Pediatric Liver Intensive Care

Naresh Shanmugam
Anil Dhawan
Editors

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To my mentors Prof. Anil Dhawan and Prof. Mohamed Rela who inspired me in every aspect of life and made me look beyond the horizon.

Naresh Shanmugam

Preface

Pediatric hepatology has evolved into a distinct subspecialty, and pediatric liver transplant care has become an integral part of it. Intensive care management of children with liver disease requires the coordination of a multidisciplinary team as decisions have to be made regarding the need for transplantation, strategies to be used during transplantation, and post-transplant care. Though there are several standard textbooks available on pediatric hepatology, this manual on *Pediatric Liver Intensive Care* is unique as it is written from an intensivist perspective that helps in the management of common liver problems to complex hepatobiliary/peri-transplant care. This manual has been written in a ready reckoner format that could be used at the bedside. The editors have taken into consideration a wide variety of readers including transplant surgeons and anesthetists who deal with pediatric transplants and have incorporated management protocols, common pediatric drug dosages, etc. for their easy use. The chapters have been written by experienced authors who have both intensive care and pediatric hepatology knowledge from high volume pediatric liver transplant centers. Some of the authors across specialties such as radiology, cardiology, and anesthesia have shared their insights regarding decision-making and management principles from their perspective.

The practical knowledge of the authors in the field of pediatric hepatology is reflected by "practical tips" and "caution alert" provided by them in each chapter. We sincerely hope that this manual would bridge the knowledge gap between various specialists, such as pediatrician, intensivist, metabolic consultant, transplant surgeon, and anesthetist, and help in the management of children with liver disease.

Chennai, India — Naresh Shanmugam
London, UK — Anil Dhawan

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About the Editors

Naresh Shanmugam is a highly qualified pediatric hepatologist and heads the Paediatric Liver, GI and Nutrition unit at Dr. Rela Institute and Medical Centre, Chennai, India. He is also the director of the Institute of Advanced Paediatrics, which specializes in multi-organ transplantation in children. He has worked at King's College Hospital and Chelsea and Westminster Hospital, both in London. His areas of special interest are metabolic liver diseases and liver intensive care. He is a fellow of the Royal College of Paediatrics and Child Health, UK, and alumnus of the University of Surrey, Guildford, Madras Medical College and Research Institute, Chennai, and Stanley Medical College, Chennai. Dr. Shanmugam has written several publications related to pediatric liver diseases.

Anil Dhawan is a consultant in pediatric hepatology at King's College Hospital, London. He is the head of the Liver GI and Nutrition Centre and MowatLabs and the Corporate Medical Director of the Variety Children's Hospital, London. Prof. Dhawan is the founder and head of the Basic Science Laboratories (Mowat Labs) at the Institute of Liver Studies, King's College Hospital, London.

He has held board-level appointments at the European Society of Pediatric Gastroenterology, Hepatology and Nutrition, International Liver Transplantation Society, and Cell Transplantation Society. He was the president of the Cell Transplant and Regenerative Medicine Society. He is on the editorial board of several journals and has published more than 300 peer-reviewed articles in the field of hepatology and hepatocyte transplantation and has edited four textbooks on liver disease in children and hepatocyte transplantation. He is a regular invited speaker at prestigious adult and pediatric liver meetings across the world.

Abbreviations

99mTc-MAA	Technetium-99m-labeled macroaggregated albumin
ABG	Arterial blood gas analysis
ACD	Acid citrate dextrose
ACR	Acute cellular rejection
ADA	Adenosine deaminase
AED	Antiepileptic drug
AGT	Alanine: glyoxylate aminotransferase
AKI	Acute kidney injury
ALF	Acute liver failure
ALT	Alanine aminotransferase
APTR	Activated partial thromboplastin ratio
aPTT	Activated partial thromboplastin time
ASD	Atrial septal defect
ASFA	American Society for Apheresis
ATG	Anti-thymocyte globulin
ATN	Acute tubular necrosis
BA	Biliary atresia
BASM	Biliary atresia splenic malformation
BCAA	Branched chain amino acids
BCKD	Branched chain keto-acid dehydrogenase
BiPAP	Bi-level positive airway pressure
BNP	Brain natriuretic peptide
CBD	Common bile duct
CIT	Cold ischemic time
CLTK	Combined liver and kidney transplants
CNNA	Culture negative neutrocytic ascites
COG	Children Oncology Group
CPM	Central pontine myelinolysis
CPS	Carbamoyl phosphate synthase
CPT	Cryoprecipitate
CRS	Cytokine release syndrome
CT	Computed tomography
CVVH	Continuous veno-venous hemofiltration

CVVHD	Continuous veno-venous hemodiafiltration
DBD	Donation after brain death
DCD	Donation after cardiac death
DEXA	Dual energy X-ray absorptiometry
DIC	Disseminated intravascular coagulopathy
DiSA	Digital subtraction angiography
DO	Drain output
DSA	Donor-specific antibody
DSU	Doppler ultrasound
Dv	Diastolic velocity
ECG	Electrocardiography
ECHO	Echocardiography
ECV	Extracorporeal volume
EF	Ejection fraction
EFAs	Essential fatty acids
EMG	Electromyogram
ESLD	End-stage liver disease
ESPEN	European Society for Clinical Nutrition and Metabolism
EST	Endoscopic sclerotherapy
EVL	Endoscopic variceal ligation
FHVP	Free hepatic venous pressure
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GIR	Glucose infusion rate
GRWR	Graft to recipient weight ratio
HA	Hepatic artery
HAS	Human albumin solution
HASt	Hepatic arterial stenosis
HAT	Hepatic artery thrombosis
HB	Hepatoblastoma
HCC	Hepatocellular carcinoma
HD	Hemodialysis
HE	Hepatic encephalopathy
HME	Heat moisture exchange
HOGA1	4-Hydroxy-2-oxoglutarate aldolase
HPS	Hepatopulmonary syndrome
HR	High-risk
HRS	Hepatorenal syndrome
HV	Hepatic veins
HVPG	Hepatic venous pressure gradient
ICA-AKI	International Club of Ascites–Acute Kidney Injury
ICP	Intracranial pressure
IMV	Inferior mesenteric vein
INR	International normalized ratio

KT	Kidney transplant
LAI	Liver Attenuation Index
LB	Liver biopsy
LCT	Long chain triglyceride
LDH	Lactate dehydrogenase
LDLT	Living donor liver transplantation
LOLA	L-ornithine L-aspartate
LPV	Left portal vein
LT	Liver transplantation
MAC	Mid-arm circumference
MB	Methylene blue
MCT	Medium chain triglyceride
MDT	Multidisciplinary team
MFD	Minimal fat diet
MHV	Middle hepatic vein
MMA	Methylmalonic acidemia
MMF	Mycophenolate mofetil
MNB	Monobacterial non-neutrocytic ascites
MRI	Magnetic resonance imaging
MSBOS	Maximum surgical blood ordering schedule
NAGS	*s*-acetyl glutamate synthase
NIV	Noninvasive ventilation
OGD	Esophagogastroduodenoscopy
OLT	Orthotopic liver transplantation
ORS	Oral rehydration solution
OTC	Ornithine transcarbamylase
PA	Propionic acidemia
PD	Peritoneal dialysis
PDA	Patent ductus arteriosus
PH	Primary hyperoxaluria
PHT	Portal hypertension
PI	Pulsatility index
PNF	Primary nonfunction
POD	Postoperative day
POPH	Portopulmonary syndrome
PPHT	Portopulmonary hypertension
PRES	Posterior reversible encephalopathy syndrome
PRETEXT	Presurgical pretreatment extent of disease
PSv	Peak systolic velocity
PT	Prothrombin time
PTBD	Percutaneous transhepatic balloon dilation
PV	Portal vein
PVT	Portal vein thrombosis
RDP	Random donor platelets
REE	Resting energy expenditure

RI	Resistive index
ROTEM	Rotational thromboelastography
RPF	Renal plasma flow
RRT	Renal replacement therapy
SAAG	Serum-ascites albumin gradient
SB	Sengstaken–Blakemore
SBP	Spontaneous bacterial peritonitis
SDP	Single donor platelets
SD-SST	Standard dose-short synacthen test
SIOPEL	Société Internationale d'Oncologie Pédiatrique–Epithelial Liver Tumor Study Group
SNS	Sympathetic nervous system
SR	Standard risk
SR	Sustained release
TEE	Total energy expenditure
TEG	Thromboelastogram
TEG	Thromboelastography
TIBC	Total iron-binding capacity
TIPS	Transjugular intrahepatic portosystemic shunt
TJ	Transjugular
tLPV	Transverse portion
TPE	Therapeutic plasma exchange
TST	Triceps skinfold thickness
TT	Tracheostomy tubes
UO	Urine output
USG	Ultrasonography
VAP	Ventilator-associated pneumonia
VSD	Ventricular septal defect
WHVP	Wedged hepatic venous pressure
WIT	Warm ischemic time

Liver Anatomy for Pediatric Intensivist

1

Mettu Srinivas Reddy

Children have a larger liver in relation to their body weight as compared to adults. While the liver to body weight ratio in adults is around 2%, it is around 4% in infants. The segmental anatomy in children is very similar to that in adults.

1.1 Attachments of the Liver

The liver is located in the right subphrenic space and kept in position through its attachment to the cava and the peritoneal folds or ligaments which continue as the Glisson's capsule over the surface of the liver and parietal peritoneum on the abdominal cavity. These ligaments are usually thin and avascular in the healthy state. Dividing these ligaments is the initial step in any major liver surgery or liver transplantation.

1.2 Vascular and Biliary Anatomy

The vascular anatomy of the liver in children is every similar to that in adults.

- The common hepatic artery arises as a branch of the coeliac artery and proceeds to the liver after giving the gastroduodenal artery.
- The portal vein is formed by the confluence of the superior mesenteric vein and the splenic vein.
- Both these structures enter the liver at the hilum after passing through the left edge of the gastrohepatic ligament.

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- The bile duct, formed by the confluence of the right and left hepatic ducts at the hilum, courses through the free edge of the gastrohepatic ligament, anterior to the portal vein and to the right of the common hepatic artery. It receives the cystic duct from the gallbladder en route before joining the medial side of the second part of the duodenum.
- The liver is drained by the left middle and right hepatic veins, which drain into the anterior surface of the IVC just before it pierces the central tendon of the diaphragm to join the right atrium. In addition, a variable number of smaller veins may be present draining the caudate lobe and parts of the posterior segments (segments 6 and 7) directly into the IVC.

1.3 Segmental Anatomy

The liver is divided internally into segments each supplied by its own portal radical and hepatic artery branch and a segmental bile duct, with adjacent segments separated by hepatic veins.

- There are eight segments organized into two lobes—the left lobe containing segments 2, 3, and 4 and the right lobe containing segments 5, 6, 7, and 8 (Fig. 1.1; Table 1.1).
- There is no surface landmark for the right and left lobes; the Cantlie's line, which separates the left and right lobes, extends from the base of the gallbladder to the right border of MHV.
- Segment 1 or caudate lobe is unique as it has blood supply from both left and right sides and drains into the cava via multiple short caudate veins.

1.4 Changes in Cholestatic Liver Disease

Cholestatic liver disease is the most common liver disease in children. The liver is grossly enlarged and hard in consistency.

- Portal hypertension can lead to splenomegaly and enlarged collateral veins around the gastroesophageal junction, lesser sac, retroperitoneum, and anterior abdominal wall.
- The peritoneal ligaments supporting the liver become highly vascularized and can house large collateral vessels. These can present with problematic bleeding during surgery and should be carefully divided with diathermy or ligation.
- The hepatic artery hypertrophies as it attempts to perfuse a stiff liver with arterialised blood and the portal vein becomes thick walled due to the high portal pressure.
- In biliary atresia, the early onset of cholestasis and inflammation results in atretic changes in the portal vein including complete thrombosis. Hepatic artery in these cases may be larger than the portal vein itself. Other changes in biliary atresia

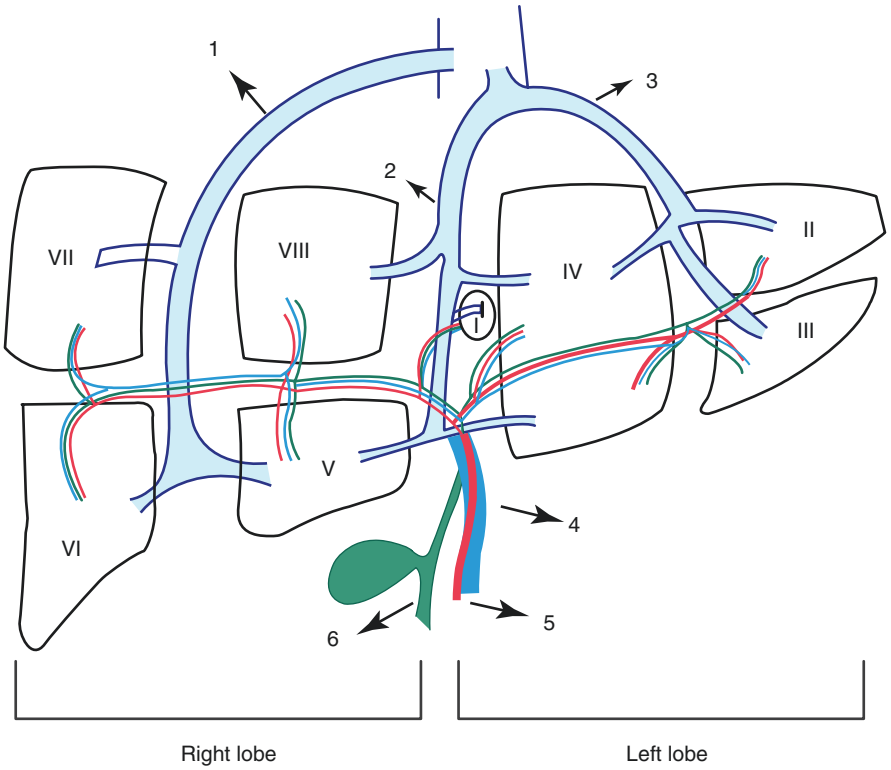

Fig. 1.1 Schematic diagram of the liver showing eight segments: segments I (caudate lobe), II, III, and IV form the left lobe, and segments V, VI, VII, and VIII form the right lobe. (1) Right hepatic vein, (2) middle hepatic vein, (3) left hepatic vein, (4) portal vein, (5) hepatic vein, and (6) common bile duct

Table 1.1 Couinaud classification of the liver

Right lobe		Left lobe	
Right posterior section	Right anterior section	Left medial section	Left lateral section
Segments 6 and 7	Segments 5 and 8	Segment 4	Segments 2 and 3

include the absence of the biliary tree and the gallbladder, large cystic spaces containing bile-stained fluid in the hilum, and large lymph nodes around the hepatic artery.

- Children with congenital liver disease have a higher incidence of malformations involving other organs. These can be minor such as polysplenia or major such as caval malformations, gut malrotation, and situs inversus.
- A detailed assessment of the liver and abdominal anatomy on a CT scan or MRI is essential for planning major liver surgery or liver transplantation.

1.5 Anatomy of the Left Lateral Segment of the Liver

Liver transplantation in children usually involves transplanting a part of an adult liver as size-matched pediatric deceased donors for whole liver transplant are very uncommon. The aim is to provide a graft size around 2–4% of body weight. Transplanting larger grafts can cause graft compression, portal vein thrombosis, and difficulties in wound closure.

The adult left lateral segment is the most common graft used in pediatric liver transplantation. This includes segments 2 and 3 and forms around 25% of total liver volume. The adult LLS weighs 200–250 g and is suitable for children weighing 5–20 kg. Smaller children will need further reduction of this graft, while larger children may need a left lobe or right lobe graft.

The LLS can be obtained by splitting an adult deceased donor liver or can be retrieved from a live donor by standard left lateral segmentectomy.

1.6 External landmarks of Left Lateral Segment

Left lateral segment is externally demarcated from the rest of the liver anterosuperiorly by the attachment of the falciform ligament. This ligament identifies the separation between segment 4 on the right and segments 2 and 3 on the left. Inferiorly, the LLS is demarcated by the insertion of the ligamentum teres. This contains the left umbilical vein which attaches to the left portal vein again separating segments 3 and 4. The ligamentum venosum arising from the left portal vein then passes along the groove separating the caudate lobe from left lateral segment before joining the left hepatic vein.

1.7 Vascular and Biliary Anatomy of Left Lateral Segment

Left hepatic artery originates from the common hepatic artery usually beyond the origin of the GDA. It reached the hilum and then enters the Rex recess to supply segments 2, 3 and 4. It may give a separate middle hepatic artery to segment 4 and an artery to the caudate lobe before it enters the Rex recess. In 15% of patients, the left hepatic artery is replaced and arises as a branch of the left gastric artery. In these cases, the LHA arises from the LGA along the lesser curve of the stomach and travels to the Rex recess through the gastrohepatic ligament.

Left portal vein (LPV) arises as a branch from the main portal vein high in the hilum. The LPV has two parts, a transverse portion (tLPV), where it travels along the inferior border of segment 4, and an umbilical portion, where the LPV turns into the umbilical fissure and travels from posterior to anterior giving branches to segments 2, 3, and 4.

The left hepatic vein is formed by the confluence of segment 2 and 3 veins. It joins the IVC either separately or after joining with the MHV. Occasionally a small superficial segment 2 vein joins the LHV late in its course just prior to the IVC confluence. Similarly, a marginal vein may be present draining part of segment 4 and joining the LHV just prior to its confluence with the IVC.

Left hepatic duct is formed by the confluence of segment 2 and 3 ducts. The segment 4 duct joins it prior to the former's confluence with the right hepatic duct to form the common hepatic duct. The distance of the segment 2 and 3 duct confluence and the CHD origin is variable. Occasionally, segment 4 and segment 3 ducts can form a single duct and then join segment 2 duct close to or at the CHD confluence.

1.8 Donor Surgery

Left lateral segment donation involves careful identification and dissection of the left hepatic structures while confirming safe preservation of the right-sided structures. Transection of hepatic parenchyma is usually carried out 1 cm to the right of falciform ligament, through segment 4 and finally division of the left hepatic vein away from the MHV trunk. The segment 4 pedicles are carefully ligated or transfixed to prevent bile leaks from the graft or the remnant right lobe. Similarly special care should be taken to identify any caudate ducts arising from the left hepatic duct and suture them, as these can be a source of troubling postoperative bile leaks.

Ischemia of segment 4 is inevitable after left lateral segment donation, unless the segment 4 artery arises separately from the CHA or the RHA and is preserved. However, this presents only as transient transaminitis and does not need any further intervention.

In the deceased donor setting, the whole liver can be split into the left lateral segment and extended right lobe by in situ techniques or bench surgery. In situ split is similar to live donor surgery and is performed before aortic cross-clamp. This reduces cold ischemia time. Bench split is performed on the back table after whole liver recovery. This is logistically easier if the donor hospital is at a distance from the transplant center and may not have the equipment and/or personnel to perform in situ splitting.

1.9 Graft Size Reduction

A standard LLS graft may not fit into the abdominal cavity of very small children (<5 kg). Graft reduction is necessary in such cases. Graft reduction can be nonanatomical where parenchyma from the margins of the graft is resected to reduce the volume or anatomical where resection proceeds along anatomical planes to produce a monosegment (segment 2 or 3) graft. The latter provides greater reduction in graft size and is the preferred approach in neonates and very small infants.

Acute Liver Failure in Children: Intensive Care Management Protocol

2

Naresh Shanmugam and Anil Dhawan

2.1 Definition

The practical definition of acute liver failure (ALF) suggested by the Pediatric Acute Liver Failure study group is "coagulopathy with INR $\geq$ 1.5 with encephalopathy or INR $\geq$ 2 without encephalopathy due to a liver cause, not correctable by intravenous vitamin K, along with biochemical evidence of acute liver injury."

Approach to children with biochemical evidence of liver injury is outlined in Fig. 2.1.

2.2 Transfer to a Transplant Center

INR is used as surrogate marker for prognosis. Infectious hepatitis is the common cause of ALF in developing countries but rarely needs transplantation. If there is a progressive worsening of INR, these children would require hospitalization and transfer to higher center.

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Tips

Ultrasonography (USG) of the abdomen showing coarse liver with or without enlarged spleen hints toward chronic diseases that have presented acutely. The classical examples of chronic liver disease presenting as ALF in children are acute fulminant Wilson and autoimmune liver disease. These diseases are refractory to medical management when present as ALF and would require liver transplantation.

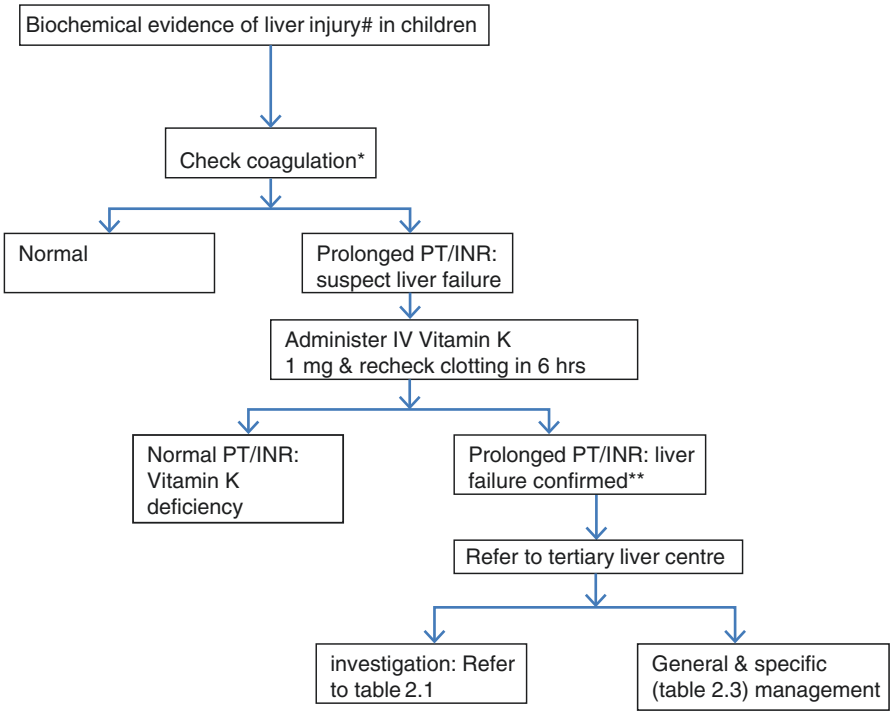

Fig. 2.1 Approach to children with biochemical evidence of liver injury (Reproduced with permission from Shanmugam et al. Neonatal liver failure: aetiologies and management—state of the art. Eur J Pediatr. 2011 May;170(5):573–81). #raised alanine aminotransferase (ALT), bilirubin, gamma-glutamyltransferase (GGT). *Check prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin ratio (APTR), fibrinogen, and d-dimers. Isolated prolonged APTR is not due to liver disease. In disseminated intravascular coagulopathy (DIC), there will be low fibrinogen levels and increased d-dimers. **INR $\geq$ 1.5 with encephalopathy or INR $\geq$ 2.0 regardless of the presence or absence of encephalopathy

2.3 Transport

- The aim of transporting a child with ALF is to ensure safe and timely transfer to a higher center, preferably with liver transplant facilities before onset of encephalopathy.
- Encephalopathy is a late sign in children, and once it sets in, it is associated with high mortality and morbidity.
- Any child with ALF who has worsening of coagulopathy or develops encephalopathy should be transferred.
- Any child who has grade III or IV encephalopathy should be intubated and airway secured before transport.
- A continuous monitoring of heart rate, rhythm, pulse oximetry and blood pressure should be available.
- Facilities for infusion of vasoactive drugs, with spare supplies, should be available during transport. Well-secured vascular access must be assured prior to the transfer (at least two wide bore cannula must be kept).
- In developing countries majority of LT are from live donors due to nonavailability of cadaver organs in emergency. Transfer of these children to transplant center should be initiated at the earliest, as the patients have to arrange altruistic live donor and finances, which could cause considerable delay.

Tips

Arrange early transfer and do not wait until these children fulfill LT criteria. When they fulfill the LT criteria, they might be unstable for transfer due to multi-organ involvement.

2.4 General Measures

- Close monitoring in quiet setting.
- Vital parameters such as saturation, pulse, blood pressure and CRT should be assessed on regular basis.
- Oral/NG feeds if neurology is normal and no impending plan for intubation.
- Any child with INR > 4 or any grade of encephalopathy should be transferred to intensive care.
- Etiological evaluation (Table 2.1) has to be carried out in parallel with general assessment and stabilization.

Table 2.1 Etiological evaluation in pediatric liver failure

Etiology	Investigations
Infective	
Hepatitis A	Anti-HAV IgM antibody
Hepatitis B	HBsAg, HBcAb (IgM), HBeAg
Hepatitis C	Anti-hep C antibody, hep C PCR
Hepatitis D	Anti-hep D antibody
Hepatitis E	Anti-HEV antibody (IgM)
Herpes simplex virus (neonates)	PCR
Cytomegalovirus, Epstein-Barr virus	PCR
Measles/varicella/adenovirus/echovirus/ dengue/malaria/scrub typhus	Serology/PCR (If needed)
Blood, urine, stool, throat swab, sputum, skin lesion if present, ascitic fluid if present	Serology/microscopy in tropical countries' culture
Metabolic	
Galactosemia	Galactose-1-phosphate uridyl transferase
Tyrosinemia	Urinary succinylacetone
Fructose intolerance	Quantitative enzyme assay, q22.3 band mutation in chr 9
Mitochondrial disorders	Quantitative mitochondrial DNA assay, mutation analysis, lactate, lactate/pyruvate ratio, CK
Congenital disorders of glycosylation	Transferrin isoelectrophorosis
MCAD deficiency	Plasma acylcarnitine
Urea cycle defects	Ammonia, serum amino acid profile
Wilson's disease	Serum copper, ceruloplasmin and 24-h urinary copper pre- & post-penicillamine
Autoimmune	Immunoglobulins
	Antinuclear antibodies
	Smooth muscle antibody
	Liver cytosol antibodies
	Soluble liver antigen
	Liver kidney microsomal antibody
	Antineutrophil cytoplasmic antibodies
Hematological malignancy	
	Bone marrow examination Ascitic or cerebrospinal fluid cytospin Genetics for HLH
Neonatal hemochromatosis	
	Serum ferritin MR of the liver, pancreas Lip biopsy
Budd-Chiari syndrome	Ultrasound, echocardiography, computer tomography
Drugs and toxins	*History*, *drug levels*

HAV hepatitis A virus, *HEV* hepatitis E virus, *HBcAg* hepatitis B core antigen, *HBsAg* hepatitis B surface antigen, *HLH* hemophagocytic lymphohistiocytosis, *IgM* immunoglobulin M, *MR* magnetic resonance

2.5 Airway and Ventilation

- Elective intubation in grade III or IV encephalopathy; if a child in grade I or II encephalopathy requires sedation due to agitation, it is better to intubate them (agitation can increase ICP).
- Lidocaine, fentanyl, midazolam, and vecuronium are drugs commonly used to intubate them by RSI technique.
- Lung protective ventilatory strategy with tidal volumes to ~6–8 mL/kg and PIP to <30 cm H20.
- Maintain saturations more than 96% and PaCO2 between 35 and 40 mmHg.
- Hypercapnia could be associated with a concomitant rise in ICP, while hypocapnia causes vasoconstriction and decreased brain perfusion so maintain normocapnia.
- Hyperventilation should be reserved for the emergency treatment of raised ICP.
- High PEEP should be avoided, as it could increase hepatic venous pressure and intracranial pressure (ICP).

Tips
- Endotracheal intubation should be done by experienced personnel as these children are coagulopathic and any trauma would be detrimental.
- Oral intubation with cuffed tube is preferred than nasal for the same reason.
- Induction of anesthesia should be smooth (cough and gag can increase ICP).

2.6 Sedation

- A combination of opioid such as fentanyl 1–4 μg/kg/min and benzodiazepine as lorazepam (0.01–0.1 mg/kg/h) is used for sedation. The reason is both are metabolized by phase II glucuronidation and thus can be used even in advanced liver disease.
- Regular chest physiotherapy while on ventilator to prevent chest infection (caution as patient is coagulopathic).
- Use sedation bolus (fentanyl 1–2 μg/kg and lidocaine 1 mg/kg) prior to suctioning/physiotherapy to minimize stimulation and thus ICP surges.
- Cluster nursing care is best. This is to avoid frequent stimulation and surges of ICP.

Tips
- Stop sedation every 24 h to assess neurology.

2.7 Fluids and Electrolytes

- Fluids should be restricted to 2/3 maintenance. The composition of maintenance fluids can be tailored based on the electrolytes, glucose requirement, and renal status of the patient.
- Normal saline with 10% dextrose and potassium as additive should be used as maintenance fluids.
- Maintain serum sodium between 145 and 155 mEq to prevent cerebral edema. This might require slow 3% saline infusion to achieve this. Maintain GIR between 4 and 6 mEq.
- Despite edema, there could be intravascular volume depletion causing hypotension. Appropriate fluid bolus should be given before considering vasopressors. Using various dynamic indices of fluid responsiveness may help in assessing the need for volume expansion.
- In metabolic acidosis, look for fluid deficit and sepsis.

Tips
- As lactate is metabolized by the liver, in ALF lactate should not solely be used as surrogate marker of intravascular fluid status.

2.8 Inotropes

- Adequate fluids should be given before starting inotropes.
- Noradrenaline is the preferred first-line inotrope due to peripheral vasoconstriction properties as there will be peripheral vasodilatation in liver failure.
- Its alpha effect increases both systolic and diastolic blood pressure. Dose is titrated to maintain required MAP.
- Vasopressin or its synthetic analogue terlipressin is used as second-line. It has been found to be effective when hypotension secondary to decreased SVR is refractory to norepinephrine.
- Start vasopressin infusion at 0.0001 U/kg/min after noradrenaline has reached a dose of >0.3 μg/kg/min and clinical evidence of vasodilation. Alternately terlipressin can be used intermittently *IV*: 1 or 2 mg 4–6 hourly.
- In resistant hypotension start stress dose hydrocortisone (2 mg/kg every 6 hourly).

2.9 Coagulation

- As trend of INR is used as prognostic marker and for transplant listing in children, coagulopathy should not be corrected unless for invasive procedures such as insertion of central line/intubation or patient is actively bleeding.

- As both procoagulant and anticoagulant are decreased in patients with ALF, they usually do not spontaneously bleed.
- Look for DIC (fibrinogen levels, d-dimers, etc.) which can cause coagulopathy.
- Thromboelastogram (TEG) could be helpful in deciding about blood component to be used to correct coagulopathy.
- Vitamin K1 is recommended empirically in all patients with ALF.
- Usually correction of coagulopathy is not needed but has to be done before transfer or if INR > 4 to prevent IC bleed (not evidence based) and before any invasive procedures like central lines.
- A dose of 10 mL/kg of FFP and cryoprecipitate if fibrinogen <100 mg/dL could be given, but it is unlikely that it would completely normalize INR.
- Factor VII concentrate (40 μg/kg) can also be used in circumstances when FFP and cryoprecipitate fail to normalize INR and in fluid-overloaded patient.
- Platelet transfusion if platelet count is 10,000–20,000/mm^3 is reached, or there is bleeding and platelet count <50,000/mm^3. A platelet count of >50,000/mm^3 is usually considered adequate when an invasive procedure is to be performed. When ICP monitor insertion is needed, target platelet >100,000/mm^3.
- Prophylactic use of acid-reducing agents like H2 blockers or proton-pump inhibitors to prevent bleed due to stress ulcers.

2.10 Renal

- Acute kidney injury (AKI) in patients with hepatic failure might be pre-renal (hypovolemia) or secondary to acute tubular necrosis or hepatorenal syndrome. Determination of the fractional excretion of sodium helps to differentiate pre-renal causes (hypovolemia, hepatorenal syndrome) from acute tubular necrosis.
- Functional renal failure or hepatorenal syndrome (HRS) is a condition seen only in liver failure group. HRS is secondary to intense renal vasoconstriction and intravascular fluid depletion.
- Patients with prerenal AKI respond to expansion of intravascular compartment with intravenous fluids. Optimize fluid intake so as to maintain a urinary output of 1–2 mL/kg/h.
- The indications for initiating renal replacement therapy include arterial ammonia >150, severe or persistent hyperkalemia (>6 mEq/L), uremia, fluid overload (pulmonary edema, severe hypertension), severe metabolic acidosis (to reduce lactate), hyponatremia (120 mEq/L or symptomatic), or hypernatremia.
- Continuous venovenous hemofiltration (CVVH) is the preferred method as it causes less hemodynamic change.

Tips

Never try low-dose dopamine to increase urine output as it can have deleterious effects due to profound vasodilatation that prevails in ALF.

2.11 Sepsis and Antibiotic Prophylaxis

- Empirical administration of antibiotics is recommended in advanced-stage (III/IV) HE, refractory hypotension, renal failure, presence of systemic inflammatory response syndrome components (temperature >38 °C or <36 °C, white blood count >12,000 or <4000/mm^3, tachycardia), or positive surveillance culture.
- Empirical antibiotics are also recommended for patients listed for liver transplantation (LT), since infection often results in delisting and immunosuppression post-LT is imminent.
- Broad-spectrum coverage with a third-generation cephalosporin is usually the first choice. Piperacillin-tazobactam is an alternative. All patients to be started on fluconazole 6 mg/kg/day.
- All newborns with acute liver failure has to elevated enzymes to be started on acyclovir.
- High-dose (60 mg/kg/day) acyclovir for 21 days or till PCR is negative.

2.12 Raised Intracranial Pressure

- ICP >20 mmHg or intracranial hypertension ICH occurring as a consequence of cerebral edema is one of the most dreaded complications of ALF.
- Method of diagnosing ICH is by direct ICP monitoring using catheters. However, since ICP monitoring is associated with risk of local complications and has no survival benefit, it is not routinely recommended. Serial transcranial Doppler may be used for noninvasive monitoring of ICH.
- The induction of hypernatremia has the potential to decrease water influx into the brain and thereby reduce cerebral edema. Prophylactic infusion of 3% saline to maintain sodium at 145–150 mmol/L in patients with severe encephalopathy is associated with fewer episodes of ICH and is preferred over mannitol.
- When neurological signs of raised ICP (irregular respirations, bradycardia, systolic hypertension) develop or ICP is above 25 mmHg for over 10 min, a bolus over 15 min of IV mannitol (0.25–1 g/kg, 20% mannitol) is recommended. This can be repeated if serum osmolality is less than 320 mOsmol/L. Three percent saline could be used as well.
- Hyperventilation with reduction of pCO2 to <35 mmHg decreases cerebral blood flow and may be used temporarily in patients with impending herniation where mannitol therapy fails.
- At present there is no evidence to support use of hypothermia, prophylactic phenytoin or corticosteroids in the management of raised ICP in ALF.

Tips

- Continuous mannitol infusion can increase serum osmolarity and can cause diuresis resulting in intravascular volume depletion.

2.13 Neuroprotection Strategies

General neuroprotective measures to be implemented in all ventilated patients:

- Head end of bed elevated (30–45°).
- Neck in neutral position.
- Normothermia (temp 36–37.5 °C). Avoid fever or hyperthermia.
- Normoxemia (PaO2 > 60 mmHg or SpO2 > 94%).
- Normocarbia (PaCO2 35–40 mmHg).
- Normoglycemia (6–10 mmol/L).
- Sedation (narcotics and benzodiazepines administered judiciously).
- Use of fentanyl and lidocaine boluses pre-procedure/pre-suction.
- Actively look for seizures and consider antiseizure drugs if clinical or EEG evidence of seizures.
- Ammonia scavenging strategy if >150 (CVVH).
- Modalities of ICP monitoring are outlined in Table 2.2.

2.14 Nutrition

- ALF is a catabolic state characterized by a negative nitrogen balance. Oral or nasogastric feeding is usually well tolerated and should be started as early as possible.
- Continuous NG feed is preferred over bolus feeds in infants, to prevent fluctuations in glucose levels during the initial phase.
- Enteral or parenteral infusions are started at a rate to provide 8–9 mg/kg/min of glucose for infants, 7 mg/kg/min for toddlers, and 4 mg/kg/min for adolescents at the same time to maintain glucose level between 6 to 10 mmol/L.
- There is no role of protein exclusion in children with HE as it will only cause catabolism of muscle protein and worsen HE. Infants should be given 1.5–1.9 g protein/kg/day and children 0.8–1.0 g protein/kg/day, based on the minimum

Table 2.2 Modalities of ICP monitoring

Invasive ICP monitoring: • CPP = MAP-ICP (target 40–50 mmHg; age-based cutoff available).
Cranial Doppler: • Pulsatility index (PI) of middle cerebral artery through temporal window. • PI = Vmax−Vmin/mean velocity (V = height of pulse wave). • Normal PI is 0.8–1.2, low PI in hypercapnia/vasodilation, high PI in hypocapnia/vasoconstriction/brain death.
Reverse jugular saturation (SjVo2): cannula in jugular bulb and regular sampling of venous oxygen level (Fig. 2.2) • Normal value SjVo2 60–75% • SjVo2 < 55% suggestive of cerebral hypoperfusion (inadequate CPP/hypocapnia) • SjVo2 > 80% suggestive of cerebral hyperperfusion (neuronal death/hypercapnia)

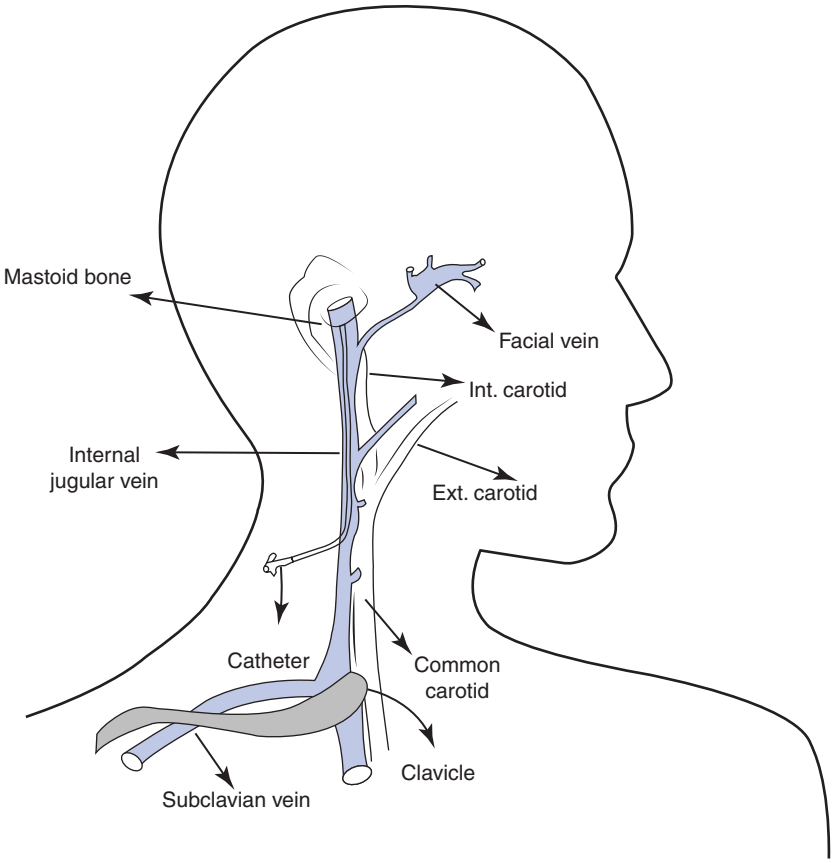

Fig. 2.2 Tip of catheter should be above the C1/C2 intervertebral disk on lateral neck X-ray (in jugular bulb)

protein requirements suggested by the WHO. Those with HE must be given at least 0.5–0.8 g/kg/day of protein.

- If there is a suspicion of a metabolic condition, then all protein/fat should be stopped for 24 h and then restarted keeping the specific condition in mind.

2.15 Specific Therapies

- Specific therapies for some of common etiologies of ALF in children are outlined in Table 2.3.

2.16 Bridging Therapy

- These therapies provide stability and act as a bridge while the patient awaits transplantation.

Table 2.3 Specific therapies for ALF

Autoimmune hepatitis: steroids (methylprednisolone 2 mg/kg/day, max 60 mg/day)
Acetaminophen toxicity: *N*-acetylcysteine (100 mg/kg/day) until INR is normal
Mushroom poisoning: benzylpenicillin (1,000,000 U/kg/day) or thioctic acid (300 mg/kg/day)
Galactosaemia/hereditary fructose intolerance: elimination diet
Hereditary tyrosinemia: NTBC (0.5 mg/kg bd) + elimination diet
Hemophagocytic lymphohistiocytosis: Chemotherapy ± hematopoietic stem cell transplantation (familial/genetically verified and persistent/reactivation of secondary HLH)
Neonatal hemochromatosis: Double volume exchange transfusion and intravenous immunoglobulin (1 g/kg)

Table 2.4 Wilson's disease index: score of 11 or more indicates high mortality

INR	Bilirubin (μmol/L)	AST (IU/L)	WBC (10^9/L)	Albumin (G/L)	Score
0–1.2	0–100	0–100	0–6.7	>45	0
1.3–1.6	101–150	101–150	6.8–8.3	34–44	1
1.7–1.9	151–200	151–200	8.4–10.3	25–33	2
2.0–2.4	201–300	201–300	10.4–15.3	21–24	3
>2.5	>300	>300	>15.4	0–20	4

AST aspartate transaminase, *INR* international normalized ratio, *WBC* white blood cell count

- Arterial ammonia levels directly correlate with cerebral edema and encephalopathy. Ammonia more than 150 μmol is an indication for CRRT. Details are provided in chap. 10.
- Plasmapheresis and high-volume plasma exchange are helpful in patients with high bilirubin, active hemolysis (as in Wilson's disease), etc. and provide stability. The stability provided is partly due to the removal of circulating toxins and cytokines. Details are provided in chap. 11.

2.17 Liver Transplantation: Indication

- In children with non-acetaminophen poisoning INR >4 or factor V concentration of <25% as the best available criteria for listing for LT.
- For acetaminophen-induced acute liver failure, arterial pH < 7.3 (after fluid resuscitation) or the presence of all three of the following criteria.
  - INR > 6.5
  - Serum creatinine >300 μmol per liter (>3.4 mg/dL)
  - Encephalopathy (grade III or IV)
- Special prognostic scores are available for acute fulminant Wilson's disease (Table 2.4), and a score of 11 or more indicates high mortality without LT.
- Contraindications for pediatric LT are active uncontrollable and untreatable sepsis, extrahepatic malignancy, generalized mitochondrial disease, fixed dilated pupils, etc.

Chronic Liver Disease: Diagnosis and Management of Complications

3

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Diseases of liver parenchyma or biliary tree ultimately lead to progressive fibrosis of liver resulting in cirrhosis. Disruption of the liver architecture by fibrous strands that connect between portal tracts or between portal tract and central venule resulting in nodule formation is defined as cirrhosis. The speed and severity of progression of cirrhosis depend upon the etiology of liver disease. Cirrhosis leads to several complications, some of which are outlined in Fig. 3.1.

3.1 Electrolyte Imbalance in CLD

Hyponatremia and hypokalemia are the two common electrolyte imbalances seen in CLD.

1. Hyponatremia in CLD is multifactorial:
   - Hyperaldosteronism (renin-angiotensin activation)
   - Arginine vasopressin (non-osmotic release)
   - Antidiuretic hormone (non-osmotic release)

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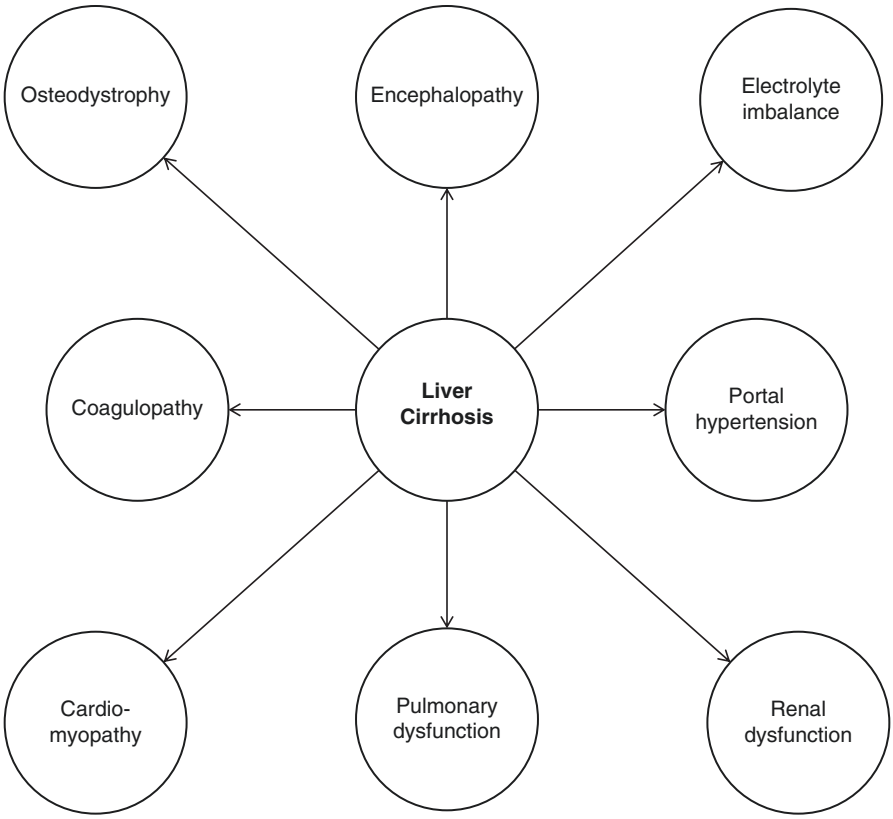

Fig. 3.1 Complications of cirrhosis

Serum sodium[a]	Management
130–135 mmol/L	• Continue diuretic therapy and no need for water restriction
125–129 mmol/L	• If creatinine is normal: continue diuretic therapy and no need for water restriction • If creatinine is raised: discontinue diuretics; give volume expansion if child progresses toward HRS
111–124	• If asymptomatic: discontinue diuretics and restrict water. Repeat serum sodium levels in 24 h • If symptomatic: admit, IV sodium correction targeting, sodium raise not more than 9 mEq/L per 24 h
<110	• Admit, IV sodium correction targeting, sodium raise not more than 9 mEq/L per 24 h

[a]Correction of hypokalemia helps in concomitant increase in serum sodium concentration

Caution

- Rapid serum sodium could result in central pontine myelinolysis, quadriplegia, coma etc.
- In pretransplant scenario, it is ideal to gradually raise serum sodium to 125 mEq/L before surgery, as usage of blood products, albumin, and other colloids intraoperatively would inadvertently raise serum sodium dramatically over a short period of time.

2. Hypokalemia

Hypokalemia is common with loop diuretics and can precipitate hepatic encephalopathy by:

- Increasing renal ammonia synthesis.
- Increasing unionized ammonia in the plasma by concomitant alkalemia.
- Correction of hyponatremia, hypokalemia, and other electrolyte imbalance is outlined in Chap. 31.5.

3.2 Hepatic Encephalopathy (HE)

In acute liver failure, HE is of rapid onset, often requiring urgent liver transplant. In CLD it could present for a long time without being noticed clinically as minimal HE. Overt manifestation of HE could happen with sudden liver decompensation due to precipitating events. The management principles outlined here are applicable only to HE in CLD (for HE management in ALF, see Chap. 2).

3.2.1 Common Precipitating Factors

- Bleeding
- Electrolyte imbalance (check if on diuretics)
- Infection (especially SBP, *C. difficile*)
- Dehydration
- Diarrhea

3.2.2 Management Principles

- Assess airway, breathing, and circulation. Intubation if grade 3–4 encephalopathy.
- Bleeding: correct hemoglobin/coagulation with transfusion, emergency endoscopy.

- Gradual correction of electrolyte disturbance.
- Neuroprotective measures (see HE under acute liver failure).
- Fluid resuscitation if dehydration and hypovolemia.
- Intravenous antibiotics.
- Reducing ammonia load.
- Liver transplantation: synthetic liver failure with encephalopathy is an indication for liver transplantation in chronic CLD.

3.2.3 Fluid and Electrolytes

- Hydration status is difficult to assess with ascites and edema.
- Hydration to be monitored by CVP (ideally 6–8 cm of H_2O), echocardiography, USCOM, etc.
- Fluid resuscitation with isotonic crystalloids (0.9% NaCl) or colloids.
- Maintenance fluids: 10% dextrose with 1 mmol/kg of Na and 1–2 mmol/kg potassium.
- Maintenance fluids at 70% of daily requirement providing GIR of around 5 mg/kg/min to maintain normoglycemia.
- Assess fluid balance regularly and titrate.
- Enteral feeds with no added salt.

Caution
- Low serum Na in CLD is usually dilutional due to free water retention.
- Attempts to normalize Na by increasing total intake can lead to water retention and worsening of edema.

3.2.4 Reducing Ammonia Load

- *Lactulose*
  - Colonic bacteria ferment lactulose and reduce the luminal pH. At lower pH ammonia (NH3) is converted to ammonium (NH4+) which is excreted with stools.
  - Ideal dose of lactulose is the amount that produces three soft stools/day (titrate the dose).
  - Diarrhea can cause electrolyte disturbance and intravascular volume depletion, so avoid excessive lactulose.
- *Lactitol*
  - Less sweet and more palatable. Action similar to lactulose.

- *Gut decontamination*: Nonabsorbable antibiotics reduce the load of ammoniagenic bacteria in the gut. Rifaximin has the best risk-benefit ratio.
- *L-ornithine L-aspartate (LOLA)*: Facilitates the action of enzyme ornithine and aspartate transaminases in the brain and peripheral tissues that convert ammonia to non-toxic glutamate.
- *Enhancing alternate pathways of nitrogen excretion*: Drugs such as sodium benzoate, arginine hydrochloride, etc. are helpful only in metabolic condition associated with raised serum ammonia such as urea cycle defects. No proven benefit in hyperammonemia due to CLD.
- *Zinc*: Deficiency state can affect conversion of ammonia to urea as zinc is an integral part of metalloenzyme that stimulates production of ornithine transcarbamylase.

3.3 Ascites and Spontaneous Bacterial Peritonitis (SBP)

Ascites and SBP are common complications of CLD. Occurrence of ascites in CLD hints toward decompensation.

3.3.1 Ascitic Fluid Analysis and Interpretation

Sent fluid for albumin levels, glucose, lactate dehydrogenase, cell count, and culture

1. *Serum-ascites albumin gradient* (SAAG).
   SAAG = serum albumin–ascites albumin
   - SAAG value (>1.1 g/dL) indicates ascites from portal hypertension.
   - SAAG value (<1.1 g/dL) suggests tuberculous peritonitis, pancreatic ascites, biliary leak ascites, nephrotic syndrome, and peritoneal carcinomatosis.

2. *Glucose*: (7–10 mmol) usually reflects serum value. Low levels suggestive of infection.
3. *Lactate dehydrogenase (LDH)*: Ascitic fluid LDH > 400 or ascitic fluid LDH/serum LDH >0.6 is associated with infection/TB and pancreatitis/malignancy.
4. Adenosine deaminase (ADA): <39 IU/mL (increased in TB).
5. In case of hemorrhagic ascites (ascites RBC count >10,000/mm^3), detecting one PMN per 250 RBC should give adjusted value of PMN in blood.
6. In cloudy ascitic fluid, neutrophil leukocytosis >250/cu.mm is suggestive of SBP. Lactate >25 mg/dL + ascitic fluid pH <7.35 is adjunctive evidence. Use of reagent strips that detect leukocyte esterase (correlates well with lab PMN) leads to a rapid diagnosis. Based on cell count and culture results, ascitic infection can be categorized into three types (Table 3.1).

Table 3.1 Ascitic fluid nomenclature based on bacterial culture and ascitic cell count

	Ascitic fluid bacterial culture	PMN cell count/MM3
Culture negative neutrocytic ascites (CNNA)	Negative	>250
Spontaneous bacterial peritonitis	Positive	>250
Mono-bacterial non-neutrocytic ascites (MNB)	Positive	<250

CNNA represent one end of spectrum where patient immunity is good, and so there is leukocytic response, and bacterial culture is negative, while MNB represent another end of spectrum with poor patient immunity and so no leukocytic response with positive culture

3.3.2 Principles of Management of Asities

- Limit sodium intake (may be difficult to achieve in children).
- Increase sodium and water excretion (judicious use of diuretics).
- Maintain plasma oncotic pressure (albumin infusion).
- Increase caloric content of feeds.
- Mild ascites with no discomfort requires no specific treatment in majority of patients apart from above measures.
- Monitor weight, fluid balance, and blood pressure.

Nutritional support: Restrict dietary sodium to <2–3 mmol/kg/day.

3.3.3 Diuretics

- Aldosterone antagonist ± thiazide diuretics:
  - Spironolactone 3 mg/kg bd up to 6 mg/kg/day when age < 10 years. 100–200 mg BD up to 600 mg when age > 10 years.
  - Spironolactone takes 2–4 days to have an optimal effect.
  - Spironolactone and frusemide have good synergistic effect when given together at a dose ratio of 2.5:1.
  - Potassium loss by frusemide is counteracted by potassium conservation by spironolactone.
- Frusemide as monotherapy is not recommended as chronic use can electrolyte disturbance and volume depletion. This can trigger prerenal failure, encephalopathy, and arrhythmias.
- Rapid diuresis will lead to plasma volume depletion and prerenal failure.
- Goal of diuretic treatment:
  - Negative balance of 10 mL/kg/day.
  - Urinary sodium excretion >15 mmol/day or urinary sodium > potassium indicates diuretic response.
- Albumin infusions 1 g/kg + frusemide 2 mg/kg over 4–6 h. IT could be repeated if albumin remains <2.0. This will help in maintaining intravascular fluid volume while diuresing extracellular water.

3.3.4 Paracentesis

- Indications for therapeutic paracentesis are gross tense ascites, breathing difficulties, prerenal azotemia, etc.
- Diagnostic paracentesis for suspected SBP.
- Albumin is usually given at the time of paracentesis. Albumin infusions at 1 g/kg is given over 4–6 h along with stat dose frusemide 2 mg/kg in the middle. This will help in maintaining intravascular fluid volume while diuresing extracellular water.
- In refractory symptomatic ascites, large-volume paracentesis combined with albumin infusion is usually helpful. Continuous drainage is not encouraged due to risk of bacterial peritonitis.

3.3.5 Severe Refractory Ascites

There are two types:

Diuretic-resistant ascites: Defined as no clinical response despite maximal diuretic therapy along with appropriate salt restriction.
Diuretic-intolerant ascites: Optimal diuretic dosage could not be used due to drug complications.

Liver transplantation is the only definitive therapy in refractory ascites. Transjugular intrahepatic portosystemic shunt (TIPS) temporarily decreases portal pressure and could act as a bridge to transplant.

3.3.6 SBP

- Fever in the background of ascites, suspect SBP.
- Specific risk factors being low serum albumin, GI bleeding, and recent therapeutic endoscopy.
- Usually caused by single species (*Streptococcus pneumoniae*, *Klebsiella*, *E. coli*, *Enterococcus*).
- Multiple species suggests bowel perforation and secondary peritonitis.

3.3.6.1 Prevention of SBP

- Pneumococcal and HiB vaccination,
- Prophylactic antibiotics for invasive procedures.
- Nutritional support.

3.3.6.2 Management of SBP

- Early institution of antibiotics with third-generation cephalosporin (IV cefotaxime, cefoperazone, etc.) in countries with less ESBL prevalence and piperacillin-tazobactam in countries with high ESBL prevalence. Then treat as per culture results. Duration: 14 days.

- Supplemental albumin infusion to support intravascular volume can reduce renal impairment.
- AASLD practice guidelines on adults with ascites suggest longterm antibiotic prophylaxis in high-risk patients which include ascitic fluid protein less than 1.5 g/dL along with at least one of the following:
  - Serum creatinine ≥1.2 mg/dL
  - Blood urea nitrogen >25 mg/dL
  - Serum sodium ≤130 mEq/L
  - Child-Pugh score ≥9 with bilirubin ≥3 mg/dL
- Recurrent SBP: In children with recurrent SBP cyclical antibiotics could be used (Institutionl policy). Fig. 3.2 shows some common antibiotics used on cyclical basis.

3.4 Cirrhotic Cardiomyopathy

Definition*
- Impaired contractile response of heart to stress in cirrhosis and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease.

Diagnostic criteria*
- Evidence of systolic dysfunction such as blunted cardiac response to exercise, volume challenge, or drugs with resting ejection fraction <55%.
- Evidence of diastolic dysfunction such as prolonged isovolumetric relaxation time (>80 ms), prolonged deceleration time (>200 ms), and early diastolic/atrial filling ratio < 1.0 (age-corrected).
- Supportive criteria
  - Electrophysiological abnormalities: prolonged QTc interval, electromechanical uncoupling/dyssynchrony, and chronotropic incompetence
  - Enlarged right atrium, increased myocardial mass
  - Increased brain natriuretic peptide (BNP), pro-BNP, and troponin

3.4.1 Management

- Beta blockers: Reduce hyperdynamic load, improves prolonged QT, lowers portal pressure, and thus prevents variceal bleed.
- Diuretics: Decrease volume overload; however prolonged use causes electrolyte disturbance, worsening renal function, and neurohormonal activation.
- Aldosterone antagonists and ACE inhibitors: Inhibit renin-angiotensin-aldosterone system overactivity, reduce LV dilatation and wall thickness, and improve diastolic function. No proven long-term benefit.

* As proposed by Working Party at the 2005 World Congress of Gastroenterology in Montreal.

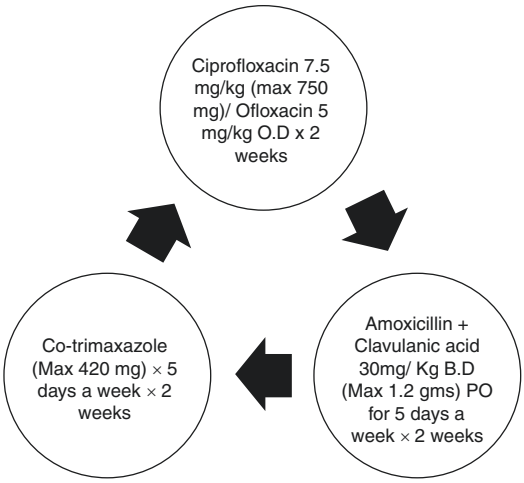

Fig. 3.2 Prophylactic oral antibiotics (cotrimoxazole, ciprofloxacin, and norfloxacin)

- Cardiac glycosides: No proven benefit.
- Gold Standard Curative Therapy: Liver Transplantation.

Caution
ACE inhibitors may aggravate systemic vasodilation.

3.5 Hepatoadrenal Syndrome

- Adrenal insufficiency occurs both in acute and chronic liver diseases.
- Pathogenesis of adrenal insufficiency in liver disease is unclear and thought to be multifactorial (increased cytokines, decreased levels of cholesterol (mainly HDL cholesterol), circulating endotoxin, etc. may play a role).
- Signs: Prolonged vasopressor-dependent hypotension, hypotension refractory to vasopressors, and fluid resuscitation.
- Diagnosis:
  - Measurement of baseline serum total cortisol at or following stimulation by the standard-dose short synacthen test (SD-SST).
  - In SD-SST serum, cortisol is measured after 30–60 min of administering 250 μg of cosyntropin.
  - Delta cortisol is the difference between peak and basal cortisol.

Reference cortisol values are outlined in Table 3.2.

Table 3.2 Reference cortisol values

	Cortisol levels in μg/dL	Cortisol levels in nmol/L
Baseline serum total cortisol (8.00 am)	>10	>275
Peak cortisol level SD-SST	>18	>495
Delta cortisol	>9	>250

Treatment:

- Low dose (physiologic dose or stress dose) and supraphysiological doses of corticosteroids have been tried in vasopressor-resistant shock in patients with liver disease.
- Beneficial effect has not been proven by randomized controlled trials in children.

Caution

- Cortisol is mainly albumin bound and low serum albumin levels in CLD could account for low cortisol levels in these patients, but there is no validated reference range for cortisol in liver disease.
- Delta cortisol levels would be helpful in CLD.

3.6 Hepatic Osteodystrophy

- Refers to metabolic bone disease in CLD that occurs as a result of osteomalacia and osteoporosis.
- Multifactorial pathogenesis: Deficiency of insulin-like growth factor, vitamins D and K, gonadotropic hormones, and drugs such as cholestyramine, frusemide, etc.
- Monitoring: Serum vitamin D levels and bone mineral density using dual-energy X-ray absorptiometry (DEXA) scan.
- Treatment: Supplementation of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) to achieve serum 25-OH vitamin D level >20 ng/ml.
- Bisphosphonates indicated if low-impact fractures (≥1 vertebral or ≥1 lower limb or ≥2 upper limb) and low bone mineral density. Intake of calcium, phosphate, and vitamin D to be optimized before commencing bisphosphonates.

Caution

- Vitamin D in the form of alfacalcidol and calcitriol increases intestinal calcium absorption but is not stored in the body. These can also cause hypercalciuria and nephrocalcinosis in higher doses.

For HPS, HRS and varicial bleed, see specific Chaps. 6, 7 and 8 respectively.

Further Reading

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Nutrition in Paediatric Liver Diseases

4

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4.1 Introduction

Liver plays a key role in anabolism, catabolism and storage of macronutrients (carbohydrates, proteins, fats, etc.) and micronutrients (vitamins and minerals). In diseased liver, the fine balance between anabolism, catabolism and storage of nutrients is disturbed. The problem is further aggravated by insufficient nutrient intake and malabsorption. Malnutrition is an independent predictor of mortality and morbidity in liver diseases.

Causes for Malnutrition in Liver Disease

(a) Increased nutritional requirement due to increased resting energy expenditure (REE) and total energy expenditure (TEE).
(b) Bile salts are required to activate lipase, and in their absence as in chronic cholestasis, large proportion of fat is excreted and unabsorbed.
(c) Drugs that are used to decrease bile acid pools such as cholestyramine interfere with fat-soluble vitamin absorption.
(d) Decreased nutritional intake due to early satiety, nausea and vomiting.
(e) Decreased absorption due to intestinal mucosal oedema secondary to portal hypertension.
(f) Decreased glycogen store in advanced liver disease leading to fat and protein utilization.

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4.2 Assessment of Nutritional Status

Isolated weight provides a false impression of adequate nutrition because of organomegaly/ascites.

Serial height/length measurement helps in chronic malnutrition, but of less value in acute liver disease. *Serial measurement of triceps skinfold thickness* (*TST*) *to estimate body fat and midarm circumference* (*MAC*) *to estimate muscle bulk and comparison to normal values is helpful*.

As albumin, prealbumin, transferrin, etc. are influenced by liver synthetic insufficiency, these biochemical parameters cannot be used as surrogate markers for nutritional deficiency.

4.3 Acute Liver Failure

4.3.1 Carbohydrates

Hypoglycemia is present in around 40% of patients with ALF on initial presentation due to reduced gluconeogenesis and increased plasma insulin levels. *Enteral or parenteral infusions / bolus are started at a rate to provide 8–9 mg/kg/min of glucose for infants*, *7 mg/kg/min for toddlers and 4 mg/kg/min for adolescents*. The infusions could be titrated using frequent blood glucose levels.

4.3.2 Proteins

The idea of protein restriction to limit the possibility of hepatic encephalopathy (HE) has now been disregarded, and adequate proteins should be supplemented. *Infants should be given 1.5–1.9 g protein/kg/day and children 0.8–1.0 g protein/kg/day*, *based on the minimum protein requirements suggested by WHO*.

4.3.3 Fat

Medium-chain triglyceride (MCT) fat with or without long-chain triglyceride (LCT) could be added to feeds to increase the caloric content. Along with MCT/LCT, essential fatty acids (EFAs) such as linolenic (omega 3) and linoleic (omega 6) fatty acids have to be supplemented. Flaxseed oil is a very good source essential fatty acids (EFAs) followed by mustard, walnut, wheat germ, rice bran and sunflower oil.

4.4 Chronic Liver Disease

Due to prolonged course of illness, malnutrition is much more of a problem in CLD than in ALF, and it is an important determinant of post-transplant mortality and morbidity.

4.4.1 Energy

The caloric intake in CLD should be 130–180 kcal (545–750 kJ)/kg/day for infants and 120–150% EAR for age in children, to compensate for increased TEE and fat malabsorption. If there is difficulty in oral route, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines support the use of NG feeding. NG tubes made of polyurethane/silicone are well tolerated and have low risk of bleed. Continuous feeds are better tolerated than bolus feeds. Gastrostomy is usually contraindicated in CLD due to the associated portal hypertension and bleeding risk.

4.4.2 Protein

To overcome the effect on negative nitrogen balance and need of protein for growth, infants have to be supplemented with 3–4 g/kg/day and children with 2 g/kg/day of proteins.

4.4.3 Fat

The severity of jaundice might not correlate with the degree of fat malabsorption. MCT could be absorbed without the need of bile acids and hence greater bioavailability. About 30–60% of total fat should be provided as MCT oil. *MCT oil can be supplemented separately in a total daily dose of 1–2 ml/kg/day divided in 2–4 doses*.

4.4.4 Carbohydrates

Hypoglycemia is common in CLD due to decreased glycogen stores and increased energy requirement. *Carbohydrates should provide 40–60% total energy*.

4.5 Minerals and Vitamin

Sodium should be restricted to 1.5–2 mEq/kg/day, as salt could cause water retention and worsens oedema and ascites. Fat-soluble vitamins should be supplemented on regular basis.

4.5.1 Post-liver Transplantation

There will be an increased energy and protein requirement immediately following liver transplantation. In infants and malnourished children, it is better to start on total parenteral nutrition on postoperative day 1 based on their RDA and continue until full feed is established. Electrolyte imbalance could happen similar to refeeding syndrome, which has to be managed appropriately.

Vitamin and Mineral Supplementation

Vitamin A

Dose of 5000–25,000/day. Serum retinol <20 μg/dL or retinol-retinol-binding protein molar ratio <0.8 indicates deficiency.

Vitamin D

Ergocalciferol (vitamin D2) 3–10 times the RDA for that age group, cholecalciferol (vitamin D3) 50–100 units/kg/day, and in severe resistant cases 1–25-dihydroxy vitamin D of 0.05–0.20 μg/kg/day should be administered.

Vitamin E

A dose of 25–50 IU/kg/day of α-tocopherol or 15–25 IU/kg/day of water soluble TPGS is needed.

Vitamin K

Vitamin K: 2.5–5 mg, 2–7 times/week.

Water-Soluble Vitamin

Water-soluble vitamin deficiency could occur due to the decrease in overall food consumption.

Trace Elements and Mineral Deficiency

If plasma zinc concentration is <60 μg/dL, supplementation with 1 mg/kg/day elemental zinc is recommended. The diet should meet daily requirement of selenium (1–2 μg/kg/day), calcium (50–100 mg/kg/day) and phosphate (20–50 mg/kg/day); otherwise it has to be supplemented.

Microcytic anaemia with low iron level and increased total iron-binding capacity (TIBC) indicates iron deficiency. Elemental iron at 5–6 mg/kg/day should be supplemented.

Conclusion

A multidisciplinary team should be involved in nutritional rehabilitation. Adequate protein and caloric intake is essential to prevent catabolism, even in the presence of encephalopathy.

Coagulopathy in Liver Disease

5

Naresh Shanmugam and Vimal Kumar

Liver plays an important role in coagulation. Apart from von Willebrand factor, all the other clotting factors are synthesized by the liver. Coagulopathy in liver disease is a reflection of synthetic liver failure. The normal coagulation cascade is outlined in Fig. 5.1. Always look for superimposed causes of coagulopathy such as vitamin K deficiency, infections, and renal failure.

The standard lab test for coagulation such as prothrombin time (PT)/international normalized ratio of PT (INR)/activated partial thromboplastin time (aPTT) assess only plasmatic events in hemostasis. They do not reflect how platelets and other cellular components contribute to coagulation. In liver disease there is concomitant decrease of both procoagulant and anticoagulant levels, platelets, etc.; and the hemostasis is altered. Using PT/aPTT as surrogate marker for bleeding risk is not advocated in liver disease. It can overrate bleeding risk resulting in administration of unneeded or even harmful prohemostatic factors. In liver disease there is concomitant decrease of both procoagulant and anticoagulant levels, and the hemostasis is rebalanced, and so these patients usually do not spontaneously bleed.

Hemostasis in liver disease is best assessed using thromboelastography (TEG). TEG is a point-of-care assay using a specialized machine that assesses clot formation in whole blood, including plasmatic and cellular components. TEG provides a graphical representation (Fig. 5.2) of assembly of a clot in whole blood and provides an assessment of overall hemostasis. Table 5.1 shows TEG parameters and its correlation with coagulation cascade. Anesthetist usually relies on TEG in choosing

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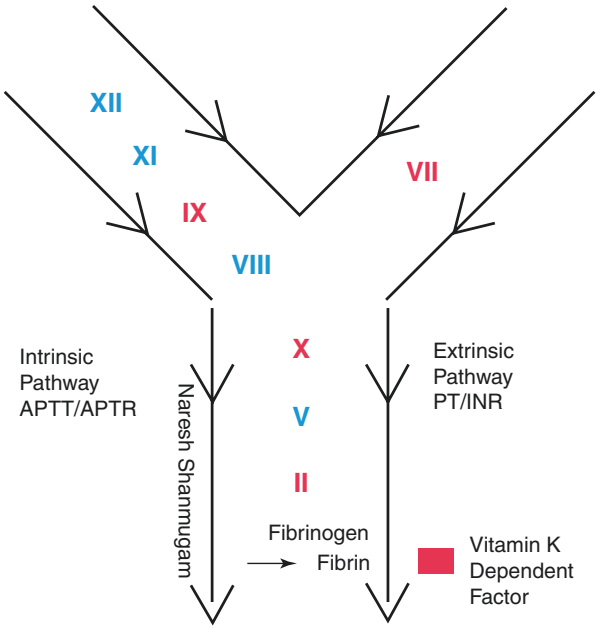

Fig. 5.1 Diagram showing factors involved in intrinsic and extrinsic pathway

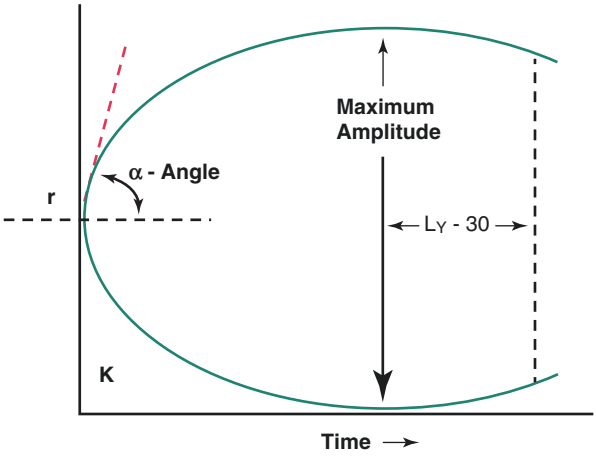

Fig. 5.2 Figure showing standard TEG in a normal person

the appropriate blood components for correcting coagulopathy during liver transplantation.

Tests prior to any surgical procedure:

- CBC, platelet count
- PT/INR, aPTT, fibrinogen
- FDP
- Thromboelastography

Table 5.1 TEG parameters and its correlation with coagulation cascade

TEG parameters	Normal range	Corresponds to	Correlates with
Reaction time in minutes (*r*)	2.5–7.5 min	Time between beginning of the clotting cascade to the initial formation of fibrin	Procoagulant factor levels, INR and aPTT
Kinetic time in minutes (*k*)	0.8–2.8 min	Time between initial fibrin formation to reach a specific clot firmness	Fibrinogen levels and platelet function/ number
α-Angle in degrees	55.2–78.4	Deals with kinetics of clot formation. Rate of fibrin formation and cross-linking of platelets	Fibrinogen levels and platelet function/ number
Maximum amplitude in mm	50.6–69.4	Measures the maximum clot strength	Fibrinogen levels and platelet function/ number
Clot lysis at 30 min (Ly-30; in percentage)	0.0–7.5	Percentage of clot dissolution within 30 min of maximum amplitude	Fibrin degradation products

- Blood group, antibody screen

Treatment options:

- Vitamin K: 2–5 mg IV OD for 3 days corrects vitamin K deficiency associated with decompensated liver disease.
- Platelet transfusion: if platelet count is <50,000/cu/mm in case of bleeding or prior to any invasive procedure.
- Fresh frozen plasma: advantages—contains all coagulation factors, inhibitors of coagulation, and fibrinolytic factors. Disadvantages: volume overload, exacerbation of portal hypertension, risk of infection, risk of transfusion-associated acute liver injury, and transient therapeutic improvement. This may be used when volume expansion is not a concern.
- Cryoprecipitate: hypofibrinogenemia (fibrinogen <100 mg/dL) treated with cryoprecipitate until normal fibrinogen levels reached.
- Recombinant factor VIIa: the most efficient use of this product is in intracranial pressure monitor placement. It may have efficient role in controlling active variceal bleeding when there is no clear endoscopic view. Disadvantages: thrombotic complications and high cost of the therapy.
- For treating local bleeding: aprotinin, tranexamic acid, epsilon aminocaproic acid.
- DDAVP: releases vWF and factor VIII. No benefit with variceal bleeding and after liver surgery.
- Red blood cell transfusion: note that transfusion should be minimum, not allowing Hb to increase more than 8–9 gm/dL.

Pulmonary Complications of Liver Disease

6

Karthick Sundaram, Akash Deep, and Naresh Shanmugam

Two major pulmonary complications of liver disease are hepatopulmonary syndrome and portopulmonary hypertension.

6.1 Hepatopulmonary Syndrome

6.1.1 Definition

Hepatopulmonary syndrome (HPS) is defined by decreased arterial oxygenation (increased alveolar arterial gradient) in room air with right to left shunting (intrapulmonary vasodilation) occurring in patients with liver disease in the absence of intrinsic lung disease.

6.1.2 Incidence/Prevalence

During transplant evaluation in cirrhotic patients, HPS was found in around 32%. Since routinely underdiagnosed, furter studies are needed to determine HPS incidence/prevalence in cirrhotic patients.

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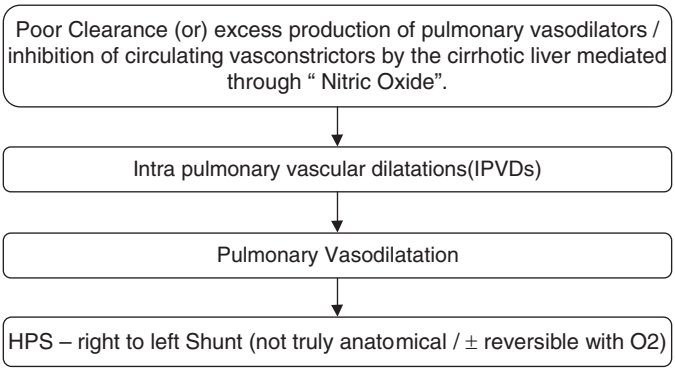
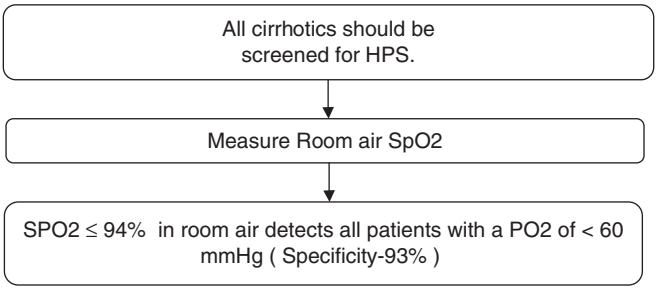
6.1.3 Etiopathogenesis



6.1.4 Presentation/Clinical Features

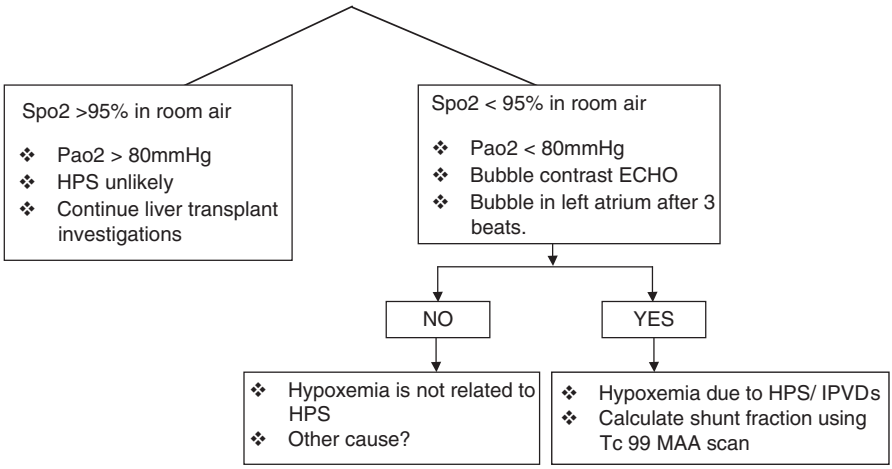
- High index of suspicion required.
- Usually no pulmonary symptoms.
- Fatigue, clubbing and cyanosis are usual symptoms.
- Spider naevi tend to be more numerous.
- HPS can occur in non-cirrhotic portal HT as well as in ischemic hepatitis.

6.1.5 Screening for HPS



6.1.6 Diagnostic Algorithm

- Suspect HPS in cirrhotic patients with dyspnoea (orthodeoxia can be present).
- Check SpO2 in room air.



Bubble Contrast Echo

- Confirm normal cardiac anatomy.
- Inject rapidly 10 cc of agitated saline via peripheral cannula.
- Record echocardiographic images digitally.
- The time interval and number of cardiac cycles between appearance of microbubbles in right ventricle and left ventricle are noted.
- Appearance of microbubbles in left ventricle in three cardiac cycles after its appearance in right ventricle is considered abnormal. Usually it takes 20 cycles for its appearance in left ventricle.
- Positive bubble contrast echo is suggestive of IPVD.

Technetium-99m-Labeled Macroaggregated Albumin (99mTc-MAA) Scan

- Using this method shunt fraction could be quantified.
- ^{99m}Tc-MAA is injected through peripheral cannula.
- Quantitative whole-body imaging was performed with gamma camera.
- Uptake of 6% or more of traced by the brain is abnormal and suggestive of shunts (it will not differentiate between intracardiac and intrapulmonary shunt and this is why echo should be done first).

Once screening with bubble echo is positive, proceed with Tc-99 MAA scan to quantify shunt fraction:

- Tc-99 MAA brain uptake ≥6%: *PaO2 in arterial blood gas more than 60 mm of hg and can proceed with liver transplantation.*
- Tc-99 MAA brain uptake ≥6%: *PaO2 in arterial blood gas less than 60 mm of hg proceed to CT pulmonary angiogram to look for diffuse (type 1) or localised (type 2) HPS. Interventional coiling of large localised AV shunt could improve oxygenation.*

6.1.7 Differential Diagnosis

- COPD (pulmonary function testing/lung imaging)
- Recurrent pulmonary emboli (lung perfusion scan)
- Portopulmonary HT (its pulmonary arterial HT in the setting of portal HT)

6.1.8 Treatment

- LT is the only option that would reverse HPS
- Resolution of HPS after LT can take several months.
- Treatment measures used in management of severe hypoxemia in HPS post-liver transplantation are outlined in Table 6.1.
- Post-transplant severe hypoxemia is defined as an SpO2 <85% for ≥1 h despite an FiO2 of 100% and a PEEP of ≥10 mmHg.
- Intensive care management of severe post-transplant hypoxemia is outlined in Table 6.2 and Fig. 6.1.

Table 6.1 Treatment modalities used in management of severe hypoxemia post-liver transplant

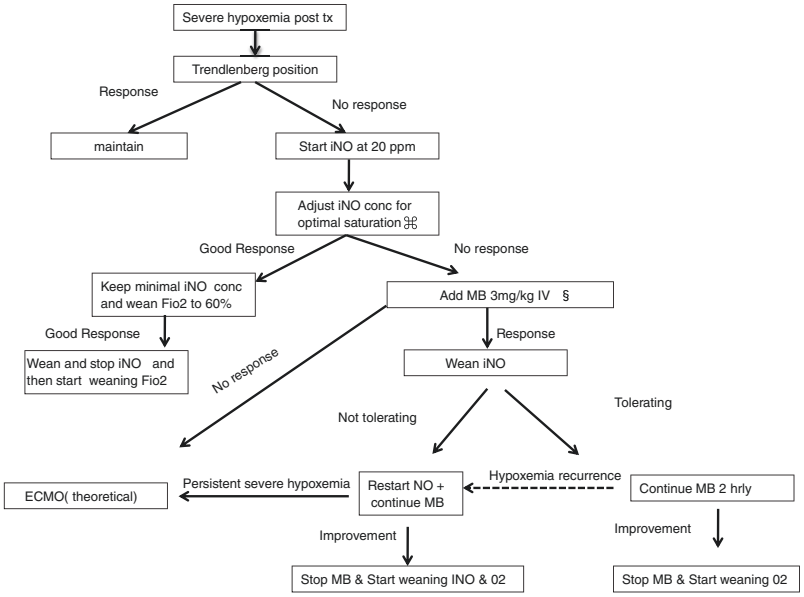
Treatment	Onset and peak	Mechanism of action
Trendelenburg position	Minutes	Gravitational redistribution of blood flow from basilar IPVDs
Inhaled nitic oxide	Minutes	Redirects blood flow from maximally dilated IPVDs
Inhaled epoprostenol		Paediatric experience with inhaled epoprostenol in HPS is limited
Methylene blue	30 min to 5 h	Methylene blue blocks NO-induced vasodilation and reduces flow through IPVDs
ECMO (theoretical)	Hours to sustained	Sustained oxygenation till IPVDs reverse

Table 6.2 Practical tips in managing HPS in post-transplant patient

Cautious and minimal use of oxygen is the key to successful outcome in transplant for HPS. Patient's body is used to low oxygen levels but not the donor liver, and so the balance has to be maintained (not too much, not too low)
Pre-op: Usually these patients are asymptomatic without tachypnoea or increased work of breathing. Do not start supplemental oxygen just for low saturation (it will only open up new shunts)
Intra-op: Immediately after intubation there would be a rise in PaO2 levels and saturation, titrate FiO2 to minimal to maintain PaO2 of 80–90 mmHg and sats of 92% during intraoperative period
Post-op • Keep the child flat or slightly head down position (make sure cuffed ET tube is used to prevent aspiration) • Titrate FiO2 to keep saturation of just above 88% • When saturation is persistently lower than 85% despite 100% oxygen, add nitric at standard dose (Max 20 ppm). There would be rise in saturation with in few minutes. Leave the child undisturbed for couple of hours. Keep that saturation as baseline try to titrate nitric down to minimal where you would notice saturation starts falling from baseline. That would be the baseline nitric oxide requirement. • Response is measured in the improvement or deterioration of P/F ratio (partial pressure of arterial oxygen/fraction of inhaled oxygen) by 20% in 30 min of intervention • Then, as the saturation improves titrate FiO2 down gradually (might take hours to days), once FiO2 reaches 60% try to wean off nitric. At this point non-invasive ventilation is possible • Sometimes it might be difficult to wean off iNO towards the end, in such scenario intravenous L-arginine infusion 15 mg/kg/min given over 20 min + sildenafil in the dose of 0.3 mg/kg has been shown to be helpful • Despite iNO if the child has persistent hypoxia, methylene blue could be given a at a dose 3 mg/kg IV. Patient could be kept in reverse Trendelenburg position to increase the blood flow to the lung bases where methylene blue could act locally • HFOV could be tried if still the child has severe hypoxemia
Don't look at Pao2—look at saturation and patients comfort in breathing. If the patient is comfortable and not tachypnoeic, do not increase the oxygen concentration

6.2 Portopulmonary Hypertension

Portopulmonary hypertension (PPHT) is defined as development of pulmonary arterial hypertension associated with severe liver disease or portal hypertension. The criteria for PPHT include an elevated mean pulmonary arterial pressure of >25 mmHg at rest, increased pulmonary vascular resistance with normal pulmonary capillary wedge pressure in the background of portal hypertension. The classification of PPHT is outlined in Table 6.3.



	iNo: inhaled nitric oxide
	FiO2 : fraction on inspired oxygen;
	¶ Inhaled epoprostinal could be tried based on local expertise
	⌘ HFVO could be tried if hypoxemia persists
	§ Try *reverse Trendelenberg position so that higher dose* Methylene Blue (MB) *is deliverd to the lung base where* majority of intrapulmonary vascular dilatations (IPVDs) are found
	Response is measured improvement or deterioration of P/F ratio (partial pressure of arterial oxygen/fraction of inhaled oxygen) by 20% with in 30 mins of intervention
	MB 3 mg/kg in 50–100cc's normal saline IV over 15 min. Peak effect can be seen between 30 mins to 5 hrs so might need to wait 5 hrs to see response
	Withhold MB after 3 doses and see response but not recommended for more than 24 to 48 hrs usage
	Try to keep the patient dry (fluid equibalance or slightly negative balance)
	Keep HB≥ 10 gm/dl for adequate systemic oxygen delivery

Fig. 6.1 Practical management protocol of hepatopulmonary syndrome during post-transplant (Tx) period. *iNo*-inhaled nitric oxide, *FiO2* fraction on inspired oxygen, ¶ inhaled epoprostenol could be tried based on local expertise, ⌘ HFVO could be tried if hypoxemia persists, and § Try *reverse Trendelenburg position so that higher dose* of methylene blue (MB) *is delivered to the lung base where* majority of intrapulmonary vascular dilatations (IPVDs) are found. Response is measured improvement or deterioration of P/F ratio (partial pressure of arterial oxygen/fraction of inhaled oxygen) by 20% within 30 min of intervention. *MB* 3 mg/kg in 50–100cc's normal saline IV over 15 min. Peak effect can be seen between 30 min and 5 h so might need to wait 5 h to see response. Withhold MB after three doses, and see response but not recommended for more than 24–48-h usage. Try to keep the patient dry (fluid equibalance or slightly negative balance). Keep HB ≥10 gm/dL for adequate systemic oxygen delivery

Table 6.3 Classification of PPHT

Portopulmonary hypertension	Mean pulmonary arterial pressure (mmHg)	Cardiac index (l/min/m^{-2})	Pulmonary vascular resistance (dyness·cm^{-5})	Right arterial pressure (mmHg)
Mild	25–34	>2.5	240–500	0–5
Moderate	34–44	>2.5	500–800	5–8
Severe	>45	<2	>800	>8

6.2.1 Clinical Features

- Dyspnoea on exertion
- Syncope
- Chest pain
- Fatigue
- Haemoptysis
- Loud P2, systolic murmur (TR), oedema, and ascites

Investigation requires cardiac catheterisation studies to confirm the diagnosis.

6.2.2 Management

- May show good response to medical management (however, prognosis with LT is worse when compared to HPS).
- Medication:
  - Prostacyclin analogues (epoprostenol: 30–90 ng/kg/min as continuous infusion).
  - Endothelin receptor antagonists (bosentan: 31.25 mg BD for wt 10–20 kg, 62.5 mg BD for wt 20–40 kg, 125 mg BD if wt is >40 kg).
  - Phosphodiesterase inhibitor (sildenafil: 0.5–1 mg/kg/dose 3–4 times/day).

Liver transplantation as therapeutic option could be offered to patients with mild to moderate PPHT responding to medication, while severe PPHT would remain as a contraindication of LT.

Caution

- Elevated right heart pressure is associated with passive congestion of transplanted liver, which could lead to graft loss.

Hepatorenal Syndrome in Children: Diagnosis and Management

7

Sukanya Govindan and Chandrasekaran Venkataraman

7.1 Introduction

Acute kidney injury (AKI) frequently complicates the clinical course in children with advanced liver disease and results in high morbidity and mortality. Hepatorenal syndrome (HRS) is an important cause of AKI, and the diagnoses of HRS are made after excluding other potential etiologies like sepsis, drugs, and hypovolemia. HRS is potentially reversible but carries a poor prognosis as pathogenesis is poorly understood and management is complex.

7.2 Definition

HRS is a "reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure." There is marked reduction in GFR and renal plasma flow (RPF) with no other identifiable causes of renal failure.

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7.3 Pathophysiology

Studies have identified four interrelated pathways that could cause HRS in liver patients. They are:

1. Peripheral arterial vasodilation associated with hyper dynamic circulation
2. Renal vasoconstriction probably due to stimulation of the renal sympathetic nervous system (SNS)
3. Above circulatory changes resulting in cardiac dysfunction and renal hypoperfusion
4. Action of various vasoactive mediators on different vascular beds including the renal vasculature

In addition, certain factors like spontaneous bacterial peritonitis, large volume paracentesis, and gastrointestinal bleeding may further complicate the clinical condition.

7.4 Clinical Presentation

The following features are characteristic of HRS in patients with established acute or chronic liver disease.

1. A progressive rise in serum creatinine
2. Bland urinary sediment
3. Proteinuria <500 mg per day
4. Low urine sodium
5. Oliguria (not all patients are oliguric)

7.5 Types of Hepatorenal Syndrome

1. *HRS type I* (*acute*)
   - Doubling of serum creatinine in <2 weeks.
   - Most children with HRS will have one or more precipitating event(s).
   - Response to diuretics.
   - Ten percent survival in 90 days without treatment.
2. *HRS type II*
   - Renal impairment is gradual and progressive.
   - No precipitating events.
   - Diuretic-resistant ascites.
   - Median survival (6 months).

The international club of ascites–acute kidney injury (ICA-AKI) criteria for diagnosis of HRS are the following:

- Presence of cirrhosis and ascites.
- Diagnosis of AKI according to ICA-AKI criteria.
- Absence of shock.
- No recent or current use of nephrotoxic drugs.
- No response to diuretic withdrawal for 2 consecutive days and plasma volume expansion with albumin (1 g/kg of body weight).
- No macroscopic signs of structural kidney injury defined as absence of microhematuria (>50 red blood cells per high power field), absence of proteinuria (>500 mg/day), and normal renal ultrasound.

In addition to these criteria, a definitive diagnosis of HRS can only be made by kidney biopsy especially in the presence of proteinuria and hematuria (after correcting coagulation abnormalities). Kidney histology will be essentially normal in HRS.

Tips

- HRS is a diagnosis of exclusion of other causes of renal impairment that may be found in cirrhosis.
- Cutoff value for s-Cr is difficult to apply to pediatric age group particularly in infants and young children.
- Doubling or more of their baselines-Cr values could be considered as an equivalent criterion (rather than a value of 1.5 mg/dl).

7.6 Differential Diagnosis

HRS is a diagnosis of exclusion. The following important conditions must be ruled out before making a diagnosis of HRS.

1. Glomerulonephritis
2. Vasculitis
3. Infection-related kidney injury
4. Pre-renal acute kidney injury
5. Acute tubular necrosis (ATN)
6. Nephrotoxins like NSAIDs, diuretics, aminoglycosides, etc.

Although infection should be ruled out before diagnosing HRS, presence of spontaneous bacterial peritonitis should not exclude diagnosis of HRS.

7.7 Treatment

The aim of medical therapy is to improve kidney perfusion by increasing mean arterial pressure and intravascular volume expansion with combination of vasoactive agents and IV human albumin. Liver transplant should be considered at the earliest.

- Norepinephrine (0.1–0.7 μg/kg/min IV) or vasopressin with albumin (1 g/kg/day IV) in critically ill patients.
- Terlipressin (0.5–2 mg tds S.C.,) with albumin (1 g/kg/day IV) in noncritical patients.
- Midodrine (2.5–10 mg tds PO) + octreotide (25–50 μg/h IV) with or without albumin (1 g/kg/day IV) can be used as alternatives to terlipressin in countries where it is not available.
- Medical therapy is usually futile if there is no improvement within 2 weeks of starting treatment.

In selected patients who do not respond to medical therapy, and who are clinically stable, transjugular intrahepatic portosystemic shunt (TIPS) can be considered but is associated with high complication rate. Dialysis can be used as a bridge till recovery of hepatic function along with medical measures or until the child undergoes a liver transplant. Combined liver kidney transplant is an option for patients with no recovery of renal function and on long-term dialysis.

7.8 Prevention of HRS

Risk factors for HRS include diuretic refractory ascites, spontaneous bacterial peritonitis, and progressive liver dysfunction. The following strategies have been used to prevent HRS in children and are typically the same as in adult patients.

- IV albumin therapy especially in patients with SBP
- Antibiotic prophylaxis for SBP
- Pentoxifylline

7.9 Prognosis

HRS increases the overall mortality rate in children with liver disease. The outcome of these patients is strongly dependent on recovery of liver failure either by medical therapy or liver transplantation. The rate of renal recovery following improvement in liver failure is unpredictable. However a significant proportion of patients show recovery of renal function after successful liver transplantation.

Management of Acute Portal Hypertensive Bleed

8

Naresh Shanmugam

8.1 Introduction

- Portal hypertension (PHT) is defined as elevation of portal pressure more than 5 mm of Hg.
- Direct measurement of portal pressure is difficult, and so hepatic venous pressure gradient (HVPG) is measured which is reflective of portal pressure.
- HVPG is pressure difference between wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP).
- HVPG of more than 10 mm of Hg is associated with the development of varices, and pressures more than 12 mm of Hg is associated with variceal bleed.

Tips

- Invasive methods of measuring portal pressure are not essential in clinical practice.
- Splenomegaly, thrombocytopenia and oesophageal varices hint towards presence of PHT.

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8.2 On Arrival of Patient with Haematemesis

- Assess airway, breathing and circulation and act appropriately.
- Assess conscious level for encephalopathy.
- Intubate and ventilate (in case of poor GCS).
- Check BP/pulse/temperature.
- Site 2 large bore IV cannulas.
- FBC, INR, renal, liver, and bone profiles; blood cultures and urinalysis.
- Chest X-ray and arterial blood gas if intubated.
- Fluid bolus until circulation stabilises.
- Strict fluid balance, 40–60 mL/kg/day crystalloid using 5 or 10% dextrose with 2 mmol/kg/day (Na restriction in CLD).
- Nasogastric (soft silicone) tube placement and gastric lavage help to quantify the blood loss as well as to remove blood from the stomach that could precipitate encephalopathy.
- Crossmatch 2 units of packed cells (1 unit if <1 year of age).
- Give all patients
  - IV antibiotics.
  - Ranitidine 1 mg/kg TDS IV or omeprazole IV BD.
  - Vitamin K 1 mg/day IV.
  - Sucralfate 1 g qds if alert and conscious.
- Start octreotide in a dedicated line. Start at 25 μg/hr in 0.9% sodium chloride and increase to 50 μg/h. Continue for 48 h after bleeding is controlled. Do not stop suddenly due to risk of rebound increase in portal pressure. Wean gradually and stop.
- Commence transfusion of packed cells slowly, sufficient to maintain adequate circulation and urinary output.
- Target HB around 8–9 g/dL and do not transfuse too rapidly as this will lead to increase in portal pressure, risking further bleeding.
- Check blood glucose 2–4 hourly to maintain between 6 and 9 mmol/L, increase dextrose concentration if needed.
- After adequate fluid resuscitation if BE remains <−10 mmol, correct metabolic acidosis with bicarbonate infusion.

Tips

- Most of PHT variceal bleed stops spontaneously.
- Stabilise the child and then transfer to the centre with endoscopic facility.

Caution

- Never shift unstable child for endoscopy.
- Endoscopy in actively bleeding child is very difficult, as the blood would obscure the field of vision.

8.3 Sengstaken–Blakemore (SB) Tube Placement

Original SB tube has only three lumens (gastric balloon port, gastric aspiration port and oesophageal balloon port). There is no oesophageal aspiration port and so high risk of aspiration from oesophageal pooling of salivary secretions. Minnesota tube or modified SB tube (Fig. 8.1) has four lumens (additional oesophageal aspiration port). It is used in life-threatening upper GI bleed where EVL/ESL failed or not available. In the era of modern endoscopy and intervention, pressure tamponades using these tubes are rarely needed.

1. Usually these patients are intubated and ventilated. Trained personnel should insert the Minnesota tube.
2. Minnesota tube has to be stored in freezer so that it is stiff and easy to insert.
3. Choose appropriate tube size according to weight.

Patient weight	Sengstaken tube size
10–25 kg	Paediatric, size 14 FG WSP
25–30 kg	Paediatric, size 16 FG WSP
30–45 kg	Adolescent, size 18 FG WSP

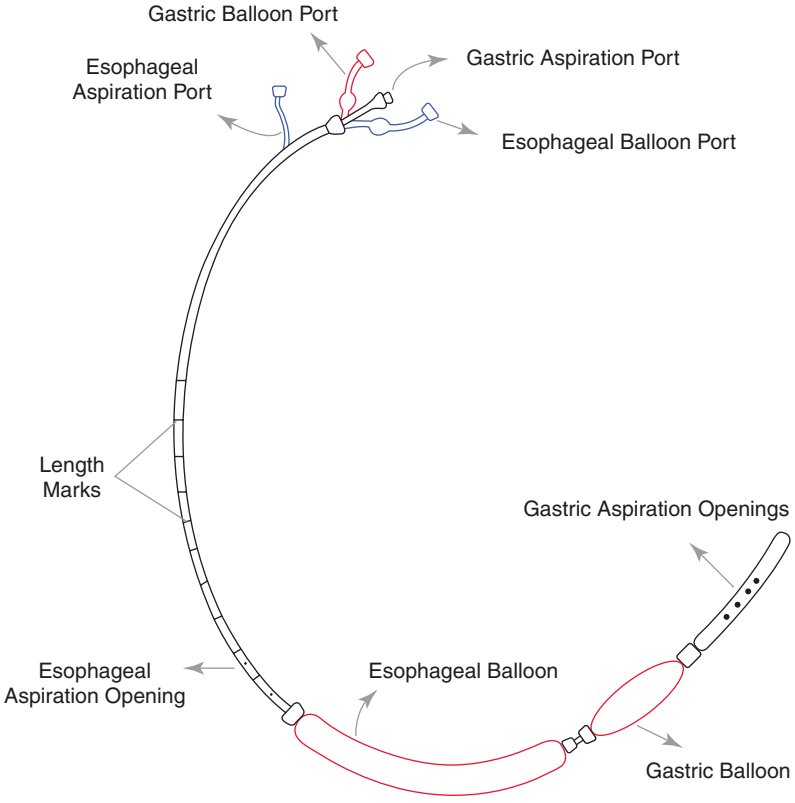

Fig. 8.1 Sengstaken-Blakemore

4. Determine correct volume of gastric balloon. Air or diluted contrast solution could be used to inflate the gastric balloon.
5. Insert the tube through one of the nostrils, and once sufficient length is inside, check whether tip is in the stomach by aspiration and checking pH. Once you are sure that it is in the stomach, fill the gastric balloon with air/contrast solution (100–150 cc) and then slowly apply traction so that the distended gastric balloon hinges against gastro-oesophageal junction. Perform chest X-ray.
6. Now inflate the oesophageal balloon to a pressure of 35–40 mm Hg. Pressure could be checked using a sphygmomanometer attached to the oesophageal lumen through a three-way tap.
7. With traction pressure, stick the catheter to the cheek with tape.
8. Release traction after 12 h for 1 h and for 1 h every 6 h thereafter (to prevent pressure necrosis).
9. Leave on free drainage; do not aspirate gastric balloon for 24 h.
10. Once the bleeding is controlled and patient is stable (usually 48 h), remove the tube in theatre, followed by endoscopy and intervention (EVL/ESL).

Caution

- Migration of gastric balloon to the oesophagus can cause respiratory distress and pressure necrosis.
- Too much traction can cause pressure necrosis gastro-oesophageal junction.

8.4 Endoscopic Intervention in Variceal Bleed

8.4.1 Endoscopic Variceal Ligation (EVL)

- This is a procedure where elastic band is applied under direct endoscopic vision over engorged varix, so that it obliterates the varix.
- Usually this procedure is used in oesophageal varix as the bands slip when applied over the gastric varix.
- Endoscopic Band Ligation Kit is available. This consists of a short plastic tube with elastic bands mounted on it. This unit is inserted at the distal end of standard endoscope. A wire from the unit is attached to a rotating knob at the proximal end of the endoscope. Turning the knob can deploy the elastic bands.
- Under direct vision a small loop of varix is sucked into the plastic mount, and the elastic band is deployed. The number of bands in the applicator is based on the manufacturer. Usually there would be six bands.

8.4.2 Endoscopic Sclerotherapy (EST)

- Using a flexible shielded injection needle, each varix was injected individually with 1–2 ml of 5% ethanolamine oleate at a level of about 2–3 cm above the GOJ junction.

Tips

1. Avoid nasogastric tube or feeding tube placement for 24–48 h.
2. This can dislodge the necrosed varix and cause severe bleed.
3. Avoid repeat endoscopy for the first few days for the same reason.

8.4.3 *n*–Butyl Cyanoacrylate Glue (Histocryl)

Bleeding from gastric varices is difficult to control with EST/EVL. In such cases cyanoacrylate glue is injected into the varices for haemostasis. Usually it is mixed with lipoidal oil and injected.

8.4.4 Hemospray®

Hemospray is a powder, which could be sprayed over bleeding site via the endoscope. It acts by forming a barrier over the bleeding site, increasing local concentration of clotting factors and activating the intrinsic clotting cascade. It is primarily approved for non-variceal GI bleed, but it is widely used in emergency when the gastric variceal bleeding is not controlled by cyanoacrylate glue.

8.4.5 Transjugular Intrahepatic Portosystemic Shunt (TIPS)

It is a procedure where a bypass channel is created by interventional radiologist between portal vein and hepatic vein resulting in decompression of portal pressure. In case of intractable portal variceal bleeding, TIPS is used as second-line therapy.

8.4.6 Surgery

Emergency shunt surgery to decompress portal vein is rarely used.

8.5 Secondary Prophylaxis

Patients who have bled may require secondary prophylaxis with propranolol 0.5–1 mg/kg/dose twice a day.

Acute Metabolic Decompensation: Crisis Management

9

Naresh Shanmugam and Roshni Vara

This chapter outlines diagnosis and management of hypoglycaemic and hyperammonaemic crisis in children.

9.1 Hypoglycaemic Crisis Beyond Newborn Period

9.1.1 Definition

Blood glucose level of <2.6 mmol in newborn and level of <3.0 mmol at any age is defined as hypoglycaemia in nondiabetic person.

9.1.2 Presentation

Usually these children are brought to the emergency department with lethargy, feed refusal and/or seizures and confirmed with bedside glucometer.

Approach to hypoglycaemia in child:

- Check ABC and act appropriately.
- Insert wide bore cannula and collect blood samples. Give glucose bolus not more than 200 mg/kg (10% glucose, 2 mL/kg), and start infusion at rate given in Table 9.1.

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Table 9.1 Dextrose infusion rates for various age groups

Age (years)	Glucose infusion rate (GIR) (mg/kg/min)	10% glucose infusion rate (mL/kg/day)
Up to 2 years	10	150
2–6 years	8	120
>6 years weight <30	6	90
>6 years weight 30–50	4.5	67

Aim to keep blood glucose between 4 and 7 mmol/L, adjusting infusion accordingly

- Sent blood for free fatty acids, 3-beta-hydroxybutyrate, acylcarnitines, insulin, cortisol, lactate, liver function test, electrolytes+ arterial blood gas + urine ketones as first line+ infection screen.
- Blood ammonia, serum amino acid profile + urine organic acid as second-line investigations.
- Genetic study for fructose intolerance if suspected from clinical history.

9.1.3 Background

- Patients with GSD (glycogen storage disorder) can have hypoglycaemic episodes, particularly when they are unwell with fever, vomiting and decreased food intake and can present to emergency department with drowsiness and seizures.
- Seizures are almost always due to hypoglycaemia and the initial treatment should be glucose rather than anticonvulsants.
- Check blood sugar upon arrival in the emergency department, insert cannula, send blood for electrolytes and laboratory glucose and give bolus dextrose followed by infusion rates shown in Table 9.1.
- Check blood glucose, U&Es, blood gas and other tests as appropriate. Monitor BM stix two hourly if the child's condition is stable. If unstable, monitor BM hourly with blood glucose.
- *Add appropriate electrolytes to the 10% dextrose to avoid hyponatraemia and hypokalaemia and monitor electrolytes.*
- If the patient is not improving, consider cerebral oedema and seek specialist help.
- Allow the child to eat and drink when they wish (unless further vomiting seems likely) and, once they tolerate enteral feeds, discontinue IV.

9.1.4 Differential Diagnosis

Figures 9.1 and 9.2 showing common conditions presenting with hypoglycaemia and their associated biochemical and clinical findings.

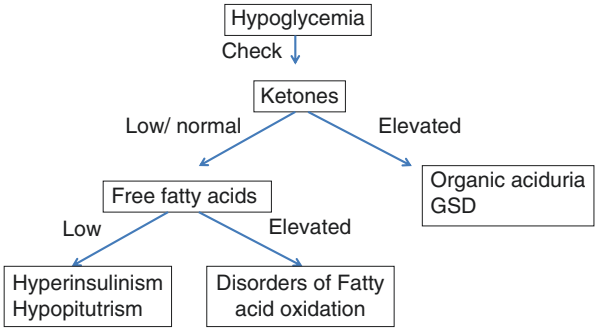

Fig. 9.1 Diagnostic algorithm in children presenting with hypoglycaemia based on ketones and free fatty acids

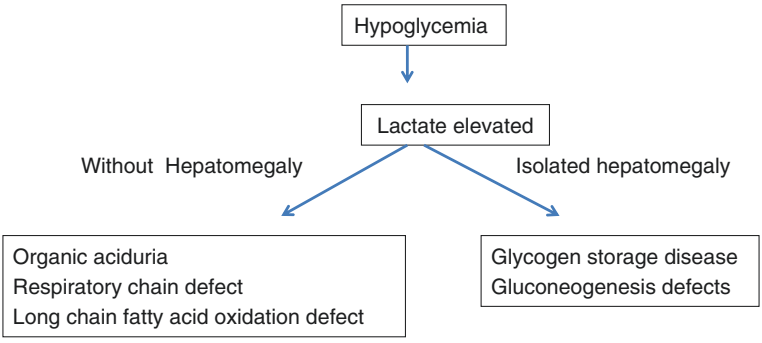

Fig. 9.2 Diagnostic algorithm in children presenting with hypoglycaemia based on liver enlargement

9.2 Hyperammonaemic Crises

Ammonia is produced from deamination of amino acids to non-toxic urea by the urea cycle, based in the liver. Ammonia should be measured in any sick neonate or any child with unexplained reduced level of consciousness.

- Early recognition and treatment of hyperammonaemia is vital in order to reduce morbidity and mortality.
- Normal values generally are <100 μmol/L for neonates and <50 μmol/L for infants and the older child.
- Any ammonia level >200 μmol/L requires immediate action. Always repeat with a free-flowing sample, taken to the laboratory on ice and alert the laboratory.
- Table 9.2 highlights few of the common condition that presents with hyperammonaemic crisis.

Table 9.2 Differential diagnosis in hyperammonaemic crisis

Metabolic Disorders
1. Urea cycle defect
• Carbamoyl phosphate synthase (CPS) deficiency
• Ornithine transcarbamylase (OTC) deficiency
• *N*-acetyl glutamate synthase (NAGS) deficiency
• Argininosuccinate synthase deficiency (citrullinemia)
• Argininosuccinate lyase deficiency (argininosuccinic aciduria)
• Arginase (argininaemia)
2. Organic acidurias
• Propionic acidaemia, methylmalonic acidaemia, etc.
3. Disorders of fatty acid oxidation
4. Others
• Lysinuric protein intolerance
• Hyperinsulinaemic hyperammonaemia
• Mitochondrial respiratory chain defect
• Citrin deficiency (citrullinaemia type 2)
• Congenital lactic acidosis
• Pyruvate dehydrogenase deficiency
Acquired
1. Liver failure
2. Infections—sepsis, urinary tract infections, bacterial overgrowth, etc.
3. Reyes syndrome
4. Transient hyperammonaemia of newborn
Artefactual increase
1. Poor specimen quality/haemolysis
2. Improper transport (not on ice)
3. Delayed analysis

9.2.1 Investigation

- All patients with hyperammonaemia should have additional biochemical tests: blood glucose, blood gases, urea and electrolytes, calcium, liver function tests, clotting studies, glucose and lactate and urine ketones as first line.
- *Metabolic investigations* to be sent are plasma amino acids, urine organic acids and blood spot acylcarnitines. A DNA sample should be stored prior to transfusion.
- Tables 9.3 and 9.4 suggest differential diagnosis of urea cycle defects and organic acidaemias based on metabolic profile, respectively.

9.2.2 Management

Management of child with hyperammonaemia and crisis management in known metabolic patient with hyperammonaemic crisis:

1. Usually parents would have been instructed to bring the child to the hospital if child is unwell and not able to take oral medication. This could be vomiting, diarrhoea, fever, etc. Sometimes the child could be brought with seizures, encephalopathy, shock, etc.

Table 9.3 Differential diagnosis of urea cycle defects based on metabolic profile

Disorder	Urine orotic acid	
CPS deficiency	N or ↓	Citrulline N or ↓ Arginine N or ↓
NAGS deficiency	N or ↓	Citrulline ↓ Arginine ↓
Citrullinemia	↑	Citrulline ↑↑ Arginine ↓
Argininosuccinic aciduria	↑	Argininosuccinate ↑↑ Citrulline ↑ Arginine ↓
OTC deficiency	↑↑	Lysine ↑ Citrulline ↓ Arginine ↓
Argininaemia	↑↑	Arginine ↑↑

Table 9.4 Differential diagnosis of common organic aciduria on metabolic profile

Disorder	Urine orotic acid	
Propiopnic aciduria	↑ or N	Propionylcarnitine ↑↑ Carnitine/acylcarnitine ↓ C5 and C6 ketones (low)
Methylmalonic aciduria	↑ or N	Methylmalonic acid ↑↑ Carnitine/acylcarnitine ↓

2. On arrival assess the child (airway, breathing, circulation). If needed intubate and ventilate. Give glucose 200 mg/kg as a bolus (2 mL/kg of 10% glucose or 1 mL/kg of 20% glucose) over a few minutes. This should be followed up with fluid resuscitation.
3. If the problem is feed refusal with normal GCS, the child can be offered carbohydrate drink orally/NG tube.
4. If child is encephalopathic or in shock with low GCS, incubate and ventilate.

Tips

- Avoid ringer lactate solution as patients with metabolic defects might not able to clear lactate efficiently.
- Avoid propofol as anaesthetic agent as it can interfere with mitochondrial function.

5. If there are signs of raised ICP, give mannitol or 3% saline, and arrange for haemodialysis urgently.
6. Sent blood investigations: blood glucose, blood gases, urea and electrolytes, calcium, liver function tests, clotting studies, ammonia, lactate and urine ketones as first line. Ammonia may be normal in early decompensation.

Table 9.5 Common drugs used in hyperammonaemia

Drug	Loading dose over 90 min (mg/kg/day)	Followed by maintenance dose over 24 h (mg/kg/day)	Thereafter maximal daily dose (Oral)
Sodium benzoate	250	250 (maximum 500)	500 mg/kg/day in four divided dose
Sodium phenylbutyrate	250	250 (maximum 500)	600 mg/kg/day in four divided dose
Carbaglu			100 mg/kg/day in four divided dose
Arginine	150	150–300	500 mg/kg/day in three divided dose
Carnitine	100	100–200	300 mg/kg/day in three divided dose

Note: 1 g sodium benzoate and phenylbutyrate contain 7 mmol Na and 5.4 mmol Na, respectively Hydroxocobalamin 1 mg/day IV or IM (helpful in MMA) and biotin po or iv 10–40 mg/day (helpful in PA)

7. Most children will require an IV infusion of glucose, which should be started immediately.
8. Start with an infusion of 10% glucose, at the rates suggested in Table 9.1.
9. Sodium benzoate and phenyl butyrate should be given as continuous intravenous infusions, unless mild elevation and able to tolerate oral medications. These drugs can be given together—the maximum concentration for infusion being no more 50mg per ml of 10% dextrose. Drug dosage is given in Table 9.5.
10. *If there is any hint of encephalopathy, start neurological observations and seek specialist help. Under these circumstances, fluid volumes should be reduced to minimise the risk of cerebral oedema. Intubate and ventilate if the GCS is poor and the child cannot maintain airway.*
11. Monitor ammonia, urea, electrolytes, glucose, blood gas, etc., every 4–6 hours according to the clinical state.
12. If the patient deteriorates or the ammonia has not started to fall within 6–8 h, seek specialist help; haemodialysis may be needed.
13. Extracorporeal detoxification should be started in neonates and infants who have blood ammonia levels >400–500 μmol/L. In children if ammonia exceeds 200 μmol/L, preferred method is continuous venovenous hemodiafiltration (CVVHD).
14. If the child improves, allow enteral feeds.

Further Reading

http://www.bimdg.org.uk/site/guidelines.asp
http://www.metbio.net/metbioGuidelines.asp

Renal Replacement Therapy in Liver Disease

10

Bogdana Sabina Zoica and Akash Deep

10.1 Introduction

Liver failure is associated with secondary organ dysfunction which includes renal impairment. Coexisting and/or independent liver and renal dysfunction impacts significantly on hospital and intensive care mortality. Renal replacement therapy (RRT) is used either to support the failing kidney or to facilitate excretion of toxic products such as ammonia that can have detrimental effect on other organ systems.

10.2 Indications of RRT

The following are considered indications for initiation of CRRT in ALF:

- Metabolic abnormalities (hyponatremia Na < 130 mEq/L, metabolic and or lactic acidosis resistant to fluid therapy)
- Hepatic encephalopathy grade 3–4
- NH3 > 150 mmol/L increasing progressively or an absolute value >200 mmol/L
- Renal dysfunction (oligo-anuria, hyperkalemia, fluid overload)
- Fluid overload

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10.3 Types of RRT with Advantages/Disadvantages

10.3.1 Slow Continuous Ultrafiltration

- The simplest form of CRRT removes water + some solutes from the blood via convective process.
- Nowadays mostly used for patients on ECMO (by only placing a filter within the circuit).
- Can be used with either a venoarterial or a veno-venous system.
- May result in dangerously high fluid removal rate, shock, and severe electrolyte anomalies.

Solute removal can be achieved by

- Convection = CVVH
- Diffusion = dialysis (CVVHD)
- Dialysis and convection combined = CVVHDF

10.3.2 Continuous Veno-venous Hemofiltration

- Uses convection for solute removal. Convection is the transfer of a solute in a stream of solvent, across a semipermeable membrane, mediated by a hydrostatic force (fluid added pre or post filter).
- Bigger molecules are easier to filter because there is a force added to the motion of the blood across the membrane.
- This is important because all inflammatory mediators are middle-sized molecules.

10.3.3 Continuous Veno-venous Hemodialysis

- Diffusion is the movement of solute across a semipermeable membrane from an area of high concentration to an area of lower concentration. It relies on the random Brownian movement of the molecules. The smaller the molecule, the faster it moves and therefore the more chances to encounter the pores of the membrane. The larger molecules move slower, and when they do hit the membrane, they do not always pass through. Therefore, CVVHD is suitable for removal of small molecules and most middle molecules.
- Clearance is proportional to dialysate flow rate. In conventional HD clearance is proportional to blood flow.
- Countercurrent dialysis flow.
- CVVHD dialysate flow = 2 L/1.73 m^2/h and can be steadily increased depending on clearance of the solutes, especially ammonia.

10.3.4 Continuous Veno-venous Hemodiafiltration

- Combination of the 2 methods. Uses convection + diffusion together

10.4 Equipments Needed (Catheter Types, Size, Machines)

(a) *Vascular access*

- The efficacy of RRT relies on your vascular access.
- The size and the site of the access both influence the adequacy of blood flow and filter life.
- Which vein is used and which size of catheter are based on patient characteristics and expected duration of treatment (short or long term).

Weight	Catheter size
<3 kg	Double lumen 6.5 Fr jugular
3–5 kg	6.5–8 Fr
5–15 kg	8–10 Fr
15–30 kg	8–10 Fr
>30 kg	10-11.5 Fr 12 and 15 cm

- The length of catheter is also important.
- Measure from site of insertion to navel for femoral catheters and from site of insertion to upper third of the sternum for internal jugular catheters. Adjust lower depending on available sizes. You may have to withdraw your catheter after X-ray check.
- Adjust lower depending on available sizes.
- You may have to withdraw your catheter after X-ray check.

(b) *Machines*

- Discuss with management and purchase machines as per departmental needs.
- Make sure staff are well trained and able to troubleshoot.
- Make sure that you have access to spare machine in case of failure.
- Discuss and create simulation cases specific for RRT in which staff participate in order to further familiarize team with potential complications.

10.5 How to Run It and Monitor It (Priming, Anticoagulation)

- Aim for an extracorporeal circuit volume of <10% total circulating volume.
- If more than 10% consider blood prime or albumin 5% prime depending on Hb levels.
- Blood flows 4–5 mL/kg/min.
  - 0–10 kg—>50 mL/min (minimal flow used)
  - 11–20 kg—>80–100 mL/min
  - 21–50 kg— > 150 mL/min
- Flows also depend on catheter size.
  - 6.5 Fr—>8–12 mL/kg/min
  - 8 Fr —>5–8 mL/kg/min
  - 10 Fr —>4–6 mL/kg/min
  - 11.5 Fr—>2–4 mL/kg/min

- Blood flows do not determine clearance on CVVH/CVVHD. They are important in determining the filtration fraction to avoid hemoconcentration and increased risk of clotting.
- The risk of clotting goes up with lower flows.
- The starting dialysate flow is 2 L/1.73 m^2/min. This is standardized and therefore allows comparison of patients and prediction of results in terms of toxin removal but more importantly in terms of drug clearance.
- *Circuit priming*
  - Use 1 L 0.9% saline to prime circuit. *Do not prime anticoagulation line*.
  - Run in recirculation for minimum 10 min.
  - If patient is <10 kg, prime circuit with blood.
  - Do not blood prime circuits in children immediately post liver transplant or those at risk of GVHD or hemolytic disease.
  - For septic shock and acute liver failure, electively change circuit every 24 h for first 3 days.
- *Anticoagulation*
  - Unfractionated heparin, regional anticoagulation dose: 10–30 U/kg/h. Monitor with 4–6 hourly ACT.
  - LMW heparin
  - Citrate regional anticoagulation – rarely used as citrate is metabolized by the liver and there is a risk of citrate toxicity in liver failure.
  - Prostaglandins: PgI2, PgE1.

Troubleshoots

- Most heparin products are phosphate bonded.
- Cross-contamination of blood samples will end up with abnormal phosphate levels. This is especially important in patients with tumor lysis syndrome.

Prostacyclin is a useful option in bleeding or at risk of bleeding children.

Dose 2–8 ng/kg/min, no complex monitoring tests required except thromboelastogram (TEG) or rotational thromboelastography (ROTEM) in case of clinical bleeding.

- *Replacement fluid*
  - Accusol 35 with potassium if serum potassium is ≤5 mmol/L.
  - Accusol 35 if the child's serum potassium level is >5 mmol/L.
  - Polyfusor phosphate to achieve serum level 1.1–1.8 mmol/L.
  - Prescribe polyfuser phosphate 1 mmol/h per 1000 mL/h pre-dilution fluid.
  - Aim serum potassium 4 mmol/L, phosphate.
- *Removal of fluids/blood products*
  - Fluid boluses to improve blood pressure should not be removed.
  - Blood products should be removed exactly mL/mL at the time of the administration.

- *How to remove products*
  - Record current totals and reset.
  - For FFP, cryoprecipitate, and platelets, add prescribed volume of transfusion to half of hourly fluid loss.
  - Set hourly rate at double the volume of transfusion.
  - Commence infusion. On completion, reset totals again and carry on with previous prescribed treatment.
  - For blood transfusions add the hourly rate of blood to hourly fluid loss rate, over prescribed time.
  - Do not remove product volume after administration.
- *Blood tests*
  - Check U&Es, Ca, Mg, PO4, albumin and ammonia, prior to commencement of CRRT, after 6 h of therapy and every 12 h afterwards repeat check. Then every 12 h.
  - If any CNS involvement (head injury, encephalopathy, seizures), check urine and serum osmolality prior to CRRT, after 6 h of therapy and then daily.
  - FBC, coagulation profile (INR, APTR, fibrinogen) every 12–24 h.
  - Check blood gases as a baseline, every 1–4 h while on CRRT.
  - ACT should be performed according to local anticoagulation guidelines.
  - In babies <10 kg send a cross-match to blood bank as per local protocol to ensure blood is constantly available for emergency blood priming.

Tips

- Intensivist to be physically present at initiation as hypotension is a common complication.
- Start without removing fluid and reassess in a few hours then gradually increase your fluid removal as tolerated.
- Internal jugular vein catheters are associated with longer circuit life and less problems related to kinking, infection, or impaired flow.
- CVVH and CVVHD are equivalent in performance for small molecules.

Extracorporeal Support in Liver Disease: Plasma Exchange/Plasmapheresis

11

Deepti Sachan

Plasmapheresis is the removal or exchange of blood plasma. Therapeutic plasmapheresis and therapeutic plasma exchange (TPE) are terms that are often used synonymously. TPE has been increasingly used over the past decade as a first-line and lifesaving treatment for various conditions classified by the American Society for Apheresis (ASFA).

11.1 Indications in Pediatric Liver Disease

Indication	ASFA category	Remarks
1. Wilson disease fulminant hepatic failure	Category I	It can rapidly remove significant amount of copper and thereby reduce hemolysis, prevent progression to renal failure, and provide clinical stabilization. It has been reported to be used as a bridge to LT or can led to elimination of the need for urgent LT
2. ABO incompatible liver transplantation	Category I	Used as a preconditioning protocol to reduce anti-A or anti-B antibody titers below a critical threshold in peri-transplant period with the goal of preventing rejections and facilitating graft survival Frequency depends upon patient's ABO titers and rate of antibody production
3. Early humoral graft rejection	Category III	Decreases level of ABO antibodies
4. Acute liver failure due to viral hepatitis, drug induced hepatitis, etc.	Category III	TPE removes albumin bound and large molecular weight toxins – aromatic amino acids, ammonia, endotoxin, indols, mercaptans, phenols, and other factors

(continued)

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Indication	ASFA category	Remarks
5. Sepsis with multi-organ failure	Category III	Remove pro-inflammatory mediators and, when using plasma replacement, provide anti-inflammatory factors, immunoglobulins, procoagulants, and natural anticoagulants as well as ADAMTS 13 in an effort to restore pathobiological process and restore hemostasis
6. Thrombotic microangiopathy drug-associated	Category I–III	Removal of plasma protein-bound drug
7. Familial homozygous hypercholesterolemia	LDL apheresis I TPE-II	Reduces time-averaged total cholesterol >50% and LDL >60% from baseline

11.2 Methods

- Spectra optia cell separator is based on centrifugation technology.
- Vascular access: Central venous access. The adequacy of venous access will vary according to the age, gender, and size of the child. Normally, a 17 gauge or larger gauge needle is needed for the draw line and a 19 gauge or larger gauge needle is needed for the return line.
- Anticoagulation: Acid citrate dextrose (ACD) in 1:8 to 1:15 ratio depending on clinical condition of patient and desired procedure. A preprocedure hematocrit, platelet count, and prothrombin time are required. Ionized calcium levels should be obtained before treatment and repeated once or twice during procedure, depending on its duration and the dose of citrate administered. Calcium supplementation is given slowly intravenously to maintain an ionized calcium >1,00 mmmol/L.
- Red cell prime: In adults and older children, saline is used to prime extracorporeal circuit. A blood prime is required in children weighing <20 kg or if the extracorporeal volume (ECV) exceeds 10–15% of the child's TBV and/or if hematocrit decreases below 20% to prevent large shifts in fluid balance and maintain a hematocrit during the procedure.
- The patient's plasma volume can be estimated either by using nomogram (gender, height, weight, hematocrit) or by making calculations based on weight and hematocrit.
  - TBV can be calculated according to the following estimated blood volume per kg of body weight: neonates = 100 mL/kg, infants and smaller children = 80mL/kg, older children =70 mL/kg.
  - The formulas are as follows: TBV = volume/kg × kg of body weight.
  - PV = TBV X (1-hematocrit).
- Plasma volume process: 1.0–1.5 PV is processed with replacement fluid as 5% albumin, fresh frozen plasma, or cryo-poor plasma. The procedure is repeated daily or on alternate days based on indication.
- Flow rate: 20–30 mL/min.

TPE seems to be an effective approach for clearing toxins, immune-mediated antigens, and other particles from the circulation. The increase in plasma of these toxic substances may be responsible for hepatic coma, hyperkinetic syndrome, decreased systemic vascular resistance, and cerebral blood flow. TPE restores hemostasis by supplying the coagulation factors and removing activated clotting factors, tissue plasminogen activator, fibrin, and fibrinogen degradation products. Improved cerebral blood flow, mean arterial pressure, cerebral perfusion pressure, and cerebral metabolic rate and increased hepatic blood flow are also reported after TPE.

12 Perioperative Management of Kasai Portoenterostomy and Liver Resection in Children

Naresh Shanmugam and Alastair Baker

12.1 Kasai Portoenterostomy/Hepaticojejunostomy

12.1.1 Background

Biliary atresia (BA) is obliteration of part of or the entire extrahepatic biliary tree.

- Incidence is 1: 9,000–16,000 live births. Aetiology is unknown.
- Type III is commonest (atretic common bile duct extending to porta hepatis).
- Surgery entails dissecting the portal plate and anastomosing jejunal loop of intestine, so that bile can drain directly into intestine. Possible consequences include generalised third spacing of fluids and ileus.
- Hepaticojejunostomy for biliary lesions including choledochal cysts are based on the Kasai protocol modified for patient size.

12.1.2 Biliary Atresia (BA) Medical Management

12.1.2.1 Pre-op Bowel Prep

Oral bowel prep begins 48 h pre-op which may be given at home.

1. Metronidazole	7.5 mg/kg	TDS oral
2. Lactulose	5 mL	BD oral
3. Gentamicin	2.5 mg/kg	TDS oral

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12.1.2.2 Pre-Kasai on Admission

- Patient admitted the day before surgery.
- Pre-op crossmatch of one adult unit of blood.
- Make sure blood for CMV IgM is sent to virology.

12.1.3 Kasai Procedure

Day 1 (0–24 h post op)

- Patient is usually extubated in theatre.
- Continue IV antibiotics: (first dose given presurgery) piperacillin-tazobactam is usually used as monotherapy at 90 mg/kg TDS (max 4.5 g TDS) for 5 days (aminoglycosides could be added based on local recommendation).
- Maintenance fluids: 10% dextrose + 1.5 mmol/kg/day NaCl + 1 mmol/kg/day K at 70 mL/kg/day. Add potassium as guided by blood tests.
- Strict input/output monitoring.
- NG losses replaced mL for mL with 0.9% saline + 10 mmol KCl.
- Drain losses replaced mL for mL with 4.5% human albumin solution (HAS).
- Stat of 10 mL/kg FFP or 4.5% HAS or NS on return from theatre (this is to replace insensible loss and fluid lost due to liver congestion during surgery).
- If operative blood losses are moderate/high. Will need deficit correction.
- Check U + E/blood gas on return from theatre, 4 hourly blood glucose.
- Start IV vitamin K (1 mg OD) and IV ranitidine (1 mg/kg TDS). Not for oral medications for 4 days.
- Monitor effectiveness of analgesia (epidural or morphine infusion). May need further analgesia if required.

Day 2

- Maintenance fluids: 10% dextrose + 1.5 mmol/kg/day 30% NaCl at 90 mL/kg/day (+K if required).
- Discuss NG/drain replacement regime and when to remove.
- Check FBC, U + E, albumin, and Ca.
- Second dose of 10 mL/kg FFP or 4.5% HAS or NS is given if needed.
- Reduce analgesia as appropriate.
- While analgesia is still effective, parenteral fat-soluble vitamins could be given to improve stores:
  - Vit D 30,000 iu IM (60,000 if radiological rickets is present)
  - Vit E 10 mg/kg IM
  - Vit A 10,000 iu IM

Day 3/Day 4

- Maintenance fluids: increase to 120 mL/kg/day (10% dextrose + 1.5 mmol/kg/day of NaCl+ K if needed).

- To start some enteral feeds (unless advised otherwise from surgical team).
- Usually start with oral rehydration solution (ORS) at 5 mL/h and gradually increase as tolerated.
- If ORS tolerated, to start milk (e.g. EBM/Pregestimil/Heparon Junior) and build as tolerated.
- Central lines to be removed if not used.
- Discuss NG/drain replacement regime and when to remove.
- Check FBC, U + E, Ca + albumin (stop monitoring if blood reports are stable and off IV fluids).
- Wean/stop analgesia as appropriate.
- Once oral milk feeds are being established, change to oral antibiotics, and start oral medications (see below).

12.1.4 Oral Medications

- Multivitamin drops/syrup.
- Alpha tocopheryl acetate liquid 10 mg/kg OD.
- Phenobarbitone 15 mg nocte increasing to 45 mg in steps of 15 mg/week as tolerated (until jaundice clearance).
- Ursodeoxycholic acid 10 mg/kg BD (can be increased to TDS).
- Vitamin K 1 mg daily (phytomenadione 2 mg/0.2 mL).
- Cefalexin (125 mg/5 mL). Dose 25 mg/kg/day in two divided doses. Doses should be rounded to a volume easy to administer. For total 1 month.

12.1.4.1 Steroid Protocol

To start oral steroids based on hospital policy (make sure that CMV IgM status is negative):

- Prednisolone tablets (5 mg/kg) for 5 days reducing by 1 mg/kg every 5 days and then stop and start hydrocortisone as below. Doses should be rounded to multiples of 2.5 mg.
- Once prednisolone course is complete, start hydrocortisone tablets 2.5 mg BD for 3 days and then OD for 3 days and then STOP.
- Ranitidine should be prescribed for gastro-protection at a dose of 2 mg/kg TDS when steroids are prescribed.

Patient to be discharged on above medications.

12.1.5 Discharge Planning

- OPD appointment in a week's time and then at 4–6 weeks postop.
- Reassure parents that stool colour might not change to yellow immediately and might take a few weeks. If bilirubin level falls below 2 mg/dL at 3 months after surgery, it is considered as successful Kasai surgery.

- In children with successful Kasai surgery, though the bilirubin would be normal, their AST and ALT might not normalise. These children are to be followed up on a regular basis as they can develop features of decompensated liver disease such as portal hypertension, ascites, hepatopulmonary syndrome, etc. without developing jaundice.
- These children can develop recurrent cholangitis and develop jaundice. Recurrent cholangitis management is outlined in CLD Chap. 3.
- Those children with failed Kasai have to be referred to transplant centre so that parents could be counselled regarding liver transplantation.
- Need regular growth monitoring and vaccination.

12.1.6 Follow-up

- Successful Kasai is defined as clearance of jaundice with serum total bilirubin level below 2 mg/dL within 3 months postoperatively.
- Though the bilirubin could be normal in successful KPE, AST/ALT might not normalise, and all children require regular follow-up.
- KPE is more or less a palliative surgery, and these children might require LT without development of jaundice (Fig. 12.1).
- Children with BA follow more or less a predictable course which is outlined in Fig. 12.1.

12.2 Medial Management in Post-Liver Resection

As hepatoblastoma (HB) is the most common cause for liver resection in children, HB management is outlined in detail along with post-liver resection management protocol.

12.2.1 Hepatoblastoma

Hepatoblastoma (HB) is the most common primary malignant liver tumour in children with a reported incidence of 1.6–2 per million children in Western countries. Several staging systems exist for HB, of which presurgical pretreatment extent of disease (PRETEXT) staging devised by the ***S***ociété ***I***nternationale d'***O***ncologie ***P***édiatrique–***E***pithelial ***L***iver Tumour Study Group (SIOPEL) is widely used (Table 12.1 and Fig. 12.2).

The SIOPEL suggests preoperative chemotherapy (neoadjuvant) chemotherapy followed by definitive surgery, while the Children Oncology Group (COG) suggests primary tumour resection whenever possible.

The standard neoadjuvant chemotherapy is termed as PLADO which consists of cisplatin (80 mg/m^2) and doxorubicin (60 mg/m^2). Each cycle comprised of cisplatin given as a 24-h IV continuous infusion followed by doxorubicin as a continuous

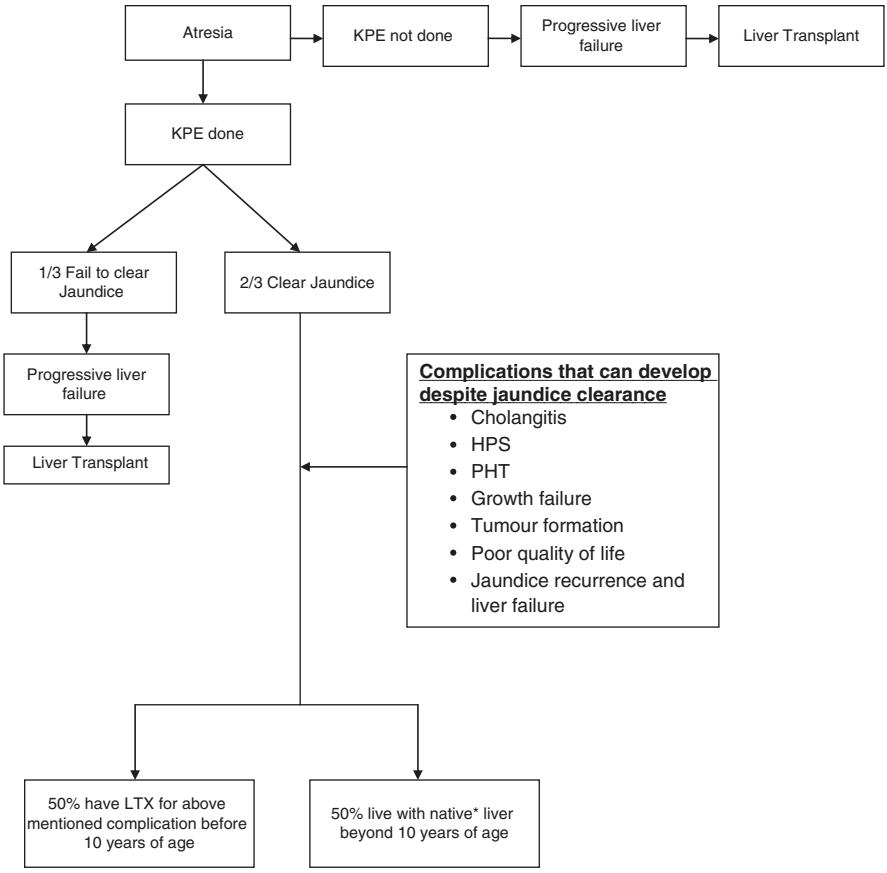

Fig. 12.1 Showing possible outcomes in biliary atresia. * can have the above mentioned complications to variable extent but not warranting transplant. *HPS* hepatopulmonary syndrome, *PHT* portal hypertension. Image reproduced with permission. Shanmugam et al., Sri Lanka Journal of Child Health, 2016;45(2):116–122

Table 12.1 PRETEXT staging

Pretext 1	3 contiguous sectors are tumour-free
Pretext 2	2 contiguous sectors are tumour-free
Pretext 3	1 sector is tumour-free
Pretext 4	No sector is free of tumour

M—Distant metastases
V—Ingrowth into the IVC or all three hepatic veins involved
P—Ingrowth into portal vein or involvement of portal bifurcation
E—Extrahepatic contiguous tumour
C—Involvement of caudate lobe
The alphabets are added along with PRETEXT stage based on involvement

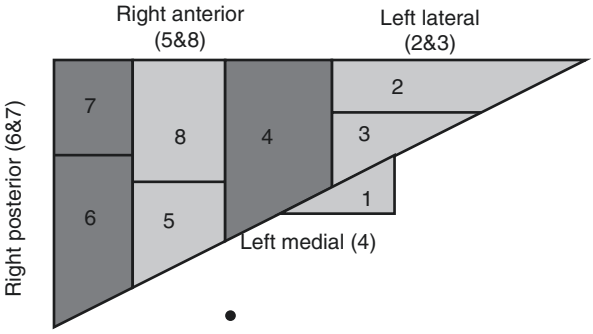

Fig. 12.2 Schematic diagram of liver showing four sectors. Segments 5, 6, 7, and 8 form the right lobe. Segments 2, 3, and 4 form the left lobe

Table 12.2 Definitions of surgical names for hepatectomy procedures

Right hepatectomy	Right lobe (segments 5, 6, 7, 8)
Left hepatectomy	Left lobe (segments 2, 3, 4)
Extended right hepatectomy	Right lobe (segments 5, 6, 7, 8) + segment 4
Extended left hepatectomy	Left lobe (segments 2, 3, 4) + segments 5 and 8

48-h IV infusion. Four cycles are given at three weekly intervals followed by either resection or liver transplantation, and the chemotherapy course is completed with further two cycles. In case of unresectability at the end of four cycles, reassessment was done after further two cycles. High-risk protocol consists of alternate cisplatin and carboplatin along with doxorubicin. Types of liver resection are outlined in Table 12.2.

HB confined to the liver and involved no more than three hepatic sections is considered as "standard-risk (SR) HB", and HB extending into all four sections and/or with lung metastases or intra-abdominal extrahepatic spread or tumour rupture at presentation or with serum AFP < 100 units at presentation is considered as "high-risk (HR) HB".

12.2.2 Perioperative Care of Hepatic Resection

- Usually surgery is planned 3–4 weeks after chemotherapy.
- Pre-op crossmatch of two to four adult units of blood depending on extent of surgery.
- Make sure the white cell count has recovered post-chemotherapy.
- Occasionally GCSF has to be given to allow timely surgery.

Procedure day (D0)

- Patient is usually extubated in theatre.
- In case of large-volume blood loss, high blood lactate, ionotropic requirement, or extended right hepatectomy, patient might be shifted ventilated.

- Extubation is done once hemodynamic parameters are stabilised (usually the next day).
- *On arrival to PICU*
  - Get handover.
- *From surgical team*
  - Extent of surgery
  - Any diaphragmatic involvement/diaphragmatic repair
  - Use of any interposition vascular grafts and thus need of any anticoagulation
- *From anaesthetic team*
  - Blood loss and fluid balance
  - Peak lactate and shifting lactate

Day 1 (0–24 h postop)

- Continue IV antibiotics: (first dose given presurgery)
- Tazocin 90 mg/kg TDS (max 4.5 g TDS) for 5 days.

Maintenance fluids: 10% dextrose + 1.5 mmol/kg/day NaCl + 1 mmol/kg/day K at 2/3 of total maintenance. Add potassium as guided by blood tests.

- Strict input/output monitoring.
- NG losses replaced mL for mL with 0.9% saline + 10 mmol KCl.
- Drain losses replaced mL for mL with 4.5% human albumin solution (HAS).
- If operative blood losses are moderate/high. Will need deficit correction.
- Check U + E/blood gas on return from theatre, 4 hourly blood glucose.
- Start IV vitamin K (1 mg OD) and IV ranitidine (1 mg/kg TDS).
- Monitor effectiveness of analgesia (epidural or morphine infusion). May need further analgesia if required.

Tips

If there was any bowel resection or perforation, then post-Kasai protocol has to be followed.

Day 2

- Maintenance fluids: 10% dextrose + 2 mmol/kg/day of NaCl at 2/3 of total maintenance. Discuss NG/drain replacement regime and when to remove.
- Check FBC, U + E, albumin, and Ca.
- Reduce analgesia as appropriate.
- If bowels are opened, start sips of clear fluid/oral rehydration solution (ORS) and gradually increase as tolerated (check with surgeons).
- *Day 3/Day 4*
- Maintenance fluids: Increased to full maintenance 10% dextrose + 2 mmol/kg/day NaCl (+K if needed).

- To start some enteral feeds.
- Taper down maintenance fluid.
- Remove central line if not used.
- Discuss NG/drain replacement regime and when to remove.
- Check FBC, U + E, Ca + albumin (stop monitoring if blood is stable and off IV fluids).
- Wean/stop analgesia as appropriate.
- Stop prophylactic abx after 5 days.

Tips

- After extended right hepatectomy, the remaining left lateral segment might act as "small for size" resulting in jaundice and increased drain output.
- This should not be confused with biliary complication due to duct bile damage/blockage.

12.2.3 Discharge

Patients are discharged typically on days 6–8 depending on extent of hepatectomy and rate of recovery. Those requiring subsequent chemotherapy should have a treatment plan already in place with the oncology service.

Management of Children with Metabolic Disease Undergoing Surgery/Procedure

13

Roshni Vara and Naresh Shanmugam

Metabolic disorders are group of inherited disorders where there is specific enzyme defect leading to various physical and physiological manifestations. These manifestations could vary from subtle defects that go unnoticed to life-threatening defects resulting in early abortions. Patients with metabolic defects have very little tolerance to stress, and they could decompensate during perioperative period as it is a stressful event. Few of common metabolic defects and anticipated problems are outlined in Table 13.1

Table 13.1 Common metabolic disorders and anticipated problems during stress/surgery

Metabolic disorder	Common problems encountered during perioperative period
Disorders of amino acid metabolism	Seizures and encephalopathy due to elevated toxic products such as ammonia, leucine, etc. causing cerebral oedema Acidosis due to lactic acidosis and other fixed acid production
Disorders of carbohydrate metabolism	Hypoglycaemia and myopathy
Mitochondrial disorders	Hypoglycaemia, seizures unmasked by drugs, prolonged anaesthetic recovery time
Mucopolysaccharidosis	Difficult airway
Hyperoxaluria	Excessive bleeding due to poor arterial vasoconstriction due to oxalate deposits in blood vessels. Conduction defects and cardiomyopathy due to oxalate deposit in myocardium

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Table 13.2 Dextrose requirements in children

Age and weight	Glucose infusion rate (GIR)	10% glucose infusion rate
Up to 2 years	10 mg/kg/min	150 ml/kg/day
2–6 years	8 mg/kg/min	120 ml/kg/day
>6 years weight <30	6 mg/kg/min	90 ml/kg/day
>6 years weight 30–50	4.5 mg/kg/min	67 ml/kg/day

The principles of perioperative management of any child with metabolic disease are similar.

13.1 Preoperative Considerations

- Elective procedures should be discussed in multidisciplinary team consisting of metabolic physician, anaesthetist and intensivist, and individualized plan has to be made for each patient.
- Preoperative cardiac assessment is essential.
- Avoid perioperative fasting – start intravenous dextrose as mentioned in Table 13.2.
- Do not skip routine medication – discuss with metabolic consultant.

Anticipate metabolic crisis and be prepared with emergency drugs (intravenous sodium benzoate, phenylbutrate, etc.) and dialysis if needed.

13.2 Intraoperative Considerations

- Avoid lactate-containing fluids.
- Continuous bicarbonate infusion helps in compensating acidosis due to stress.
- Regular blood gas and electrolyte checking helps in adjusting fluids. There is risk of hyperkalaemia with succinylcholine in myopathies.
- Avoid albumin for colloid infusion in disorders of amino acid metabolism.

13.3 Postoperative Considerations

- Keep in ICU for recovery.
- Restart their regular medications through NG at the earliest.
- If they are on special feeds, it should be started at earliest.

13.4 Salient Points in Specific Disorders

13.4.1 Glycogen Storage Disease

- Cardiac assessment in Cori, Anderson and Tauri due to associated cardiomyopathy
- Respiratory depression due to myopathy, particularly Pompe disease
- Airway difficulty due to macroglossia in Pompe disease
- Tight tourniquet could cause muscle lysis in McArdle's disease

13.4.2 Mucopolyscharidosis

- Short neck, micrognathia, macroglossia, etc. can make airway management difficult in these patients.
- Cervical spine assessment has to be carried out carefully as cervical spine instability is common.
- Might require smaller endotracheal tube, face masks and nasopharyngeal airways and might not fit properly, and it is always better to have backup for emergency tracheostomy.
- Atlanto-occipital subluxation is common in Morquio syndrome (type 4 MPS).
- Check for cardiac valve prolapse.

13.4.3 Porphyria

- Unique intraoperative complication of erythropoietic porphyria is the photoactivation of protoporphyrin by the operating room lights, which can cause tissue burns. Special filters should be used to cover the lights.

Disorders of amino acid metabolism are discussed in detail in individual chapters.

Further Reading

Stuart G, Ahmad N. Perioperative care of children with inherited metabolic disorders. Contin Educ Anaesth Crit Care Pain. 2011;11(2):62–8. https://doi.org/10.1093/bjaceaccp/mkq055.

Cardiac Evaluation of Paediatric Liver Transplant Recipients

14

Arul Narayanan

14.1 Introduction

Cardiac evaluation before liver transplant and subsequent follow-ups are important in children with end-stage liver disease. Detecting cardiac abnormalities during evaluation can help in anticipating and rectifying major haemodynamic instability during transplantation. Abnormalities identified during evaluation include:

1. Structural heart diseases
2. Myocardial abnormalities
3. Conduction defects

Diagnostic tests include pulse oximetry in both the upper and lower limbs, electrocardiography (ECG), echocardiography (ECHO), contrast-enhanced ECHO, and cardiac catheterisation, if necessary.

14.1.1 Structural Heart Diseases

Children with structural heart diseases can have major haemodynamic challenges during or after the transplant. For the liver transplant graft to function well, the right atrial pressure should be within normal range during immediate postoperative period.

Simple cardiac lesions like atrial septal defect (ASD), patent ductus arteriosus (PDA), and moderate ventricular septal defect (VSD) can be corrected after the liver transplant depending on the symptoms. If there are complex cardiac lesions like transposition of the great arteries or total anomalous pulmonary venous drainage, it

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Table 14.1 Pressure within cardiac chambers in mm of Hg

Chamber measured	Systole	Diastole	Mean	End diastole
Right atrium			2–6	
Right ventricle	25			4–6
Pulmonary artery	25	10	15	
Left atrium			8	
Left ventricle	100–120			8–10
Aorta	100–120	60–80	70–90	

has to be corrected as soon as possible. Conditions that cause elevated right heart pressure like tetralogy of Fallot, severe pulmonary valvar stenosis, and branch pulmonary artery stenosis should be corrected before the transplant.

ECHO measurement of RV pressure more than 60 mm of HG may be considered as severe obstruction. Any lesions with potential for right-to-left shunt can cause major problems during or after the transplant. This shunt can cause embolism and stroke.

Pressure in heart chambers and blood vessels depends on the age of the child. Values in children are outlined in Table 14.1

Tips

- Alagille syndrome is known to be associated with verity of cardiac malformation. Pulmonary artery abnormalities are the most common lesions. Cardiac catheterisation should be considered for detailed evaluation.
- Biliary atresia splenic malformation (BASM) could be associated with situs inversus and cardiac abnormalities.

14.1.2 Cardiomyopathy

Cardiomyopathy is more common in children with ESLD than in general population. Viral hepatitis can precipitate immune-mediated myocarditis or fibrosis leading to restrictive cardiomyopathy. Storage disorders like amyloidosis, hyperoxaluria type 1, haemochromatosis, Wilson's disease, etc. can cause infiltration in the heart leading to cardiomyopathy. Features of hypertrophic and dilated cardiomyopathy are also seen in children with liver failure. Symptoms of liver and heart failure are not entirely different. Shortness of breath, fatigue, oedema, and ascites can be seen in both conditions. Routine screening with ECHO is essential to rule out cardiomyopathy. Even though the cardiac illness may not be significant at the time of screening ECHO, it is important to find out the co-morbid conditions so that appropriate counselling may be given. Some investigators have suggested that mild degree of dilated cardiomyopathy improves after liver transplant. But if the cardiomyopathy is significant, then combined heart and liver transplant should can be considered.

A few patients with cirrhosis may not have features of cardiomyopathy on routine cardiac ECHO. Generally, the cardiac workload is reduced because of significant vasodilatation in children with liver failure. So the myocardial function may seem to be normal on ECHO. Nevertheless, prudent examination will reveal the presence of vasodilation, in keeping with low systemic vascular resistance. Moreover, they may also have mild left heart dilation. In such situations, reperfusion of the new organ can be compromised due to the significant changes in the afterload causing inadequate cardiac output, acidosis, and end-organ dysfunction. This type of cardiomyopathy is called cirrhotic cardiomyopathy. It involves poor cardiac contraction, dilated peripheral vasculature, decreased diastolic relaxation, repolarisation anomalies, and blunted response to catecholamines.

In healthy children adrenergic stimulation causes increase in heart rate as well as cardiac contraction. On the other hand, children with cirrhosis have decreased action to physiological and pharmacological adrenergic stimulation. It is shown to be a bad prognostic marker in heart failure. This abnormality is also likely to contribute to increase mortality in patients with ESLD. These findings occur to some degree in all patients with liver disease.

Tips

- Some of the patients with propionic academia can have cardiomyopathy and could reverse after LT.
- Oxalate deposits in myocardium in primary hyperoxaluria can impair contractile function of the heart.

14.1.3 Electromechanical Disorders

Actual systole takes place immediately after electrical stimulation/depolarisation. They are closely linked to each other. Ventricular repolarisation also happens instantly. This stalls the next depolarising current from getting into a partially depolarised conduction system, thereby preventing re-entry arrhythmias. Children with ESLD are likely to have cardiac abnormalities such as electromechanical dissociation, long ventricular repolarisation (prolonged QT interval), and chronotropic ineffectiveness.

The time lag between electrical and mechanical systole can be higher in children with liver cirrhosis. If the conduction system is still partially depolarised during the next action potential arrival, electrical depolarisation will not be able to pick up all the mechanical activity of the heart muscle. This may cause poor systolic function in cirrhosis since all available heart muscles cannot be used for the next ventricular systole. As the dissociation worsens, the time required for repolarisation (QT interval) increases. These abnormalities in the QT interval can alter cardiac rhythm and contribute to life-threatening illnesses such as ventricular fibrillation. In severe liver disease, this electromechanical disassociation can cause major problems.

Tips

- Wolff-Parkinson-White syndrome is seen in some of the children with Alagille syndrome.
- Cardiac conduction defects are seen in primary hyperoxaluria defects are seen in primary hyperoxaluria.

14.1.3.1 Pre-transplant Assessment

Simple screening tests like ECG and ECHO can help us identify most of the cardiovascular abnormalities in children with ESLD.

In the event of any ECHO evidence of abnormal pulmonary vascular disease, such as a tricuspid regurgitation velocity >3 m/s, predicted right ventricular pressure >50% systemic, or other minor evidence of high right ventricular pressure, then invasive tests including cardiac catheterisation will help in assessing the haemodynamic data in detail.

Patients with no structural heart defect and having saturation <95% in room air should have contrast ECHO/CT pulmonary angiogram to look for HPS (Hepato pulmonary syndrome).

Early detection of cardiac problems and appropriate treatment can assure successful liver graft function.

Caution

During transplant, air enters the vena cava during caval anastomosis and usually is filtered by the lung with no apparent consequences. The presence of right-to-left shunts can result in fatal paradoxical air embolism.

Anaesthesia in Paediatric Liver Transplantation

15

Ilankumaran Kaliamoorthy

15.1 Introduction

Biliary atresia, inborn errors of metabolism, autoimmune and Wilsons' disease are some of the common indications for liver transplantation in children. The anaesthetic team dealing with paediatric transplantation should be able to anticipate problems and try to avert it with pre-emptive strategies. Securing a vascath pre-emptively in child with urea cycle defect so that CRRT could be initiated if there is any hyperammonic crisis is a classical example.

15.2 Preoperative Assessment: Key Points

The following points will be considered while assessing the child for fitness for liver transplantation from the anaesthetist viewpoint.

1. General health, well-being and nutritional status of the child.
2. Severity of the liver disease: This could be assessed using standard scoring systems such as Child-Pugh scoring system. This helps in counselling patents about recovery period as hospital stay could be prolonged in patients who has advanced liver disease.
3. Some of these diseases have extrahepatic manifestations or associated congenital anomalies where the anaesthetist should be aware of while assessing the child for liver transplantation. Cardiac malformations in Alagille syndrome, poor cardiac ejection fraction and cardiac conduction defects in primary hyperoxaluria due to oxalate deposits in the heart are few of the examples.

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4. Assessment of cardiopulmonary involvement in cirrhosis:
   (a) Hepatopulmonary syndrome (HPS) and portopulmonary syndrome (POPH) should be ruled out. If the child has got SpO_2 of <96%, arterial blood gas analysis (ABG) should be done in room air and with 100% oxygen. Any abnormality in the ABG would warrant further investigation to quantify pulmonary shunting. If arteriovenous shunt is present, it will result in increased venous saturations and decreased arteriovenous difference in oxygen content.
   (b) 2D echocardiogram is a very good screening tool to identify POPH. If pulmonary arterial systolic pressure is >45 mmHg, a child might need right heart catheterization once volume overload is ruled out. 2D echocardiogram will also be useful in identifying any congenital cardiac abnormality.
5. Renal dysfunction if any should be noted and the cause should be identified, as it could be multifactorial.
6. History of any previous surgery should be documented. Children, who underwent previous surgeries like Kasai procedure, might have significant, blood loss. The size of the endotracheal tube used and information regarding any adverse reactions during anaesthesia would be useful in the planning.
7. Presence of varices: Gastric, oesophageal, abdominal wall or rectal. The date of the most recent sclerotherapy should be documented.
8. Any history of septic episodes and antibiotic therapy should be documented.
9. Documentation of any allergies is important.

15.3 Preoperative Instructions

Anaesthetist will see the child the day before the liver transplantation and give instructions. This will normally include the following.

1. Blood and blood products reservation: It will be written based on the weight and complexity of the surgery. If the donor blood group is different from the recipient, donor blood group PRCs will be used for the recipient post-implantation. Advanced communication to the blood bank is mandatory while dealing with complex situations.
2. Blood investigations required include a full blood count for haemoglobin, platelets and white cell count, INR, fibrinogen, liver and renal function tests including electrolytes.
3. Fasting for at least 6 h. For breast milk, 4 h.
4. Antibiotics and anxiolytics.
5. Other regular medications: ideal to skip beta-blockers from the previous night of the surgery.

15.4 Intraoperative Management

Anaesthesia for paediatric liver transplantation is a challenging event. The planning for conduction of anaesthesia varies based on the type and complexity of the procedure.

1. Invasive monitoring is essential. All lines should be placed in the upper limbs or neck. Peripheral venous access should involve one or two good lines.
2. Arterial cannulation of the radial artery (sometimes femoral artery) with a 22–24 g cannula is optimal based on the weight and size of the child. Some children will require two arterial cannulas.
3. Central venous cannula should be placed in the internal jugular vein. Usually performed with ultrasound guidance with 4.5 Fr or 5 Fr catheters. If peripheral venous access is difficult, two lines will be required.
4. Micro-cuffed endotracheal tubes are preferable.
5. Usually, inhalational induction is with sevoflurane. Sometimes with intravenous induction with propofol.
6. Normally, atracurium, fentanyl, morphine, sevoflurane or isoflurane will be used intraoperatively for maintenance.
7. A convection forced air warmer with the appropriate blanket and underbody warming blanket is used in maintaining normothermia.
8. Based on the requirement, noradrenaline (first choice) and adrenaline will be used to maintain adequate blood pressure. In extreme situations, vasopressin will be added.
9. Antibiotics will be repeated every 4 h intraoperatively.
10. Piperacillin-tazobactam and fluconazole are used for prophylaxis
11. Complete blood count, INR, fibrinogen and thromboelastogram (TEG) will be done at regular interval.

15.5 Postoperative Care

1. All children will be transferred to the liver intensive care with ventilator support once the surgery is completed.
2. Usually, they will be off ventilator on the next day morning when all parameters are found to be satisfactory.

Paediatric Liver Transplantation: Perioperative Management

16

Anil Dhawan and Naresh Shanmugam

16.1 Pre-transplant: Assessment

- Patient to be admitted a day prior to liver transplant (living donor) or once the alert for possible cadaver organ availability.
- Routine nursing observations and doctors' clerking.
- Inform blood bank and reserve necessary blood products and liaise with anaesthetist.
- Venous gas, FBC, PT, INR, U+E and CXR taken.
- Formal consent for surgery is taken.
- Transplant theatres should inform PICU approximately half an hour before the child is duly back.

Tips

- Rule out electrolyte imbalance and infection before posting patient for surgery.
- Hyponatraemia is associated with increased mortality, and slow correction to >125 meq/l is preferable before surgery.

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16.2 Preparations to Be Done Before Receiving Patients

Once the call from OT is received regarding patient shifting:

- Prepare drug chart—Check patient's weight and drug allergies. Based on weight prescribe antibiotics, antifungal, vit. K, antacids, H2 blocker (to prevent stress- and steroid-induced ulcers) and immunosuppressants (dose after consulting consultant hepatologist).
- Prepare infusion chart—inotropes (usually noradrenaline), sedatives (fentanyl/midaz/propofol as appropriate) and maintenance fluids.
- Keep ventilator ready (initial vent settings, FiO_2, as required; TV, 6–8 ml/kg, peak pressure <20; PEEP, 3–4) and check air, O_2 and suction line.
- Check emergency drugs.
- Anticipate issues specific to the case (crisis in metabolic liver disease, hypoglycaemia, fluid overload status).
- Prepare maintanance fluids.

16.3 Handover

Once the child is shifted to liver ICU/PICU, the ventilator is connected, monitors are attached and bed is parked.

The handover is given by anaesthesiologist conducting the case to PICU team (includes consultant intensivist, paediatric on-call registrar, nurse taking care of the baby).

Receive patient in a space with good barrier nursing and strict asepsis.

Handover includes:

1. Name, age, sex and weight
2. Donor and recipient blood group
3. DDLT / LDLT / auxiliary /reduced liver/ split / combined (liver and kidney)
4. Preoperative diagnosis and status
5. Planned and performed operations
6. Issues at induction, ET size, central lines and arterial lines
7. Donor issues and condition of donor liver
8. Cold ischaemic time, GRWR and graft weight
9. Portal pressures and time of reperfusion
10. Duct to duct or Roux-en-Y anastamosis of bile duct
11. Type of abdominal closure and airway pressures on closure
12. Blood loss, amount of blood products transfused, fluid balance and requirement of inotropes
13. Urine output and electrolyte imbalances
14. Peak INR, peak lactate, shifting INR, platelet and lactate and TEG report

15. Immunosuppression: As per hospital protocol
    (a) Intraop methylprednisolone dose to be noted
16. Last antibiotic and antifungal dose
17. Special precautions (G6PD deficiency, avoid propofol, albumin, etc. in propionic academia patients)

16.4 ICU Monitoring

On handover check:

- *Airway* (*tube position*, *leaks*)
- *Breathing* (*air entry*, *chest rise*)
- *Circulation* (*CRT*, *BP*)
- Temperature (need for warmer/Hemotherm)
- ABG on receiving (see for BE , pH,lactate)
- X-ray chest (line position, ET position, NG position)
- Send blood for urea and electrolytes, full blood count and INR

16.4.1 Elective Ventilation Overnight

- Continuous HR, RR, $ETCO_2$, SpO_2, IBP, ECG, CVP and U/O monitoring.
- Strict I/O chart (maintain equibalance, avoid negative balance to prevent HAT).
- Drain fluid (serous/serosanguinous/chyle/bilious), and drain replacement (initially 100% replacement with 5% albumin, later optimized as per fluid balance).
- If abdomen is closed with a mesh, fluid loss from dressing pad has to be included.

Notify transplant physician if:

1. Hb >11 or <9. Ideally Hb is maintained between 9 and 10.5. Polycythemia is a risk factor for vascular thrombosis; hence partial venesection of approx. 4 ml/kg of blood would decrease HB by 1 g. Serial Hb monitoring is required.
2. Platelets <20,000 (hypersplenism/sepsis/platelet dysfunction).
3. Electrolyte imbalances.
4. Drain fluid is bloody.
5. Increasing blood lactate.
6. Increased resistive index (RI) in liver (>0.8).
7. Capillary blood sugar < 4.5 or >11 mmol/ L. Maintain sugars between 7 and 10 mmol/ L.

16.4.1.1 Airway and Ventilation

- Optimal endotracheal tube position (check X-ray).
- Patient is usually ventilated overnight.
- Lung protective strategy should be adopted where possible.
- Tidal volumes 6–8 ml/kg with plateau pressure <30 cm H_2O.

- PEEP, 5–8 cm: inadequate PEEP will lead to alveoli collapse, and high PEEP can cause decreased vascular return.
- Mode of ventilation based on local expertise usually volume guarantee is used.
- Pressures and FiO_2 should be adjusted so as to maintain arterial saturations more than 95% and $PaCO_2$ between 35 and 45 mmHg.
- Use sedation bolus (fentanyl 2 mcg/kg) prior to suctioning/physiotherapy to minimize stimulation and coughing.
- While on mechanical ventilation, ensure regular chest physiotherapy to prevent chest infection.
- Bronchodilators and Mucomix as indicated.

Caution

- Desaturation/increased O_2 requirement—check for tube displacement/pneumothorax (during transport and hand ventilation).
- Right basal collapse and pleural effusion common after liver transplantation.
- Chest drain for pleural effusion if significant (causing respiratory compromise).

Tips

- Post-transplant intra-abdominal pressure affects ventilation, and so volume guarantee is a better modality to achieve optimal ventilation.

16.4.1.2 Fluids and Nutrition

- On arrival, start with 10% dextrose solution as maintenance fluid, and once serum electrolytes are available, change to fluid with additives as suggested in Table 16.1.
- Two-third fluid maintenance with GIR of 4–6 mg/kg/h, 2–4 meq/kg/day of sodium and 1–2 meq/kg/day of potassium.

Table 16.1 Post-transplant maintenance fluid

Daily maintenance fluid = 2/3 maintenance (dextrose 10%) along with
Sodium—2.0 mmol/kg/day
Potassium—1.0 mmol/kg/day
Magnesium—0.5 mmol/kg/day
Calcium chloride—1 mmol/kg/day
Based on the regular blood results, the additives can be adjusted

Tips

- Most of the CLD patients have hyponatraemia; rapid correction leads to central pontine demyelination, and so low sodium fluid is used.
- Underfilling can cause low blood pressure and reduce perfusion to graft, and overfilling can cause passive graft congestion. Keep CVP around 8–10 cm.
- Strict input/output chart.
- Input includes IVF, IV infusions and IV medications, and output includes drains, dressing, NG aspirations, bile, loose stools and emesis.
- Try to maintain equibalance.
- Potent diuretics has to be avoided as large volume dieresis can cause hypotension and decreased graft perfusion and increase the viscosity of blood and can predispose to vascular thrombosis.
- Consider TPN from day 1 for malnourished children as usually feeding would be commenced only on day 4 or 5 postsurgery due to hepaticojejunostomy rather than duct-to-duct anastomosis in majority of children**.**
- In case of IEM, TPN has to be started on D1 to prevent catabolism (dealt in detail in Chap. 20)

Caution

- Lactate is used as surrogate marker of liver graft recovery. It reaches peak before reperfusion of the graft and then gradually comes down. Overall trend is more important than absolute values.
- Progressive raise in lactate is of serious concern.
  1. Give trial of 10 ml/kg of colloid fluid bolus to improve peripheral perfusion and recheck lactate.
  2. Get urgent Doppler ultrasound to look at the flow in hepatic artery, hepatic vein and portal vein.
  3. Consider insulin dextrose drip as there can be transient postsurgical insulin resistance leading to anaerobic metabolism and raise in lactate.
- In case of hyperglycaemia, calculate the glucose infusion rate in mg/kg/min. Infants and children require a GIR of 4–6 mg/kg/min. If hyperglycaemia is due to high GIR for their age, there is a need to decrease the dextrose concentration in their intravenous fluid, but if hyperglycaemia is present while on recommended GIR, start on insulin sliding scale rather than decreasing the dextrose concentration.

16.4.1.3 Sedation

- Child would arrive to the PICU intubated, before starting any sedation or pain medications, to assess sedation score. Start sedation in intensive care when score is −2 or −3 of Richmond Agitation-Sedation Scale.

- This is to prevent oversedation.
- Usually started with fentanyl and midazolam or propofol (if >6 years) and muscle relaxant SOS (atracurium 0.2–0.5 mg/kg) when on ventilator.

Tips
- Titrate to optimal sedation, where the child is comfortable with appropriate heart rate and spontaneous breaths are more than the ventilator set rate.

16.4.1.4 Inotropes

- Vasopressors should be used once the patient is fluid unresponsive but ensure adequate fluid are given before labelling patient as fluid unresponsive (IVC collapsibility on USG, response to fluid bolus and USCOM if available).
- Noradrenaline is the vasopressor of choice. Mainly alpha effects increase both systolic and diastolic blood pressure. Dose is titrated to maintain required MAP.
- Vasopressin or its synthetic analogue terlipressin is used as a vasoactive drug in the management of hypotension. It has been found to be effective when hypotension secondary to decreased SVR is refractory to norepinephrine.
- Start vasopressin infusion at 0.0001 U/kg/min as second line if needed.

Tips
- What is the ideal post-transplant blood pressure?
- Blood pressure that is good enough to produce urine of 1 ml/kg/h is considered to be ideal. It indirectly reciprocates end-organ perfusion pressure (and of course you have to use the standard nomogram as well as a guide).

16.4.1.5 Immunosuppression (Protocols can vary with Institutions)

- Methylprednisolone 2 mg/kg/day IV Q24H (max 40 mg/day). Commence day after transplant (D1) as large dose (D0) given following reperfusion of liver in theatre. Start weaning slowly after 5 days.
- Liaise with hepatologist regarding tacrolimus dose. Usually 0.15 mg/k is given in two divided doses, titrate to maintain tacrolimus trough levels between 8 and 12 ug/l during first few weeks. Watch for prograf toxicity. (Varies from severe renal failure to neurotoxicity. Watch for hyperkalaemia, decreased urine output, seizures, anaemia, fluid retention, hyperglycaemia and hypomagnesaemia.)
- MMF is added based on institutional protocol.

Tips
- Usually tacrolimus is started at half the recommended dose, as most of the paediatric transplant has Roux loop and has delayed gut motility that can cause toxic tacrolimus levels in the first few days.
- Trough tacrolimus levels can be checked after three doses (time taken to reach a steady state), and dosage titration can be done.

16.4.1.6 Renal

Renal Dysfunction

1. Liver transplant patients are at a risk of ATN due to the vena cava being clamped above the renal veins during traplant surgery.
2. Measure urine sodium to distinguish between hepatorenal syndrome (HRS) and ATN.
   (a) Urine sodium will be low in HRS and high in ATN.
   (b) HRS is a diagnosis of exclusion; if urine sodium is low, other causes must first be ruled out.
   (c) Urine sodium concentration is similar to ½ NS; to replace urine output, always use ½ NS.
   (d) Indications for haemodialysis (HD/CVVH without heparin):
   - Acidosis
   - Electrolyte imbalance
   - Intoxicants (hyperammonaemia)
   - Overload (fluid)
   - Uraemia

Tips
- For patients who are at high risk of renal problems (Alagille syndrome, PFIC, etc.), try to add mycophenolate, and run low tacrolimus levels.

16.5 Neuroprotection

Neuroprotective measures are to be implemented (*if transplanted for ALF*).

- Head of bed at 30°.
- Neck in neutral position.
- Sedation (narcotics and benzodiazepines administered cautiously).
- Use of fentanyl boluses or propofol pre-procedure/pre-suction.

- Actively look for seizures and consider antiseizure prophylaxis with leveracetam if there is clinical or EEG evidence of seizures.
- Aggressive temperature control (36–37 °C).
- Mechanical ventilation to normal pH and $PaCO_2$.
- Normoglycaemia.

Tips
- Plan extubation 48–72 h after transplant as it could take some time for cerebral oedema to settle.
- Patient who had sedation for ventilation for a long time can have withdrawal, so wean the medications slowly.

16.5.1 Imaging

- Daily Doppler imaging for the first 5 days post-op. In high-risk patient (small vessels, interposition graft, etc.), Doppler imaging should be performed twice daily.
- If arterial/venous flow signals are not present or diminished, CT may have to be performed after discussion with surgeons.

16.5.2 Infection Control

- *Strict asepsis and barrier nursing*
- *Antibiotic prophylaxis*
- Antibiotic prophylaxis is instituted as a matter of routine in all patients. Patients are prone to infections because of impaired polymorphonuclear leukocyte function, impaired cell-mediated and humoral immunity and diminished opsonic and complement activity. Some of the factors that predispose to infection are presence of indwelling catheters, H2-receptor blockers, steroid and tacrolimus. Antibiotics are given for 5 days and stopped and no need for longterm propylactic antibiotics.
- *First line*: Piperacillin-tazobactam (+gram-positive cover with vanc or teic if needed) and metronidazole if hepaticojejunostomy is done.
- *Second line*: Meropenem (metronidazole not needed here).
- *Antifungals*: Choice of antifungal is based on hospital policy. Usually IV fluconazole at 6 mg/kg/day is given for 5 days and then changed to oral. It could be stopped after 2 weeks.
- *Antiviral drugs*: Ganciclovir treatment if recipient is negative and donor is positive for CMV IgG, started after D3 of transplant (sent baseline EBV, CMV quantitative PCR). Treatment is usually given for 2 or 3 weeks. (Prophylaxis is a once-a-day dosage for 3 months depending on local hospital policy.)

Tips

- If hyperthermia/hypothermia and unexplained tachycardia/tachypoenia are present, suspect sepsis. Subtle signs like sudden-onset food intolerance, hypoglycaemia and irritability could be early sign of sepsis.
- Send blood & urine culture, blood count, CRP and procalcitonin and results of chest X-ray and US to look for any intra-abdominal collection, and start antibiotics.
- Based on physical, biochemical and culture reports at 48 hours, antibiotics could be altered or stopped.

16.5.3 Extubation

Patients are usually ventilated overnight; if haemodynamically stable with decreasing LFTs & lactate with normal liver doppler imaging, child is gradually weaned off ventilator support and extubated. Good chest physiotherapy, nebulisations as required and incentive spirometry started. Post-extubation child respiratory status is monitored along with ABGs.

Right hemidiaphragm elevation and right lower lobe atelectasis are common and should be treated conservatively; bronchoscopy is indicated if conservative measures fail or the atelectasis is thought to be the cause of delay in extubation.

Start paracetamol at the time of weaning of sedation, so that the child is comfortable post-extubation and SOS oromorph if pain is persistent.

Tips

Extubation Failure

- Better to reintubate and have protected airway rather than try CPAP immediately during transplant period particularly in small infants.
- Consider diaphragmatic palsy, increased intra-abdominal pressure due to large graft and bowel perforation along with common causes of extubation failure.

16.5.4 Removal of Central Lines

Arterial lines are removed by D3 if haemodynamically stable and central lines by D5. Central lines are retained with difficult IV access, need of inotropes or fluid replacement (high drain output).

Tips

- Never try to remove arterial lines in a coagulopathic child.

16.5.5 Anticoagulation

Anticoagulation is indicated in all liver transplant patients to prevent thrombosis of hepatic vessels.

When to start: When INR <2, platelets >50,000 and if drains are clearing up (earlier if high risk after consulting surgeons)

Options:

1. Heparin: For high risk or re-thrombosis, 75 U/kg loading followed by 20 U/kg/h. Maintain a PPT level between 80 and 100.
2. Low-molecular-weight heparin (Fragmin) 50 U/kg/dose Q12H or Clexane 1 mg/kg/dayQ24H.
3. Once haemodynamically stable and no planned procedures (Intervention for pleural fluid/abdominal collections/liver biopsy) can change over to oral aspirin 3–5 mg/kg/day (aspirin and LMH are overlapped for 48 h).

16.5.6 Drain Replacement

- Usually one drain is inserted before closing the abdomen.
- Drains are emptied and recorded q 2 h.
- The physician is notified if there is change in drain output colour and/or amount.
- Initially 100% drain replacement done with 5% albumin/Gelo. Based on fluid balance, drain replacements are gradually reduced.
- If drain output is high, then oral propranolol (provided no surgical issues with portal flow) or SC/IV octreotide is started.
- In case of bilious drain, drain bilirubin and serum bilirubin are sent (usually drain bilirubin is <2/3 of serum bilirubin, unless there is bile leak). USG is done to rule out bilious collection (aspirated if present). Might need further MRCP/cholangiogram/CT with contrast.
- If chylous drain, dietician is involved for fat-free diet (milky drain with high-drain triglycerides).

Tips

- Patients sometimes complain of right shoulder pain, and this can be due to drain tube irritating the diaphragm or presence of sub-diaphragmatic collection.
- Octreotide is helpful in case of persistent chylous drain.

16.5.7 Nutrition

- Usually enteral feeding is commenced on postoperative day 2 or 3 for duct-to-duct anastomosis and day 4 or 5 for Roux-en-Y hepaticojejunostomy.

- For all practical reasons, it would be D7 or D8 to establish full feeds in children.
- It is better to start TPN of D1 for children who are malnourished and in children with special metabolic condition.
- supplementation with appropriate vitamins and minerals is essential as there would be a rapid catch-up growth after liver transplant.

Tips

- Initial few days after transplant are crucial period for liver regeneration and wound healing. Providing plain dextrose as maintenance fluid will only lead to muscle catabolism to compensate the requirement.

16.5.8 Shifting to Ward

Twenty-four hours after extubation, child could be shifted to HDU, and once all the central lines are removed and child has achieved full oral feeds (usually D7), child could be shifted to ward.

ABO-Incompatible Liver Transplantation: Perioperative Management

17

Deepti Sachan and Naresh Shanmugam

17.1 Introduction

- Just like blood transfusion, organ transplantation has to be blood group matched.
- In liver transplantation, blood groups A and B could donate liver to similar blood groups. Blood group O are universal donors (can donate organ to A, B, AB, and O) and blood group AB are universal recipients (can receive organs from A, B, AB, and O) (Table 17.1).
- Rhesus compatibility and HLA matching are not required in liver transplantation.

Table 17.1 Blood group compatibility and organ compatibility

Blood group	A	B	AB	O
Antigens in RBC	A antigen	B antigen	A+B antigen	None
Antibodies[a] in plasma	Anti-B	Anti-A	None	Anti-A+ Anti-B
Can donate organ to	A	B	AB	A, B, AB, O
Can receive organ from	A, O	B, O	A, B, AB, O	O

[a]Antibodies are called isohemagglutinin as they cause hemagglutination when mixed with other blood group

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17.2 ABO-Incompatible Liver Transplant

- In living donor scenario where ABO-compatible donor is not available, ABO-incompatible liver transplantation could be done safely, provided isohemagglutinin in plasma is removed and its production is prevented by adequate immunosuppression.
- Infants less than 1 year old usually do not develop significant isohemagglutinin production (titers less than 1:8 standard) in whom ABO-incompatible transplant could be considered, without the need for preconditioning.

17.3 Newer Blood Antigen Adsorption System

- Conventionally several cycles of plasma exchange were performed to bring down the ABO antibody titer.
- Newer ABO antibody adsorption circuit is available which can be used in standard plasmapheresis machine (Fig. 17.1).

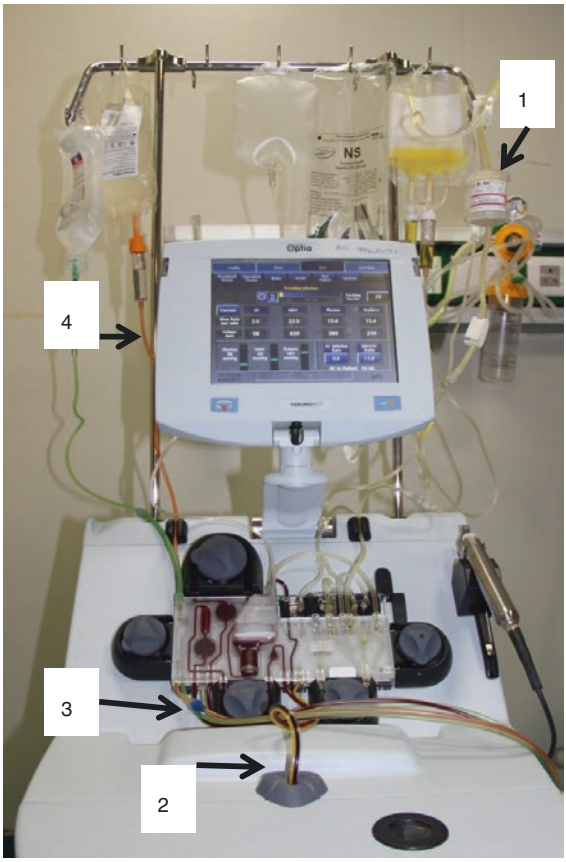

Fig. 17.1 Image showing plasmapheresis in a patient with ABO-incompatible transplant. (1) ABO antibody adsorption column (attached to standard circuit). (2) Inlet line. (3) Return line. (4) Anticoagulation line

- The active ingredient is an oligoconjugate immobilized on inert saccharose matrix.
- The active ingredient of column binds the anti-A/B antibodies according to the principle of affinity chromatography by antibody-antigen interaction.
- There are separate circuits for anti-A or anti-B or anti-A/B antibodies
- The adsorbed antibodies could be eluted by glycine buffer (pH 2.5) and the regenerated column could be reused for same patient.
- In between the treatments, columns could be stored in storage solution (provided in the kit) at 2–8 °C.

Two commercially available ABO antibody adsorption kits are:

- ABO Adsopak® (POKARD Ltd. Moscow, Russia).
- Glycosorb®-ABO (Glycorex Transplantation AB)

17.3.1 ABO-Incompatible Liver Transplant Protocols

- There are several protocols used at different centers. Table 17.2 shows one such protocol. The basics is to stop antibody production by giving rituximab, to remove preexisting circulating antibodies by plasmapheresis, and postoperative higher immunosuppression to prevent antibody-mediated rejection.

Caution

- ABO antigens are present on most epithelial and endothelial cells.
- This increases the risk of vascular and biliary complications in ABO-incompatible transplant particularly during the first 2 weeks after LT.

Table 17.2 ABO-incompatible liver transplant protocol

Day	Lab tests	Medications	Procedure
D–14 (14 days before liver tx)	• Screen the patient for infection • Base line: CD4, CD19, CD20, CBC, CRP, PCT, LFT, RFT, anti-ABO antibody titer	Rituximab intravenous infusion	None
D–7 (7 days before liver tx)	• Anti-ABO antibody titer • CD-19 cell count	• Start MMF 10–15 mg/kg BD orally	
D–4	• Anti-ABO antibody titer • CBC, CRP, PCT, LFT, RFT • Blood/urine c/s		
D–3	• Collect reports • Make sure infection screen negative		If anti-ABO titers >1:8[a] • Admit in ICU • Insert vascath • Plasmapheresis using special filters
D–2	Anti-ABO antibody titer CBC, CRP, PCT, LFT, RFT CD-19 cell count		• Plasmapheresis if titers >1:8
D–1	Anti-ABO antibody titer		• Plasmapheresis if titers >1:8 • Proceed to TX if anti-ABO antibody titer <1:8
D0 day of transplantation	Anti-ABO antibody titer (make sure titers < 1:8)	Methyl Prednisolone 10 mg/kg at perfusion • Start tacrolimus, with target trough levels of 10–12 • Continue MMF	
First 7 days	Anti-ABO antibody titer/LFT daily	• Methylprednisolone 2 mg/kg OD (max 40 mg/day). Start weaning after 5 days • Tacrolimus: target level 10–12 • MMF • Inj Fragmin 50 IU/kg BD • Ganciclovir[a]	• Daily ultrasound Doppler of liver • Plasmapheresis if titers >1:8

Table 17.2 (continued)

Day	Lab tests	Medications	Procedure
D8–D14	Anti-ABO antibody titer daily	• Change to oral prednisone • Gradually wean prednisolone to 1 mg/kg (20 mg/day max) • Inj Clexane 20 mg BD • Tacrolimus: target level 10–12 • MMF • Ganciclovir[a]	Ultrasound Doppler of liver every other day Plasmapheresis if titers >1:8
3rd/4th week after transplantation	Anti-ABO antibody titer, LFT on alternate days CD-19 cell count (once on week)	• Oral prednisolone 1 mg/kg (20 mg/day max) • Tacrolimus: target level 10–12 • Swap Inj Clexane to aspirin • MMF • Valganciclovir	Ultrasound Doppler of liver twice a week Plasmapheresis if titers > 1:8
5th–8th week after transplantation (weekly)	Anti-ABO antibody titer, LFT twice a week	• Oral prednisolone 0.5 mg/kg (10 mg/day max) • Tacrolimus: target level 7–10 • Aspirin • MMF • Valganciclovir	
3rd month (weekly)	LFT, anti-ABO antibody titer. CD-19 cell count	• Oral prednisolone 0.2 mg/kg (5 mg/day max) • Tacrolimus: target level 7–10 • Aspirin • MMF	
Month 4–6 (monthly)	• Anti-ABO antibody titer, LFT monthly • CD-19 cell count (once)	• Oral prednisolone 0.1 mg/kg (5 mg/day max) • Tacrolimus: target level 7–10 • Aspirin • MMF	Stop aspirin at 6 months
Month 6–12	• LFT, anti-ABO antibody titer once in 2 months	• Long-term maintenance prednisolone (0.05 mg/kg–2.5 mg max) based on hospital policy (some centers stop) • Tacrolimus: target level 5–7 •MMF	

Percentage of CD19+ B cells among the total lymphocytes (%CD19) in the peripheral blood ≤1.2% is associated with lower risk of AMR compared to >1.2%

Antibody titer threshold for plasmapheresis is usually based on local hospital policy, with few centers having slightly higher cutoff

[a]Treatment with IV ganciclovir for 3 weeks if donor is CMV+ and recipient is CMV−. At the end of 3 weeks, check CMV PCR, if positive continue treatment until it turns negative, and if negative oral prophylactic dose could be given based on hospital policy.

MMF (mycophenolate mofetil) 10–15 mg/kg BD orally.

18 Combined Liver and Kidney Transplantation: Perioperative Management

Chaya Kelegari, Gomathy Narasimhan, and Chandrasekaran Venkataraman

18.1 Introduction

Common indications for combined liver and kidney transplants (CLKT) in children are the following:

- Primary hyperoxaluria (PH) type 1
- Congenital hepatic fibrosis with polycystic kidney
- Methylmalonic acidemia (MMA)
- Atypical hemolytic uremic syndrome

Isolated liver transplantation (LT) could be done in the above mentioned conditions, provided the kidney function was preserved. Isolated kidney transplant (KT) could be done in congenital hepatic fibrosis with polycystic kidney and MMA. In this chapter, we discuss combined liver kidney transplantation (CKLT) with emphasis on PH, as it is the most common cause for CKLT in children. The options in these patients are either for a simultaneous or sequential liver followed by kidney transplant based on availability of cadaveric organs, living donors, and plasma oxalate levels in PH. Advantage of CLKT from a single donor is the additional immunogenic protective effect of the liver over kidney rejections, but if the organs are

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from two different donors as in live donor situation, this protective effect is lost. The protocol for CKLT in other condition is more or less similar apart from monitoring oxalate levels.

18.2 Classification of Primary Hyperoxaluria

PH is classified based on specific enzyme deficiency and confirmed on genetic mutation analysis. Table 18.1 shows differential values of oxalate levels in urine and plasma in normal person and in patients with PH. There are three types of PH, with type 1 being the most severe form.

(a) PH type 1: Absent hepatic peroxisomal enzyme alanine/glyoxylate aminotransferase (AGT). Based on GFR the definitive treatment option could be combined liver kidney transplant or preemptive liver transplant.
(b) PH type 2: Absent D-glyceric dehydrogenase enzyme. PH2 patients with kidney transplant alone appear to have a more favorable course than PH1 patients as enzyme is not liver specific. Benefit of liver transplant in such patients is still unclear.
(c) PH type 3: Increase in hepatic or renal mitochondrial 4-hydroxy-2-oxoglutarate aldolase (HOGA1) resulting in increased oxalate production. Significant renal disease is uncommon in this condition.

Table 18.1 Oxalate levels in normal and diseased state

Normal urinary oxalate levels	0.11–0.46 mmol/24 h or 9.7–40.5 mg/24 h The reference value is for a 24 h collection
In the background of normal kidney function suspect primary hyperoxaluria if	Urine oxalate >0.7 mmol/1.73 m/24 h or spot urine oxalate/urine creatinine > normal for age[a]
In the background of poor kidney function or renal failure suspect primary hyperoxaluria if	Urine oxalate >0.5 mmol/1.73 m^2/24 h and/or plasma oxalate >20 μmol/l
Alternative definition that corrects for size differences	30 mg of urinary oxalate per 24 h/g of excreted creatinine
Spot urine oxalate/urine creatinine values	• Age <2 years, <300 mmol/mol • Age 2–5 years, <130 mmol/mol • Age 5–15 years, <70 mmol/mol • Age >16 years, <40 mmol/mol Suspect PH if values are beyond reference range

[a]Spot urinary oxalate over creatinine ratios may be used for screening in children

18.3 Treatment Options in PH Type 1

- Treatment options in PH type 1 are outlined in Table 18.2.
- Avoid isolated kidney transplant except in selected pyridoxine responsive patients.
- Preemptive isolated liver transplant in selected patients with GFR ≥45 ml/min/1.73 m^2, to avoid the complications of systemic oxalosis.
- Combined liver-kidney transplant is either simultaneous or sequential.
  1. *Simultaneous liver-kidney transplant*
     (a) When GFR 15–30 ml/min/1.73 m^2
     (b) May be appropriate for low-risk patients with GFR <15 l/min/1.73 m^2 without any features of systemic oxalosis
     (c) An abdominal cavity large enough to hold both organs
     (d) With separate donors for each organ
     (e) In case of cadaveric transplants (immunological advantage)
     (f) Infantile form (ESRD <2 years of age)

Table 18.2 Management options in PH1

	Transplant strategy			
	Simultaneous liver + kidney	Sequential liver followed by the kidney	Isolated kidney	Isolated liver
Stage 3 moderate CKD (GFR = 30–59 ml/min)	Not indicated	Not indicated	Not indicated	Consider in selected patients (stage 3b)
Stage 4 severe CKD (GFR = 15–29 ml/min)	Indicated	Not indicated	Consider in selected B6 responsive pts	Not indicated
Stage 5 end-stage CKD (GFR <15 ml/min)	Indicated	Indicated	Consider in selected B6 responsive pts	Not indicated
Infantile form (ESRD <2 yrs)	Indicated	Indicated	Not indicated	Not indicated
	Pre ± postoperative HD according to POx and GFR	HD following liver Tx aiming at POx <20 µmol/l	Preoperative and perioperative HD	Sometimes perioperative HD
	Hemodialysis (HD) strategy			

2. *Sequential liver-kidney transplant*
   (a) When GFR <15 ml/min/1.73 m^2.
   (b) In case of severe systemic oxalosis.
   (c) Infantile form (ESRD <2 years of age).
   (d) The rationale is to prevent kidney damage due to mobilization of tissue oxalate. LT halts further production of oxalate, and total body oxalate load can be decreased by dialysis, and KT can be done safely at latter date.
   (e) When the organ is harvested sequentially from the same live donor liver followed by the kidney 6 weeks later.

Tips

In PH, independent of the transplant strategy medical management should be initiated in all feasible patients to prevent further tissue oxalate crystallization and protect the kidney. Despite supportive measures the disease could progress based on phenotypic severity.

- Fluid intake (2–3 l/1.73 m^2/day)
- Pyridoxine: 5 mg/kg/day up to 20 mg/kg/day (maximum 1 g/day)
- Crystallization inhibitors
  - Alkalization with oral potassium citrate 0.10–0.15 g/kg/day (in renal failure use sodium citrate)
  - Orthophosphate: 30–40 mg/kg/day
  - Magnesium oxide: 500 mg/day/m^2

18.4 CLKT Preoperative Management

- Intensive hemodialysis (HD) regimen, five to six times per week, each with 4–5 h session, with high-flux dialyzer or intense peritoneal dialysis (PD) preferably with continuous ambulatory PD with frequent exchanges or a combination of PD and HD is used.
- Suggested urine and plasma oxalate levels to prevent systemic oxalosis are outlined in Table 18.3. If it exceeds the suggested levels, more aggressive management with HD is to be considered.
- Aim to keep plasma oxalate (POx) level <45–50 μmol/l.

Table 18.3 Suggested urine and plasma oxalate levels to prevent systemic oxalosis

Treatment	Conservative	Dialysis	Transplantation
Urine oxalate	<0.5 mmol/l or <45 mg/1.73 m^2		<0.5 mmol/l or <45 mg/1.73 m^2
Plasma oxalate (POx)		<45–50 μmol/l	<20 μmol/l

- Check cardiac ejection fraction (EF), as oxalate deposits in the heart can cause decreased EF and conduction blocks. In our practice EF should be more than 40% to undergo surgery. Vigorous hemodialysis five to six times/week with high-flux dialyzer for 4 to 6 weeks prior to transplant helps in reducing oxalate load and improve the cardiac EF.
- Check ECG for heart block due to oxalate deposits.
- Check blood pressure as most of the patients with kidney disease would be hypertensive.
- Minimal heparin is used to avoid systemic anticoagulation.
- In patients with primary hyperoxaluria, preoperative dialysis is initiated to decrease the oxalate load and prevent injury to the transplanted kidney graft. Last dialysis to be completed at least 4–6 h before the scheduled time of transplant to avoid oxalate rebound.
- Per operative fluids are calculated and prescribed depending on the urine output and insensible losses.
- As a protocol we initiate CRRT intraoperatively and continue postoperative period until plasma creatinine is <2 mg/dl, good diuresis (urine output >3l/m^2/day), and plasma oxalate less than 20 μmol/l (to protect transplanted kidney).
- Switch over to intermittent hemodialysis if the patient is stable and requiring dialysis for longer periods in case of allograft dysfunction or high plasma oxalate after transplant.

18.5 CLKT Postoperative Management

Posttransplant management is similar to standard OLT apart from fluids and immunosuppression. Check ABG; CBC; BUN; creatinine; electrolytes Ca, PO_4, and Mg; INR; glucose; albumin; and osmolarity. The frequency of these tests depends on the stability of the graft and the patient. Plasma oxalate levels are to be monitored additionally in primary hyperoxaluria patients.

18.5.1 Fluid Balance

- Too much fluid will increase CVP and can cause congestion in liver graft and could be detrimental to the liver graft.
- Inadequate fluids could cause intravascular fluid depletion and could affect transplanted kidney and could be detrimental to the kidney graft.
- Postoperative fluid balance is vital with fluid status assessed every 4 h to maintain CVP of 8–10 cm of water.
- Fluid requirement is calculated as urine output (UO) + wound/drain output (DO) + insensible losses.
- As UO and DO are highly variable during initial postoperative period, it has to be replaced on an hourly basis.

- Urine output is replaced ml for ml with 0.45% normal saline every hour.
- Drain losses are replaced ml for ml with 5% human albumin solution.
- Insensible losses are calculated as 400 ml/m^2/day which are generally 20–25 ml/kg/day and are replaced with 10% dextrose. Look for other signs of hypovolemia (like low peripheral temperature, tachycardia, hypotension) and hypervolemia and act accordingly. Err on the side of overhydration than under hydration.
- In children who is having posttransplant polyuria (due to poor concentrating ability of the new kidney), consider replacing a proportion of the urine output than full replacement after discussing with the nephrologist.
- For primary hyperoxaluria type 1, aim for urine output of at least 6 ml/kg/h, and consider frusemide infusion if urine output is less than 3 ml/kg/h

18.5.2 Immunosuppression

- Basiliximab IV on day 0 and day 4 (see Chap. 23).
- Tacrolimus dose is initiated as in liver transplant patients, but the trough level is maintained at 7–9 ng/ml.
- Mycophenolate mofetil (MMF): MMF will be prescribed in conjunction with tacrolimus and methyl prednisolone on day 1.
- Starting dose: 5 mg/kg orally BD.
- Increase to 10 mg/kg orally BD.
- Gradually increasing to 20 mg/kg orally BD (maximum 1 g) based on tolerance.

18.5.3 Other Drugs

In children with primary hyperoxaluria, additional drugs used are:

- Bendrothiazide 2.5–5 mg daily or twice daily. Avoid furosemide if possible.
- Restart pyridoxine 500 mg/m^2 if sensitive.
- Avoid vitamin C.

18.5.4 Hypertension

Hypertension may occur in the immediate posttransplant period.

- If the CVP is low, the raised BP may reflect vasoconstriction in response to hypovolemia.
- If the CVP is normal, vasodilate with hydralazine (0.1–0.5 mg/kg IV to be given slowly over 1–3 min) or nifedipine 0.25–0.5 mg/kg PO every 4–6 h. Max: 10 mg/dose. To be repeated as necessary (total 1–2 mg/kg/day in total).

- If hypertension persists and the patient is adequately vasodilated, then regular nifedipine sustained release (SR) may be used.
- If blood pressure remains elevated and the patient has a tachycardia, then consider use of labetalol. This is both an alpha- and beta-blocking agent with a short half-life and should be infused at 1 mg/kg hourly as initial dose. Titrate the infusion according to clinical response with a maximum dosage of 3 mg/kg/h. Make up in glucose/saline or glucose 5% (*not* saline alone) at a concentration of 1 or 2 mg/ml.

18.5.5 Diagnostic Imaging

- If primary kidney function has been achieved, a baseline ultrasound scan with Doppler is done. DTPA scan should be obtained within the first week posttransplant.
- If there is primary graft nonfunction, an ultrasound scan with Doppler tracing plus a DTPA scan must be obtained as soon as possible posttransplant. Discuss the result with the nephrologist and surgeon.
- DMSA scan at 3 weeks posttransplantation to be requested.
- Subsequent investigation will be requested according to individual need and postoperative complications.

18.5.6 Acute Rejection Episodes

Renal biopsy is essential if renal function is deteriorating as this could be due to rejection or oxalate deposits. Treatment protocol for acute rejection (kidney or liver) is outlined in Chap. 23

Liver Transplantation for Metabolic Disorders: Perioperative Management

19

Roshni Vara

19.1 Perioperative Management of Patients with Urea Cycle Defect

Urea cycle disorders are group of inherited disorders due to absence of one of either six enzymes or two amino acid transporters involved in urea cycle. The urea cycle in its complete form is present only in the liver, and it is the main pathway for the disposal of excess nitrogen. A defective urea cycle results in hyperammonaemia of various severities with a wide variety of clinical manifestations. In these conditions, alternative pathway medications for nitrogen excretion could be used to conjugate glycine (sodium benzoate) and glutamine (sodium phenylbutyrate) for the treatment of hyperammonaemia.

19.1.1 Preoperative Management

1. Child should ideally be metabolically stable.
2. Check blood gas, blood glucose, ammonia, plasma amino acids and urine organic acids including routine pre-liver transplant (LT) bloods. If ammonia >80 μmol/l, discuss with metabolic team and may need to consider postponing surgery.
3. Ensure minimal fasting time—start IV 10% dextrose at 8–10 mg/kg/min for neonates and 6–8 mg/kg/min for older children with additional electrolytes.
4. Continue all routine medications such as sodium benzoate, Carbaglu, etc.
5. Total daily dose of oral sodium benzoate and/or phenyl butyrate could be converted to equivalent dose of intravenous preparation and could be given as a 24 h

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infusion (max concentration 50 mg/ml in 10% dextrose of sodium benzoate/phenyl butyrate, both can run in the same IV line).
6. In case of non-availability of intravenous preparations, these drugs could be given through nasogastric tube as bolus doses.
7. If blood glucose level is >10 mmol/l, start IV insulin. Do not reduce dextrose concentration.
8. If on arginine and metabolically stable, run total daily dose IV over 24 h (max concentration 50 mg/ml)—needs to run through a separate line. If unwell consider increasing to 150–200 mg/kg/day.
9. Consider continuous veno-venous hemofiltration (*CVVH*) if ammonia is above 300 μmol/l and rising—discuss with metabolic consultant.

19.1.2 Intraoperative Management

1. Consider two central lines with one being vascath, which could be used for renal replacement therapy (RRT) if metabolically unstable.
2. Check ammonia; if on increasing trend from the baseline, consider interoperative CVVH.
3. Avoid acidosis by correcting with IV sodium bicarbonate or THAM (trometamol; tris-hydroxymethyl aminomethane).
4. Avoid albumin as resuscitation or replacement fluid as it can increase the protein load.

19.1.3 Postoperative Management

1. Check blood gas, blood glucose, ammonia, acylcarnitines, plasma amino acids, urinary ketones and urinary organic acids along with routine post-LT bloods.
2. If ammonia remains <80 μmol/l, ammonia-lowering agents could be stopped and repeat ammonia levels in 6 h.
3. Maintain dextrose at 8–10 mg/kg/min for neonates and 6–8 mg/kg/min for older children.
4. Start intravenous lipid at 2 g/kg/day on receiving the patient from theatre.
5. Add protein at 1 g/kg/day on first postoperative day.
6. Avoid albumin as drain replacement as it increases protein load.
7. Protein intake can be liberlised to normal once good graft function is acheived.
8. Ammonia - lowering agents can be gradually tapered and stopped.

19.2 Perioperative Management of Propionic Acidemia and Methylmalonic Acidemia (Organic Acidemias)

Propionic acidemia (PA) and methylmalonic acidemia (MMA) are organic acidemias which characteristically present in the neonatal period with encephalopathy, acidosis and hyperammonaemia. The long-term management involves a protein-restricted diet, carnitine (which conjugates propionic acid) and ammonia-lowering agents.

- The hyperammonaemia in PA and MMA is a secondary phenomenon in which a build-up of propionic acid and methylmalonic acid inhibits the proximal part of the urea cycle.
- Any form of stress such as fever, infection, etc. can trigger metabolic decompensation in a stable child (under treatment).
- The long-term outcome despite medical therapy is suboptimal due to neurological involvement. It is essential to consider LT before permanent neurological damage happens.

19.2.1 Preoperative Management

1. Child should be metabolically stable.
2. Check blood gas, blood sugar, urine ketones, ammonia, blood spot acylcarnitine, plasma amino acids and urine organic acids including routine pre-LT bloods.
3. If ketones are positive, ammonia >80 μmol/l or presence of metabolic acidosis is discussed by the metabolic team as it could indicate catabolic state.
4. Ensure minimal fasting—start IV 10% dextrose at 8–10 mg/kg/min for neonates and 6–8 mg/kg/min for older with added sodium and potassium. If blood glucose level is >10 mmol/l, start IV insulin. Do not reduce dextrose concentration.
5. IV carnitine at 100–200 mg/kg/day as a continuous infusion (made up using 10% dextrose solution).
6. Give the usual dose of hydroxocobalamin 1 mg/day IV or IM in MMA.
7. Sodium benzoate: Make up equivalent total daily oral doses as a 24 h infusion (max concentration 50 mg/ml in dextrose of sodium benzoate).
8. If intravenous preparation is not available, sodium benzoate could be given through nasogastric route.

19.2.2 Intraoperative Management

1. Continue IV medications as continuous infusion is preoperatively prescribed.
2. Consider two central lines with one being vascath, as in case of metabolic decompensation RRT could be done.
3. Maintain IV dextrose as above.
4. Check intraoperative ammonia, if more than 200 μmol/l and rising might need haemodialysis.
5. Avoid metabolic acidosis by correcting with IV sodium bicarbonate or THAM.
6. Check urine ketones every 2 hours.

19.2.3 Postoperative Management

1. Check blood gas, blood sugar, urine ketones, ammonia, blood spot acylcarnitines, plasma amino acids and urine organic acids including routine post-LT bloods.
2. If ammonia remains <80 μmol/l, ammonia-lowering agents could be stopped.
3. Continue IV carnitine at 100 mg/kg/day for at least 48 h.
4. Maintain dextrose at at 8–10 mg/kg/min for neonates and 6–8 mg/kg/min for older children.
5. Start total parenteral nutrition at 1 g/kg/day of protein and 1–2 g/kg/day intravenous lipid on postoperative day 1.
6. Protein intake could be gradually increased based on tolerance. May consider post-operative moderate restriction (i.e. 2.5 - 3g/kg/day) particularly in MMA

Tips
- Liver transplantation only partially corrects the defect.
- For the same reason, isolated kidney transplantation can give partial metabolic control in MMA. More specific considerations are required in MMA.
- Continue L-carnitine postoperative period as there will be secondary carnitine deficiency caused by urinary loss of carnitine-bound to organic acids.

19.3 Perioperative Management of Patients with MSUD (Maple Syrup Urine Disease)

MSUD is due to a deficiency of branched chain keto acid dehydrogenase (BCKD) which is involved in the breakdown of branched-chain amino acids (BCAA): leucine, valine and isoleucine. Leucine is neurotoxic and causes encephalopathy. The

management is to minimise fasting, BCAA-restricted protein diet and adequate calorie intake with carbohydrate and fat. Sometimes, supplementation of isoleucine and valine might be required in case of essential amino acid deficiency.

Patients decompensate with a leucine encephalopathy (levels normally kept in the range of 150–350 μmol/l) and ketosis. Hyperammonaemia, metabolic acidosis and hypoglycaemia can sometimes be present.

19.3.1 Preoperative Management

1. Child should be metabolically stable.
2. Fasting should be minimal and IV dextrose commenced as soon as possible.
3. Check blood gas, blood sugar, urine ketones, ammonia, plasma amino acids or blood spot BCAA.
4. Make arrangements so that BCAA is reported the same day. Valine/leucine/isoleucine has to be measured and reported individually as some labs report leucine + isoleucine together. Optimal levels of BCAA are given below.
   - Leucine <300 μmol/l
   - Isoleucine—200-400 μmol/l
   - Valine—200–400 μmol/l
5. If ketones are positive, ammonia >80 or metabolic acidosis could indicate catabolic state.
6. During preoperative fasting, start IV 10% dextrose at 8–10 mg/kg/min for neonates and 6–8 mg/kg/min for older with added sodium and potassium. If BM's >10, start insulin, do not reduce dextrose concentration. Never fast these children for more than 2 h.
7. If on a BCAA-free supplement and isoleucine/valine supplementation, ensure these are given pre-op.

Tips

- In MSUD, the ammonia can be normal, and so it should not be used as a surrogate marker for metabolic control.

19.3.2 Intraoperative Management

1. Consider two central lines with one being vascath, as in case of metabolic decompensation, RRT could be done.
2. Maintain IV dextrose as above.
3. Avoid metabolic acidosis by using maintenance sodium bicarbonate or THAM infusion if required.

19.3.3 Postoperative Management

1. Check blood gas, blood sugar, urine ketones, ammonia and blood spot BCAA initially once daily.
2. Make sure to maintain dextrose at 8–10 mg/kg/min for neonates and 6–8 mg/kg/min for older.
3. Consider TPN at 1 g/kg/day of protein and 2 g/kg/day of intralipid.
4. Once feeds are started, protein restriction could be gradually relaxed while monitoring blood BCAAs.

Caution

- While LT completely replaces the enzymes in urea cycle defect (as the enzymes are present only in liver), LT in PA, MMA and MSUD, only partially corrects the defect (due to significant extra-hepatic enzyme expression).
- Post-LT patients can still have metabolic decompensation during stress and intercurrent illness, so warn them to use emergency regimen (oral glucose) during stress or fasting.

- Long-term follow up with metabolic and hepatology specialists is required

Post Liver Transplantation Complications: Early Surgical Complications

20

Gomathy Narasimhan

20.1 Introduction

Early recognition and appropriate management of post-operative complications are largely facilitated by having adequate information on intraoperative details. Paediatric recipients often have congenital anomalies which may require variations in surgical technique, and hence this information is very vital.

The operating room to ICU handover should include the following information:

- Type of liver graft (whole/split/auxiliary/lobe) used.
- Quality of liver graft.
- Graft to recipient weight ratio (GRWR >4 may cause large for size which is elaborated later).
- Previous surgeries leading to bowel adhesions/diaphragmatic adhesions.
- Details of implantation—hepatic vein/portal vein/hepatic artery/bile duct. If bile duct reconstruction was hepaticojejunostomy, Whether a new loop was created? Details regarding use of vascular interposition graft.
- Number and location of the drains.
- Nature of abdominal closure/any significant change in respiratory pressure as the abdomen was closed.

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20.2 Post-transplant Complications

20.2.1 Primary Non-function (PNF) of Graft

Graft does not begin to function in immediate post-operative period in the absence of rejection or vascular issues.

Causes: More common with cadaver transplant with incidence of 2–6%. Older donor age, prolonged donor ICU stay, and prolonged cold ischemic time are some of the predisposing causes.

Clinical course: Progressive increase in liver enzymes, coagulopathy, increasing lactate leading to encephalopathy, and multiorgan failure during post-operative period

Treatment: Emergency re-transplantation

20.2.2 Vascular Complications

Hepatic artery thrombosis and portal vein thrombosis should be closely monitored, especially in the first 5 days following transplantation. Hepatic vein issues are quite uncommon and rarely manifest in the immediate period. Any deviation from the normal course in the first 5 days by way of rising lactate/persistent tachycardia warrants an immediate Doppler study of the hepatic vessels. On a normal course:

1. Doppler ultrasound once a day for the first 5 days (twice a day in patients with interposition graft or intraoperative difficulties in vascular reconstruction). Scan result to be available during morning rounds to help with decision making.
2. If Doppler signal of hepatic artery or portal vein is not seen, discuss with surgeon for any other possibilities and proceed with CT scan with IV contrast.
3. Prepare for re-laparotomy if CT shows no flow in hepatic artery or portal vein.
4. Patients with positive procoagulant status or technically difficult vascular anastomosis or having interposition graft need anticoagulation with low molecular weight or unfractionated heparin as early as the clinical situation would allow.
5. Acute portal vein thrombosis or portal stenosis can occasionally present as variceal bleeding. Hence any gastrointestinal (GI) bleeding in the post-operative period would need an immediate Doppler evaluation of the vascularity to the transplanted liver in addition to planning for an esophagogastroduodenoscopy (EGD).
6. If re-vascularisation of the transplanted liver following hepatic artery thrombosis (HAT) is unsuccessful or re-thrombosis occurs after initial success, the graft should be monitored for possible progression to graft dysfunction leading to retransplant. The need for urgent relisting for a deceased donor graft or possibility of evaluating a live donor should also be anticipated.
7. Long-term follow-up of liver graft which has sustained hepatic artery thrombosis would need monitoring for biliary strictures and abscess in the liver.

8. Venous outflow obstruction is the least frequently encountered vascular complication. It may present as large volume drain output/graft dysfunction with biopsy showing sinusoidal dilatation. Wave pattern (mono-, bi-, or triphasic on Doppler) can help identify the problem. Triphasic pattern with good respiratory variation excludes an outflow problem. If in doubt, further confirmation is by CT scan and pressure studies with the possible requirement for hepatic vein stenting, but these are very rarely performed in paediatric patients.

Tips

- The Doppler ultrasound should provide clear information about the hepatic artery, portal vein, and hepatic venous flow in addition to information about any collection or clot.
- The frequency of liver Doppler is usually based on individual unit policy. We suggest that it has to be done daily for at least the first 5 days.

Fig. 20.1 Showing mesh closure due to large-for-size graft

20.2.3 Complications Due to Large Graft

Graft to recipient weight ratio (GRWR) is a ratio of graft weight in kg/body weight in kg × 100, e.g. 250 g graft in a 10 kg child gives a GRWR of 2.5. When a large graft with GRWR >4 is used, anticipate the following problems:

1. Large graft can make abdominal closure difficult, which can cause abdominal compartment syndrome and respiratory compromise.
2. In case of difficult abdominal closure, certain techniques are used such as partial or no muscle closure or the use of a mesh for a temporary period (Fig. 20.1). The mesh could be removed in 2 weeks' time, and muscle or skin closure could be done. Mesh closure can lead to significant fluid losses and possibility of infection.
3. Large for size can also result in portal hypoperfusion manifesting as significantly high AST, ALT, and INR in the first few days following surgery. Frequent Doppler evaluation with portal flow measurement is required.

Tips
Large grafts in small recipients need close observation for respiratory compromise or abdominal compartment syndrome—watch for increased airway pressure/reduced urine output.

20.2.4 Functional Small-for-Size Syndrome

In paediatric liver transplant setting, the donor graft is usually of adequate size, but certain other factors can cause functional small-for-size syndrome. The graft can be functionally small either because of portal hyper-perfusion (severe pre-existing portal hypertension) or due to steatotic donor liver.

Signs: Progressive cholestasis, intractable ascites and coagulopathy leads to increased mortality and morbidity. This usually happens in the first week after surgery.

Treatment: Measures to decrease portal flow such as propranolol, octreotide or terlipressin could be tried. Splenic artery embolisation or ligation is helpful in extreme cases.

20.2.5 Bleeding

At the time of transfer to the ICU from the operating room, the abdominal drain fluid is more or less clear:

1. Any sudden change in the colour/volume of the drain fluid should be intimated to the surgical team. Coagulation parameters may need correction prior to decision about reoperation. It is important to do this in consultation with the surgical team to prevent over-/under-correction keeping in mind the intraoperative technical details.

2. Acute portal vein thrombosis or portal stenosis can occasionally present as variceal bleeding. Hence any post-operative GI bleeding warrants an immediate Doppler evaluation of the vascularity to the transplanted liver in addition to upper GI endoscopy.
3. Bleeding from bile duct anastomosis (the Roux-en-Y hepaticojejunostomy) may also present as malena. This cannot be visualised on routine upper GI endoscopy. This is usually secondary to persisting portal hypertension and may need treatment with beta-blockers or octreotide.
4. Stress-induced/steroid-induced ulcers can also lead to GI bleeding. In addition, viral ulcers can cause ulceration in the GI tract. Possibility of any of these as a cause usually follows a timeline from the first week to several weeks after transplantation.

20.2.6 Biliary Complications

Bile leak from the bile duct anastomosis or from the cut surface may be diagnosed from the colour of the drain output . It may also present as a loculated collection which may be asymptomatic or manifest systemic symptoms. Tissue oedema at the site of biliary anastomosis could temporarily increase intrabiliary pressure and and aggravate a cut surface leak. Waiting for few days could help the oedema to settle down and re-establish patency of anastomosis:

1. Cut surface leaks invariably settle with conservative management in a few days to a couple of weeks.
2. Any symptomatic collection has to be aspirated and if it shows bile, a pigtail should be placed.
3. Large volume bile leaks or leaks which lead to systemic signs like tachycardia or fever or biliary peritonitis in the early post operative period may need more aggressive treatment like stenting or surgical re-exploration.
4. As opposed to bile leak, bile duct obstruction due to stricture usually manifests much later and may need revision of the bile duct anastomosis or PTBD (in hepaticojejunostomy) or ERCP (in duct-to-duct anastomosis). Stricture dilatation and stenting may be tried as a first step before surgery in selected patients.

Tips

- Bile leak should be suspected in recipients with unexplained fever, especially in the context of an intra-abdominal collection.
- In a patient with bile leak, if the stool is pigmented, no intervention is needed in most instances and is likely to settle with conservative management.
- If there is persistent high bile output in the drain along with pale stools, consider redoing hepaticojejunostomy or stent in case of duct to duct.

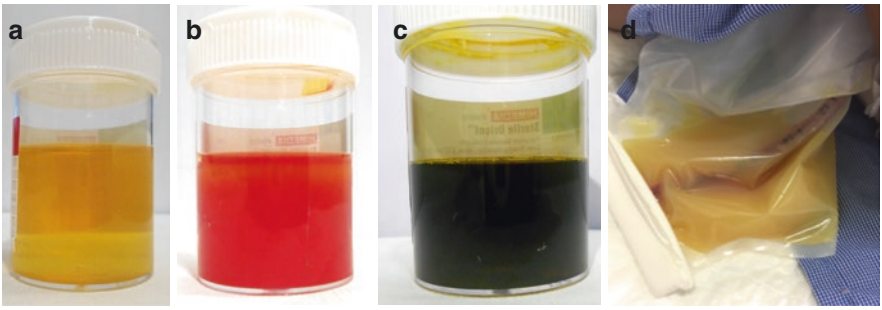

Fig. 20.2 (**a**–**d**) Showing various types of post-LT abdominal drain fluid. (**a**) serous drain fluid (normal), (**b**) haemorrhagic drain fluid, (**c**) bilious drain fluid, and (**d**) chylous drain fluid

20.2.7 Drain Output

Attention should be paid to colour, consistency, and volume of drain output. Figure 20.2a–d shows various types of post-LT abdominal drain fluid:

1. High volume drains can be seen in children with severe pre-existent portal hypertension. With extensive dissection of the retrocaval space, especially in children who have had previous surgeries, lymphatic leak may be encountered. This may not be evident in the first few days when the child is not fed but becomes apparent when feeding is initiated. The drain fluid is usually milky. Management of chylous drain is outlined in Chap. 22
2. Turbid drain fluid may indicate intestinal perforation. The incidence of intestinal perforation is higher in post Kasai children undergoing transplantation due to the extensive adhesions which are released at the time of transplant. This may or may not present with the usual symptoms of guarding/rigidity/fever/rise in white count as these patients are on immune suppression. The key is to maintain a low threshold in suspecting these complications. Clinical parameters in addition to radiological imaging (with an X-ray or CT of the abdomen if required) will confirm the diagnosis, and the child will need a re-laparotomy.

Tips

- Transplant recipients may not manifest with the typical signs and symptoms of an acute abdomen even in case of perforation.
- High degree of suspicion, especially in patients who have had a laparotomy prior to transplantation, may help in early diagnosis.
- Elevated abdominal drain amylase is suggestive of perforation.

21 Post Liver Transplantation Complications: Diagnosis and Management of Seizures

Joseph J. Varamphil and Naresh Shanmugam

21.1 Introduction

Seizures during posttransplant period are not uncommon. The reported incidence after liver transplantation ranges from 5 to 25%. There are currently no specific guidelines in selection of antiepileptic drug (AED) therapy in transplant recipients. In post liver transplant patients, AEDs without substantial hepatic metabolism should be chosen as first line.

21.2 Etiology

The most common causes of seizure during posttransplant period are as follows:

- Dyselectrolytemia: hypomagnesemia, hyponatremia, hypernatremia, hypocalcemia, hypophosphatemia, and hypoglycemia.
- Hypertension (steroid induced during postoperative period).
- Calcineurin inhibitor toxicity: pretransplant hepatic encephalopathy, posttransplant hyponatremia, and surgical time more than 7 hrs predispose to CNI-related neurotoxicity.
- Posterior reversible encephalopathy syndrome (PRES). Features of PRES are outlined in Table 21.1.
- Cerebrovascular: acute cerebral infarctions, hemorrhages, subdural hematomas, and hypoxic encephalopathy.
- Central pontine myelinolysis (CPM).

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Table 21.1 Posterior reversible encephalopathy syndrome (PRES)

• PRES can present with headache, seizures, and focal neurological deficits particularly visual loss or altered mental status
• PRES is often associated with hypertension, CNI[a], hypomagnesemia, etc. Serum CNI levels need not be high
• PRES usually happens within 4 weeks of CNI institution and may manifest as GTC or complex partial status
• On CT affected areas appear as white-matter hypodensity, and on MRI they appear as (T1) hypo- and (T2) hyperintense areas
• These changes are usually seen in parieto-occipital, cortical, and subcortical areas
• Start antihypertensives in case of hypertension
• Dose reduction in case of high CNI levels facilitates recovery. Usually resolves within 2 weeks
• There are no recommendations either to stop or switch CNI in PRES
• If the patient continued to be symptomatic with seizures despite AED, then withdrawal of the CNIs should be considered

[a]*CNI* calcineurin inhibitors

- Coexisting seizure disorder.
- Infectious: septicemia and focal or diffuse infections of CNS.

Tips

- Though serum electrolytes could be within normal range, rapid fluctuations in levels due to blood, blood products, colloids, and crystalloids during intraoperative period could cause seizures.
- Calcineurin inhibitor toxicity need not be dose dependent.

21.3 Laboratory Tests

- Complete blood cell count, CRP
- Arterial blood gases
- Coagulation profile
- Ammonia
- Liver enzymes
- Electrolytes including calcium and magnesium
- Blood cultures for bacteria, viruses, and fungi (if febrile)
- Blood levels of administered drugs (cyclosporine/tacrolimus)
- Electroencephalography
  - Routine awake and sleep recordings
- Imaging studies (in recurrent seizures, focal seizures, focal neurological deficits, etc.)
  - Magnetic resonance imaging (MRI) or computed tomographic scan with and without iodinated contrast (if MRI cannot be done)

21.3.1 Management

1. Management of posttransplant seizure is outlined in Figs. 21.1 and 21.2.
2. If blood CNI (cyclosporine/tacrolimus) levels are high, then skip three doses and recheck. Restart at a lower dose.

Tips

- It is not necessary to stop or change CNI with single episode of posttransplant seizures.
- Consider stopping or changing CNI only in case of recurrent seizures despite on AED treatment as there is remote possibility of CNI-induced seizure with normal serum drug levels.

3. For recurrent seizures or a single seizure with potentially epileptogenic abnormalities on brain imaging or EEG, AED therapy should be initiated. AEDs can usually be discontinued after 1–3 months without significant risk of seizure recurrence. However, patients with potentially epileptogenic brain lesions may benefit from continued AED therapy.
4. Self-limiting brief seizures usually do not require treatment. Seizures lasting more than 5 min should be considered as evolving status, and treatment should be initiated as mentioned in diagram.
5. For recurrent seizures or a single seizure with potentially epileptogenic EEG, AEDs can usually be discontinued after 1–3 months provided the repeat EEG is normal.
6. Phenytoin, phenobarbital, and carbamazepine all have significant drug interactions with immunosuppressive agents, increasing metabolism of CNIs and corticosteroids via induction of the hepatic cytochrome P450 enzymes.

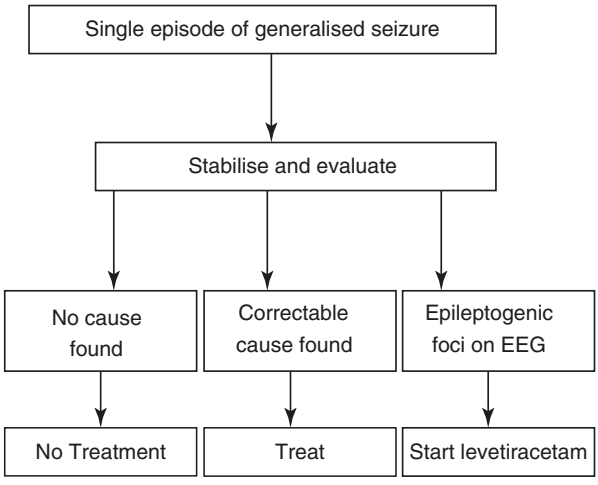

Fig. 21.1 Showing management of single seizure episode in post liver transplant patient

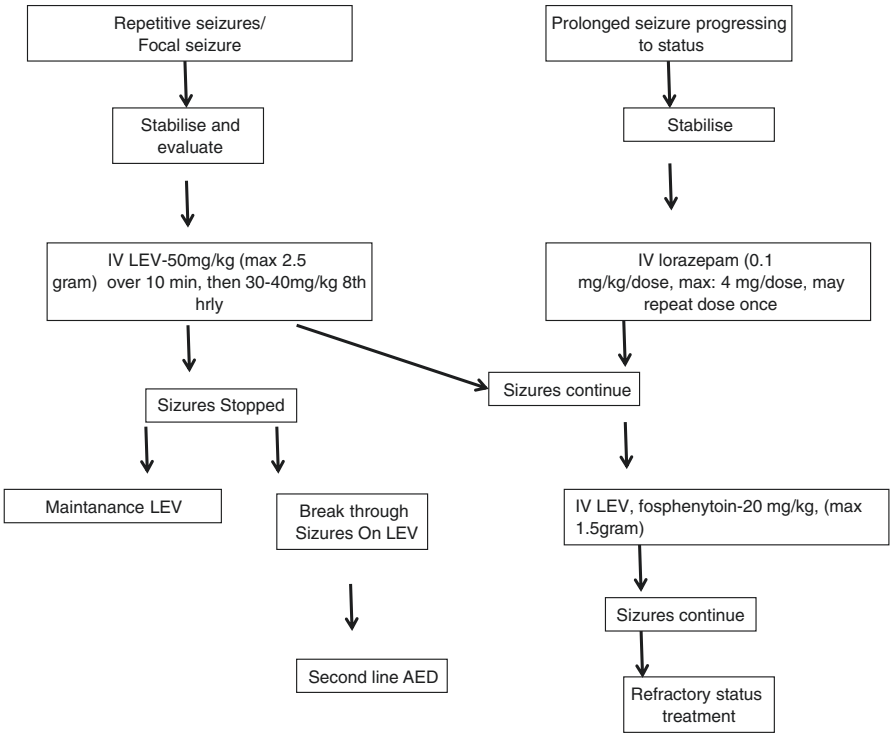

Fig. 21.2 Showing management of repetitive seizures/status epilepticus in post liver transplant patient

7. The use of valproate is not recommended, as it has hepatic metabolism and can cause liver failure.
8. Levetiracetam is the drug of choice for post liver transplant seizures due to lack of significant hepatic metabolism or drug interactions. It has broad-spectrum efficacy across a broad range of seizure subtypes and could be safely given from infants to adults.
9. Gabapentin is a newer AED that could be used in children as adjunctive therapy to control partial-onset seizures in patients >3 years of age and pregabalin for patients >12 years of age.

22 Post Liver Transplantation Complications: Diaphragmatic Palsy and Chylous Ascites/Effusion Management

Nataraj Palaniappan

22.1 Diaphragmatic Palsy

22.1.1 Introduction

Although diaphragmatic paresis or paralysis is fairly common following cardiac surgical procedures, it is a less common complication following liver transplantation (LT). Unilateral diaphragm paresis, usually right sided, has been described following LT. The effects of diaphragmatic palsy are more marked in pediatric LT recipients as usually they are malnourished with muscle wasting and weakness of the accessory respiratory muscles. Postoperative gastrointestinal ileus and ascites exacerbate the respiratory distress. Diaphragmatic palsy may complicate post LT recovery and prolong the hospital course. Young children and infants are especially intolerant of phrenic nerve injury due to their:

- Greater chest wall compliance
- Underdeveloped intercostal musculature
- Mediastinal hypermobility

22.1.2 Causes

Diaphragmatic dysfunction can occur as a consequence of dissection, stretch, contusion, thermal injury, or hypothermic damage. LT may be complicated by a degree of phrenic nerve injury owing to its close anatomical proximity to the inferior vena cava (usually the right phrenic nerve is injured during application of the caval clamp).

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22.1.3 Clinical Clues

Symptom depends on the preexisting cardiorespiratory status, the extent of paralysis, the unilateral or bilateral diaphragmatic involvement, and the nature of the dysfunction (paralysis/paresis). Patients with unilateral diaphragm palsy are usually asymptomatic, and this may be discovered as an incidental radiographic finding with an elevated hemidiaphragm. Often the first sign of diaphragmatic palsy following an operative procedure is the inability of the patient to be weaned off of ventilator support despite having good gas exchange.

The most characteristic sign on physical examination is respiratory distress and paradoxical breathing in bilateral phrenic nerve paralysis. Respiratory distress and difficulty to extubate or requiring noninvasive ventilation (NIV) in the form of bi-level positive airway pressure (BiPAP) post-extubation are pointers for diaphragmatic palsy.

22.1.4 Diagnosis

1. *Imaging*
   - Chest X-ray may reveal basilar atelectasis with asymmetric elevation of the hemidiaphragm in unilateral diaphragmatic palsy (absent in bilateral paralysis, rendering recognition more difficult)
   - Fluoroscopy/ultrasound study of excursion of the diaphragms (off positive pressure ventilation) will reveal diaphragmatic paresis as no movement of involved diaphragm will be seen.
   - Diaphragmatic fluoroscopy also called sniff test or ultrasound visualization of diaphragmatic movement is a sensitive tool in diagnosis, and the transcutaneous phrenic nerve conduction will help in confirming the diagnosis.
2. *Transdiaphragmatic Pressure Studies*
   - Intrathoracic and intra-abdominal pressure measurements during respiration using balloon catheters help in diagnosis of bilateral diaphragmatic paralysis.
   - During inspiration, pleural pressure, reflected by esophageal pressure, becomes more negative, while the pressure in the abdomen, measured via a gastric balloon, becomes more positive (abdominal content is compressed by the descending diaphragm).
   - In bilateral diaphragmatic paralysis, the pressure tracing in both organs will move to the negative direction. It is difficult to diagnose unilateral paralysis.
3. *Electromyogram (EMG)*
   - The EMG response of the diaphragm can be measured at the muscle insertion; however, these studies need expertise

22.1.5 Differential Diagnosis

- Subpulmonic effusion.
- Eventration of the diaphragm is a localized fibrous replacement of part of the diaphragm.

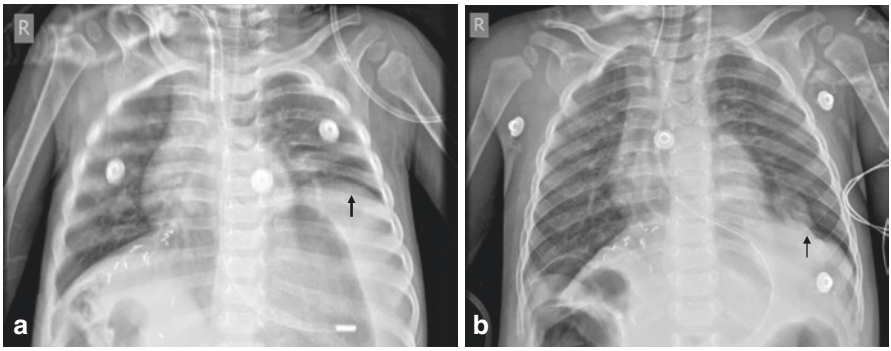

Fig. 22.1 (**a**) Showing elevated left diaphragm (thick arrow) due to left diaphragmatic palsy in a post liver transplant patient. (**b**) Showing (thin arrow) diagram after plication

22.1.6 Treatment Options

- Treatment options should be individualized and be dependent on the severity of symptoms and duration of diaphragmatic palsy. It is also important to note that the return to normal diaphragm function depends on the location and severity of the nerve injury and may take months to years to recover.
- Over time it is possible for diaphragmatic function to resolve with NIV support.
- Plication of the diaphragm is a procedure in which the flaccid hemidiaphragm is made taut by oversewing the membranous central tendon and the muscular components of the diaphragm (Fig. 22.1). It is accepted as standard of treatment for children under 12 months of age because it allows rapid weaning from mechanical ventilation.
- Permanent phrenic nerve pacing is possible only if the phrenic nerve is fully intact and the deconditioned muscle fibers needs programmed gradual reconditioning.

22.2 Postsurgical Chylous Ascites/Effusion

22.2.1 Introduction

Chylous ascites/effusion refers to the accumulation of lipid-rich lymph in the peritoneal/thoracic cavity due to disruption of the lymphatic system secondary to traumatic injury or obstruction. As the treatments for both chylous ascites and *chylous effusion* are similar, they are dealt together. Chylous ascites after liver transplant is a common complication.

22.2.2 Overview

- Test ascitic fluid (chylomicrons, lymphocytes, and triglycerides) on POD#3 or later if there is milky drainage or persistent drainage ≥4 mL/kg/day
- A positive diagnosis is made when chylomicrons are positive, triglycerides >110 mg/dL, or lymphocytes are greater than 80%.

- Observe drainage each day until POD#5; if drainage is <4 mL/kg/day, pull out the tubes; and if on POD#5 drainage is ≥4 mL/kg/day, start treatment as outlined below.

22.2.3 Management

Management algorithm for chylous ascites/effusion is outlined in Fig. 22.2.

1. *Nonchylous Fluid*
   If the patient has been tested and the results are negative for chyle but the drainage is persistent (≥ 4mL/kg/day), continue diuretics (spironolactone). Pull out drain tubes if drainage is <4 mL/kg/day. After every 7 days of persistent drainage, resend the testing for lymphocytes, chylomicrons, and triglycerides and proceed with appropriate treatment.
2. *Minimal Fat Diet (MFD)*
   Monitor drainage daily for up to 6 days (the day you start MFD is considered as day 0); if the drainage is less than 2 mL/kg/day, drain tubes can be pulled out; and patient will continue MFD for 6 weeks from the last tube removed.
3. *Medication*
   After 6 days of greater than 2 mL/kg/day of drainage on MFD, start octreotide and continue MFD. Once full dose of medication is reached, treat for 5 full days and monitor drainage.

   On day 6 of medication: if drainage is <2 mL/kg/day, stop/wean octreotide, and monitor drainage for 48 hours after medication is stopped. If the volume remains <2 mL/kg/day, pull drain tubes, but if drainage is ≥2 mL/kg/day, stop MFD, stop/wean octreotide, and move to the next step.
4. *Nil per Oral/Total Parenteral Nutrition*
   Treatment with NPO/TPN for 5 full days. On day 6 if drainage is ≥2 mL/kg/day, restart MFD, and move to the next medication (if not previously used). If the drainage is less than 2 mL/kg/day, restart MFD and wean TPN, and monitor drainage 48 h off TPN. If, after 48 h, the drainage remains less than 2 mL/kg/day, pull tube and keep on MFD for 6 weeks.
5. *Thoracic Duct Ligation*
   If the drainage continues to persist after all of the above treatments, consider thoracic duct ligation after lymphangiogram.

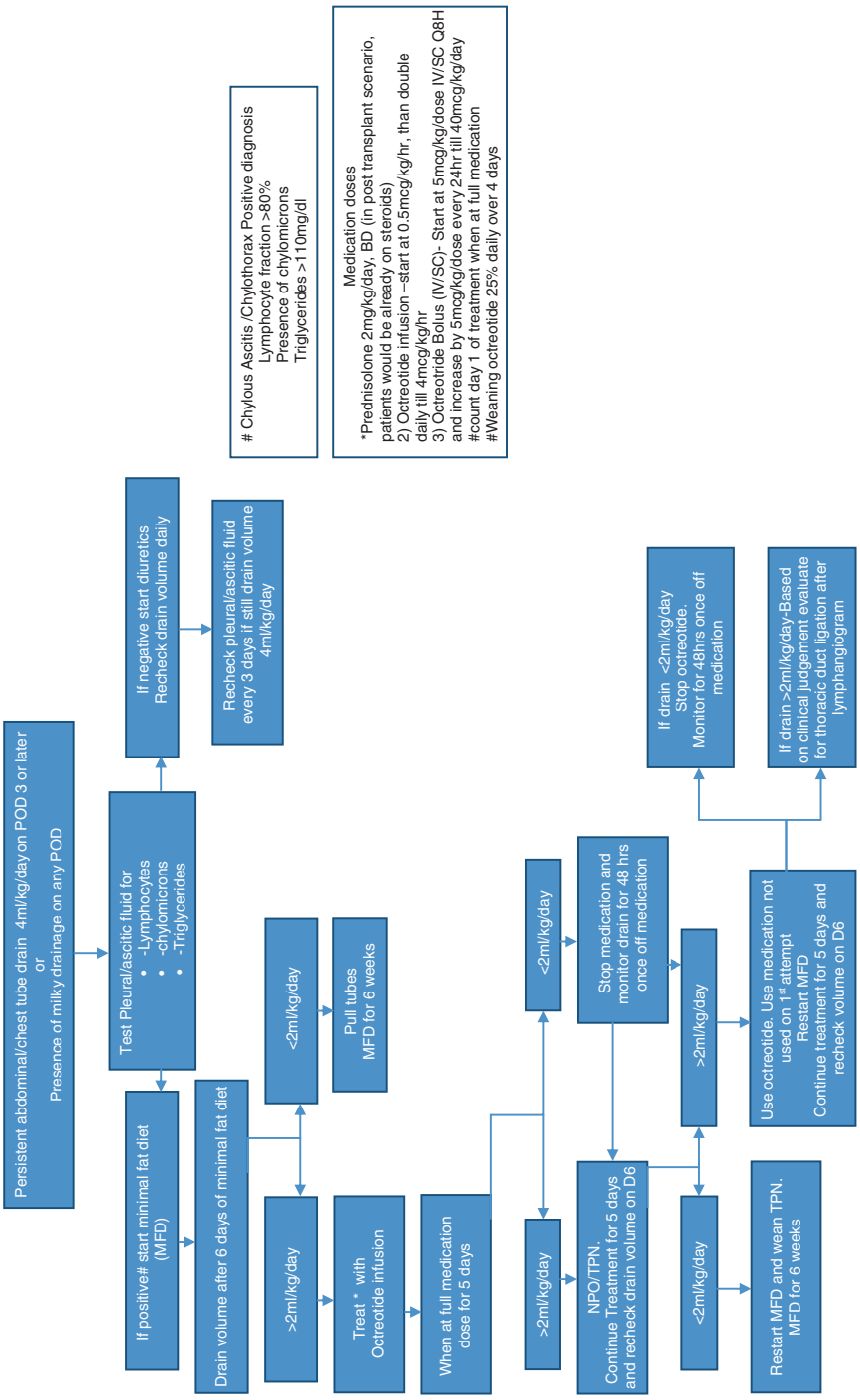

Fig. 22.2 Treatment algorithm for chylous ascites/effusion is outlined in Fig. 22.2

Immunosuppression Protocol in Liver Transplantation

23

Emer Fitzpatrick

23.1 Introduction

Advancement in the field of immunosuppression has reduced morbidity and mortality in organ transplantation. The aim of immunosuppression management is to maintain the balance between preventing rejection and minimising drug side effects.

23.2 Standard Immunosuppression Protocol for Liver Transplantation (LT) in Children

There is no universally agreed immunosuppression protocol for LT. The standard LT immunosuppression protocol described below reflects the practice of a quartenary paediatric liver transplant referral centre.

23.2.1 Induction and Immunosuppression During Immediate Post-Transplant Period

- All LT patients will receive IV methylprednisolone at a dose of 10 mg/kg at induction of anaesthesia.
- On postoperative day (POD) 1, a dose of 2 mg/kg (max 40 mg) is given as a single dose IV in the morning and continued for 3–5 days. Then it is gradually weaned by 5 mg every 2 days down to a maintenance dose of 1 mg. Once the patient can tolerate feeds, steroids may be given orally. Patients may be kept on long-term low dose prednisolone. Prednisolone generally ranges from a dose of 5 mg daily in the

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immediate post-transplant period for older children (>20 kg) and 2.5 mg for younger children (<20 kg) and weans down to a maintenance dose of 1 mg daily thereafter.

- Tacrolimus is the drug of choice as first-line immunosuppression as it has maximum efficacy with a relatively low side effect profile. Starting dose is between 0.075 mg/kg and 0.15 mg/kg BD with a maximum starting dose of approximately 3mg BD. Target trough levels are discussed in drug section below; however important modifications must be made according to the phenotype of the child. For example, it could be modified if there is renal dysfunction or frequent infection/high viral titres of EBV/CMV (as in sections below), or with late acute cellular rejection a decision may be made to run lower or higher levels of tacrolimus.
- Cyclosporine is now rarely used as a first-line agent due to its nephrotoxic effects. The exception is when tacrolimus is contraindicated (e.g. following tacrolimus-induced cardiomyopathy).

23.2.2 Second-Line Agents: Renal Sparing

- One of the major side effects of tacrolimus is renal dysfunction. Either mycophenolate mofetil (MMF) or azathioprine (or in certain cases sirolimus) may be added to tacrolimus once full feeds are established (in the case of sirolimus this should be done only after the 28th POD as there is an association with hepatic artery thrombosis in this time period), thus allowing a lower level of tacrolimus without loss of efficacy.
- In children with significant renal dysfunction prior to transplant, basiliximab may be used day 0 and day 4 again with the intention of running lower levels of tacrolimus in the first few weeks. Though basiliximab may decrease the incidence of acute cellular rejection (ACR) significantly, the incidence of infectious complications may be increased in those treated, and thus it must be used judiciously.
- MMF or another add-in agent is usually started once full feeds are attained.

23.3 Immunosuppression in Rejection

23.3.1 Acute Cellular Rejection (T Cell-Mediated Rejection)

- Occurring commonly between day 7 and 14 post-transplant, acute cellular rejection (ACR) affects in 40–60% recipients and in the most part is steroid responsive. Often presents with rising transaminases plus/minus fever.
- ACR is best confirmed by liver biopsy as infection can also present in a similar fashion. Findings on biopsy are often characteristic but can coexist with viral infection or sepsis.

- Late ACR is less characteristic on liver biopsy, and viral infection or antibody-associated rejection may also be suspected. Hepatitis viruses including hepatitis E PCR in addition to CMV and EBV should be checked and antibody-mediated rejection also considered.
- Management of ACR is with high-dose intravenous methylprednisolone at 10 mg/kg OD for 3 days. Thereafter the patient is converted to oral prednisolone and weaned from a dose of 2 mg/kg OD (max 40 mg) by 5 mg every 2 days down to a maintenance dose between 1 mg and 5 mg OD.
- If Tacrolimus levels are low in the context of ACR, the dose is adjusted to maintain appropriately higher levels; however, in some situations, this may not be appropriate, for example, if the patient is already running high tacrolimus levels or if there is renal dysfunction necessitating lower levels. In this case a second agent should be added as below. In addition, if the rejection is severe or if it is the second episode or subsequent, then a second agent may be added in.
- The second agent of choice is usually mycophenolate mofetil (MMF). Starting dose is usually 5 mg/kg BD increasing after 5 days to 10 mg/kg BD and then after another 5 days to 20 mg/kg BD as tolerated. Side effects (detailed in drug section below) such as diarrhoea may not allow rapid increase in dose. Bone marrow activity should be monitored, and if white cells are $<1.5 \times 10^9$/L or neutrophils $<0.5 \times 10^9$/L, MMF should be decreased or stopped. A trough dose at 12 h post-dose may be checked, and if >2 mg/mL, evidence of possible toxicity should be ascertained, and to decrease dose should be considered, though this is not always necessary.
- Azathioprine is a once-a-day alternative to MMF and can be started at a dose of 0.5 mg/kg OD increasing after 5 days to 1 mg/kg OD and then 1.5 mg/kg OD as tolerated monitoring white cells as above and other possible side effects (see section on drugs below).

23.3.2 Steroid-Resistant Rejection

- In the case of steroid-resistant rejection, a second liver biopsy is usually undertaken to confirm that blood tests reflect rejection rather than another process. If this indicates poor or inadequate response to steroids, an agent such as antithymocyte globulin (ATG) is considered.
- ATG is given over 10–14 days as a once-a-day infusion IV (see section below on special medications). Response is reassessed in the form of liver function tests and often a liver biopsy after 10 doses, and if adequate, the course of ATG may be terminated at this point. Otherwise the course continues for a full 14 days.
- A second-line agent such as sirolimus may be added in especially if the severity of the rejection is such that bile duct loss is seen on liver biopsy. Sirolimus is added in at a dose of 1 mg/m^2, and troughs are taken after 5–7 doses aiming

usually for a level between 4 and 6 mg/L in the first instance. Side effects of sirolimus are by nature its strong immunosuppressive effect and its propensity for hyperlipidaemia. The child needs to be monitored closely clinically and with blood tests (see section drugs below).

Tips

- Severe ACR accompanied by bile duct loss may take 6 months or more for liver function tests to normalise even with ATG and sirolimus treatment.

23.3.3 Chronic (Ductopenic) Rejection

- Ductopenic rejection may arise from an episode of very severe ACR (leading to duct loss) or multiple episodes of ACR. The patient may present with jaundice, and findings on biopsy are characteristic.
- If there is a significant inflammation present on liver biopsy, methylprednisolone and/or ATG may be considered and response monitored. Sirolimus should generally be added into the immunosuppression regime, but this may take months to demonstrate effect as above.

23.3.4 Antibody-Medicated (B Cell-Mediated) Rejection

- There is much controversy over this entity on paediatric liver transplantation; however the possibility is increasingly recognised. The entity may coexist with ACR but has some characteristic features on liver biopsy. The patient donor-specific antibody (DSA) titre should be measured, and C4d staining on liver biopsy is a non-specific but can be a relevant finding accompanying positive DSA.
- Treatment is not evidence based in liver transplantation. Steroids are the first line of treatment as in ACR. A course of plasmapheresis and intravenous immunoglobulin and/or rituximab is a second-line approach. A complement inhibitor such as eculizumab is used in renal transplant practice but not routinely in liver transplantation.

23.4 Special Circumstances

23.4.1 Retransplantation

- In the event that a second or subsequent liver transplant is required, the focus of immunosuppression regime will be based on the aetiology of graft loss and any existing co-morbidities of the patient.

  For example, if the first graft was lost because of uncontrolled rejection which was resistant to treatment, immunosuppression post subsequent transplant would be tailored as such running higher levels of immunosuppression together with an induction agent (basiliximab) and/or a second agent such as MMF in addition to tacrolimus.
- The recipient will invariably have some degree of renal dysfunction as he/she will have been treated with tacrolimus for a period of time, and thus, an induction agent may allow reduction of the usual target levels of tacrolimus post-transplant.

23.4.2 EBV Viraemia/Post-Transplant Lymphoproliferative Disease

- This subject is wide, and at present there is no consensus as to optimal management.
- In the patient with *EBV viraemia*, check for pyrexia, lymphadenopathy, faecal occult blood, anaemia, hypoalbuminaemia, etc. based on symptoms and proceed

Common Immunosuppression Medications Used in LT: Drug Dosage, Monitoring and Side Effects

Tacrolimus

Indication: Primary immunosuppression

Brands: Prograf®, Modigraf®, and Advagraf®

Formulation:

Prograf® capsule (twice-a-day dosage) – 0.5 mg, 1 mg, and 5 mg

Modigraf® sachets (TWICE-a-day dosage) – 0.2 mg and 1 mg

Advagraf® capsule (ONCE-a-day dosage) – 0.5 mg, 1 mg, and 5 mg

Dose: Initial starting dose post-transplant (Prograf or Modigraf) 0.075 mg/kg/dose–0.15 mg/kg/dose BD to achieve levels indicated above. Maximum dose 3 mg BD

Monitoring: Tacrolimus trough levels (EDTA sample). Should be taken immediately before the next dose is due. Aiming for levels as stated above according to time post-transplant and other complications.

Dose adjustments: The half-life of tacrolimus is 12–18 h, and thus any dosage adjustments would ideally reflect on trough levels done at 48 h (when dose adjustment done to check trough levels after three doses).

Administration: Recommended to take tacrolimus on an empty stomach or at least 1 h before or 2–3 h after a meal in order to maximise the absorption.

In patients who are nil by mouth, Prograf® capsules may be opened, contents dissolved in water, and the dose given via the NG route.

Side effects:

Gastrointestinal—diarrhoea, gastrointestinal ulceration, stomatitis and oral ulceration, vomiting, dyspepsia, constipation, flatulence, bloating, loose stools

Infectious—increased susceptibility to infection

Blood—anaemia, leucopenia, thrombocytopenia

Neoplasia—benign and malignant neoplasia including EBV-associated lymphoproliferative disorders, skin malignancies

Cardiac—ischaemic heart disease, tachycardia, arrhythmia, cardiomyopathy

Vascular—hypertension, haemorrhage, thromboembolic and ischaemic events, peripheral vascular disease

Nervous system—tremor, headache, seizures, disturbance in consciousness, paraesthesia, dysaesthesia, peripheral neuropathy, dizziness, impaired writing, insomnia, anxiety, confusion, disorientation, depression, hallucination, nightmares

Metabolic—hyperglycaemia, diabetes mellitus, hyperuricaemia, metabolic acidosis, hyperlipidaemia

Fluid and electrolyte imbalance—hyperkalaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload

Eye—blurred vision, photophobia

Ear—tinnitus

Hepatobiliary—cholestasis, hepatocellular damage, cholangitis

Skin—pruritis, alopecia, acne, rash, sweating increased

Musculoskeletal—arthralgia, muscle spasms, back pain, limb pain

Respiratory—dyspnoea, parenchymal lung disorders, pharyngitis, cough, nasal congestion

Renal—renal impairment, renal failure, oliguria, renal tubular necrosis

Interactions: Tacrolimus is metabolised by hepatic and intestinal CYP3A4. Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect metabolism of tacrolimus. Note fluconazole which may be frequently used post-transplant will result in increased levels of tacrolimus. This effect is usually seen after about 5 days of treatment.

Concurrent use of medicines with nephrotoxic or neurotoxic effect may increase these effects, e.g. aminoglycosides, vancomycin, and acyclovir.

with further investigations such as CT scan of the chest and abdomen to look for lymphadenopathy, upper and lower gastrointestinal endoscopy, bone marrow aspiration, to obtain a histopathological diagnosis.

- EBV viraemia with no symptoms/signs of PTLD: In our practice if EBV levels increase by a log of 2 or more within 3 months without symptoms or signs of PTLD, then the immunosuppressive therapy is minimised accordingly. Steroids and any second-line drugs may be withdrawn initially. Tacrolimus levels are then run as low as tolerated anticipating ACR. In the event of a rise in transaminases, the patient will have a liver biopsy and treatment will be managed accordingly.
- EBV viraemia with symptoms/signs of PTLD: If histology reveals a pre-PTLD or PTLD-like lesion, immunosuppression will usually be weaned and stopped, and the patient may also undergo a course of rituximab.

  Based on histopathology, further chemotherapy may be planned. While off immunosuppression, the patient will undergo close surveillance for ACR.

23.4.3 ABO Incompatibility

There is no consensus in terms of an alternative IS regimen in the event of ABO mismatch of donor and organ (A or B liver into recipient whi may have anti-A or anti-B antibodies respectively. Generally ABO incompatible organ transplant is undertaken in only very young children (mainly infants) and/or in those with low anti-agluttinin antibodies. Anti-A antibodies (in the case of an A liver into an O or B donor) and anti-B antibodies in the case of a B liver into an O or A donor are checked. The higher the antibody titre the more likely the complicaitons. Different centres consider agents such as rituximab and high dose steroids as an adjunct to immunosuppression. Plasmapheres is has also been used to decrease antibody titres in cases of dire need. There is no deviation to normal IS in our centre in this case however close surveillance for rejection and for haemolysis (treated with steroids) is maintained. Increased incidence of biliary stricture remains a risk.

Corticosteroids: IV Methylprednisolone (Sodium Succinate) and Oral Prednisolone

Indication: Primary immunosuppression and used as first-line treatment of rejection.

Dose: Initially all patients will be prescribed with IV methylprednisolone and then switched to oral prednisolone once feeding enterally.

Post-Liver Transplant

2 mg/kg (max 40 mg) once daily for 3 days, and then reduced by 5–10 mg every 2 days down to a maintenance corticosteroid dose of 1–2.5 mg/day.

Treatment of Rejection

IV 10 mg/kg (max 1 g) for three doses followed by oral 2 mg/kg (max 60 mg) once daily weaning by 5–10 mg every 2 days down to maintenance dose as above.

Formulations: IV = 40 mg, 100 mg vials; PO = 1 mg, 5 mg, and 20 mg tablets

IV methylprednisolone: PO prednisolone 1:1 conversion for practical purposes

Administration: IV – *give as an infusion*. Dilute to a practical volume (e.g. 50–100 mL) and give over 30 min. Tablets may be halved or dissolved in water for children who are unable to swallow whole doses.

Side Effects:

GI: dyspepsia, ulceration, pancreatitis, candidiasis

Infectious: increased susceptibility to infection

Vascular: hypertension

Metabolic: growth suppression, menstrual irregularity, hirsutism, weight gain, hyperglycaemia

Fluid and electrolyte balance: sodium and water retention, potassium loss, hypokalaemic alkalosis, oedema

Neurological/Psychiatric: irritability, anxiety, depression, sleep disturbance

Eye: glaucoma, papilloedema, cataracts

Skin: impaired healing, skin atrophy, bruising, telangiectasia, skin thinning, hyperhidrosis, acne

Musculoskeletal: osteoporosis, fractures, tendon rupture

Interactions: Hepatic microsomal enzyme inducers may decrease the therapeutic effects of prednisolone; drugs include rifampicin, carbamazepine, and phenobarbitone. The desired effects of hypoglycaemic agents (including insulin), antihypertensives, and diuretics are antagonised by corticosteroids.

Mycophenolate Mofetil (MMF)

Indication: Secondary immunosuppression as a renal-sparing agent and/or adjuvant agent in rejection.

Dose: 5 mg/kg BD and gradually titrate to 20 mg/kg BD (max 1 g BD). Monitor GI side effects.

Formulation: Suspension 1 g/5 mL, Capsule 250 mg, Tablet 500 mg.

Monitoring: Trough levels may indicate toxic effects. If trough level is >2, review side effect profile and other bloods, and consider decreasing dose. This may not be necessary in certain cases.

Administration: The tablets and capsules may NOT be opened/split; therefore, in patients who cannot swallow whole, the suspension must be prescribed.

Side Effects:

GI: vomiting, abdominal pain, diarrhoea, ulceration, dyspepsia

Infections: increased susceptibility to infections

Blood disorders: leucopoenia, thrombocytopenia, anaemia, pancytopenia, leucocytosis

Neoplasia: skin cancer, benign neoplasm of the skin

Cardiac: tachycardia

Vascular: hypotension, hypertension, tremor, somnolence, myasthenic syndrome, headache, paraesthesias

Metabolic: acidosis, hyperglycaemia, hypercholesterolemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia

Fluid and electrolyte imbalance: hyperkalaemia, hypokalaemia, hypomagnesaemia, hypocalcaemia

Psychiatric: agitation, confusion, depression, insomnia

Hepatobiliary: hepatitis, jaundice

Skin: skin hypertrophy, rash, acne, alopecia

Musculoskeletal: arthralgia

Respiratory: pleural effusion, dyspnoea, cough

Renal: renal impairment

Interactions: Caution should be used with medicinal products that interfere with enterohepatic circulation because of their potential to reduce the efficacy.

Sirolimus

Indications: Secondary immunosuppression as a renal-sparing agent and/or adjuvant agent in rejection (particularly ductopenic rejection) and/or alternative agent in PTLD

Dose: This is a once-daily drug. Initially all patients will be prescribed 1 mg/m^2.

Subsequent/maintenance dose will be dependent on levels.

Monitoring: Trough levels should be taken 7 days after initiation as this drug has a long half-life.

Target Levels: In combination with tacrolimus – 4–12 ug/L.

If being used as sole immunosuppressive agent: 12–20 ug/L.

Dosage adjustments: May take up to seven doses to equilibrate levels. Frequent manipulation of dose is not recommended within this period.

Formulations: Rapamune® liquid 1 mg/1 mL, Rapamune® tablets 0.5 mg, 1 mg, 2 mg

Administration: The tablets must be swallowed whole; they may not be crushed or dissolved.

The liquid can be diluted in an equal measure of water or orange juice if required.

Sirolimus should be taken consistently either with or without food to minimise variability in absorption.

Side Effects:

GI: abdominal pain, diarrhoea, constipation, nausea, pancreatitis, stomatitis

Infectious: increased susceptibility to infections

Blood: thrombocytopenia, anaemia, leucopenia, haemolytic uraemic syndrome, neutropenia

Neoplasms: skin cancer

Cardiac: tachycardia, pericardial effusion

Vascular: hypertension, lymphocele, thrombosis

Nervous/psychiatric: headache

Metabolic: hyperlipidaemia, hyperglycaemia

Fluid and electrolyte imbalance: hypokalaemia, hypophosphatasemia

Skin: rash, acne

Musculoskeletal: arthralgia, osteonecrosis

Respiratory: pulmonary embolism, pneumonitis, pleural effusion, epistaxis

Renal: proteinuria

Interactions: Sirolimus is extensively metabolised by the CYP3A4 isozyme in the intestinal wall and liver. Sirolimus is also a substrate for the multidrug efflux pump, P-glycoprotein (P-gp), located in the small intestine. Therefore, absorption and the subsequent elimination of sirolimus may be influenced by substances that affect these proteins.

Basiliximab

Basiliximab (Simulect®) is a monoclonal antibody that is directed against the interleukin-2 receptor, which is expressed on the surface of T lymphocytes in response to antigenic change. Basiliximab specifically binds to the CD25 antigen on activated T lymphocytes expressing the high affinity interleukin-2 receptor and thereby prevents binding of interleukin-2, the signal for T cell proliferation.

Indications: Primary immunosuppression in all intestine and kidney transplant recipients. It is also used as a renal-sparing immunosuppression, i.e. in patient with renal impairment undergoing liver transplant and/or adjuvant immunosuppression for graft rejection.

Dose: The patient should receive two doses, one dose on day 0 (usually within 2 h prior to surgery) and one dose on day 4

>35 kg: 20 mg per dose for two doses

<35 kg: 10 mg per dose for two doses

<1 year old: 12 mg/m^2 per dose for two doses

Formulation: Simulect® (Basiliximab) 20 mg vial

The reconstituted solution should be diluted to a volume of 50 mL or greater with normal saline or dextrose 50 mg/mL (5%) for infusion over 20–30 min.

Side Effects:

Hypersensitivity reactions, neoplasms, malignancy, malignant neoplasms

Interactions:

Due to the potential for hypersensitivity reactions, all patients should receive a dose of IV chlorpheniramine and PO paracetamol 30 min prior to each basiliximab infusion.

Rabbit Antihuman Thymocyte Globulin (ATG) Thymoglobuline®

Rabbit antihuman thymocyte globulin (ATG) Thymoglobuline® is an infusion of rabbit-derived antibodies against human T cells which is used in the treatment of acute rejection in organ transplantation. It acts by destroying T cells.

Indication: Steroid-resistant graft rejection.

Dose: 1.5 mg/kg/dose once a day for a minimum of 5 days and maximum of 14 days (maximum cumulative dose 21 mg/kg).

Formulation: Thymoglobuline® 25 mg vials. The daily dose is diluted in an infusion solution (0.9% sodium chloride or 5% glucose solution) so as to obtain a total infusion volume of 50–500 mL (usually 50 mL/vial).

Adjust the infusion rate so that the total duration of infusion *is not less than 6 h*. Give through a 0.22 μm in-line filter.

Side effects:

Interactions: none expected

Prophylactic medications: orally 6 hours or IV if NBM, and continue 1–3 months post-transplant

Due to the immunosuppressive effect, all patients should be prescribed:

Fluconazole 6 mg/kg daily (max 400 mg)

Cotrimoxazole dosing based on body surface area; give once daily three times a week:

<0.25 m^2: 120 mg

0.25–0.39 m^2: 240 mg

0.4–0.49 m^2: 360 mg

0.5–0.75 m^2: 480 mg

0.76–1 m^2: 720 mg

>1 m^2: 960 mg

Valganciclovir: 520 mg/m^2 once daily (max 900 mg)

Premedication: Due to the potential for hypersensitivity reactions, all patients should receive a dose of IV hydrocortisone, chlorpheniramine, and PO paracetamol 30 min prior to each ATG infusion.

Side effects:

Immune-mediated reactions: anaphylaxis or severe cytokine release syndrome (CRS)

Infection

Malignancy: lymphoma or post-transplant lymphoproliferative disease (PTLD)

Haematological effects: thrombocytopenia and/or leucopenia (including lymphopenia and neutropenia)

Role of Radio Imaging in Liver Transplantation

24

Sandeep Botcha and T. Deepashree

24.1 Introduction

Over the past five decades, liver transplantation (LT) has evolved from an experimental to an established procedure for treatment of children with liver disease. Various operative techniques such as liver reduction, split and living donor liver transplantation (LDLT) have increased organ availability to children. Radiological diagnosis and interventions play a valuable role in pre- and posttransplant follow-up care.

24.2 Role of Ultrasound

Ultrasonography (USG) is the preferred post-LT screening method as it can be easily performed at bedside. It can detect parenchymal (hematomas and collections), vascular (stenosis and thrombosis), biliary (e.g., stenosis), and abdominal cavity (collections and abscess) complications.

Doppler ultrasound (DUS) plays an important role in assessment of blood flow dynamics in transplanted organs. During routine post-LT DUS, the hepatic artery and its intrahepatic branches, main portal vein and its branches, hepatic veins, and IVC are screened. Blood vessel dimensions and various arterial flow parameters are measured.

24.2.1 Doppler of Hepatic Artery (HA)

Resistive index (RI) of the hepatic artery is a calculated index using the following Doppler parameters:

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- Peak systolic velocity (PSv)
- Diastolic velocity (Dv)
- Systolic acceleration time (Sat) (the time taken to reach PSv after trough Dv)
- RI = (PSv – Dv)/PSv usually range between 0.6 and 0.8 in a normal liver:

1. The nontransplant HA values for PSv range from 40 to 80 cm/s, and Sat lies below the range of 0.08 s.
2. High RI indicates resistance to arterial flow and reflected as a large difference between PSv and Dv.
3. Low RI and prolonged Sat are reflected as a minimal difference between the PSv and trough Dv as seen in arterial stenosis.
4. In the presence of proximal stenosis, a characteristic pattern of a slow Sat and diminished PSv called *tardus et parvus* waveform is seen. It can be accessed by the arterial waveform distal to the stenosis.
5. DUS of a high-velocity segment shows elevated RI proximally and decreased RI and prolonged Sat distally.

24.2.2 Doppler of Veins

Thrombosis and anastomotic stenosis are the common complications affecting the portal vein (PV) after LT. They are detected by the absence or acceleration of blood flow.

24.3 Postoperative Doppler Evaluation of Allograft Liver

Post-LT DUS is often carried out within the first day (before extubation of patient), with follow-up exams as clinically indicated.

24.3.1 Hepatic Arterial Flow

The immediate postoperative Doppler often shows transient hepatic arterial abnormalities that resolve on follow-up scans.

- Increased RI (RI > 0.8, absent or even reversed diastolic flow) due to decreased diastolic flow (secondary to allograft edema, increased portal flow, or vessel spasm) is seen in almost half of the patients.
- A decreased RI (RI < 0.55) due to increased diastolic flow (probably due to anastomotic edema in the postoperative period) is usually of concern for arterial complications. Arterial waveform abnormalities in immediate postoperative scans should be followed up and correlated with the patient's clinical findings and liver function tests [4].
- Transient waveform usually resolves in 7–15 days; any deterioration of a waveform on a follow-up study is highly suggestive of an arterial complication [7].

24.3.2 Portal Vein (PV) and Hepatic Veins (HV)

- Increased portal venous flow due to reduction in portal venous resistance manifests as high portal venous velocity in the immediate post-LT period.
- As the body adapts to the new hemodynamics, it normalizes in the postoperative period.
- Increased portal venous velocity can also be caused secondary to PV compression by transient postsurgical intra-abdominal collections.
- Hepatic veins (HV) normally have a triphasic waveform, but monophasic or biphasic waveforms are commonly seen postoperatively either due to early graft edema or by the adjacent intra-abdominal collection compression; it usually normalizes on subsequent DUS studies.

24.4 Radiological Evaluation of Postoperative Complications

24.4.1 Arterial Complications

24.4.1.1 Hepatic Arterial Thrombosis (HAT)

It is a devastating complication that usually occurs in the first few weeks after LT. Delayed occurrence of thrombosis has more devastating clinical outcomes. It is usually diagnosed by the absence of flow in the hepatic arteries on DUS.

High-resistance waveform (RI = 1) can be obtained in the site proximal to the HAT when sampled. Computed tomography (CT) or digital subtraction angiography (DSA) is usually performed for diagnosis confirmation. When the diagnosis is established early in the postoperative course, surgical revascularization may be attempted, or re-transplantation is required in majority of the cases.

Hepatic arterial collaterals can develop after HAT, particularly in the late cases which can produce a "tardus parvus waveforms" in the right and left hepatic arteries which may also indicate the presence of either upstream stenosis or thrombosis.

24.4.1.2 Hepatic Arterial Stenosis (HAS)

Timely detection of HAS on a postoperative Doppler is extremely important. HAS can occur anywhere in the graft artery with increased predilection for the anastomotic site. Direct demonstration of the stenotic segment clinches the diagnosis:

- DUS shows an area of turbulence and aliasing with elevated PSV (greater than 200 cm/s) at the stenotic segment.
- Secondary changes such as decreased resistance (RI < 0.55) of the arterial tree along with a tardus parvus waveform (occasionally) distal to the stenotic segment can be seen.
- It can be treated by percutaneous angioplasty, and stenting with DSA being the preferred modality as diagnosis and treatment can be done in the same setting.

24.4.1.3 Hepatic Artery Pseudoaneurysm

It's a rare complication either due to infection or of iatrogenic cause (secondary to a biopsy or angioplasty). On Doppler ultrasound it is identified as a cystic structure along the hepatic artery, with a disorganized flow within it.

24.4.1.4 Splenic Artery Steal Syndrome

In some patients following LT with pre-existing portal hypertension and splenomegaly, the hypertrophied splenic artery may shift the blood flow away from the liver toward the spleen, resulting in hepatic hypoperfusion. This is known as the splenic artery steal syndrome. On DUS, a presence of high-resistance waveform in the main, left, and right hepatic arteries, increased portal vein velocity and hyperdynamic splenic arterial flow should raise the possibility even though these findings may present in normal patients in the immediate postoperative period which usually normalize on follow-up imaging. Angiography is performed to confirm the diagnosis, and the condition is treated by splenic arterial embolization.

24.4.2 Venous Complications

24.4.2.1 Portal Vein Thrombosis (PVT)

It is frequently encountered post surgery. The normal portal vein has antegrade flow posttransplantation, and its velocity is variable and tends to decrease on serial examinations after transplantation. In a majority of the patients, it is diagnosed within 1 month of transplantation and may present with indirect signs of portal hypertension or nonspecific abnormalities of liver function tests.

On grayscale imaging it is identified as either anechoic or echogenic material within the portal vein, with no flow on DUS. Acute cases of thrombosis can be treated with catheter-guided thrombolysis and thrombectomy. Anastomotic revision and re-transplantation can also be performed based on the severity.

24.4.2.2 Portal Vein Stenosis

Stenosis after transplantation is rare and usually occurs (within 6 months, a more delayed presentation is due to neointimal hyperplasia) in the pediatric and living donor population, due to the small graft vein size.

Its clinical presentation is similar to portal vein thrombosis showing portal hypertension or hepatic failure. DUS is useful in assessing the velocity and pressure gradient across at the stenotic segment which could be treated with catheter-guided angioplasty or stenting.

24.4.2.3 Hepatic Venous and Inferior Vena Cava Complications

- The posttransplant venous complications tend to occur at the anastomosis few months to years posttransplantation with thrombosis and stenosis being rare complications of the IVC and hepatic veins.

- The incidence of stenosis is higher in living donors and split graft liver pediatric grafts than in whole liver grafts, likely due to the size mismatch and small anastomosis.
- Normal hepatic veins have a triphasic waveform. However loss of triphasicity is a very nonspecific finding and is often seen in normal postoperative patients. Therefore, loss of triphasicity should be correlated with the patients' clinical presentation. Venous angioplasty and stenting can be performed in cases of clinically significant hepatic stenosis.

24.5 Biliary Complications

Biliary complications such as leak and stenosis occurring within the first 3 months is around 25% of liver transplant recipients. Biliary tree of allograft liver is critically dependent on the hepatic artery, and any disruption of hepatic arterial flow is associated with bile duct ischemia.

24.5.1 Bile Leak

It's an early complication occurring at the anastomotic site. Small leaks usually close spontaneously, but a large biliary collection requires percutaneous drain insertion. CT and ultrasound help in localizing peri- or subhepatic space collections. Less frequently bile leaks (non-anastomotic) due to necrosis of bile ducts (e.g., HAT) generally require re-transplantation. T-tube cholangiogram or contrast-enhanced ultrasound cholangiography can show evidence of dynamic contrast leak.

24.5.2 Biliary Duct Obstruction

Bile duct stenosis can occur at the site of anastomosis or anywhere along the biliary tract. Magnetic resonance cholangiography (MRCP) has good sensitivity and specificity in showing focal narrowing at the level of the anastomosis with upstream dilatation of biliary tract.

- *Anastomotic biliary stenosis*: MRCP should be done in all patients where routine ultrasound shows dilated biliary system. Percutaneous transhepatic balloon dilation (PTBD) could be done in hepaticojejunostomy or balloon dilation by ERCP in duct-to-duct anastomosis.
- *Non-anastomotic biliary strictures occur* due to HAS or HAT leading to biliary ductal ischemia, resulting in fibrosis and stenosis. It can occur anywhere in the biliary tree and can be usually seen in hilar region. Temporary stenting can be done while awaiting re-transplantation.

Conclusion

DUS plays an important role in routine assessment and surveillance of patients post-LT. CT and MRI are used as definitive modalities to confirm the diagnosis.

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Blood Product Usage in Liver Transplantation

25

Deepti Sachan

25.1 Introduction

Liver transplantation has emerged as an increasingly successful treatment for patients with end-stage liver disease (ESLD). The operative procedure is extensive, complex and technically challenging, with multiple vascular transections and anastomoses. Historically, liver transplantation was associated with massive blood loss and requires maximum component support amongst all organ transplants. Over the last few decades, with the continuous improvements in surgical techniques, use of pharmacological alternatives of blood and availability of potent immunosuppressive agents, there are remarkable improvements in survival outcomes of liver transplantation. General instructions on usage and handling of blood components handling and storage are outlined in Table 25.1.

The liver is an extremely vascular organ and site of synthesis of various coagulation factors and protein. Preoperative coagulopathy, portal hypertension, thrombocytopenia and blood loss during transplant surgery create a challenge to blood transfusion services. At majority of instances, it is difficult to predict the perioperative requirements of blood transfusion and required adequate blood inventory to support liver transplant programme.

25.1.1 Pre-transplant Immunohaematological Workup

ABO and Rh typing plays an important role during the liver donor selection as well as for blood transfusion; alloimmunization of red cell antigens is one of the major risks of blood transfusion. It results from the antigenic disparities between the donor

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Table 25.1 General instructions on usage and handling of blood products

Component	Indications	Shelf life and storage	One adult unit is equivalent to mL (approx.)	Recommended time for 1 unit transfusion	Therapeutic effect of one unit in an average adult
Packed red blood cells (in SAGM)	Surgical/non-surgical acute blood loss, chronic anaemia	42 days at 2–6 °C	250 mL	1–2 h	Increase Hb by 1 g/dL, in paediatric age 10–15 mL/Kg increase 2–3 g/dL
Single donor platelets (SDP)	Bleeding due to thrombocytopenia, platelet dysfunction or both	5 days at 22 °C under agitation	200 mL	60–90 min	Increase the platelet count by 40,000–60,000/mm^3
Random donor platelets (RDP)	Bleeding due to thrombocytopenia, platelet dysfunction or both	Same	50 mL	15–30 min	Increase the platelet count by 5000/mm^3
Fresh frozen plasma	Liver disease with INR > 1.5 and active bleeding or invasive procedure	1 year at −30 °C. After thawing, within 24 h (in 4 °C)	200 mL	30–60 min	One unit—5–7% augmentation of clotting factors 15 mL/kg bwt provides 20–30% augmentation of clotting factors
Cryoprecipitate (Cryo)	Liver disease with hypofibrinogenaemia (<1 g/L), DIC, bleeding	1 year at −30 °C	CPT—20 mL (1 unit)	5–10 min	Each unit of cryo augments the fibrinogen levels 6–7 mg/dL in an average adult
			Pooled CPT—120 mL (6 units)	30–60 min	

and recipient. Immunization may be influenced by the number and frequency of the transfusions as well as recipient's gender, age and underlying disease. Patients undergoing liver transplant may be suffering from primary or secondary autoimmune haemolytic anaemia.

As per hospital protocol, ABO blood grouping, Coombs test (direct and indirect) and cold antibody detection tests are performed to rule out the presence of any significant irregular red cell antibodies free in serum or coating red cells which may interfere during crossmatching and may cause haemolytic transfusion reactions.

25.1.2 Inventory Management

Maintenance of an adequate blood component inventory is critical to the success of a liver transplant programme. Optimal inventories of blood components necessary to support institutional needs and the day's liver transplant case(s), should be available before any case starts. General instructions on blood product handling and storage are outlined in Table 25.1. Every transplant facility should develop guidelines for blood reservation for liver transplant surgery based on utilization practices, facility experience and needs of individual patients. Maximum surgical blood ordering schedule (MSBOS) for a liver transplant surgery usually consists of 15 units of crossmatched leucodepleted packed red cells, 15 units of FFP, 4 units of single donor platelets and 4–6 adult doses of cryoprecipitate which are reserved for an adult liver transplant surgery.

25.1.3 Blood Product Specifications

Patients undergoing liver transplant have specific and specialized blood requirements before, during and after the transplantation. This is to reduce the adverse consequences of alloimmunization to human leukocyte antigens, immunohaematologic consequences of ABO-mismatched transplantations or immunosuppression.

25.1.3.1 ABO Blood Group Compatibility

Blood components PRCs, PLTs, FFP and cryoprecipitate are transfused which are compatible with both donor organ and the recipient whenever feasible. Table 25.2 shows guidelines on choosing appropriate blood and components to be used in LT based on recipient and donor blood groups.

25.1.3.2 Rh Compatibility

- Rh-negative patients should be provided with Rh (D)-negative RBCs to avoid sensitization to D. However, in case of excess requirements (>10 units) or non-availability of Rh-negative blood, patients can be switched to Rh(D)-positive RBCs, provided anti-D is not detected in patient before transfusion.
- Rh-positive units can be transfused to the patient for 24–48 h or until sufficient Rh-negative inventory is available.
- Although the risk of alloimmunization is low in OLT due to postoperative immunosuppression, efforts should be made to give Rh-negative children and women of child-bearing age with Rh-negative blood.

25.1.3.3 Leukoreduced Blood Products

- Cellular blood components used in the perioperative setting should be leukocyte depleted to reduce the occurrence of febrile reactions, HLA immunization and CMV transmission and prevent post-perfusion complications after liver transplant surgery. Nowadays, with the use of integrated inline leukocyte filters, prestorage leukodepletion is ensured.

Table 25.2 Blood and component selection in liver transplantation based on recipient and donor blood group

Recipient	Donor	PRBC—compatible choices	FFP/PLT compatible choice
A	A	A	A, AB
A	B	O	AB
A	O	O	A, AB
A	AB	A, O	AB
B	A	O	AB
B	B	B	B, AB
B	O	O	B, AB
B	AB	B, O	AB
O	A	O	A, AB
O	B	O	B, AB
O	O	O	ALL GP
O	AB	O	AB
AB	A	A, O	AB
AB	B	B, O	AB
AB	O	O	AB
AB	AB	AB	AB

- In case of non-availability of leukoreduced products, non-leukoreduced products may be given with bedside leukoreduction filter.
- For platelet transfusions, single donor platelets (SDP) prepared from modern apheresis machines contain very low number of leukocytes; however, random donor platelets if transfused should be leukodepleted using platelet leukofilter.
- Cryoprecipitate and fresh frozen plasma do not contain intact or viable leukocytes, and so leukoreduction is unnecessary.

25.1.3.4 Irradiated Blood Products

- Blood products are exposed to 25 Gy of gamma irradiation to arrest the lymphocyte's ability to divide.
- Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare complication of organ transplantation but carries high mortality rate. It is debatable whether recipients of liver transplant should receive irradiated blood components due to time- and cost-consuming procedure and risk versus benefits of irradiation.
- Irradiation of RBCs can induce membrane damage and increase potassium leakage to the extracellular environment. This can increase the risk of developing hyperkalaemia especially in the setting of poor renal function and metabolic acidosis and can increase morbidity and even mortality especially in the setting of massive transfusion.

25.1.3.5 CMV-Reduced Risk Components

- As liver transplant recipients are more susceptible to CMV infection (in CMV-seronegative recipients of CMV-seronegative donors), steps should be taken to prevent CMV transmission through blood transfusion.
- Prevention can be achieved by leukocyte reduction of the cellular components and by selection of blood from CMV-seronegative donors or both.
- Cryoprecipitate and FFP are cell-free and have not been implicated in CMV transmission.

25.1.3.6 Alloimmunized Patient

- Clinically significant alloantibodies may be present in liver transplant recipients due to previous blood transfusions or pregnancies.
- Antibody identification and selection of antigen-negative and crossmatch-compatible blood are required to minimize haemolysis.
- During high blood requirements, strategies like switching from antigen-negative to antigen-unscreened/partially matched and switching back to antigen-negative units in postoperative period are utilized to prevent postoperative haemolysis.
- Preoperative plasmapheresis is also an option to reduce clinically significant antibodies. Haemolysis secondary to alloimmunization can present a challenge in OLT, and it can greatly increase requirements for transfusion.

25.1.3.7 Autologous Blood

- Intraoperative cell salvage is an effective tool in blood conservation. It allows the retrieval and reuse of blood lost in the operative field.
- Cell salvage is not indicated in the presence of sepsis and hepatocellular carcinoma (HCC).
- As the salvaged blood does not contain platelets and fibrinogen, large-volume transfusion of salvaged blood can cause cell saver-induced coagulopathy and should be prevented by simultaneous platelets and cryoprecipitate transfusions.

25.1.4 Intraoperative Period and Blood Transfusion

Preexisting abnormalities of clotting, platelets and fibrinolysis compound the problem. Addressing these abnormalities is crucial. The anaesthesiologist must aggressively attempt to correct the international normalized ratio (INR) and platelet count by transfusing plasma and platelets early in the operative procedure.

- Stage I (pre-anhepatic period): blood loss in stage I occurs mainly from transection of the fragile collateral vessels that develop as a result of portal hypertension.

- Stage II (anhepatic phase): extensive bleeding may occur from raw areas after removing the liver due to increased portal pressure.
- Stage III (reperfusion and post-reperfusion period): coagulation factors, especially factors V and VIII, may be degraded during transplantation as a result of enhanced proteolysis, and the degree of degradation correlates with the transfusion requirements during orthotopic liver transplantation (OLT).

25.1.5 Postoperative Factors Requiring High Transfusion

- *Primary non-function (PNF) of graft or delayed graft dysfunction*—Failure of graft to function contributes to postoperative bleeding, coagulopathy and thrombocytopenia. Appropriate blood component therapy is given to these patients. Plasmapheresis is also used as a supportive therapy in post-transplant graft dysfunctions.
- *Passenger lymphocyte syndrome*—It can occur from transfer of donor-derived passenger lymphocytes and manifests as haemolysis during 7–14 days after transplantation. This is usually controlled by transfusion of donor-specific RBCs.
- *Peri-operative thrombocytopenia* is commonly associated with hemodilution, reduced platelet production and/or increased platelet consumptions due to thrombosis, viral infections, medications, platelet-associated antibody production or combination of these.

25.2 Complications of Blood Transfusion

Alloimmunization to red cell antigens may cause difficulties in selecting compatible blood, while alloimmunization to HLA expressed on platelets may cause subsequent platelet transfusion refractoriness. Allergic reactions are the commonest adverse transfusion reactions seen in liver disease patients due to plasma and platelet transfusions.

Conclusion

Improvements in organ preservation, surgical technique, anaesthetic care as well as postoperative intensive care management have contributed to a steady reduction of transfusion requirements in the perioperative period and have increased the number of patients undergoing liver transplant surgery without any need for blood products.

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Antimicrobial Therapies in Pediatric Liver Disease

26

S. Subramanian

26.1 Introduction

Infections are a common cause of morbidity and mortality in children with liver disease. Early recognition and timely institution of appropriate therapy are key to improving outcomes. The risk factors for these infections include changes in the intestinal flora and the intestinal barrier, decompensated liver disease, gastrointestinal bleeding, history of invasive procedures, impaired immunity of the host defense mechanisms, and impaired function of the reticuloendothelial system, complement, and neutrophils. In addition, poor nutrition, coexisting medical and metabolic conditions, structural deformities, and missed vaccination coverage could also contribute. The common foci of infection are the peritoneum, the lung, and the urinary tract.

26.2 Choosing Appropriate Antimicrobial

Early and appropriate antimicrobial therapy is the key to improve outcomes. The therapy should be chosen based on common local pathogenic organism and guided by local antimicrobial susceptibility data (antibiogram). Blood cultures before starting intravenous antibiotics should be the standard of care, as it helps in either escalation or de-escalation of therapy based on culture report. Choosing appropriate anti-infective in specific scenarios is outlined below.

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26.2.1 Acute Liver Failure

- High risk of sepsis is a leading cause of death.
- Risk of both bacterial and fungal infection.
- Infection is usually from translocation from bowel and also from other sites—peritonitis, pneumonia, and urinary tract.
- High risk of nosocomial infections as well.
- Cultures when clinically indicated to be performed—new-onset fever, change in vital signs, worsening clinical condition, or rise in counts.
- May need to be considered for those planned for emergency liver transplant.
- Piperacillin-tazobactam with fluconazole is a common regimen used as first-line therapy.
- Newborns with acute liver failure should receive acyclovir IV till PCR negative or for 21 days.
- In patients with late or nosocomial infections, therapy as per guidelines suggested later should be considered.

26.2.2 Encephalopathy

- Infection is an important cause of encephalopathy and vice versa holds true.
- Nonabsorbable antibiotics like aminoglycosides and vancomycin are no longer preferred.
- Rifaximin is approved for this indication, but the data in children is limited, and should be kept to 7 days of therapy.

26.2.3 Bacterial Peritonitis

- Common cause of sepsis in patients with liver disease.
- Ascitic fluid can establish diagnosis.
- Unlike adults, where it is primarily enteric Gram-negative pathogens, pneumococcus and *H. influenzae* are common causes in children.
- Although pneumococcus and streptococci remain susceptible to penicillin, there is a rise in resistance in many organisms like pneumococcus, *H. influenzae*, and Gram-negative bacteria.
- Empiric therapy should cover for enteric Gram negatives, and piperacillin-tazobactam is a good choice. If drug-resistant pneumococci is a concern, vancomycin may be added.

26.2.4 Lower Respiratory Tract Infection

- Increased risk of pulmonary infections in children with liver disease.
- Viral lower respiratory disease very common with influenza being notable, especially during the winter season. Others include parainfluenza, RSV, and metapneumovirus.

- Pneumococcus is the primary bacterial cause. Others include *H. influenzae*, streptococci, and rarely *S. aureus* and enteric Gram-negative pathogens.
- Tuberculosis should not be forgotten as a cause.
- Examination of respiratory secretions can be helpful in older children.
- Radiology can be a useful adjunct to clinical presentation in determining causative agent; lobar consolidation indicates pneumococcus, diffuse interstitial presentation concerning for atypical pathogens and viral causes, and bronchopneumonia suggesting *S. aureus*. The presence of cavities or upper lobe infiltrates should trigger search for tuberculosis.
- Empiric therapy with a cephalosporin should be adequate. For children who may be sick or have additional risk factors, piperacillin-tazobactam with linezolid could be used. Role of antivirals is unclear.

26.2.5 Urinary Tract Infection

- Risk higher than in normal children.
- Usual causes are enteric Gram-negative pathogens, especially *E.coli*; enterococcus is also a concern.
- Urine analysis with Gram stain and culture should help.
- Empiric therapy with piperacillin-tazobactam is appropriate; in children who are septic or have an obstructive system, meropenem or imipenem should be preferred.
- Anatomic anomalies should be assessed for: vesicoureteric reflux may be present.

26.2.6 Skin and Soft Tissue Infections

- Usually due to Gram-positive cocci—*S. aureus* and streptococci.
- Higher risk of Gram-negative pathogens in children with liver disease.
- At risk for unusual pathogens like *Vibrio vulnificus* and *Aeromonas hydrophila* in children with iron overload.
- Empiric therapy with piperacillin-tazobactam (with vancomycin or teicoplanin in places with MRSA risk) or tigecycline is appropriate.

26.2.7 Nosocomial Infections

- Related to stay in hospital, use of invasive devices, broad-spectrum antibiotics, and immune suppressants.
- Influenced by level of infection control and antimicrobial stewardship implementation at the center.
- Guidance from microbiologist in the form of local antibiograms is helpful.
- Appropriate culture is key to individualizing therapy.

- Early appropriate antimicrobial therapy with broad-spectrum coverage, if needed as colistin-based therapy (with a secondary agent).
- Removal of focus (like infected line) key to successful outcomes.
- Centers that note candidemia should also use an echinocandin like anidulafungin as an empiric agent.
- Repeat blood cultures are mandatory if *S. aureus* or *Candida* is isolated; duration of culture positivity correlates with outcomes and the possibility of complications.
- Based on culture data and patient profile, de-escalation of therapy should be attempted.
- Duration of therapy depends on the focus of infection, but for most infections, 7 days of therapy should be adequate.
- Longer duration of therapy should be administered for *S. aureus*; non-fermenting Gram-negative bacilli like *Acinetobacter*, *Pseudomonas*, *Burkholderia*, etc.; and *Candida*.

26.3 Poor Responders

Children who do not improve with seemingly appropriate therapy should trigger a search for additional issues. These would include:

- Incorrect diagnosis
- Inadequate coverage of pathogens or unusual resistance patterns
- Novel pathogen or a new outbreak
- Inadequate dose or timing of therapy
- Complications related to the disease like abscess formation
- Complications related to therapy like line-related infection

Conclusion

Strategies such as early diagnosis and treatment of underlying disease, good nutrition, up-to-date vaccination, etc. help in preventing infections. High index of suspicion and early institution of antimicrobial help in decreasing mortality and morbidity in liver diseases.

Liver Allograft: Cadaver and Living Donor Transplantation

27

Ashwin Rammohan

27.1 Introduction

The success of organ transplantation may be attributed to many factors but ultimately depends on the quality of donor organ, either from a cadaveric or living donor. This chapter deals with principles behind case selection and organ retrieval procedure involved in deceased and living donors.

27.2 Deceased Donor Transplantation: Organ Retrieval

The whole liver can be harvested from two sources: (1) brainstem-dead, heart-beating donors/donation after brain death (DBD) and (2) non-heart-beating donors/donation after cardiac death (DCD) (at present, the Transplantation of Human Organs Act in India does not permit this type of donation). Organ retrieval is generally done at a hospital recognized and accredited with the relevant government authority. The host hospital has first choice of use in single organs and one of the paired organs being retrieved. If the harvesting hospital is not a transplant centre, the organs are allocated equitably according to a transparent rota overseen by the transplant authority of the state.

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27.3 Principles

Procurement of the cadaver donor liver is most often done in conjunction with the removal of other organs. Therefore, multiple surgical donor teams must coordinate their efforts to remove organs from the deceased donor as quickly and as effectively as possible.

The goals of liver procurement are to:

1. Determine if the liver is acceptable for transplantation. Suitability of the donor liver is determined by visually inspecting in the donor's abdomen by an experienced liver transplant surgeon. In cases of doubt, liver biopsy is performed.
2. Perform a technically perfect donor hepatectomy.
3. Avoid warm ischaemia of the organs.
4. Minimize the cold ischaemic time of the donor organs.
5. The donor and the relatives are to be treated with utmost dignity and professionalism in a fashion similar to any other surgical patient undergoing an operation. Any indiscretion may place the whole transplant system in disrepute.

27.4 The Team

1. Lead surgeon
2. Assistant surgeon
3. Operating room technician
4. Anaesthetist
5. Scrub nurse
6. Perfusionist
7. Transplant coordinator

27.5 Pre-operation

Discuss plans for the operation with the anaesthetist, cardiac and renal teams regarding (1) incision and sternotomy, (2) heparinization, (3) aortic clamping and (4) organ out. The order of organ retrieval is as follows: the (1) heart/lung, (2) liver, (3) pancreas/intestine, (4) kidneys and (5) corneas.

27.5.1 Checklist

- Check blood group again.
- Age.
- Form 6—consent including organ list (India).
- Form 8—brainstem death declaration form (India).
- List of injuries.
- Lowest BP of patient (duration of hypotension, desaturation).

- Inotropic support—vasopressin better than noradrenaline to target MAP 60.
- LFT, sodium level at retrieval.
- Positive blood cultures and antibiotic list.
- Viral markers.
- Previous operation or treatment for malignancy.
- Discuss with anaesthetic team—inform if unstable—systolic blood pressure less than 90 mm Hg and oxygen saturation less than 90%.

Before the donor is transferred, theatre should be ready; a nurse and surgical team member should be present. Donor may become very unstable during transfer, and a rapid retrieval may be needed if this happens.

27.6 The Donor Operation

The donor operation is divided into two main stages:

27.6.1 Warm Phase

Warm ischaemic time (WIT) refers to the duration of time that an organ remains at body temperature after its blood supply has been stopped. In heart-beating donor scenario, the primary WIT is practically zero as cold solution would be perfused via aortic cannulation and portal vein with the donor's heart beating. The steps in surgery include:

- Laparotomy/sternotomy.
- The liver is assessed for suitability.
- The infrarenal aorta is exposed and looped in preparation for cannulation.
- Inferior mesenteric vein (IMV) is looped in preparation for portal cannulation and perfusion.
- Common bile duct (CBD) is divided following the dissection of the hilum of the liver. Gallbladder is flushed to rid the biliary system of bile, which can crystallize and damage the biliary epithelium when frozen in the cold phase.
- The common hepatic artery, the gastroduodenal artery and the splenic artery are exposed.
- The crus of diaphragm is dissected to expose the supracoeliac aorta, in preparation for aortic crossclamping.
- Donor is heparinized—25,000 IU (300 IU/Kg)—and after 5 min, IMV (14 Fr) and aorta (22 Fr) are cannulated.
- Supracoeliac aorta is crossclamped and blood vented in the chest by the cardiac team. The abdominal organs are now perfused with ice-cold preservative solutions (IMV with 2 L of UW and aorta with 4 L of HTK).
- Ventilation is stopped and cavities are packed with ice. Adequate perfusion is ensured by visualizing the blanching of the bowel wall and clear fluid coming into the right atrium.

27.6.2 Cold Phase

Cold ischaemic time (CIT) refers to the amount of time that an organ is cooled and not receiving a blood supply. Acceptable CIT for the liver is 6–10 h. This stage of the operation involves cooling the organs and perfusing them with ice-cold preservative solutions and ends with vascular anastomosis in recipient. Procedures during cold phase include:

(a) *Organ Removal*
- The portal vein is divided inferior to the junction of the splenic vein and superior mesenteric vein(SMV).
- Gastroduodenal and splenic artery are ligated and divided.
- Supracoeliac aorta is divided and the coeliac axis is taken with a patch of aorta.
- Infra-hepatic IVC is divided above the junction of left and right renal veins.
- Diaphragm around the liver is divided to deliver the liver.

(b) *Back Table*
- After retrieving the liver, the portal vein is flushed with 2 L of UW solution.
- Bile duct is flushed with UW solution till it is clear.
- The liver is packed airtight in three layers.
- Iliac arteries, veins and superior mesenteric artery(SMA) are also retrieved.

27.6.3 Bench Procedure

This is the final part of the retrieval operation, performed at the transplant hospital. During the back table procedure, the harvested graft is prepared for transplantation:
- The liver is kept immersed in the preservation fluid and surrounded by ice slush.
- All diaphragmatic and extra fatty tissue is removed, and the vessels (IVC, portal vein and hepatic artery) are carefully bared, in preparation for the recipient operation.

27.6.4 Preservation

The traditional and time-tested method organ preservation is using ice-cold preservation solutions (UW, HTK, Celsior, etc.). Cooling an organ slows down its metabolism and thereby its deterioration. At the same time, the preservation solutions counteract the deleterious effects of interrupted blood supply and cold ischaemia.

Various newer methods of organ preservation are under development and being put through various stages of clinical trials. Machine perfusion is one of these techniques, where the machine restores blood through the liver outside the body (ex vivo), thereby providing a dynamic and real-time assessment of the likely quality of liver function. Various centres (Columbia University, University of Zurich and

Oxford University) have successfully initiated variations of the machine perfusion at hypothermic (cold), subnormothermic (below body temperature) and normothermic (body temperatures) conditions.

27.7 Live Donor Liver Transplantation: Donor Selection Criteria

Each transplant programme is required to have well-defined criteria and an algorithmic process for the selection of both recipients and donors, and patients are required to be provided with this information. The basic tenet of live donations in liver transplantation includes an altruistic desire on the part of the donor to help a fellow being, without any financial or other ulterior motives. The donor must have a sound mind and voluntarily consent to the procedure following a fully informed consent. There lies no obligation of the part of the donor to follow through with the donor operation, once donor assessments have begun. The potential donor needs to be physically and mentally healthy, in such a manner that all stipulated medical criteria for donation are met.

The following are the criteria for the selection of living donors.

27.7.1 Blood Group

The criteria are similar to those required for blood transfusion. This also means that an individual with O group is a universal donor and one with AB group is a universal recipient. ABO-identical and ABO-compatible donors are commonly chosen. ABO-incompatible donation is discussed in Chap. 17.

27.7.2 Relationship

Each country has different rules and regulations regarding this. In India, relatives of any degree can donate provided they submit the required documents to an independent authorization committee, while in Thailand, only first-degree relatives are allowed to donate. The UK and the USA allow altruistic donation from friends, while this is not possible in many developing countries.

27.7.3 Age

Donors should be between the ages of 18 and 50 years. However, caution should be exercised in selecting Indian female donors over the age of 45, since they often have poor abdominal muscle tone and are at a higher risk of postoperative respiratory complications.

27.7.4 Weight and BMI

A suitable donor should ideally have a BMI below 25 kg/m^2. However, this criterion may be relaxed up to a BMI of 27.5 for Indians and 30 for donors from the Middle East if the estimated degree of steatosis by LAI is under 20% (i.e., the liver attenuation index is above +6) and the estimated volume of the remnant liver is over 35%. If there is no other suitable donor within the family and the donor's BMI is between 30 and 35 kg/m^2, the prospective donor can be considered for donation after he/she has lost weight following a period of diet/exercise regime (usually 6 weeks).

27.7.5 Comorbidities

A donor should have no significant comorbidities. Diabetics as a rule are not accepted as donors. In practice, a donor with either mild controlled hypertension may be considered acceptable. If a donor has any comorbidity, it should be discussed in a multidisciplinary meeting before a formal decision is made. Any donor with ischaemic heart disease, COPD, chronic kidney disease or any other significant cardiorespiratory or renal morbidity is unsuitable for donation.

27.7.6 Cardiac Assessment

All donors undergo a detailed history, clinical examination, ECG, chest X-ray and a 2D echo. Subsequently, all potential donors undergo a treadmill test (preferred) or dobutamine stress echocardiogram. Donors with abnormal treadmill test or echocardiogram have to be discussed in multidisciplinary team (MDT) meetings before further evaluation. This will be in the form of a coronary angiogram, done when the donor is otherwise very well and, in most cases, the only donor available for that recipient.

27.7.7 Steatosis

The degree of steatosis in a donor is assessed by estimating the liver attenuation index (LAI). An ideal donor should have an LAI of $\geq$+6. This reliably correlates with a steatosis of <20%. LAI of <−5 indicates a possibility of >30% steatosis and is a contraindication for donation. However, if the LAI is between −5 and +5, a liver biopsy may be necessary for the assessment of steatosis. More recently, due to its accuracy and noninvasive nature, MRI fat estimation is being increasingly used.

27.7.8 Volumes

Both graft volume and remnant volume need to be estimated and taken into consideration. Adequate graft volume is assessed by calculating the GRWR (graft

weight-to-recipient's body weight ratio expressed as %). Ideally, the GRWR should be greater than 0.8. A GRWR of 0.7–0.8 can be considered adequate if the LAI is ≥+6 and the recipient's MELD is < 20. In general, any donor with an estimated GRWR of <0.7 is unsuitable for donation. In paediatric patients, the estimated GRWR should ideally be between 1 and 3. There may be a need to further reduce a left lateral section graft if the GRWR is higher than 4 or if there is a significant size mismatch.

Reduction of graft depends on various other parameters like vascular anatomy and shape of graft (reduction is not required if the graft is flat and long rather than being bulky anteroposteriorly or if recipient's abdominal compartment is large).

27.7.9 Anatomical Suitability

Anatomical suitability of the donor is assessed by a careful study of the triphasic CT scan and the MRCP. Anomalies that can increase the risk of complications in the recipient are multiple arteries requiring reconstruction, two right portal vein branches and multiple bile ducts on the graft. However, certain anomalies can increase the risk for the donor, and these should be clearly identified and such donors be avoided. Examples of these anomalies include portal supply to segment 4 of the liver from the right portal vein or a single portal vein supplying the entire liver, an artery to segment 4 originating from the right hepatic artery within the liver or a biliary radicle from the left liver (segment 4) draining into the right hepatic duct.

Hepatic venous anatomy needs to be studied in detail to determine if the middle hepatic vein (MHV) can be either completely or partially taken with the graft or left behind with the donor. Our fundamental policy is use "right liver grafts without MHV" when right lobe donation is indicated.

Tips

Acceptable donors:

- Age 18–50 years
- ABO-compatible blood group
- No comorbidities or one comorbidity such as well-controlled HT
- LAI ≥+6
- BMI < 25 kg/sq.m.
- GRWR > 0.8
- Remnant volume > 30% of TLV
- Anatomically suitable for donation

Caution

To be discussed in the multidisciplinary team (MDT) meeting before accepting for donation:

- Female aged >45 years or male aged >50 years
- Comorbidities such as systemic hypertension and bronchial asthma
- LAI between −5 and +5
- BMI 25–30 kg/m^2
- GRWR 0.7–0.8 and/or remnant volume 28–30%
- Any unusual anatomic feature

Nursing Care of Children with Liver Disease/Transplantation in Intensive Care

28

T. Ravikumar

28.1 Mouth Care

In the critical care setting, poor oral hygiene has been associated with increased dental plaque accumulation, bacterial colonization of the oropharynx, and higher nosocomial infection rates, particularly ventilator-associated pneumonia (VAP).

28.1.1 Factors Increasing Susceptibility for Poor Oral Hygiene

- Intubation (loss of protective reflex—cough and gag).
- NG/OG tubes (leads to xerostomia via open mouth).
- Medications like anticholinergic/inotropes/sedatives exaggerate xerostomia.
- Fluid restriction.
- Immunocompromised.
- Decreased mobility.
- Supine position.
- Poor nutrition.

28.1.2 Equipments Required for Cleaning Oral Cavity

- Gloves
- Plain foam swabs
- Soft pediatric toothbrush
- Oral suction brush
- Fluoride toothpaste

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- Chlorhexidine gluconate 0.2% (must be diluted 1:1)
- Gauze swabs
- Clean water/0.9% NaCl
- Yankauer suction
- Mouth moisturizer

28.1.3 Process Involved in Mouth Care

- Assess oral cavity for bleeding, redness ulceration, external factors (ETT tapes/ribbon, braces), debris, condition of the tooth (decay, loose, broken swelling abscess), etc.
- Neonates and infants: moist mouth with gauze or foam soaked in saline/normal water.
- Children <6 years: brush using soft pediatric toothbrush smeared with fluoride toothpaste. Suction out excess paste. Do not rinse.
- Children >6 years: in addition to the above, use chlorhexidine 0.2% solution diluted 1:1 to irrigate using syringe, or wipe with the use of foam swab. Suction out excess solution. Do not rinse. Do not combine brushing and chlorhexidine mouthwash together. There should be at least 30-min gap between the two. Mouthwash is done at least twice a day.
- Non-intubated conscious child can be encouraged to brush using soft pediatric toothbrush with paste and rinse mouth twice and in addition after each feed.
- Following mouthwash, use moisturizer second hourly over lip.

28.2 Skin Care

28.2.1 Factors Increasing Susceptibility for Skin Breakdown

- Poor nutrition
- Length of stay >4 days
- Device anchor such as tapes and straps
- Impaired perfusion secondary to inotropes, shock, and hypovolemia
- Decreased oxygenation
- Moisture

28.2.2 Skin Integrity Assessment

It is done at time of admission and subsequently daily during bath and also during diaper change or position change. Most vulnerable pressure points such as the buttock (ischial tuberosities), sacrum, occiput, toes, etc. should be periodically checked.

Look for:

- Redness/erythema—non-blanching when finger pressure applied
- Pain and soreness
- Warmer or cooler area over bony prominence
- Boggy feeling
- Hardened area
- Discoloration—dark red, purple, and black
- Broken skin/ulcer (look at Table 28.1 for pressure ulcer classification)

28.2.3 Precautions to Prevent Skin Breakdown

1. Skin surface protection:
   - Use barrier preparations to prevent moisture-related and mechanical skin breakdown.
   - Carefully remove adhesives and dressings with water or adhesive solvent to prevent skin stripping.
   - Use barrier products such as hydrocolloids, silicone dressings, clear adhesive dressings, or foam dressings on body surfaces susceptible to shearing forces and pressure injury to prevent skin injury.
   - Place on a pressure-reducing surface.
   - Consider the use of egg crate, sheepskin, low airflow mattress, or other pressure-reducing surface depending on availability and patient condition.
   - Use a gel pillow underneath the occiput.
2. Pressure redistribution:
   - Keep repositioning the patient every 2 h.
3. Incontinence management:
   - Urine and feces have alkaline pH unlike the skin which has acidic pH, thus causing irritation and skin breakdown; hence they must not be left to stay for a prolonged period.
   - To utilize a non-alkaline cleaning agent to minimize irritation to the skin, prevent dryness, and restore normal pH of the skin and to use protective barrier cream after each incontinent episode.

Table 28.1 Pressure ulcer classification

Grade I: Non-blanching area in the skin
Grade II: Partial thickness (partial thickness loss of the dermis presenting as a shallow open ulcer with a red pink wound bed, without slough)
Grade III: Full thickness (full-thickness tissue loss. Subcutaneous fat may be visible, but the bone, tendon, and muscle are not exposed)
Grade IV: Full thickness (full-thickness tissue loss with exposed bone, tendon, or muscle. Slough or eschar may be present)

- Ideally, the barrier cream should remain in contact with the skin despite cleansing and should have an active ingredient of zinc oxide, dimethicone, or other high-quality silicone; avoid petroleum-based barrier cream which does not stay in contact with the skin.

28.3 Oropharyngeal, Tracheal, and Endotracheal Suction

Suctioning could be performed using a Yankauer sucker to clear oral secretions from the mouth and oropharynx by passing a suction catheter into the upper airway in order to clear tracheal secretions. A sputum sample may be requested for microbiological investigation. A sputum trap should be used to collect a sputum sample.

Suction procedures should therefore be as brief as possible, lasting approximately 15 s. Installation of 0.9% saline via a tracheostomy or endotracheal tube prior to suctioning is sometimes performed; however, there is little evidence to support this practice, and it could potentially cause harm.

- The mouth is suctioned first before suctioning ETT as subglottic collection is the major reason for aspiration. During ETT suctioning, cough may increase space around the tube, thus leading to aspiration.
- Size of suction catheter (size of ETT) × 2 = size of French catheter or twice the diameter of ETT size: The suction catheter should be no more than half the internal diameter of endotracheal tube.
- Depth of suction: Oropharyngeal suction must be a deep suction to remove pharyngeal subglottic collection. ETT suction is a shallow suction as the aim is to keep airway patent, thus selecting the length of 1–2 cm beyond ETT length for suctioning.
- Suction pressure: Recommended pressure is around 80–120 mmHg (16 kPa). In practice, it is sometimes necessary to apply higher levels of negative pressure to clear thick, tenacious secretions; this should be done cautiously, and advice should be sought regarding therapies to help loosen secretions, such as mucolytic agents and sufficient airway humidity, using 2–5 ml of normal saline lavage followed by manual ventilation with bag.
- Potential indications for tracheal or endotracheal suctioning include:
  Raised respiratory rate
  Reduced air entry on auscultation
  Audible secretions
  Spontaneous but ineffective cough
  Reduced oxygen saturation levels/raising ETCO2/abnormal ABG
- Complications of tracheal/endotracheal suctioning:
  Hypoxemia when suctioning
  Vasovagal response causing arrhythmias, bradycardia, and hypotension
  Mucosal trauma
  Laryngospasm

Tips

- Need for ETT suction should be assessed on an individual basis.
- Suctioning should be performed when they need it rather than a fixed time routine.
- Suction should only be applied when withdrawing the catheter, never when inserting it.

28.4 Eye Care

Eye care is the practice of assessing, cleaning, or irrigating the eye and/or the instillation of prescribed ocular preparations.

28.4.1 High-Risk Population

(a) All unconscious, sedated, or paralyzed patients.
(b) All mechanically ventilated patients.
(c) Patients with diseases or syndromes affecting eye protective mechanism (e.g., obstruction of lacrimal ducts, etc.).
(d) Patient on medication affecting tear production (e.g., atropine, antihistamine, sedation, paralytic agent, etc.).
(e) In ICU, dryness of air occurs due to AC which leads to dryness of the eye.

28.4.2 Potential Eye Complications

(a) Conjunctivitis: inflammation of the conjunctiva.
(b) Chemosis (conjunctival swelling): the conjunctiva will often appear red, and the outer surface covering appears to have fluid in it. Often, the conjunctiva becomes so swollen that the eyes cannot close properly. Also called ventilator eye occurs due to ventilatory setting such as PEEP and drugs used to facilitate respiratory support which affects venous return and fluid stasis, thus causing increased intraocular pressure. Exacerbation of chemosis has been said to occur if the endotracheal tube is secured too tightly.
(c) Exposure keratopathy: a non-inflammatory disease of the cornea that can be recognized as an irregular reflection of light from a penlight off the corneal surface. This will place cornea at risk for infection.
(d) Keratitis: inflammation of the cornea. Bacterial keratitis is a serious infection which can result in infectious corneal ulcer that appears as a whitish area on the cornea surface.

28.4.3 Eye Care Intervention

(a) Eye hygiene regime: Gauze soaked in saline or sterile water used to wipe of eyelids from inner canthus to outer canthus to remove debris, secretions, dried ointment, and/or other ocular medications.
(b) Prevention of dry eye: Start on topical lubricant—drops/gel preparation. Every second hourly.
(c) Eyelid closure: Vast array of approach used to ensure eyelids remain closed. Adhesive tapes, gauze, eye pads/patches, eye shields, and temporary tarsorrhaphy.
(d) Do not apply dry gauze directly over open eyes as it can damage the cornea.
(e) Bedside examination with bright torch twice daily and ophthalmic consultation when needed.
(f) Clinicians should take care to ensure that patient eyes are not exposed to aspirates during tracheal or oropharyngeal suction procedures.
(g) Patients should be referred for specialist ophthalmological consultation when there is concern.

Tracheostomy and Chest Drain Care in Children

29

T. Ravikumar and Nataraj Palaniappan

29.1 Tracheostomy

Surgical tracheostomy (artificial opening in the trachea, usually between the 2nd and 4th tracheal rings) in pre-/post-liver transplant patients is required usually for respiratory failure, critical illness myopathy and prolonged ventilator support. The overall mortality rate for a complication directly related to a paediatric tracheostomy is 0.7%.

29.1.1 Types of Tracheostomy Tubes (TT)

- Shiley
- Passy Muir
- Bivona
- Jackson

29.1.2 Additional Optional Features

- Cuffed tracheostomy tubes can be chosen for ensuring a tight seal for ventilation support or to prevent aspiration.
- Fenestrations—hole(s) situated on the curve of the outer tube to allow or enhance airflow through the vocal cords.
- Speaking valve—occludes the tracheostomy tube during expiration only, to facilitate speech and swallowing.
- Extra length—either the proximal length (e.g. if obese) or intratracheal length (e.g. to bypass tracheal obstruction from tracheomalacia).

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Table 29.1 Tracheostomy tube and corresponding suction catheter selection in children

	3 month	6 month	1 year	3 years	6 years	8 years	12 years	16 years
Factors	6 kg	8 kg	10 kg	15 kg	20 kg	25 Kg	40 kg	60 kg
Trac. tube size (mm)	3.0–3.5	3.5–4.0	4.0–4.5	4.5–5.0	5.0–5.5	6.0	7.0	7.0–8.0
Suction catheter (Fr)	6–8	8	8	8–10	10	10–12	12–14	12–14

29.1.3 Common TT Used in Children

- Shiley: Disposable plastic tubes with an introducer and inner cannula, commonly used for short-term airway support. Shiley are MRI-compatible tubes.
- Bivona: Soft flexible tubes with adjustable flanges, for long-term airway support.

29.1.4 TT Size Selection in Children

- Tracheostomy tube size and corresponding suction catheter selection in children are outlined in Table 29.1.

29.1.5 Care of New Tracheostomy (Less Than 7 Days)

- Nursing care following the formation of the tracheostomy should be mainly on maintaining the correct positioning and patency of the new tube and stoma maintenance.
- Appropriate resuscitation and suction equipments must be present in dedicated bedside cart:
  1. Suction catheters—correct size
  2. Clean gauze
  3. Personal protective equipment (PPE)—protective eye wear, gloves, face mask and apron
  4. 2 mL syringe and 0.9% sodium chloride for cleaning/irrigation
  5. An emergency tracheostomy box should be prepared with:
     A spare tracheostomy tube (same size/make)
     A Shiley tracheostomy tube (half size smaller than above)
     Spare tracheostomy tapes with scissors

29.1.6 Tracheostomy Care >7 Days

After 7 days, the tracheostomy will have well-formed track. The first tracheostomy tube change is done on days 7–10 and later on every 14 days to 2 months depending

on the type of tracheostomy used. The main focus is to keep the site clean and healthy, and shallow suctioning of tracheostomy tube is required to clear secretions.

29.1.7 "TRACHE" Care Bundle

Compliance with "TRACHE" care bundle will help in better management of pedaitric tracheostomy safely.

1. *T= Tapes*. Security of the tracheostomy tube is a key principle in maintaining airway safety. Paediatric patients provide a variety of challenges in achieving this, with accidental decannulation occurring in around 5% of paediatric tracheostomies.
2. *R = Resuscitation*. BLS is similar in the sequence of skills to be performed for those with a tracheostomy. Emergency tube change is outlined in Table 29.2:
   - Safety
   - Stimulate
   - Shout for help
   - Suction
   - Airway
   - Breathing
   - Circulation
3. *A = Airway: Suctioning*
   - Suctioning when needed.
   - Correct size suction catheters—double the ID of tracheostomy tube.
   - Should have numbered graduations for accurate insertion lengths.
   - Suction should be applied only on withdrawal.
   - Observe for skin breakdown and granulation tissue and treat accordingly.

Table 29.2 Emergency tube change

• Change the tracheostomy tube immediately if the tube appears blocked or any resistance is felt and the child is in respiratory distress
• Exercise caution if stoma is less than 1 week old (with the reinsertion of the tube, this may not go back into the stoma but instead goes into the pretracheal tissue/space)
• The same size tube should be inserted
• If unable to insert the same size tube, try to insert the Shiley tube that is a half size smaller and stiffer
• If the stoma closes and the smaller tube cannot be replaced, remove the obturator from the smaller tube, and pass a suction catheter through the tube
• Attempt to insert the end of the catheter through the stomal opening, and guide the tracheostomy tube along the catheter and through the stoma (this is known as the Seldinger technique)
• If this is also unsuccessful, ventilation can be attempted via the stoma or by conventional rescue breaths (e.g. mouth-to-mouth or bag and mask over the mouth and nose). The Seldinger technique should be practised as a first-line attempt at reinserting a tracheostomy tube. Tracheal dilators have been removed from routine paediatric tracheostomy care

- Crusting may also need to be removed from the tracheostomy tube.
- If the suction length is too short, the patient is at risk of tube blockage, yet if the suction length is too long, it may lead to tracheal trauma and can result in distal soft tissue trauma and overgrowth.

4. *C = Care of the Site: Stoma and Neck*
   The recommended practice is to review the stoma, assess the skin of the neck and clean the local area around a tracheostomy thoroughly each day.
5. *H = Humidification*
   Without appropriate humidification, secretions can become increasingly thick and tenacious, making their retrieval difficult. This may lead to blockage of the tube or retention of secretions in the lower airways; hence it is recommended to use appropriate-sized heat moisture exchange (HME) device.
6. *E = Emergency Box*
   Designed to include all essential equipment in case of accidental decannulation or for emergency tube change (Table 29.2).

29.1.8 Common Complications Post-tracheostomy

1. Pneumothorax
2. Haemorrhage
3. Tube block—suction on an "on-required" basis
4. Surgical emphysema
5. Infection (chest/stoma site)

29.1.9 Prevent Accidental Decannulation

An infant with a chubby neck, use of an incorrect tube, loose tracheostomy tapes or the child/equipment pulling on the tube are common causes. Two long looped "stay" sutures extend from inside the stoma and are taped to the child's chest. These sutures are attached through the trachea on either side of the stoma.

29.2 Decannulation

Prior to decannulation, assess the following factors to ensure readiness:

- Resolution of condition that necessitated tracheostomy tube
- Adequate level of consciousness
- Effective cough
- Ability to manage secretions
- Adequate oxygenation
- Swallowing function
- Ability to tolerate tracheostomy tube occlusion

Once the evaluation is complete and the patients are ready for decannulation, the tracheostomy tube is plugged for 24 h, and patient is monitored for respiratory difficulty or suction requirement. If they tolerate occlusion, then tracheostomy tube is removed, and the stoma is covered with sterile gauze. Another common practice before trial decannulation is downsizing to a small Shiley tracheostomy for 48 h and then decannulating. Vocalization will usually return to normal once the stoma has closed completely. The tracheostomy stoma heals by secondary intention within 5–7 days in the majority of patients.

29.2.1 Post-Decannulation Issues

- Decannulation failure
- Tracheocutaneous fistula
- Tracheobronchomalacia

29.3 Chest Tube Care

29.3.1 Introduction

Chest tube insertion involves placement of a sterile tube into the pleural space to evacuate air or fluid into a closed collection system to restore negative intrathoracic pressure, promote lung expansion and prevent potentially lethal levels of pressure from developing in the thorax.

29.3.2 Indications

Tube decompression is indicated in those who are symptomatic with the following causes:

1. Pneumothorax—spontaneous/due to high ventilator setting especially PEEP/improper or overzealous bagging during resuscitation
2. Pleural effusion—transudate (due to increased hydrostatic pressure) or exudative
3. Haemothorax
4. Chylothorax

29.3.3 Drugs and Equipment Required for Chest Tube Insertion

- Chlorhexidine or povidone-iodine solution
- Sterile towels and drapes
- Sterile sponges

- 1% lidocaine without epinephrine (40 mL)
- 10 mL syringe
- 18-, 21- and 25-gauge needle
- Standard tissue forceps
- Towel forceps
- Needle holder
- 0-Silk suture with cutting needle
- Scalpel handle and no. 10 blade
- Chest tubes (24, 28, 32 and 36 French)
- Chest tube drainage system (filled appropriately)
- Petrolatum gauze
- 2 in. adhesive tape
- Sterile gowns and gloves, masks and caps

29.3.4 Procedure

- Chest drains are best inserted under ultrasound guidance using Seldinger technique.
- The tube is usually inserted through the fourth or fifth intercostal space in the anterior axillary line. Make sure all side holes are pushed inside the pleural space. In case of pneumothorax, tube is pushed anteriorly and upwards and in fluid collection posteriorly and downward.
- Chest tube must be immediately connected to underwater seal drainage. Do check chest X-ray immediately post-procedure.

29.3.5 Chest Tube Care

1. Tube must be kept always in a closed system.
2. Every shift, check for chest tube functioning or if any position change done (chest tube oscillation).
3. Suction is routinely established at 15–20 cm water, controlled by the height of the column in the suction regulator unit.
4. Daily ensure that appropriate levels are maintained in the underwater seal and suction regulator chambers.
5. Connections between the chest tube and the drainage system should be tightly fitted and securely taped.
6. For continuous drainage, the chest tube and the tubing to the drainage system should remain free of kinks, should not be left in a dependent position and should never be clamped.
7. The tube can be milked and gently stripped, although with caution, as this may generate negative pressures of up to 1500 mm Hg and can injure adjacent tissues.
8. Irrigation of the tube is discouraged.

9. Ensure that the most proximal drainage hole has not migrated from the pleural space (a situation that may result in pneumothorax or subcutaneous emphysema). This can be done by serial chest X-rays.
10. A tube should never be readvanced into the pleural space, and if a tube is to be replaced, it should always be at a different site rather than through the same hole.
11. Dressing changes should be performed every 2 or 3 days under aseptic precaution using sterile gauge and adhesive dressing.

29.3.6 Chest Tube Removal

- For a pneumothorax, the drainage system is left on suction until the air leak stops. When the leak has ceased for more than 24–48 h (or if no fluctuation is seen in the underwater seal chamber), the drainage system is placed on water seal by disconnecting the wall suction, followed by a chest film several hours later. If no pneumothorax is present and no air leak appears in the system with coughing, deep breathing and reestablishment of suction, the tube can be removed.
- For fluid collections, the tube can be removed when drainage is minimal (less than 1 mL/kg for 12 h).
- The suture holding the tube to the skin is cut. As the patient takes deep breaths, the tube is removed and the hole simultaneously covered with an occlusive petrolatum gauze dressing at peak inspiration (at which point only positive pressure can be generated in the pleural space, minimizing the possibility of drawing air in). A chest radiograph is performed immediately to check for a pneumothorax and is repeated 24 h later to rule out re-accumulation of air or fluid.

29.3.7 Complications of Chest Tube Insertion

1. Unintentional tube placement into vital structures (lung, liver, spleen, etc.)
2. Bleeding
3. Re-expansion pulmonary oedema
4. Pneumothorax
5. Haemothorax
6. Empyema

Procedural Protocols: Liver Biopsy, Abdominal Paracentesis and Elective Endoscopy

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30.1 Liver Biopsy

Liver biopsy (LB) is usually performed percutaneously, but in special situations, transjugular (TJ) approach, laparoscopic approach or even laparotomy might be required. Ultrasound-guided LB is the method of choice, particularly with "cutting needles". In this chapter, only percutaneous LB is discussed.

30.1.1 Indications

- Etiological evaluation of liver disease
- Post-transplant biopsy to rule out acute or chronic rejection, PTLD
- Bacteriological culture for recurrent or resistant cholangitis
- Liver tumours

30.1.2 Liver Biopsy Devices

"Cutting needles" (Tru-Cut, Vim-Silverman and Temno) and "suction needles" (Menghini, Klatskin, Jamshidi) are two types of needles used to perform LB. Various diameters and gauge sizes are available. Sometimes gel form is used to cover the needle track to minimize bleeding risk.

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30.1.3 Liver Specimen *Handling*

- Core specimens are "adequate" if they measure at least 2.0 cm long and 0.2 mm wide or contain at least ten portal tracts; wedge specimens are adequate if they contain at least six complete portal tracts independent of the liver capsule.
- The liver biospy specimen should be stored in formalin for histopathological investigation.
- Biopsy specimens for quantitative copper determination should be placed unfixed on a moist piece of filter paper or directly in a copper-free container.
- If possible, a portion can be snap frozen and held and stored in liquid nitrogen for additional special studies in the future.

Caution

- An INR value of >1.5 and platelet count of <50,000/mm^3 are usually regarded a contraindication for percutaneous LB.
- INR between 1.3 and 1.5 and platelets between 50,000 and 60,000/mm^3 may require correction before procedure.
- Cirrhotic liver and the liver affected by amyloidosis tend to have higher risk of bleeding.
- Percutaneous LB in a patient with ascites should be avoided due to higher risk of bleeding at the biopsy site due to the loss of tamponade effect by subcutaneous tissue.
- Duct dilatation secondary to increased intra-ductal pressure is a contraindication for liver biopsy as there is a high risk of bile leak and fistula.

30.1.4 Care Before LB

(a) Informed consent must be obtained.
(b) Check the following lab parameters before LB:
    - Complete blood counts
    - Liver function tests
    - Prothrombin time/INR
    - Fibrinogen
    - Ultrasound in post-transplant patients (to rule out duct dilatation)
(c) Check medications:
    - Low-dose aspirin, frequently given after liver transplantation, should be stopped 3 days prior and can be restarted 24 h after LB.
    - Fragmin should be stopped a day prior.
    - Warfarin administration should be discontinued 5 days before LB and may be restarted 24 h after LB; administration of low molecular heparin and related products should be interrupted 12–24 h before LB.
    - Post-liver transplant biopsies require prophylactic dose of antibiotics (piperacillin-tazobactam three doses at 8-h interval with 1st dose 1 h before biopsy).

30.1.5 Liver Biopsy Procedure

- Patients should fast (6 h for solids and 4 h for breast milk) before LB; vital signs, including heart rate, respiratory rate, arterial blood pressure and core body temperature, should be assessed 1 h before LB.
- The patient should lie supine in a comfortable position with the right arm placed behind the head. After sedation/anaesthesia, long-acting local anaesthetic should be topically infiltrated into the skin at the probable site of the liver (marked by percussion or image guided).
- The site of the needle entry must be cleaned with an alcohol-based solution and draped with sterile cloths.
- Based on local hospital policy, it could be either blind biopsy or under real-time ultrasonographic guidance.
- After split liver transplantation, image-guided LB is recommended.

30.1.6 After LB

- Immediately after LB, the needle entry site should be firmly plastered for haemostasis. The patient should fast for approximately 2 h after LB, and vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation) should be monitored closely.
- The patient should be observed for at least 6 h for signs or symptoms that suggest complications, such as severe pain, shoulder pain (in older children), irritability (in infants), bleeding, discharge at LB site, difficulty in breathing, pallor and fever.
- Complications of LB are outlined in Table 30.1.

Tips

- Routine haemoglobin and haematocrit check post-liver biopsy is not necessary unless clinically justified (tachycardia, hypotension, etc.).

Table 30.1 Complications of liver biopsy

• Bleeding including haemobilia requiring transfusion or surgery or ICU care
• Pneumothorax or haemothorax (in percutaneous LB)
• Bile leak/fistula
• Visceral perforation
• Arteriovenous fistula
• Pain at LB site and right shoulder (referred pain)

30.2 Abdominal Paracentesis

30.2.1 Drugs and Equipment Required

- Sheathed needle (Venflon or similar cannula):
  18–22 gauge for large-volume taps
  22–24 gauge for a diagnostic
- Three-way tap
- 20 mL syringe
- Urine bag with appropriate connectors to connect to three-way tap
- Betadine/sterile gauze/sterile gloves/surgical tray with sterile drape/sterile gown and mask
- 1 or 2% lidocaine and a 25-gauge needle and 2cc syringe for infiltration
- Collection bottles—aerobic and anaerobic culture/microscopy/biochemistry/cytology/special cultures like TB, fungus

30.2.2 Procedural Technique

- Explain the procedure and get consent from parents.
- Position the patient supine with head end of bed slightly elevated.
- Percuss the abdomen to determine where the fluid level exists, and roughly mark a spot in between the anterior superior iliac spine and umbilicus.
- Clean the skin thoroughly with Betadine solution.
- Infiltrate the skin and subcutaneous tissues with lidocaine, and *wait* about 3–5 minutes.
- Pull the skin up or down until it is taunt, and insert the Venflon attached to a syringe perpendicular to the skin. This is to create "Z" track where the skin would move back and closes the peritoneal puncture site once Venflon is removed. This would prevent ascitic leak.
- As you advance your needle, slowly aspirate intermittently; once the fluid comes, withdraw the needle, and advance the sheath.
- Now connect one end of three-way tap to the cannula (through an appropriate connector), one end to syringe and another end to the collection bag.
- Now ascites can be drained in a controlled way with three-way tap system. Lab samples could be sent from syringe port.

30.3 Elective Upper Gastrointestinal Endoscopy

30.3.1 Before Procedure

- Admit the child day prior. Check CBC, clotting and crossmatch blood.
- If platelets are <50, inform anaesthetist and hepatologist:
  – Ensure at least 2 adult units of platelets.
  – Give platelets just before patient is shifted to the endoscopy theatre.

- If INR >1.6, give IV vit K (dose as per weight) and recheck INR after 6 h.
- If INR is still >1.6, give 10–20 mL/kg FFP over <2 h to finish at least 2 h before theatre time.
- If fibrinogen is <100 mg/dL and INR <1.6, correction is not needed, but if it is >1.6, then give cryoprecipitate 5 mL/kg over 1 h before procedure.
- If the child is having ascites and low albumin, 20% albumin 1 g/kg over 4 h could be given along with diuretics. This would help with decreasing ascites and improve ventilation.
- Start on 10% dextrose with additives (2 mmol/kg/day of sodium and 1 mmol/kg/day of potassium), while the child is fasting for the procedure.

Caution

- Child with coagulopathy and ascites (decompensated liver disease) requires liver transplantation; unless endoscopy is absolutely necessary better to avoid.
- Anaesthesia in such children would be associated with high mortality and morbidity.

30.3.2 Procedure

- Child is usually sedated for routine surveillance endoscopy and intubated if there is plan for intervention, particularly ESL or glue injection where the risk for bleeding and aspiration is high.

30.3.3 Post-Procedure

- If no intervention is done, then the child could be discharged after 6 h of observation.
- If child had a EST/EVL/glue, keep the child overnight for observation. Semi-solid/liquid food overnight (theoretically it can dislodge the band or necrosed varix).
- Complications of EVL/EST outlined in Table 30.2.
- The child could be discharged home the following day.

Table 30.2 Complications of EVL/EST

1.	Chest pain and dysphasia
2.	Oesophageal obstruction due to oedema
3.	Oesophageal ulceration and bleeding
4.	Perforation
5.	Infection
6.	Oesophageal stricture formation (on repeated procedure)

Common Drugs Used in Liver Disease: Dosage and Calculations

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31.1 Common Drugs Used in Pediatric Liver ICU

Drug	Dose	Comment
Acetazolamide	5–10 mg/kg 6–8 h orally	
Activated charcoal	1–2 g/kg (50–100 g) then 0.25 g/kg hrly if required	
Acetylcysteine (NAC)	*Acetaminophen over dose*: 150 mg/kg over 60 min, followed by 50 mg/kg over 4 h then 100 mg/kg over 16 h *Non-acetaminophen induced hepatic disease*: 10 mg/kg/h until normalization of INR	Diluent: D5, 1/2 NS Max conc: up to 50 mg/ml for loading dose and 10 mg/ml for maintenance dose
Acyclovir	*Neonatal HSV*: 30–60 mg/kg/day divided q 8 h 3 months–12 years: 60 mg/k/day divided q 8 h >12 years: 30 mg/k/day divided q 8 h *Varicella-Zoster virus*: Immunocompetent hosts: >2 years: 30 mg/k/day divided q 8 h Immunocompromised host: <12 years: 60 mg/k/day divided q 8 h >12 years: 30 mg/k/day divided q 8 h	Adjust dosage in patients with renal dysfunction (CrCl < 50 ml/min) Diluents: Dextrose, NS, RL Maximum conc: <7 mg/ml
Alendronate	0.5 mg/kg daily orally (max 40 mg)	Bone pain, acid reflux, constipation are some of the common side effects

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Drug	Dose	Comment
Alteplase (recombinant tissue plasminogen activator)	• *0.1–0.6 mg/kg/h IV for 6–12 h (longer if no response)* • *Local intra-arterial infusion: 0.05 mg/kg/h* • *Blocked central lines: 0.5 mg/2 ml (<10 kg), 2 mg/2 ml (>10 kg) per lumen left for 2–4 h; withdraw drug; flush with saline; repeat once in 24 h if required*	• Keep fibrinogen >100 mg/dl (give cryoprecipitate 1bag/5 kg); give heparin 10 u/kg/h; give FFP 10 ml/kg daily in infants
Amikacin	Once daily dose regimen (not for endocarditis or meningitis). By intravenous injection or infusion (1 month–18 years) initially 15 mg/kg, then adjusted according to serum-amikacin concentration	Monitor serum-amikacin concentration closely (Trough level <5 mg/l) CrCl < 50 ml/min dosage adjustment is necessary Max conc: 10 mg/ml Diluent: NS, dextrose
Amlodipine	0.05–0.2 mg/kg daily oral (2.5–10 mg)	
Amoxicillin	25 mg/kg q 8 h Severe infections: 50 mg/kg (adult 2 g) q 6 h	
Amphotericin B	0.5–1.5 mg/kg q 24 h, start with lower dose, increase daily dose as tolerated by 0.5 mg/kg	Suitable diluent—D5W Max conc: 0.25 mg/ml Dose adjustment is not necessary in patients with renal insufficiency; if renal insufficiency occurs during therapy, dosing interval should be increased
Amphotericin (liposomal)	Prophylaxis: 3 mg/kg/dose q 24 h Treatment: 5 mg/kg/dose q 24 h	Dilute to 2 mg/ml with 5% glucose and infuse over 30–60 min Can be given to patients with pre-existing renal impairment Max conc: 2 mg/ml
Anidulafungin	<2 years: Loading dose 3 mg/kg Maintenance: 1.5 mg/Kg q 24 h 2–17 years: Loading dose 3 mg/kg (max 100 mg) Maintenance dose: 0.75 mg–1.5 mg/kg/ once a day	No dosage adjustment in renal or hepatic dysfunction Diluent: D5, NS Max conc: 0.77 mg/ml
Atenolol	0.5–1 mg/kg 12–24 h (max 25–50 mg)	
Azithromycin	Dosage: 10 mg/kg once daily (max. 500 mg once daily) for 3 days	Increases serum tacrolimus levels, avoid in transplant patient unless absolutely needed Diluent: D5, NS Max conc: 2 mg/ml
Bisacodyl	<12 months—2.5 mg PR 1–5 years–5 mg PR Above 5 years—10 mg PR	
Calcium gluconate (10%)	0.5–1 ml/kg (max 20 ml) slow IV Maximum dose is 800 mg/kg/day as continuous infusion or q 6 h	Diluent: D5, NS Max conc: 100 mg/ml

Drug	Dose	Comment
Calcitriol (1,25 OH vitamin D3)	0.02 mcg/kg (max 0.25 mcg/kg) daily	Adjust every 2–4 weeks based on Ca, PO4, ALP, PTH
Carnitine L form	IV 5–15 mg/kg (max 1 g) q 6 h; Oral 25 mg/kg q 6–12 h (max 400 mg/kg/day)	
Caspofungin	*Child 1 month to 17 years* 70 mg/m^2/dose (max 70 mg per dose) as loading dose followed by 50–70 mg/m^2/day (max 70 mg)	Do not use dextrose containing solution as diluent (Max conc 0.5 mg/ml) Dose adjustment is necessary in severe hepatic impairment (Child Pugh score >7–9)
Cefepime	Mild to moderate infections: 100–150 mg/kg/day divided q 8 h Severe infections: 150 mg/k/day divided q 8 h (max 6 g/day)	If CrCl < 50 ml/min, dose adjustment is needed Max conc: 160 mg/ml Diluent: D5, NS
Cefoperazone	25–60 mg/kg (max 1–3 g) q 6–8 h	
Cefotaxime	*Child 1 month–18 years* Mild to moderate infections: 75–100 mg/kg/day divided q 6–8 h Severe infections: 150–300 mg/kg/day divided q 6–8 h	Dose adjustment is needed in renal dysfunction Diluent: D5, NS Max conc: 73 mg/ml
Ceftriaxone	Infants and children Non-CNS infection: 50–75 mg/kg/day divided q 12 h up to 2 g/day CNS infection: 80–100 mg/kg/day divided q 12 h up to 4 g/day	No adjustment in hepatic dysfunction Most patients with renal dysfunction who receive <2 g/day do not require dosage adjustment. Patients with GFR <10 receive their dose every 24 h only Diluent: D5, NS Max conc: 40 mg/ml
Cefuroxime	IV 25–50 mg/kg (max 2 g) q 6 h; oral 10–15 mg/kg (250–500 mg) q 12 h	
Cholestyramine	<6 years—1 g 6–12 years—2–4 g Above 12 years—4 g daily. Increase over 4 weeks to max 2 times initial dose	
Cephazolin	Surgical prophylaxis: 50 mg/kg (max 2 g) at induction Mild to moderate infection: 10–15 mg/kg (max 1 g) q 8 h Severe infection: 50 mg/kg (max 2 g) q 6 h	
Ciprofloxacin	*Child 1 month–18 years*: Oral—10 mg/kg twice daily; dose doubled in severe infection (max. 750 mg twice daily) Intravenous—10 mg/kg every 8 h in severe infection (max. 400 mg every 8 h)	CrCl < 30 ml/min dose adjustment is necessary

Drug	Dose	Comment
Clindamycin	Mild to moderate infection: 15–25 mg/kg/day divided q 6–8 h Severe infections 25–40 mg/kg/day q 6–8 h Max single dose 1.2 g (4.8 g/day)	Diluent: NS, D5 Max conc: 18 mg/ml
Colistin	Loading dose (IV): 1.8 lakh units/kg Maintenance dose (IV): 90,000 units/kg 12 h Inhaled dose: 30,000–60,000 units/kg 8 h	Dose adjustment is necessary in renal failure Diluent: NS, D5
Co-trimoxazole	Severe infections: 8–12 mg/kg/day of TMP divided q 6–12 h *Treatment of PCP* TMP 20 mg/kg/day divided 6–8 h *Prophylaxis of PCP* TMP 5 mg/kg daily on 3 days/week	Monitor FBC In fluid restriction, Co-trimoxazole can be given undiluted via the central line Suitable diluent: D5W Max conc: 5 ml of concentrate in 75 ml of D5
Dexamethasone	Anti-emetic: 0.5 mg/kg 24 h Extubation stridor : 0.6 mg/kg stat (max 16 mg) Bacterial meningitis: 0.15 mg/kg q 6 h	Diluent: NS, D5 Max conc: 10 mg/ml
Domperidone	0.2–0.5 mg/kg (10–20 mg) 4–8 h	
Enalapril	0.1 mg/kg (2.5 mg) daily oral, increase over 2 weeks to 0.5 mg/kg (5–20 mg)	
Epinephrine	*During CPR*: 0.1 ml/kg (1:10,000) max 1 mg/dose IV/IO, ET dose 0.1 ml/kg (1:1000) max 2.5–10 mg/dose *Anaphylaxis*: 0.01 ml/kg (1:1000) max 0.3–0.5 mg/dose IM *Asthma*: 0.01 ml/kg (1:1000) max 0.3–0.5 mg/dose Sc q 20 min 3 doses	Suitable diluent: NS, D5 Max conc: 0.1 mg/ml (1:10,000) for IV push, for ET administration 1 mg/ml (1:1000)
Ertapenem	3 months–12 years: 30 mg/kg/day divided q 12 h up to 1 g/day 13–17 years: 20 mg/kg/day divided q 24 h	CrCl < 30 ml/min a dose decrease of 50% is recommended Reduces seizure threshold, hence to be avoided in CNS infections Suitable diluent: NS Max conc: 20 mg/ml
Erythromycin	Gut prokinetic 2 mg/kg 8 h	
Factor VII a (novoseven)	Dose: 90 mcg/kg q 2 h IV until hemostasis occurs	Diluent: Histidine diluent (provided with lyophilized powder) Max conc: 1 mg/ml
Fentanyl	1–2 mcg/kg (50–100 mcg) Continuous infusion: 1–10 mcg/kg/h	Diluent: NS, D5 Max conc: 50 mcg/ml
Filgrastim (G-CSF)	5 mcg/kg SC/IV (max 300 mcg/dose)	

Drug	Dose	Comment
Fluconazole	*Prophylaxis for Candidiasis in post-transplant patient* 0 month to 18 years old: 3–6 mg/kg (max 400 mg) daily *Treatment of proven fungal infection (if the isolate is susceptible)* 1 month to 18 years old: 12 mg/kg (max 400 mg) OD *Antifungal prophylaxis in acute liver failure* 1 month to 18 years old: 6 mg/kg (400 mg) OD	Renal modification needed if CrCl < 50 ml/min Increases serum tacrolimus level
Fosphenytoin (PE)	Loading dose: 15–20 mg PE/Kg (at a rate not to exceed 3 mg PE/kg/min or 150 mg PE/min) Maintenance: 4–8 mg PE/Kg/day given as 2–3 doses	Diluent: NS, D5 Max conc: 25 PE/ml
Frusemide	Dose: 0.5–2 mg/kg q 6 h (Max 20 mg/dose) Continuous infusion: 0.05–0.4 mg/kg/h	Diluent: NS, D5 Max conc: 10 mg/ml
Ganciclovir	CMV mismatch dose 5 mg/kg IV 12 h for 2 weeks CMV treatment dose 5 mg/kg IV 12 h for 3 weeks (up to 6 weeks for congenital CMV infection)	Infuse over 60 min and monitor renal function and white cell count Max conc: 10 mg/ml Diluent: NS, D5
Glycopyrolate	To reduce secretions 5–10 mcg/kg (max 0.2–0.4 mg) 6–8 h	
Hyoscine butyl bromide	0.5 mg/kg (20–40 mg) 6–8 h IV	
Ketamine	1–2 mg/kg For anesthesia induction 1–5 mg/kg Continuous infusion: 10–40 mcg/kg/min	Diluent: NS, D5 Max conc: 50 mg/ml for IV push
Lactulose	0.5–1 ml/kg q 6–8 hrly, aim for 2–4 acidic loose stools	
Lamivudine	Chronic hepatitis B infection 2–11 years 3 mg/kg once daily (max 100 mg daily) 12–17 years 100 mg once a day	Tablet: 100 mg Oral solution: 25 mg/5 ml
Lansoprazole	<30 kg–15 mg OD >30 kg–30 mg OD	
Linezolid	*IV and oral dose (same dose):* 1 month to 12 years old: 10 mg/kg 8 h (max 600 mg per dose) 12 years and over: 600 mg 12 h	Monitor for thrombocytopenia, anemia and leucopenia Oral bioavailability is 100%
Meropenem	*Non-CNS infections: 60 mg/kg/day q 8 h up to 3 g/day* *CNS infections 120 mg/kg/day q 8 h up to 6 g/day*	CrCl < 50 ml/min dose adjustment is necessary Max conc: 50 mg/ml Diluent: NS, D5

Drug	Dose	Comment
Metoclopramide	Hypomotility: 0.1 mg/kg q 4–6 h GER: 04–0.8 mg/kg/day q 6–8 h Small bowel intubation: 0.1 mg/kg single dose (max 10 mg)	Diluent: NS, D5 Max conc: 5 mg/ml
Methylene blue	HPS: 3 mg/kg in 50–100 cc's normal saline IV over 15 min Repeat 2 hourly if there is response	*Peak effect could be seen between 30 min and 5 h so might need to wait for 5 h to see response* *Not to continue for more than 24–48 h*
Metronidazole	*Oral and IV*: 15–50 mg/kg/day 8 h (max 400 mg per dose) C. difficile: 10 mg/kg 8 h IV/oral	IV dose: infuse over 20–30 min
Micafungin	<40 kg: 1.5 mg/kg/day OD (max 75 mg/day) >40 kg: 75–100 mg/day OD Prophylaxis: 1 mg/kg once daily	1.5 mg/ml Diluent: NS, D5
Midazolam	0.1–0.2 mg/kg (max single dose 5 mg) Continuous infusion 1–4 mcg/kg/min	Diluent: NS, D5 Max conc: 5 mg/ml for IV push, 1 mg/ml for infusion
Morphine	0.1–0.2 mg/kg Max single dose 10 mg Continuous infusion: 20–60 mcg/kg/h	Diluent: NS, D5 Max conc: 1 mg/ml Renal adjustment if CrCl < 50 ml/min
Naloxone	*Post op sedation*: 0.002 mg/kg/dose (0.4 mg diluted in 20 ml, give 0.1 ml/kg) repeated every 2 min for 4 doses *Opiate overdose*: 0.01 mg/kg (max 0.4 mg) repeated every 2 min for 4 doses *Continuous infusion*: 0.01 mg/kg/h	Diluent: NS, D5 Max conc: 1 mg/ml for IV push, 4 mcg/ml for continuous infusion.
Nifedipine	Cap: 0.25–0.5 mg/kg (max 10 mg) q 12 h Tab: 0.5–1 mg/kg q 8 h	
Nitroglycerine	0.5–5 mcg/kg/min (3 mg/kg in 50 ml 1 ml/h = 1 mcg/kg/min) increase 1 mcg/kg/min every 15 min up to 5 mcg/kg/min	No dose adjustment in renal dysfunction
Ofloxacin	10 mg/kg 12 h oral or IV over 1 h	Cyclical antibiotic for prophylaxis of bacterial peritonitis or recurrent cholangitis
Octreotide	*Chylothorax*: IV 0.3–4 mcg/kg/h, up to 6–12 mcg/kg/h SC 10 mcg/kg/day 8 h titrate up to 20–40 mcg/kg/day *GI bleeding*: Bolus 1–2 mcg/kg followed by 1–2 mcg/kg/h Adult dose 50 mcg bolus followed 50 mcg/h as continuous infusion	Once there is no bleeding taper the dose 50% every 12 h and can be stopped when the dose is 25% of initial dose Diluent: NS, D5
Ondansetron	0.15–0.2 mg/kg q 8–12 h (max dose 0.45 mg/kg up to 16 mg/dose)	Diluents: NS, D5 Max conc: 2 mg/ml

Drug	Dose	Comment
Pancreatic enzymes	*Infants*—2000–4000 units lipase/120 ml breast milk or formula *12 months–4 years*—1000 units lipase/kg/meal initially, then titrate per response *4 years and above*—500 units lipase/kg/meal initially, up to maximum of 2500 units lipase/kg/meal or 10,000 units lipase/kg/day *PLUS*: half the standard meal dose to be given with snacks	
Pantoprazole	Dose 1 mg/kg q 12–24 h (max dose 80 mg/dose, 160 mg/day)	Diluent: NS, D5 Max conc: 4 mg/ml
Penicillamine	5–7.5 mg/kg q 8 h (adult 250–500 mg)	• Toxic effect includes hypersensitivity reactions (i.e., Goodpasture syndrome, systemic lupus erythematosus, polymyositis) • Penicillamine is an antimetabolite of vitamin B6 (Pyridoxine),additional amounts of this vitamin is necessary • At least 4 h gap between zinc intake and penicillamine • Has to be taken 1 h after food
Piperacillin and tazobactam	Mild to moderate infections: 100–150 mg/kg/day divided q 6 h (up to 8 g/day) Severe infections: 200–300 mg/kg/day q 6 h (up to 24 g/day)	Reduce dose in renal impairment and in CVVH Diluent: NS, D5 Max conc: 200 mg/ml
Posaconazole	Prophylaxis: 230 mg/m^2 Severe infection 150 mg/m^2 (max 200 mg) q 6 h *or* 300 mg/m^2 q 12 h (max 400 mg) along with fatty meal	Avoid PPI and H2 receptor antagonist
Propranolol	Oral: 0.2–0.5 mg/kg (10–25 mg) 6–8 h, increase max to 1.5 mg/kg (80 mg)	
Racecadotril	0–8 kg: 10 mg, 9–12 kg: 20 mg, 13–27 kg: 30 mg, 28–40 kg: 60 mg, adult: 100 mg 8 h	
Ranitidine	Intravenous dose: 1 mg/kg (adult 50 mg) 6–8 h Oral dose: 2–4 mg/kg (adult 150 mg) 6–8 h	Adjust dosage in severe renal dysfunction Max conc: 2.5 mg/ml Diluent: NS, D5
Rifampicin	Pruritus due to cholestasis Orally, all ages, 5–10 mg/kg once a day (max 600 mg OD)	Monitor LFTs as potentially hepatotoxic

Drug	Dose	Comment
Rituximab	375 mg/m^2 once weekly for 4 doses. Begin with 50 mg/h and increase gradually to 400 mg/h	Premedication with acetaminophen and diphenhydramine is recommended Diluent: NS, D5 Max conc: 4 mg/ml
Sodium nitroprusside	0.5–4 mcg/kg/min (3 mg/kg in 50 ml NS/D5; 1 ml/h = 1 mcg/kg/min)	• Risk of thiocyanate toxicity in renal failure (prolonged infusion should not exceed 3 mcg/kg/min) • Photosensitive: protect from light with aluminum foil
Sodium polystyrene sulfonate	1–2 g/kg (15–30 g) 6 h NG or PR	
Spironolactone	1 month to 12 years: 1–3 mg/kg/day in 2 divided doses 12–18 years: 50–75 mg/day	
Sucralfate	1 month–2 years 250 mg po q 6 h 2–12 years 500 mg po q 6 h 12–18 years 1 g po q 6 h taken before meals	Suspension available 1 g/5 ml
Tramadol	1–2 mg/kg (50–100 mg) 4–6 h IV or Oral	
Tranexamic acid	IV: 10–15 mg/kg (0.5–1 g) 8 h Oral: 15–25 mg/kg (1–1.5 g) 8 h	
Teicoplanin	250 mg/m^2 12 h for 3 doses, then 250 mg/m^2 once daily	Diluent: NS, D5
Terlipressin	0.04 mg/kg IV (adult 2 mg) then 0.02–0.04 mg/kg 4–6 h for max of 72 h	Monitor serum sodium
Tigecycline	Loading dose: 2.4 mg/kg (max 100 mg) Maintenance dose: 1.2 mg/kg (max 50 mg) 12 h	No dose adjustment in warranted in patients with mild to moderate hepatic impairment Reduce dose by 50% in severe hepatic impairment No dose adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis Diluent: D5, NS Max conc: 1 mg/ml
Ticarcillin + clavulanic acid	Mild to moderate infection: 100–200 mg/kg/day q 6 h Severe infections: 200–300 mg/kg/day q 4–6 h	Diluent: NS, D5 Max conc: <100 mg/ml Renal adjustment is needed if Crcl < 60 ml/min
Tranexamic acid	Oral 15–25 mg/kg 8 h Intravenous 10–15 mg/kg 8 h	Avoid if any hematuria Mac conc: 100 mg/ml
Valganciclovir	Treatment of CMV: 520 mg/m^2 q 12 h CMV prophylaxis: all ages: 520 mg/m^2 daily Tablets are available as 450 mg	Reduce dose in renal impairment

Drug	Dose		Comment
Vancomycin	Mild to moderate infections: 40 mg/kg/day divided q 6–8 h up to 2 g/day Severe infections: 60 mg/kg/day divided q 6 h up to 4 g/day C. difficile: 10 mg/kg q 6 h oral		Adjust dosage if CrCl < 50 ml/min Max conc: 10 mg/ml Diluent: NS, D5
Voriconazole	IV dose: 2–12 years: 7 mg/kg q 12 h 12–18 years: 6 mg/kg q 12 h		• Hepatic impairment: in mild to moderate hepatic cirrhosis use usual initial dose then halve subsequent doses; no information available for severe hepatic cirrhosis • Oral voriconazole is preferred in patients with CrCl < 50 ml/min • Max conc: 10 mg/ml • Diluent: NS, D5
Insulin (actrapid) sliding scale	Blood glucose (mg/dl)	Insulin dose	
	90–180	0.01 u/kg/h	
	180–270	0.03 u/kg/h	
	>270	0.05 u/kg/h	
Vitamin supplements in cholestasis	*Fat-soluble vitamin*: • Vitamin A 10,000–15,000 IU/day as Aquasol A • Vitamin E 50–400 IU/day as oral α-tocopherol or TPGS • Vitamin D 400–1200 IU/day • Vitamin K 2.5–5.0 mg every other day as water-soluble derivative of menadione. Administer injectable vitamin K if PT is prolonged		
	Deficiency of water-soluble vitamins: Supplement with twice the recommended daily allowance		

31.2 Anticoagulation

31.2.1 Aspirin

2–3 mg/kg dose OD (max 75 mg)
Start once platelets > 75,000/mm^3

31.2.2 Unfractionated Heparin

Loading dose 75 units/kg IV over 10 min
Maintenance dose
<1 year of age: 28 units/kg/h

>1 year of age: 20 units/kg/h
Adjusting unfractionated Heparin dose based aPTT:

aPTT (s)	Bolus (units/kg)	Hold (min)	Rate change (%)	Repeat aPTT
<50	50	0	+10%	4 h
50–59	0	0	+10%	4 h
60–85	0	0	0	Next day
86–95	0	0	−10%	4 h
96–120	0	30	−10%	4 h
>120	0	60	−15%	4 h

CrCl < 10 ml/min/1.73 m^2, give 50% of usual dose
Diluent: D5, NS

31.2.3 Low Molecular Weight Heparin (Enoxaparin)

Treatment: <2 months—1.5 mg/kg SC q 12 h
2-months to 18 years—1 mg/kg SC q 12 h
Prophylaxis: <2 months—0.75 mg/kg SC q 12 h
2 months to 18 years—0.5 mg/kg SC q 12 h
Adjusting low molecular weight heparin dose:

Anti FXa level (units/ml)	Dose
<0.35	25% increase
<0.5	10% increase
0.5–1	No change
>1	20% decrease
>1.5	30% decrease
>2	Hold for 24 h

31.2.4 Dalteparin (Fragmin)

Prophylactic dose (subcutaneous route):
1 month to 12 years—100 units/kg OD
12–18 years—2500–5000 units OD
Treatment dose (subcutaneous route):
1 month to 12 years: 100 units/kg/dose BD
12–18 years: 200 units/kg/dose OD (max 1800 units)
In renal impairment: Dose reduction, monitoring of factor X a level is recommended

31.2.5 Warfarin

On Day 1: Loading dose 0.2 mg/kg (with baseline INR 1–1.3)

INR (day 2–4)	Loading dose
1.1–1.3	Repeat initial loading dose
1.4–1.9	50% initial loading dose
2–3	50% initial loading dose
3.1–3.5	25% initial loading dose
>3.5	Hold till INR <3.5, then restart at 50% less than previous dose

INR	Maintenance dose
1.1–1.4	Increase dose by 20%
1.5–1.9	Increase dose by 10%
2–3	No change
3.1–3.5	Decrease dose by 10%
>3.5	Hold till INR <3.5, then restart at 20% less than previous dose

31.3 Inotropes

Medication	Usual dose range	Dilute in 50 ml NS or 5% dextrose (central line)	1 ml/h will deliver	Max conc/ml
Adrenaline	0.01–1 mcg/kg/min	0.3 mg/kg	0.1 mcg/kg/min	100 mcg
Dobutamine	5–20 mcg/kg/min	15 mg/kg	5 mcg/kg/min	5 mg
Dopamine	5–20 mcg/kg/min	15 mg/kg	5 mcg/kg/min	3.2 mg
Milrinone	0.25–0.75 mcg/kg/min	1.5 mg/kg	0.5 mcg/kg/min	250 mcg
Noradrenaline	0.01–0.5 mcg/kg/min	0.3 mg/kg	0.1 mcg/kg/min	16 mcg
Vasopressin	0.0003–0.002 unit/kg/min	1.5 u/kg	2 ml/h = 0.001 units/kg/min	1 unit

In Peripheral line: Dopamine/Dobutamine dilute 3 mg/kg in 50 ml NS 1 ml/h will deliver 1 mcg/kg/min

Low dose Dopamine should be avoided in liver disease

31.4 Sedatives and Muscle Relaxants in PICU (Infusions)

Medication	Usual dose range	Dilute in 50 ml NS or 5% dextrose	1 ml/hr will deliver	Max conc/ml
Midazolam	1–10 mcg/kg/min	3 mg/kg	1 mcg/kg/min	1 mg
Fentanyl	1–10 mcg/kg/h	50 mcg/kg	1 mcg/kg/h	50 mcg
Morphine	10–60 mcg/kg/h	1 mg/kg	20 mcg/kg/h	1 mg
Ketamine	10–40 mcg/kg/min	30 mg/kg	10 mcg/kg/min	
Dexmedetomidine	0.2–0.7 mcg/kg/h			4 mcg
Propofol	1–4 mg/kg/h	Undiluted 1 ml = 10 mg		

31.4.1 Muscle Relaxants

Atracurium	PRN dose: 0.3–0.5 mg/kg Continuous infusion dose: 0.3–0.9 mg/kg/h (5–15 mcg/kg/min)	No dosage adjustment is required in hepatic or renal dysfunction
Vecuronium	PRN dose: 0.1–0.3 mg/kg Continuous infusion: 0.8–2.5 mcg/kg/min	Patients with cirrhosis and renal impairment may experience prolonged recovery time
Rocuronium	PRN dose: 0.6–1.2 mg/kg Continuous infusion 5–15 mcg/kg/min	No dosage adjustment is required in patients with renal impairment

31.5 Electrolyte Imbalance Correction

Sodium

While correcting hyponatremia, serum Sodium should not raise >8 to 10 mEq/l/24 h

- A child with severe symptomatic hyponatremia (seizures) should be given a bolus of hypertonic saline to produce a small, rapid increase in serum sodium.
- A child with active symptoms often improves after receiving 4–6 ml/kg of 3% sodium chloride
- Each ml/kg of 3% sodium chloride increases the serum sodium by approximately 1 mEq/l

The total sodium deficit can be calculated as:

0.6 × body weight (140-serum Na)

Half of the Na deficit is replaced at a rate of 0.5 mEq/h

Hypernatremia

Rapid reduction in serum sodium results in cerebral edema will manifest as seizures. The goal is to decrease the serum sodium by <8 mEq/l every 24 h, a rate of not more than 0.5 mEq/l/h with frequent monitoring of sodium and adjusting fluid therapy

This is approximately equivalent to 3–4 ml of water per kg for each 1 mEq of sodium above 145 mEq. Most patients with hypernatremic dehydration do well with half-normal saline, but with a fluid rate that is 1.25–1.5 times the maintenance fluid

Free water deficit can be calculated by the following formula

Free water deficit (L) = 0.6 × body weight (actual Na-desired Na)/ actual Na (replace free water deficit over 48–72 h)

Potassium chloride Hypokalemia 0.5–1 mEq/kg over 2 h Intermittent infusions should not exceed 1 mEq/kg/h	Diluent: NS, D5 Max conc: Peripheral IV line up to 80 mEq/l Central IV line <200 mEq/l
Phosphate Hypophosphatemia (correction using potassium phosphate) Mild (serum phosphate 2.3–3 mg/dl): 0.16–0.32 mmol/kg over 4–6 h Moderate (serum phosphate 1.6–2.2 mg/dl): 0.32–0.64 mmol/kg over 4–6 h Severe (serum phosphate <1.5 mg/dl): 0.64–1 mmol/kg over 4–6 h	Diluents: NS, dextrose Max conc: Peripheral IV 40 mEq/l of potassium = 27 mmol/l phosphate
Sodium bicarbonate *Dose*: 1–2 mEq/kg/dose (max up to 50 mEq/dose) *Urinary alkalinization*: (Salicylate poisoning) 25 mEq infused over 1 h, urine pH should be measured q 30 min and additional doses given until urinary pH 7.5–8.5.arterial pH should be <7.5 *Metabolic acidosis: HCO3 deficit(mEq): 0.3 × weight × base deficit* This will correct half of the deficit (infused over 4 h), further corrections depend on repeat blood gas analysis	Diluent: dextrose *Max conc*: infants 0.5 mEq/ml Children 1 mEq/ml • Requires adequate ventilation to release CO2 generated • Potential risk of HCO3 use is paradoxical CNS acidosis
Magnesium sulfate 25–50 mg/kg (max 2 g/dose) of magnesium sulfate q 6 h for 3 or 4 doses	Diluent: NS, D5 Max conc: 200 mg/ml

31.6 Glucose Tonicity and GIR (Glucose Infusion Rate) Calculation

The formula for preparing 100 ml of fluid with a desired concentration of glucose using 5% dextrose and 25% dextrose solutions is given by the formula $5X - 25 = Y$ where X is the required percentage of dextrose and Y is the amount of 25% dextrose (in ml) to be made up with 5% dextrose to make a total of 100 ml.

$$\text{GIR}\left(\text{mg/kg/min}\right) = \%\,\text{of dextrose being infused} \times \text{rate of infusion}\left(\text{in ml/h}\right) / \text{Body weight}\left(\text{in kg}\right) \times 6$$

$$\text{GIR}\left(\text{mg/kg/min}\right) = \text{Rate of IV fluids}\left(\text{in ml/kg/day}\right) \times \%\,\text{of dextrose infused}/144$$

$$\text{GIR} = \text{Rate of IV fluids}\left(\text{in ml / kg / day}\right) \times \%\,\text{of dextrose infused} \times 0.007$$

To prepare 100 ml of fluid with a desired concentration of glucose (7.5, 10, 12.5, and 15%) using 5% dextrose and 25% dextrose solutions:

Glucose tonicity (%)	Amount of *D5* (ml)	Amount of *D25* (ml)
7.5	87.5	12.5
10	75	25
12.5	62.5	37.5
15	50	50

31.7 Immunosuppressants

Please see Chap. 23

31.8 Accelerated Vaccination Schedule in Children with Liver Disease

Accelerated vaccination has to be done in all children with liver disease in anticipation of need for liver transplantation at any time. Liver transplantation should not be offered to anyone who had liver vaccines within a period of 4 weeks. All killed vaccines could be given after six months of liver transplantation. Though there is no absolute contraindication to give killed vaccine during immediate post-transplant period, sero-conversion is unpredictable due to higher immunosuppression during immediate post-transplant period

Age	Immunization	Date given	Serology	Comments
6 weeks	DTaP /DTwP HiB, HepB (Pentavac) PCV13 IPV			
10 weeks	DTaP/DTwP HiB, HepB (Pentavac) PCV13, IPV			
14 weeks	DTaP/DTwP Hib, Hep B (Pentavac) PCV 13, IPV			
6 months	MMR* Varicella Hep A (Havrix Junior®)		Anti-HBs	*MMR/varicella may not be given <1 month pretx
9 months	Vi-Ps conjugate Typhoid vaccine			Booster during second year of life
12 months	DTaP/DTwP HiB/Hep B (Pentavac) Hep A (Havrix Junior®) PCV13, MMR, varicella			MMR/varicella may not be given <1 month pretx #Hep B-see note below

Age	Immunization	Date given	Serology	Comments
13 months	MMR			
24 months	PPV 23 Typhoid			
6 months post Tx	Hep B—3 doses Pneumovax 23		Anti-HBs before and 1 month after initial series	If Hep B not previously given, and anti-HBs (-), give initial series, using double dose. Give second series if inadequate response to initial series
4 years	DTaP/IPV/DTwP, typhoid			
11 years	Tetanus/diphtheria booster—Consider dTap			
Annually	Influenza			Recommend for all pts and family members

Full hep B series (double dose) if HBs (-) when tested 1–2 months after initial series

If first MMR given when child is <12 months of age, child needs second dose at 2 months, and a third dose 1 month later

If not given pneumococcal pre-transplant:

If <24 months give 3 doses of conjugate vaccine (PCV 13) at monthly intervals with polysaccharide vaccine (23PPV) at 2 years

If >24 months give 2 doses conjugate vaccine (PCV 13) at monthly intervals followed by Pneumovax 23

Catch up immunizations when there has been delay; generally at least one month should occur between repeat doses of the multiple dose vaccines, but there is no restriction of the types of vaccines which can be given simultaneously apart from the comfort of the child.