, and
3. post implantation(post anhepatic) phase.

PRE-ANHEPATIC PHASE

The pre-anhepatic stage begins with surgical incision and ends with cross-clamping of the portal vein, the suprahepatic inferior vena cava(IVC), the infrahepatic IVC, and the hepatic artery. This phase involves dissection and mobilization of the liver and identification of the porta hepatis.

Hypotension is initially due to drainage of ascites, resulting in hypovolemia. Hypovolemia should be treated in an anticipatory fashion with colloid-containing fluid to minimize changes in preload. Bleeding is an ongoing problem throughout the procedure. Bleeding during this phase of surgery is related to the degree of preexisting coagulopathy, the presence and severity of portal hypertension, and the duration and complexity of the surgical procedure . The presence and severity of adhesions from previous abdominal surgery may add significantly to the complexity of the surgical dissection.

ANHEPATIC PHASE

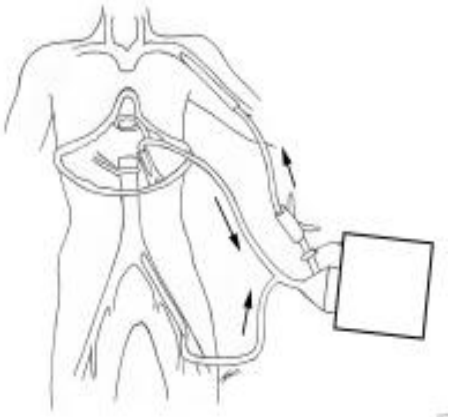
The second, or anhepatic stage, begins with devascularization of the liver and is completed when the IVC and portal vein clamps are removed and the transplanted liver is perfused, with or without unclamping of the hepatic artery.

Cross-clamping of the suprahepatic and infrahepatic vena cava (IVC) decreases venous return by as much as 50%. Venovenous bypass(VVB) maybe implemented for this stage of the procedure.

VENOVENOUS BYPASS (VVB) [20,21,22]

This involves the extracorporeal circulation of blood from the venous system below the caval clamps (inferiormesenteric and femoral veins) and return to the central veins (axillary or internal jugular veins) via a centrifugal pump and heparin bonded tubing. The use of VVB is an established practice in liver transplantation surgery, although it remains a controversial issue. Currently there is a trend to reduce its use to carefully selected indications, while many centres continue to use it routinely and others not at all.

Access to the central veins may be obtained by percutaneous cannulation or surgical cutdown with both procedures having the potential for serious complications. In a recent retrospective study of 312 cases for OLT, where percutaneous VVB was used; 5 patients had serious life threatening complications from line insertion which required urgent sternotomy/thoracotomy, of which one patient demised.



Venous Bypass

Clamping of the IVC results in the loss of venous return from the lower part of the body, and this causes a sudden and profound decrease in central

venous and pulmonary capillary wedge pressures and cardiac output (CO). The degree of cardiovascular instability depends on the extent of collateral circulation and the underlying cardiovascular reserve. The natural collateral veins (azygous, epidural,and superficial abdominal veins) are limited in their ability to increase flow. Cross-clamping of IVC typically results in a 50% reduction of cardiac index, but mean arterial pressure (MAP) is generally relatively well maintained because of the compensatory increase in systemic vascular resistance (SVR) and moderate increase in heart rate, however, there is wide variability in these responses. The majority of patients will tolerate IVC clamping for a period of about one hour. Beyond this period, decompensation becomes increasingly apparent with a fall in mixed venous oxygen saturation and MAP. Patients with cirrhosis generally tolerate portal vein clamping well due to the presence of enlarged portosystemic collaterals around the gastrooesophageal and splenic areas, which limits the fall in CO.

Indications for VVB

- *Hemodynamic Instability Following Test Clamping*.Hemodynamic instability following test clamping of IVC is the most common indication for initiating VVB in many centers, although the criteria used vary among centres. Veroli et al. suggested that hypotension(>30% decrease in MAP) or a decrease in cardiac index (>50%) during a 5-minute test period of hepatic vascular occlusion can be used to identify the group of patients who require VVB. A reduction in CO (of greater than 50%) during the anhepatic phase has been shown to be associated with an increased perioperative morbidity and mortality.
- *Impaired Cardiac Function.* Presence of pulmonary hypertension, impaired ventricular function from previous myocardial infarction, ischemic heart disease, and cardiomyopathy.
- *Impaired Renal Function***.** Most centres use VVB in patients with impaired renal function with a view to preventing further damage to the kidneys during the anhepatic phase and to reduce the need for postoperative renal support.
- *Fulminant Liver Failure***.** Many of these patients have cerebral oedema/raised ICP which leads to a compromise in cerebral perfusion pressure(CPP), resulting in neurological deficit. Hence VVB is indicated to maintain CPP.
- *Severe Portal Hypertension***.** The rationale for using VVB in this situation is to reduce portal venous pressure and mesenteric bed congestion associated with venous clamping. Large varices,

particularly those in the retroheptic area, can be associated with severe bleeding and make the hepatectomy extremely difficult. In this situation, early devascularization of the liver with clamping of the caval and portal veins is usually essential, and early institution of VVB may be helpful in these circumstances.

Complications related to VVB

- Vascular access related complications such as pneumothorax, lymphoceles, hematoma formation, air embolism, major vascular injury, nerve injury, and vessel thrombosis.
- Complications associated with extracorporeal circuit which include hypothermia and air and thrombotic pulmonary embolism.

A review article by K Reddy et al showed the following advantages, disadvantages of VVB.

Advantages of VVB
Reduces hemodynamic instability during anhepatic phase
Useful in patients with pulmonary hypertension and cardiomyopathy who tolerate anhepatic period poorly *
Has been shown to maintain intraoperative renal function†
Maintains cerebral perfusion pressure in patients with acute fulminant failure by avoiding rapid swings in blood pressure*
Facilitates difficult surgery and reduces blood loss
Disadvantages of VVB
Does not guarantee normal perfusion of abdominal organs and lower limbs
No evidence that it improves outcome
May worsen postreperfusion syndrome
No evidence that it reduces or prevents the occurrence of postoperative renal failure †
May worsen cerebral oedema following reperfusion of the graft
May potentiate bleeding by causing hemolysis, platelet depletion
Morbidity and mortality associated with its use
*Theoretical benefits.
†Randomized controlled trial.

Despite the absence of hepatic clotting factor production during the anhepatic stage, blood loss is usually limited by vascular clamping of the inflow vessels to the liver. However, fibrinolysis may begin during this stage, caused by an absence of liver-produced plasminogen activator inhibitor,

which results in the unopposed action of tissue plasminogen activator. The use of antifibrinolytics varies among centres.

POST ANHEPATIC PHASE [3,5,10,11,15,16,17]

The onset of this phase is heralded by the unclamping of the portal vein and IVC, with reperfusion of the new liver. The major anaesthetic issue during this phase is that of the so called “postreperfusion syndrome.” The hallmark of the postreperfusion syndrome (PRS) is systemic hypotension with or without pulmonary hypertension occurring within the first 5 minutes after reperfusion of the graft. Other circulatory disturbances include bradycardia, ventricular dysrhythmias, and cardiac arrest. These changes are provoked by the rapid infusion of effluent from the transplanted liver, which is high in potassium and low in pH and temperature. In addition, infusion of air and/or microthrombi into the heart may precipitate acute pulmonary hypertension. The incidence of the `postreperfusion syndrome' maybe reduced by several management strategies as outlined in the table below:

Preparation for Reperfusion[3]
Normalize arterial blood gas tensions
Normalize serum electrolytes
Achieve body temperature >35.5±36.0 °C
Discontinue anaesthetic vapour
Emergency drugs prepared
Blood prepared for transfusions

Some debate also exists on reperfusing the liver initially through the hepatic artery rather than the traditional method of through the portal vein. In a prospective non randomized, observational study which compared cardiovascular stability, acid-base status, and metabolic gas exchange between patients who underwent reperfusion through either the portal vein or hepatic artery the following results were found:

Cardiovascular changes (mean arterial pressure, cardiac output) were similar for both groups, but more epinephrine was administered to the portal-vein group (P = .014). There was a greater increase in $PaCO_2$, after portal reperfusion (median portal vein, 1.01KpA; hepatic artery, 0.29KpA ;P=.015)and a trend toward more severe academia. These observational data may suggest that hepatic arterial reperfusion may be associated with reduced epinephrine requirements and a slower rate of acid release, which could be advantageous in unstable patients. However further studies of the relative merits of each technique are warranted.

Additionally, and most importantly vigorous flushing of the liver with colloid solution followed by retrograde flushing with the recipient's blood by the surgeon prior to reperfusion (`blood flush') reduces the potassium concentration and acid content of the effluent(Flushing has been shown to decrease the incidence of post reperfusion cardiac arrest[16]) Also, the FiO2 should be increased to 1.0 and halogenated anaesthetic agents should be discontinued 3±5 min prior to reperfusion. Epinephrine and atropine should be at hand for treatment of bradycardia. Calcium chloride should also be prepared, and sodium bicarbonate, dextrose and insulin should be readily available to rapidly treat acidaemia and hyperkalaemia.

An observational retrospective study of 1124 patients was undertaken by Xia et al[15], looking at predictors of hyperkalemia in the pre-reperfusion, early post-reperfusion, and late post-reperfusion periods during adult liver transplantation. A total of 47 recipient, donor, intraoperative, and laboratory variables were initially analyzed in univariate analyses.

Results:
Pre-reperfusion 10.2% of patients were found to have hyperkalaemia, and the independent predictors for hyperkalaemia were found to be an increased baseline potassium(K+) and red blood cell transfusion.
In the early post reperfusion period there was a 19.1% incidence of hyperkalaemia with predictors in this period being a higher pre-reperfusion K+ and donation after cardiac death donor.

Late post-reperfusion hyperkalaemia was seen in 7.9% of patients and independent predictors included higher baseline K+, longer warm ischaemia time, longer donor hospital stay, low intraoperative urine output and the use of VVB.

Such information may be used for more targeted pre-emptive interventions in patients who are at risk of developing hyperkalemia during adult OLT.
Other important intraoperative considerations include the use of antibiotics, immunosuppression, cytoprotection, and adequate temperature homeostasis. Prophylactic antibiotics are used frequently and dosed around the operative procedure, which can be quite lengthy. After complete revascularization of the allograft, methylprednisolone (1 g) is administered as immunoinduction.

In addition, prostaglandin E_1 is administered at a rate of 0.3-0.6 mg/kg/h in the post anhepatic portion of the surgery as a hepatic and renal cytoprotective agent, adjusted to blood pressure levels. Finally,

maintenance of temperature is important because it plays a vital role in optimizing the function of the coagulation system. Methods to achieve this include maintenance of room temperature, warm air blankets, fluid warming via the RIS, low fresh gas flow rates, and heat-moisture exchangers. If the venovenous bypass circuit is used, a heating element may be placed in-line.

HAEMOSTATIC DISORDERS AND MANAGEMENT DURING LIVER TRANSPLANT [3,4,5,6,11,18,23,24]

Intraoperative Coagulation Changes

The pre-anhepatic phase does not induce specific changes in the haemostatic profile. Intrinsic haemostatic deficiencies can be worsened by iatrogenic haemodilution. During this stage patients may exhibit enhanced fibrinolytic activity as monitored by TEG.

Hyperfibrinolysis is the most striking abnormality of coagulation in OLT and it occurs late during the anhepatic phase and worsens with revascularisation of the new liver. Frank fibrinolysis with evidence of diffuse bleeding may occur in up to 20% of patients. Fibrinolysis is caused by abrupt increases in tissue plasminogen activator from graft endothelial cell release and the lack of hepatic clearance during the anhepatic period.

Platelet count decreases progressively during the procedure with a nadir at the time of reperfusion. Studies have shown that the transplanted liver plays a major role in thrombocytopaenia either by platelet sequestration, extravasation into space of Disse or phagocytosis by Kuppfer cells. The contribution of the thrombocytopaenia to bleeding is not clear.

Heparin activity may contribute to coagulopathy, which maybe due to a release of exogenous heparin from the graft harvested after donor heparinisation or to endogenous heparin like substances. This effect is normally short lived and does not require treatment in most case. However some OLT recipients may have a greater sensitivity to heparin and may not clear these substances adequately which may support the use of protamine when heparin activity is well documented.

It is important to remember that all these coagulation abnormalities are worsened by haemodilution, hypothermia and acidosis.

Monitoring of Coagulation Status Intraoperatively

Alterations in coagulation must be monitored closely during the intraoperative period to assist in the overall haemodynamic management of these patients and to ensure both timely and effective transfusion of blood products. With such a complex and dynamic process , the optimal means of

monitoring the coagulation system during OLT is still to be determined. Test results must be available quickly to make any meaningful contribution to the rapidly changing haemostatic process. Conventional clotting tests which are used in some centres intraoperatively include prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen concentration and fibrin degradation products. It must be remembered that most of these tests are performed at 37^0C on plasma and not on whole blood, hence neglecting the role of temperature, platelets and red blood cells in the coagulation mechanism. These test results may only be obtainable after a lag time of 35-40min which is deemed too long by many anaesthetists. This has resulted in on site monitoring by TEG or rarely sonoclot in many centres. TEG evaluates the whole process of coagulation and fibrinolysis at 37^0C. TEG may diagnose a quantitative or qualitative platelet dysfunction and fibrinogen deficiency. The TEG has been used effectively during OLT to guide transfusion of coagulation products and subsequently to confirm their effect.

Treatment Options for Haemostatic Dysfunction [5,11,18]

- Blood component transfusion
  This includes fresh frozen plasma(FFP), platelets and fibrinogen concentrates. Guidelines for substitutive therapy are lacking and practices vary widely between institutions. Red blood cells are transfused to maintain a haematocrit around 30%. FFP is given to maintain the prothrombin time below 1.2-1.5 times normal and platelets are kept above $50X10^9$ L^{-1}. TEG based coagulation therapy has also been proposed where administration of a fluid mixture of packed cells, FFP`s, and crystalloids in a ratio of 3:2:2.5 for volume replacement; the infusion of platelets for maximum amplitude less than 40mm; cryoprecipitate for poor clot formation rate and additional FFP for prolonged reaction time(>12min). Those in favour of this TEG based therapy argue that blood requirements decreased significantly compared to controls.

- Pharmacological agents
  Accelerated fibrinolysis is one of the main causes of excessive bleeding during OLT, hence the use of anti-fibrinolytics has been proposed to reduce blood loss and to treat or prevent the occurrence of intraoperative hyperfibrinolytic activity.

  - Aprotinin is a serine protease inhibitor, derived from bovine lung, is widely used to treat and prevent hyperfibrinolysis in OLT. Aprotinin

has to be administered by continuous infusion in order to achieve stable plasma concentrations. It acts as an inhibitor of human trypsin, plamin, plasma kallikrein and tissue kallikreins. The result is the formation of aprotinin-enzyme complexes at the active serine site of the enzyme. Aprotinin has a high affinity for renal tissue and is freely filtered by the glomeruli. There have been reports of renal failure however aprotinin has not shown deleterious effects on renal function in randomised placebo controlled studies. Allergic responses may occur with the administration of this drug due to it being an animal protein.

In studies carried out before 1997, the benefits of antifibrindytic drugs for OLT, typically defined as a decrease in blood loss or transfusion requirements, were not present in prospective, randomized, blinded studies. Nearly all of these studies evaluated aprotinin. In 2001, a randomized, blinded study from the Mayo Clinic showed a decrease in RBC transfusion requirements (median of 5 units versus 7 units) with aprotinin compared with placebo. The European Multicenter Study of Aprotinin in Liver Transplant (EMSALT) also showed a decrease in red blood cell usage with both high dose and regular dose of aprotinin compared with placebo (red blood cell requirements of 1500 mL versus 1750 mL versus 2450 mL, respectively). The authors report no difference in the prevalence of thromboembolic events in the aprotinin groups compared with control group. It was noted that the three patients who developed hepatic artery thromboses occurred in the control group. These three events may have been related to surgical technical issues, whereas the thrombotic events in the aprotinin group (pulmonary emboli, right coronary occlusion) were not. It is unclear whether antifibrinolytic drugs increase the risk of thrombotic events. In a retrospective analysis of 1492 patients S. Mallet et al did not demonstrate an increased risk of thrombotic complications or mortality when aprotinin is used during OLT. (there was a higher incidence of hepatic artey thrombosis and venous thromboembolic events in aprotinin treated patients but this did not reach statistical significance) Fibrinolysis is an unpredictable event, and the risks of treatment are largely unknown.

- Epsilon aminocaproic acid acts by saturating a high affinity lysine binding site of plasminogen, resulting in a delay in fibrinolysis. This drug is cheap and has few adverse effects. Its short half life requires continuous infusion of relatively large doses. Kang and his colleagues reported successful treatment of hyperfibrinolysis assessed on clinical generalised oozing and TEG changes after a bolus dose of 1g.

- Tranexamic acid which is another lysine anologue has also been used in OLT. Benefits of its use have been conflicting. A randomised placebo controlled study in 2000 showed that prophylactic administration of tranexamic acid(10mg/kg/hr) can reduce intraoperative blood requirements.[19]

It is important to remember that the use of antifibrinolytic therapy induces a shift of the haemostatic balance towards coagulation and the risk of thrombotic complications. Thrombosis of the arterial axis of the liver graft is a devastating complication, which normally leads to graft necrosis and death unless an emergency retransplantation can be performed. Some transplant recipients have an increased risk of developing thrombotic complications especially those with cancer and primary biliary cirrhosis. Post operative thrombotic complications have been described with epsilon aminocaproic acid but no increased rate in graft vascular thrombosis has been reported with aprotinin or synthetic anti fibrinolytics. With this in mind the decision to use anti fibrinolytics should be taken on an individual basis.

POSTOPERATIVE CARE [3,5,11,27]

Major considerations in the immediate postoperative period include:

a) Postoperative Bleeding
Significant coagulopathy can be present following hepatic revascularization and as mentioned previously this can be attributed to fibrinolysis, heparin-like effect, thrombocytopenia, and coagulation factor deficiencies. If ongoing bleeding, despite correction of coagulopathy and rewarming of the patient, is suspected especially if hemodynamic instability and oliguria are present, the patient should undergo immediate reoperation to identify and stop the ongoing bleeding. Postoperative bleeding is high in the differential diagnosis of early postoperative hypotension and oliguria.

b) Liver Function
Favourable signs regarding hepatic function in the immediate postoperative period include the following:
1. Hemodynamic stability
2. Awakening from anaesthesia
3. Clearance of lactate
4. Resolution of hypoglycaemia
5. Normalization of coagulation profile (prothrombin time)
6. Resolution of elevated transaminases
7. Good renal function

Causes Of Hepatic Dysfunction after Liver Transplantation

Immediate
1. Primary allograft non-function
2. Primary allograft dysfunction
3. Hepatic artery thrombosis
4. Portal vein thrombosis
5. Hepatic vein and caval thrombosis
6. Biliary tract obstruction or leak

Delayed
1. Rejection
2. Infection
3. Biliary tract obstruction
4. Recurrent disease

Graft dysfunction encompasses a spectrum ranging from mild graft dysfunction, manifested by elevated liver enzymes and poor early hepatic synthetic function, to severe dysfunction, manifested by prolonged synthetic dysfunction, hemodynamic instability, and associated multiorgan dysfunction. If the transaminase levels continue to rise beyond 12 to 24 hours after transplantation, a complete evaluation should be performed, including assessment of mental status, coagulation profile, renal function, and hemodynamic stability.

Severe liver dysfunction or primary non-function must be differentiated from technical vascular complications including hepatic artery thrombosis, portal vein thrombosis, and hepatic congestion secondary to venous outflow obstruction. Preservation injury is generally associated with improving mental status and a stable or improving prothrombin time that is easily correctable. Contrariwise, primary non-function is manifested by progressive deterioration of mental status, a worsening coagulation profile, renal dysfunction, and hemodynamic instability. The treatment of severe hepatic dysfunction is primarily supportive. Intravenous prostaglandin E1 has been shown to be beneficial. In cases of moderate liver dysfunction, the transaminases normalize over time, as do the coagulation parameters, even though these patients become severely cholestatic during the recovery period.Severe graft dysfunction and primary non-function require consideration of urgent retransplantation, whereas mild-to-moderate graft dysfunction requires close observation and supportive therapy.

Signs of Primary Liver Graft Non-function
1. Failure to regain consciousness
2. Hemodynamic instability
3. Poor quality and quantity of bile
4. Increasing prothrombin time
5. Renal dysfunction
6. Rise in serum transaminases and bilirubin
7. Acid-base imbalance
8. Persistent hypothermia

c) Vascular Complications

Hepatic artery thrombosis presents with various liver test abnormalities, including very subtle elevations in the serum transaminases, and may not be diagnosed in the early postoperative period and may manifest later in the postoperative period.

Manifestations of Hepatic Artery Thrombosis after Liver Transplantation
1. Elevation of the serum transaminases and bilirubin
2. Fulminant hepatic failure
3. Sepsis with hepatic abscesses or gangrene of the liver
4. Biliary anastomotic disruption
5. Biliary tract strictures, bile leaks, bilomas

Portal venous thrombosis is uncommon, but can occur in the setting of significant portal vein stenosis or previous portal vein thrombosis in the recipient, especially in the pediatric recipient. Typically, severe elevations in the serum transaminase levels occur early postoperatively. Ascites is a manifestation of delayed portal vein thrombosis. Also, acute portal hypertension manifested by variceal bleeding should alert the clinician to possible acute portal vein thrombosis. In the acute setting, thrombectomy should be attempted to try to save the graft, although retransplantation may be necessary.

Venous outflow obstruction is another postoperative vascular complication which should be considered.

d) Rejection

Acute Rejection

Acute (cellular) hepatic allograft rejection, an attempt by the immune system to attack the transplanted liver and destroy it, can occur in as many as 40% of patients during the first 3 months after transplantation. Acute

rejection normally occurs 7-14 days after the operation but can occur earlier or much later. Hyperacute rejection of the liver, comparable to that observed in kidney transplantation, is controversial and difficult to diagnose, but early accelerated rejection certainly occurs. Liver biopsy may be required to distinguish between rejection and viral infection. Rejection is most commonly manifested by malaise, fever, graft enlargement, and diminished graft function. In patients who have undergone LT, a rise in bilirubin and transaminase levels is observed and T-tube biliary drainage may be thin and lighter in color. Acute rejection most commonly first occurs in the second week after transplantation but can occur earlier. Graft biopsy should be performed, if safe, to document rejection. Adult liver biopsies are routinely performed at the bedside with or without ultrasound guidance.

With early suspicion and detection, most acute rejection episodes can be treated successfully. Characteristic signs and symptoms of rejection include fatigue, fever, abdominal pain or tenderness, jaundice, dark yellow or orange urine, and/or clay-colored stools. In some instances, a patient may not have any symptoms, but his or her liver function test findings may be abnormal, suggesting that rejection is occurring. Rejection episodes are managed sequentially by pulse steroids, OKT3, and/or the use of mycophenolate or a tacrolimus switch if the patient was on cyclosporine. Retransplantation is the last resort when therapy fails and the patient develops hepatic failure.

Chronic Rejection

The characteristics of chronic rejection in recipients of a liver transplant are progressive bile duct disappearance and obliterative arteriopathy, known as ductopenia, and vanishing bile duct syndrome, which results in progressive jaundice and allograft dysfunction. The ducts suffer direct immunological injury and ischemia from the obliterative arteriopathy caused by antibody-mediated intimal damage of hepatic arterioles. In the late phase of chronic rejection, diffuse hepatic fibrosis occurs. Allograft function deteriorates, marked by cholestasis and, ultimately, loss of synthetic function and portal hypertension. Heavy immunosuppression with tacrolimus, mycophenolate mofetil, and/or sirolimus may reverse chronic rejection in the early phases. Advanced chronic rejection is an indication for retransplantation.

Histologic determinants of acute liver graft rejection

1. Portal infiltrate with mixed inflammatory cells
2. Bile duct injury
3. Endothelialitis

Grading of Acute Liver Allograft Rejection–Banff Criteria

Grade	Criteria
I (mild)	Cellular infiltrate in a minority (<50%) of the portal triads, that is generally mild, and confined within the portal spaces
II (moderate)	Cellular infiltrate, expanding most (>50%) or all of the portal triads
III (severe)	As above for moderate, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis

From Demetris AJ, Batts KP, Dhillon AP, et al. Banff schema for grading liver allograft rejection: an international consensus document. Hepatology 1997;25:658–63.

IMMUNOSUPPRESSION [5,11,27,32]

Following transplantation, all patients are placed on immunosuppressive drugs to prevent rejection of the new liver. These medications are usually started in the operating room and are continued thereafter. The dose of the immunosuppression agent needed varies from patient to patient depending on the likelihood of rejection.

Immunosuppression must be balanced carefully against the patient's own immune system. Adjusting the dose specifically for each patient helps avoid the risk of postoperative infections, tumor development, and liver rejection. The dose of immunosuppression agents varies between patients and may vary with time in a particular patient. This explains the requirement of frequent blood drawing, especially early after transplantation, because absorption, metabolism, and dose requirements of these drugs can vary significantly from day to day in the early posttransplant period. As time passes, the amount of immunosuppression needed to prevent organ rejection usually decreases. Immunosuppression therapy is not without risk and must be monitored closely.

Immunosuppression management is based on the following principles:

- The doses used, adjusted over time, should be the minimum necessary to prevent rejection.
- The risk of rejection is highest (40%) during the first 3-6 months after transplantation and decreases significantly thereafter.

- Prolonged use of these medications can have severe and significant adverse effects and toxicities.
- Some disease processes (ie, autoimmune diseases) are more likely to produce rejection; drug levels in these patients should be adjusted accordingly.
- Most medications are metabolized by the liver itself; therefore, graft dysfunction can significantly alter drug levels.
- Other medications added to an immunosuppressive regimen can lead to significant toxicities or to a lack of therapeutic effect and subsequent rejection.

Induction immunosuppression is not commonly used after LT, although the recent introduction of newer IL-2 receptor-blocking antibody preparations, daclizumab and basiliximab.

Maintenance immunosuppression is usually based on a calcineurin inhibitor (ie, cyclosporine A or tacrolimus) and corticosteroids. These may be combined with newer antimetabolite compounds (eg, mycophenolate) or antiproliferative agents (eg, sirolimus, rapamycin) with the goal of decreasing steroid and/or calcineurin inhibitor use. The most important toxicities are related to steroids (eg, osteopenia, diabetes, cushingoid syndromes). Calcineurin inhibitor use is fraught mostly with neurotoxicity and nephrotoxicity. Finally, the antimetabolites can cause cytopenias, and sirolimus (rapamycin) has been associated with poor wound healing, hepatic artery thrombosis, cytopenias, and severe hyperlipidemia.

CONCLUSION

Results of orthotopic liver transplantation(OLT) have steadily improved over the years, but many questions regarding best practices persist. A thorough knowledge of the pathophysiology, intra operative problems and postoperative complications is essential to the anaesthetist. Continuing challenges, include specific indications and contraindications to liver transplantation, the optimum timing of the operation, and the most appropriate use of scarce donor organs.

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