

# PAEDIATRIC LIVER DISEASE AND LIVER TRANSPLANT

A Resource for Nurses in New Zealand



# Acknowledgements and Disclaimer

Appreciable care has been taken in the preparation of this package which Starship Children's Health provides as a tool for nurses and others to use in the nursing of children with liver disease and liver transplant.

However in view of the possibility of human error or advances in medical knowledge, Starship Children's Health cannot and does not guarantee that the information contained in this package is in every respect accurate or complete. You are encouraged to consult other sources in order to confirm the information contained in any of this package and in the event that medical treatment is required seek advice and input from an experienced medical practitioner.

This nursing resource was written by Karyn Sanson Clinical Nurse Specialist Liver / Gastroenterology Starship Children's Health 2012

This resource uses the Liver Disease Learning Package for Nurses written by me during my employment by at the Royal Children's Hospital, Melbourne, as its base.

I would like to acknowledge the following people for their contribution and support whilst writing this document:

Shared Care Nurses Review Group  
Ros Robertson (Canterbury DHB)  
Claire Hagglund (Southern DHB)  
Robyn Kelly (Southern DHB)  
Wendy Diamond (Waikato DHB)  
Donna Aitken (Waikato DHB)  
Angela Weekly (Wanganui DHB)  
Trish Silk (Wanganui DHB)

Meda Credland (Hawkesbay DHB)  
Mary Rutherford (Community Nurse Starship)

Haylee Riddell Social Worker (Starship)  
Robyn Agnew Social Worker (Starship)

Caroline De Luca Pharmacist (Starship)  
Kim Herbison Dietitian (Starship)  
Rebecca Bruce Dietitian (Starship)

Dr Jon Bishop, Gastroenterologist/ Hepatologist, for painstakingly reviewing the medical information  
Cate Fraser Irwin, CNS Liver Gastro Starship for believing it would happen and supporting me during the project in a myriad of ways.

Dr Helen Evans, Dr Simon Chin and Dr Stephen Mouat Gastroenterologists for their unfailing support The Immune Deficiency Foundation NZ (IDFNZ) who have provided the substantial funding required for the graphic design and diagram drawing, along with ongoing support and encouragement throughout the project.

The Judith Phillipson Scholarship trustees for the scholarship grant which allowed dedicated time for the project and the means to keep it current into the future

## Purpose and limitations of this resource

This resource has been developed to assist nurses in caring for children and their families through the transplant continuum; it has not been designed to meet the needs of parents and other non health professionals. Parents and families should be encouraged use the parent guide to liver transplant which has been

developed and obtain further information if required with the support of their health care team. This resource will cover the most common causes of liver disease likely to lead to transplant within childhood or adolescent years and issues related to liver transplant until transfer of the patient to adult care.

It does not cover the myriad of conditions such as Viral Hepatitis which is unlikely to ultimately lead to transplant during childhood. Nor does it include extremely rare or complex conditions that may lead to transplant for which very individualised management is required. In such cases information and support will continue to be provided to the shared care team on a case by case basis.



creativebite™  
new designers fresh ideas

Layout design, Illustrations and production by Tracey Liu

Proudly Printed by  
presentations  
design & print ltd  
www.present.co.nz

# Contents

## Part One: Liver Disease

### Section One: Anatomy

Gross Anatomy .....	06
Blood Flow .....	08
Biliary Tract .....	09
The Gallbladder .....	09

### Section Two: Function of the Liver

Bilirubin .....	10
Carbohydrate .....	10
Fats .....	10
Protein and Amino Acids .....	10
Coagulation .....	11
Vitamins and Hormones .....	11
Drug Metabolism .....	11

### Section Three: Complications of Liver Disease

Faltering growth .....	11
Glucose control .....	13
Vitamin deficiency .....	14
Portal hypertension and varices .....	15
Ascites .....	19
Spontaneous bacterial peritonitis .....	21
Hepto- renal syndrome .....	21
Hepatic encephalopathy .....	22
Hepato- pulmonary syndrome .....	24



Development.....	24
Blood tests .....	25

## Section Four: Disorders Of The Liver

Infantile Cholangiopathies .....	27
Biliary Atresia .....	28
Kasai Procedure.....	29
Alpha 1 Antitrypsin Deficiency.....	30
Alagille's Syndrome .....	31
PFICC -Bile salt transporter disorders.....	32
Metabolic Liver disease.....	33
Acute Liver Failure.....	34

## Section Five: medications in Liver Disease

## Part Two: Liver Transplant

An Overview.....	36
------------------	----

### Section One: Pre transplant

Assessment.....	37
Waiting for transplant.....	38
Donor sources .....	40
The Transplant Surgery.....	43

### Section Two: Post Liver Transplant

Recovery .....	44
----------------	----

### Section Three: Complications

Growth .....	46
Development.....	46
Biliary Strictures .....	47



Rejection.....50

Infection.....52

## Section Four: Healthy Living

Return to school .....56

Sport and swimming .....56

Other activities .....56

Diet and weight .....57

Oral health .....57

Skin Care.....57

## Section Five: Youth Health and Transition

## Section Six Medications

Immunosuppression.....60

Prednisone.....60

Tacrolimus .....61

Cyclosporin.....63

Mycophenolate Mofetil.....63

Others.....63

## Section Seven: Psychosocial aspects

Cultural considerations .....64

A social work perspective.....64

## References

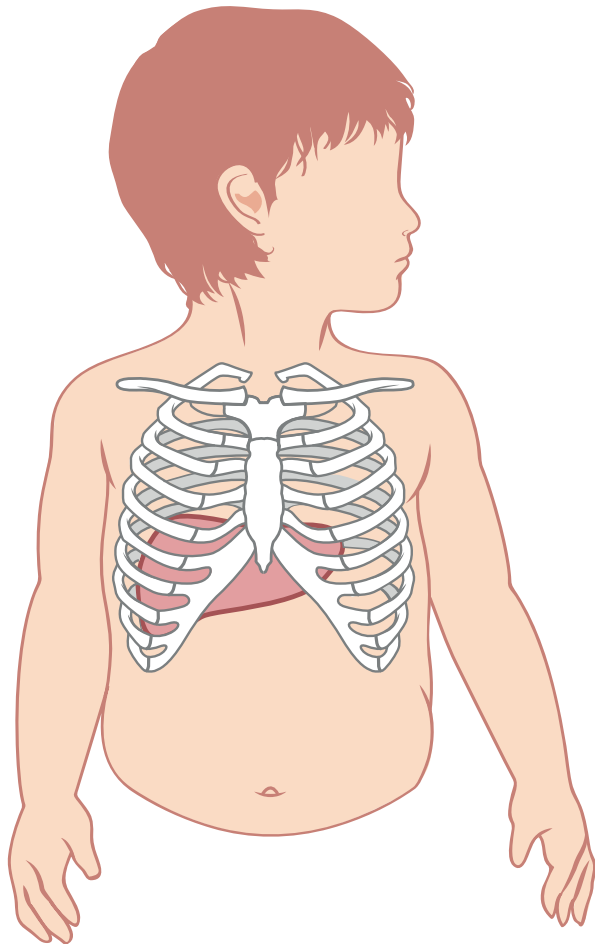
References.....66



## Section 1 Liver Anatomy

### Gross Anatomy

The liver is the largest organ in the body and in infants comprises one-eighteenth of the birth weight.



It lies in the right upper quadrant protected by the ribs. The upper border lies approximately at the level of the nipples (1).

At any one moment the liver holds approximately 13% of the body's total blood supply.

The liver is completely covered by peritoneum except in three places;

- Where it comes into direct contact with the diaphragm
- The area surrounding the entrance point for the inferior vena cava
- The area surrounding the entrance point for the gall bladder

There are 2 major anatomical lobes the

- Right
- Left

The right is approximately six times the size of the left

There is a recognised functional anatomy.

The main portal vein divides into right and left branches and each of these supplies two sectors.

Sectors on the Right Side are:

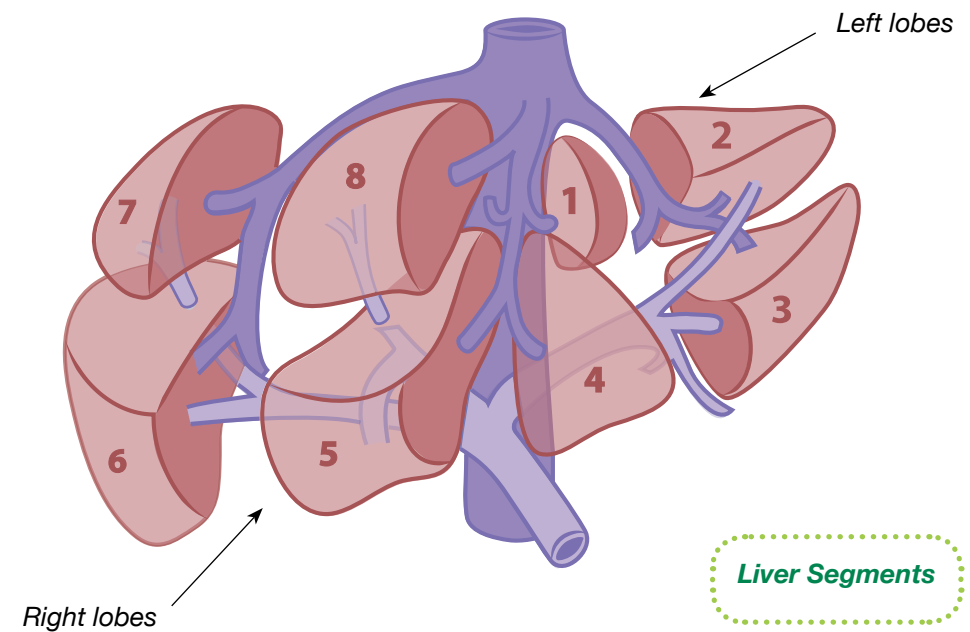
- Anterior
- Posterior

In the left lobe they are:

- Medial
- Lateral

The right and left sides are independent with regard to portal and arterial blood supply and bile drainage.

The functional anatomy is of vital importance to the surgeon who is considering liver resection or transplantation.





In 1833 Kiernan introduced the concept of hepatic lobules as the basic architecture at the microscopic level. He described circumscribed pyramidal lobules consisting of a central tributary of the hepatic vein and at the periphery a portal tract containing bile duct, portal vein radicle and hepatic artery branch.

Columns of liver cells and blood-containing sinusoids extend between these 2 systems (1).

We now know columns of liver cells radiate from the central vein and are entwined in an orderly way by sinusoids (small vessels similar to capillaries).

The liver tissue is saturated by two systems of tunnels

- The Portal tracts
- The Hepatic central canals

These are set out in such a way that they never touch each other.

Hepatocytes (liver cells) have 3 surfaces.

- One faces the sinusoid and space of Disse.
- The second faces the canaliculus and
- The third faces other hepatocytes.
- Hepatocytes are arranged in rows or sheets called plates or cords
- They comprise about 60% of the liver and have a lifespan (in experimental animals) of approximately 150 days (1).

Sinusoids are a form of terminal blood channel consisting of a large, irregular, anastomosing vessel.

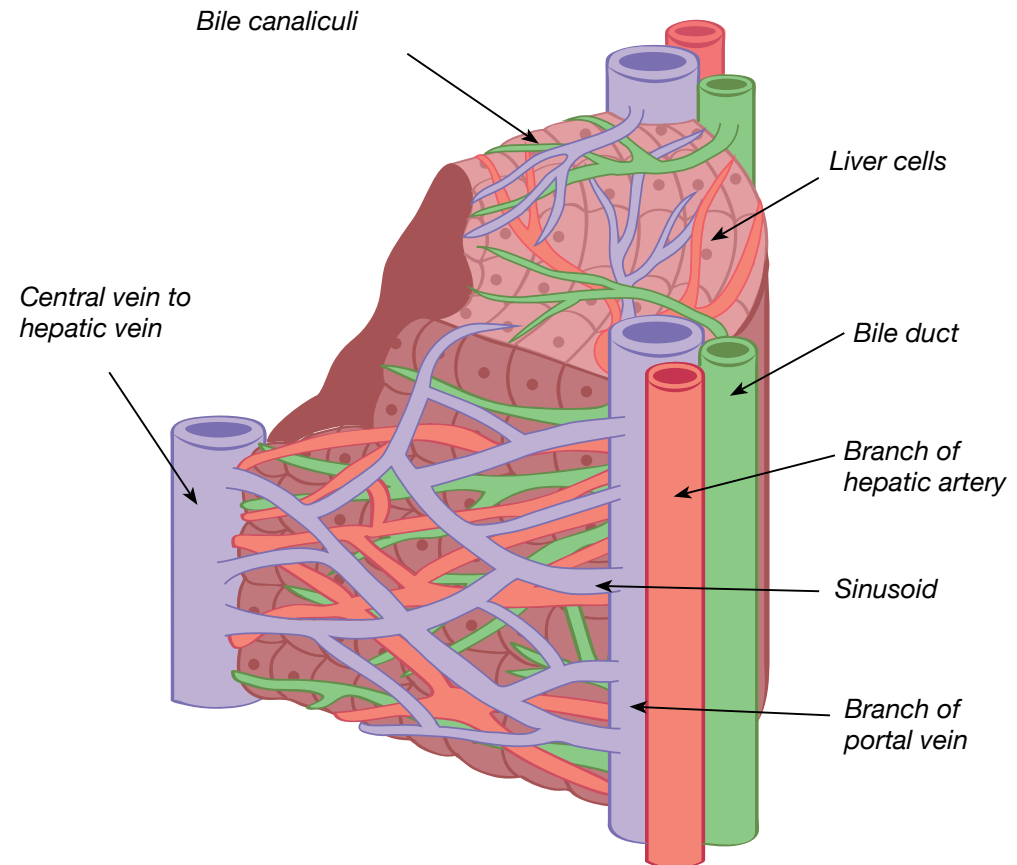
They are lined with a highly permeable endothelial cell layer which allows protein diffusion from the blood.

Substances diffuse out of the blood into the hepatocytes where they are either metabolised or altered.

Kupffer cells (a type of phagocyte) are also found in sinusoids and filter bacteria and foreign bodies.

Hepatic Stellate cells are associated with sinusoids and have also been called fat storing cells.

**Wedge Section  
Demonstrating Structure of  
The Normal Liver**



## Blood Flow

The liver is served by 2 distinct blood supplies. The portal vein and the hepatic artery.

### The Portal Vein

- Brings venous blood from the intestines and spleen
- Is formed by the junction of the superior mesenteric and splenic veins
- Carries 80% of the blood supply and nutrients to the liver
- The blood from here is not high in oxygen
- Is a low pressure vein with no valves

The nutrient composition of the blood into the liver from this vein varies substantially from hour to hour and the liver acts as a moderator of these changes protecting the systemic circulation from large fluctuations in supply of metabolites

### The Hepatic Artery.

- Delivers fully oxygenated blood at high pressure
- Is a branch of the celiac axis
- Has branches which supply the left and right lobes
- Has a variable anatomy

Both vessels enter the liver via a fissure called the porta hepatis.

Inside the porta, the portal vein and hepatic artery divide into branches to the right and left lobes. These branches continue to subdivide, ultimately delivering both oxygenated blood (in the branch of the hepatic artery) and nutrient rich blood (in the branch of the portal vein) to each hepatic lobule

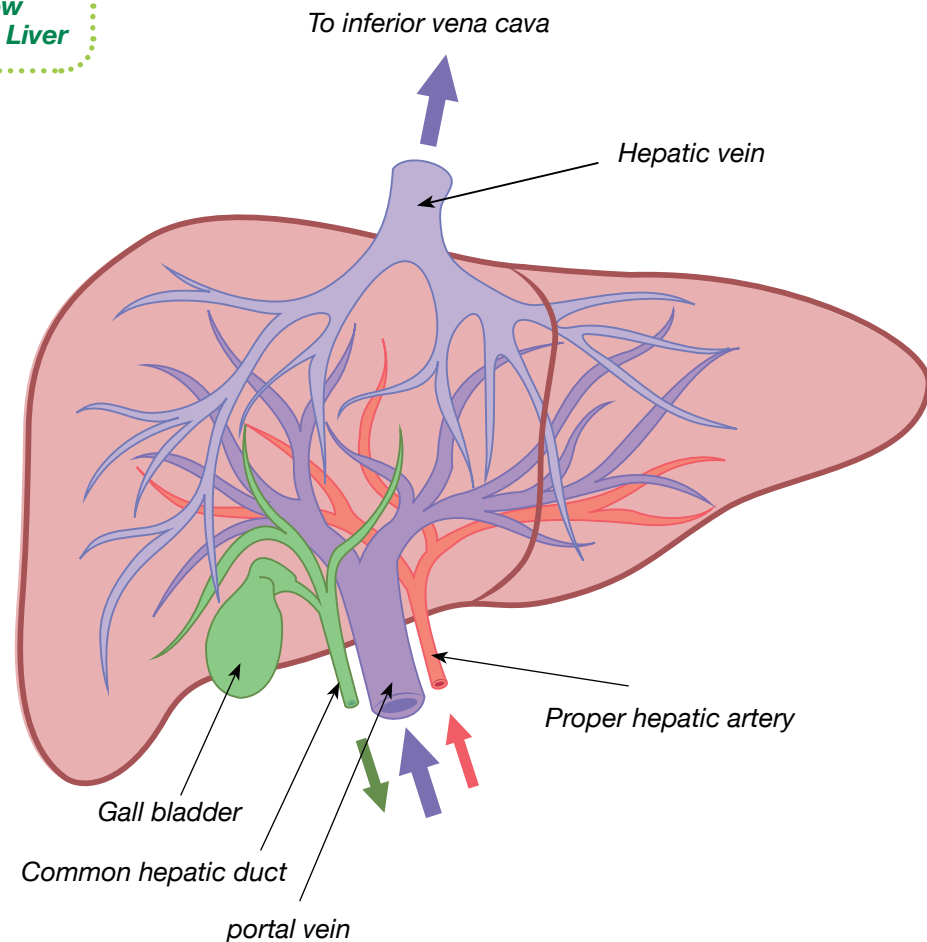
Blood from the sinusoids empty into a central vein that passes through the centre of each lobule, these then drain into the right and left hepatic veins.

The hepatic veins empty into the inferior vena cava very near where it enters the right atrium of the heart.

The composition of blood entering the liver from the portal vein varies substantially from hour to hour.

The liver dampens this fluctuation so the blood entering systemic circulation is uniform (2).

### Blood Flow Through The Liver





## Biliary Tract Anatomy

The biliary tract is the liver's excretory system.

It begins with the Bile Canaliculi.

- These are grooves on the surface of liver cells.
- Their surfaces are covered with microvilli.

This intralobular network drains into thin walled terminal bile ducts.

- These are sometimes called Ductules, Cholangoles or Canals of Hering.

These drain into larger interlobular bile ducts in the portal canals.

Bile flows in the opposite direction to flow of blood in the sinusoids.

The right and left hepatic bile ducts join to form the common hepatic duct in the porta hepatis.

It is then joined by the cystic duct from the gall bladder to form the common bile duct.

This runs behind the posterior wall of the second part of the duodenum.

It usually joins the main pancreatic duct to form the Ampulla of Vater.

In a small proportion of children the pancreatic and bile ducts open into the duodenum separately.

The junction of the common bile duct and duodenum is surrounded by muscle fibres. This is the Sphincter of Oddi.

When this sphincter relaxes bile flows into the duodenum. Contraction causes bile to flow into the gallbladder where it can be stored between meals.

Hormones released from the duodenal wall control this

process allowing accurate mixing of food and bile in the upper small intestine.

## The Gallbladder

The gallbladder is a pear shaped bag with a capacity of approximately 5 - 50 ml in children depending on age and size.

The fundus is the wider end.

The body extends into a narrow neck which continues into the cystic duct.

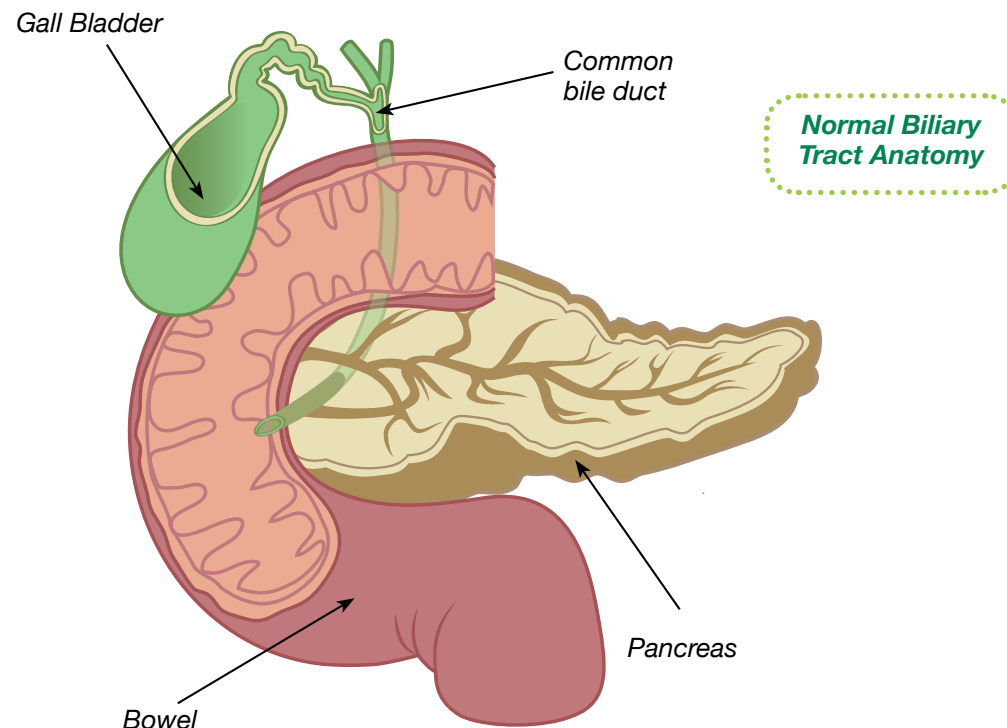
The Valves of Heister are spiral folds of mucous membrane in the walls of the cystic duct and neck of the

Gallbladder (1). The Hartmann's pouch is a sacculatation at the neck of the gall bladder.

Gallstones commonly occur in this part. The gallbladder concentrates bile (5-10 fold) while it is storing it.

It receives blood from the cystic artery. There are many lymphatic vessels within the walls of the gallbladder. These drain through the cystic gland at the neck, to the glands along the common bile duct where they join with the lymphatics from the pancreas.

The Gallbladder and bile ducts are profusely supplied with nerves from the parasympathetic and sympathetic systems.



## Section 2 Functions of the Liver

The liver plays a vital role in human metabolism. It has over 500 functions.

It plays a major role in many biochemical conversions and syntheses in the body.

In other areas it has a regulatory function.

The liver is involved in;

- The metabolism of all three food groups.
  - Protein
  - Fats
  - Carbohydrates.
- Chemical transformation of endogenous and exogenous substances
- Storage of
  - Glycogen
  - Fat-soluble vitamins A, D, E and K,
  - Vitamin B 12
  - Iron

### Bilirubin

Bile formation and Bilirubin excretion;

Are major contributing factors in digestion and absorption of fats.

- Bile has 3 main components.
  - Bile salts
  - Bile pigments
  - Cholesterol.

Bile salts are the most essential part and are manufactured in the liver from cholesterol.

Up to 95% of excreted bile salts are reabsorbed by the small intestine, recycled in the liver and used again in the bile.

### Bilirubin Formation

- Haemoglobin from old red blood cells is broken down to form haem.
- Haem is converted to bilirubin.

Unconjugated bilirubin (indirect) is fat soluble and bound to plasma proteins.

- Within the hepatocytes, bilirubin disassociates with the protein and is attached to glucuronic acid, thus becoming conjugated.

Conjugated bilirubin (direct) is water soluble in hepatocytes.

- It is actively secreted by hepatocytes into bile and removed from the body exiting as the pigment in faeces. (Foods also contribute to the pigment in faeces.)

Bilirubin is yellow and jaundice occurs due to the imbalance between bilirubin production and clearance.

### Carbohydrates

- Are absorbed from the intestinal tract and are either used immediately or stored in the form of glycogen.

The liver will break down glycogen to normalise blood glucose levels and prevent hypoglycemia.

This process is called gluconeogenesis.

### Fats

- Are synthesised in the liver and components are absorbed from the small intestine.

They are recycled between the liver and adipose tissue.

- They can be used as an alternative energy source to glucose when needed.

Bile plays a very important role in emulsifying fats (excluding medium chain triglycerides, which do not require emulsification) in the small intestine and helping their absorption.

- Some fats are necessary for normal growth and development.
- Bile salts help bile flow.
- Cholesterol is also synthesised by the liver as well as by the intestinal wall. The reaction which occurs in this process is an important control point for blood cholesterol levels.

### Protein and Amino Acids

The liver rapidly takes up protein and amino acids absorbed from the intestine.

Proteins and Amino acids are deaminated, transaminated or utilised in protein synthesis.

Ammonia is produced in the deamination process, converted to urea and excreted by the kidneys.

Albumin is one specific protein that is synthesised and stored in the liver.

The most important regulators of albumin synthesis are the state of nutrition (adequate dietary protein intake) and a liver healthy enough to make normal quantities of albumin.

## Coagulation

Fibrinogen, prothrombin and many other proteins which are vital clotting agents, are formed in the liver.

- Adequate absorption of Vitamin K requires the presence of bile salts in the gut
- There are a number of Vitamin K dependent clotting factors
- Vitamin K must be present in the liver for those clotting factors to become activated

## Vitamins and Hormones

Normal bile production is essential for efficient absorption of fat-soluble vitamins;

- The liver stores the fat-soluble vitamins A, D, E and K and produces essential active metabolites of vitamins E and D.
- The liver controls the levels of many hormones in the body including glucagon and growth hormone.
- It also inactivates hormones via a complex feedback system

## Drug Metabolism

The liver is responsible for the metabolism of many drugs and dangerous body toxins.

Drugs are changed through a series of chemical reactions into non toxic compounds, and then excreted.

## Section 3 Complications Of Liver Disease

### Faltering Growth

Previously referred to as failure to thrive

Improving nutritional status can slow progression of liver disease and decrease risk of mortality (3).

This makes nutrition one of the most powerful tools in supporting children with liver disease (3).

Nutritional requirements in children with liver disease are increased and even if appropriate feed changes have been made, energy supplementation is required.

There are a number of barriers to optimal nutrition which include:

#### • Impaired digestion

- Reduced bile salt availability, particularly in cholestatic liver disease leading to malabsorption of fats.
- Reduced ability for absorption related to changes in blood flow through the gut lining and atrophy of the villi when malnutrition is present in spite of adequate intake.

#### • Decreased intake

- Anorexia, nausea and poor volume tolerance causing vomiting.
- Organomegaly of the liver and spleen crowding the stomach and diaphragm.
- Frequent need to restrict fluid intake to limit ascites formation.

#### • Increased energy expenditure

- Can drive requirements up to 175% of normal (4)
- Through a hyper metabolic state where there is increased protein breakdown and a decrease in protein synthesis
- Respiratory splinting by enlarging organs can also increase effort.

The aims of nutritional management in children with liver disease who require transplant are:

- To meet the increased nutritional requirements
- Reduce fat malabsorption
- Prevent nutritional deficiencies

## Faltering Growth (Continued)

The babies shown in Photos 1 and 2 below show the difference in growth between twin boys at age 6 months– one of whom had liver disease.



Nutritional assessment cannot be based solely on the child's weight. Increasing size of liver and spleen, development of ascites and use of diuretics make weight of limited nutritional assessment value. Head circumference, length (or height in older children) fat and protein stores give a much more accurate assessment of nutritional state (5).

As a general rule there are no set diets for the different diagnoses which cause liver disease.

Management is determined on an individual basis, according to the presenting symptoms of the child.

Scenarios that will require nutritional intervention include:

- Jaundice (particularly in association with pale stools)
- Hyperbilirubinemia
- Fat digestion decreases and malabsorption and poor weight gain result. (eg: Extra Hepatic Biliary Atresia)

There are a number of strategies used to maintain and improve nutrition and children are managed with the active input of specialist paediatric dieticians.

Early intervention and close monitoring is imperative to obtaining good nutrition and maximising growth.

### Breast feeding and solids:

Children with cholestatic liver disease are generally ravenous feeders taking far more than normal volumes. They are often unsettled, feeding frequently and have diarrhoea secondary to fat malabsorption. Whilst breast milk has a number of advantages normally, in this setting specialist formula is required. By the time diagnosis of chronic liver disease is made mothers are often exhausted and breast feeding should be allowed after bottle feed for comfort and bonding only.

Many mothers find that this induces vomiting and it is rare to see breast feeding maintained as liver disease progresses.

However, oral intake remains important for oro-motor skill development and prevention of oral aversion. Solids are introduced at the normal age but the purpose is for taste and skill rather than nutrition so volumes are kept very small.

### Specialist feeds

- Pepti Junior
  - Is a feed based on hydrolysed protein and medium chain triglycerides (MCT) which is more easily digested in children with little or no bile flow through the intestine.

This is the first line treatment in NZ.

- Generaid Plus
  - Is available to children in NZ waiting for transplant and when synthetic liver function begins to fail.
  - It contains whole protein rather than hydrolysed protein making it more palatable than Pepti Junior.
  - Has a higher MCT component.
  - Contains branch chain amino acids which can be used directly for muscle growth without liver involvement.
  - Low sodium component assisting in reducing ascites formation.

Feed supplementation and concentration of calories.

- Adding products such as Liquigen to increase calories per ml.
- Increasing concentration of feed can reduce volumes required and increase tolerance.

## Nasogastric feeding

The team will consider the disease, the symptoms, and the child's intake when making the decision to place a nasogastric tube. The risks and benefits of NG feeding needs to be weighed up in children with known varices present and we always recommend the placement of long term tubes and strategies to reduce the need for frequent tube replacement.

These same needs are taken into consideration for its removal.

- Many babies and children will struggle to take and tolerate the volumes required to meet nutritional needs orally even when calorie density is maximised.
- Bolus feed top ups
  - Generally need to occur at every feed
  - Given after the child has had the opportunity to feed orally for a short period (10 mins)
  - Often not well tolerated
  - Can be given over a few minutes or via a pump over a longer period (30-60 mins)
  - Can be difficult for parents to manage due to restrictions on mobility imposed by equipment and time involved.
  - Generally smaller and more frequent feeds than a well child of the same age.
- Continuous feeds
  - Generally given over night, over a number for hours, at a low rate.
  - Can improve absorption due to small volumes slowly moving through
  - Usually better tolerated when organomegaly is present

- Protective against hypoglycaemia.
- Generally easier for parents to manage
- May be extended through the full 24 hour period

Diseases that always require nutritional intervention include:

- Biliary Atresia, post Kasai,
- Alpha -1 Anti trypsin deficiency
- Alagille's syndrome
- Neonatal hepatitis
- PFIC

### SHARED CARE NOTE

**In a child with documented varices it may be appropriate to have nurse replace any dislodged tubes in the hospital setting rather than by a parent in the community.**

**If concerned please discuss with the Starship CNS service.**

## Glucose Control

After absorption from the intestine, food does not pass directly into the general circulation. Instead it travels first by way of the portal system to the liver.

During intestinal absorption, blood entering the liver via the portal vein has varied concentrations of glucose.

One function of the liver is to control this variation to provide a more uniform concentration to the systemic circulation.

Children with advanced stages of liver disease will have impaired gluconeogenesis.

They cannot make glucose from protein and have little stored glucose (Liver glycogen)

They have difficulty in maintaining their blood glucose levels during even short periods of starvation,

e.g. When fasting for theatre.

They may become hypoglycaemic and become unconscious or have seizures. Intravenous fluids containing glucose must be given when fasting to prevent hypoglycaemia.

The same twin boys at 10 months of age after maximising nutrition.

3



4



## Vitamin Deficiency

In children with cholestasis, fat soluble vitamin absorption is severely affected.

Even with vigilant monitoring of levels and extensive supplementation, diseases of vitamin deficiency can occur specially if the child has chronic liver disease.

Some of the common deficiencies we see in children with long term cholestasis include:

- Vitamin A - night blindness and the skin becoming dry and pimply.
- Vitamin C - Haemorrhages, loose teeth and gingivitis.
- Vitamin D - rickets (Calcium malabsorption contributes to this) or osteoporosis with brittle bones. ( This risk remains for up to 6 months post liver transplant.
- Vitamin E - Red blood cell haemolysis and if severe; impairment of muscle power and peripheral nerve function in feet.

Vitamin K- Clotting abnormalities

All children with jaundice will require fat soluble vitamin supplementation and the dosing is likely to be significantly higher than what is generally recommended.

Vitamin K deficiency causes coagulopathy, putting infants and children at risk of intracranial bleeds(6). Many children will require regular IV Vitamin K (usually weekly) in addition to daily oral administration to assist in the maintenance of safe clotting levels.

### SHARED CARE NOTE

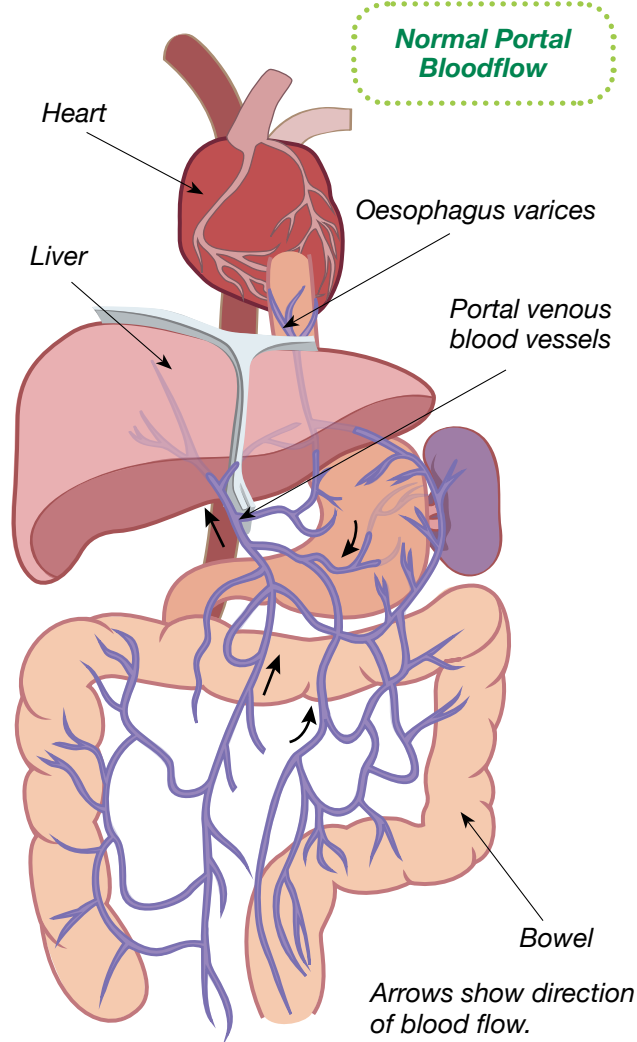
**The frequency of Vitamin k administration is important in maintaining clotting at a safe level. Any planned delays in administration should be discussed with the Starship team.**

**Vitamin levels should be monitored routinely every three months. Vitamin K is measured through clotting not as a vitamin K level.**



## Portal Hypertension (and Varices)

The portal system includes all veins that carry blood from the abdominal part of the alimentary tract, the spleen, pancreas and gall bladder.



Portal hypertension is increased pressures within the portal circulatory system.

In health, the portal venous system is a low pressure system (<10mmHg) which does not contain valves. In the context of progressive fibrotic liver disease, the resistance to blood flow within the liver increases. This increased pressure is transmitted back into the portal vein. Portal hypertension may also arise secondary to problems in the pre-hepatic (eg portal vein thrombosis) or post-hepatic (eg Budd-Chiari syndrome) parts of the circulation.

There is continued debate in the literature as to the exact mechanisms involved but it is clear that there are multiple factors contributing to the development of portal hypertension. These include:

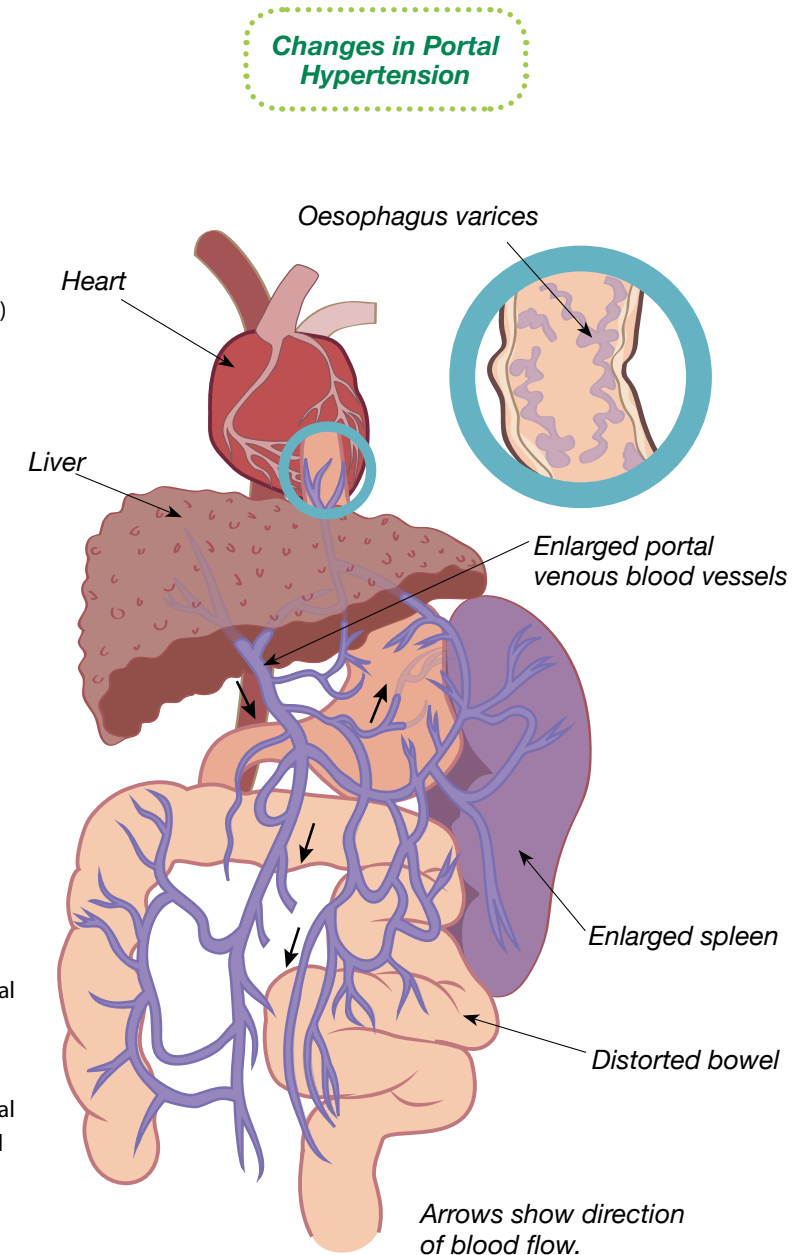
- Increased resistance within the portal system
  - Usually the liver itself.
- Haemodynamic changes

Hyper dynamic circulation increases the portal flows required

- Changes in vasodilator levels
  - Through a number of hormonal and chemical mediator changes(6)

When the portal circulation is restricted or obstructed, whether it is from within or outside the liver, a remarkable collateral circulation develops to carry portal blood into the systemic veins (1, 6).

Note the visible superficial veins radiating from the umbilicus in the picture, this is commonly seen collateral circulation and is consistent with the presence of portal hypertension.



Collateral Vessels are tortuous and fragile; they have minimal elasticity and are called Varices.

Collaterals are classified into 4 collateral systems.

Three of the systems which develop cause less critical clinical problems, although may be associated with other complications of liver disease e.g hepatopulmonary syndrome and renal impairment (6).

The fourth collateral system is through the abdominal alimentary tract and carries significant morbidity and mortality risk.

Varix development and variceal bleeding can occur from a number of sites including;

- Oesophagus
- Stomach
- Duodenum
- Previous surgical sites e.g. Roux en Y loop and Gastrostomy stomas
- Rectum (6)

Because oesophageal varices are superficial, distended, thin walled vessels, covered only by mucous membrane, they are liable to ulcerate and rupture and massive bleeding can occur (7).

There are 2 additional pathogenic mechanisms that appear to operate which contribute to the risk of significant haemorrhage.

First, the liver dysfunction interferes with the production of a number of clotting factors.

Secondly in obstructive jaundice, vitamin K is poorly absorbed from the gut. This leads to a deficit in Vitamin K dependent factors (2).

Clinical signs which may indicate the development of

portal hypertension include increasing spleen size on examination and a dropping platelet numbers on FBC.

Bleeding oesophageal varices can be life threatening. Mortality rates associated with acute large bleeding episodes range from 0-8% (8)

Factors, which contribute to bleeding, include straining to pass stool, sneezing, coughing, vomiting, and eosophagitis. Increased cardiac output associated with over hydration or sudden fluid shifts, or febrile illness. Inflammation of vessels by irritating fluids, passing a nasogastric tube and poorly chewed food may also be factors (6, 7).

The child with haematemesis from bleeding oesophageal varices can be critically ill requiring aggressive medical care and expert nursing care.

The immediate goals are maintaining a patent airway, ensuring adequate circulating blood volume and stopping the bleeding.

- Initially normal saline is used for circulating volume replacement, followed by a combination of blood products to maintain haemoglobin and boost clotting factors.
- The size of a bleed can vary substantially from slow ooze presenting as melaena with minor changes in clinical state only, to the massive bleeds described earlier.
- Melaena is also associated with large bleeds.
- Bleeds can be a combination of haematemesis and melaena.

A child with any form of intestinal bleeding and liver disease is an extremely high-risk patient requiring vigilant monitoring and care.



## Management of Oesophageal Varices

There are a number of options for management of varices to help control bleeding and prevent further episodes.

They include medications, endoscopic surgery and ultimately liver transplant.

### Medications:

Used in the treatment of portal hypertension and variceal bleeding.

### Prevention:

- Omeprazole and Ranitidine (Oral and IV) are used to reduce gastric acidity.
- Propranolol is a beta blocking agent used to lower portal hypertension and prevent increases in portal pressure during physical exercise. Patients with severe cirrhosis are less responsive to beta blocker therapy (9).

### Active bleeding

- Octreotide is a vaso active medication that can be used for bleeding varices. The mechanism of action is not certain, however it may be due to reduced portal pressures and blood flow (9)

### Endoscopy

Endoscopy is the best method of visualising oesophageal varices and offers several treatment options;

These include

- Band ligation
- Sclerotherapy
- Tissue adhesive

There is a strong correlation between variceal size and the probability of bleeding (7).

Once the varices have been sighted and assessed then the most appropriate method of treatment is decided.

Band Ligation is the preferred option as it has greater efficacy in ensuring obliteration of varices and less complications. However it is technically not possible in infants or small children (10).

Band ligation involves the application of bands to large varices. The applicator attaches to a flexible endoscope through which the lumen can be visualised. When the varix has been identified, suction is applied. This draws the varix into the lumen of the overtube and the applicator is activated releasing the band which is applied to the varix.

Tissue adhesive can also be used to obstruct large vessels.

In injection sclerotherapy a sclerosing agent is injected into the varices to cause thrombosis and scarring. This reduces or completely stops flow through the effected blood vessel.

These methods can be used prophylactically to prevent of bleeding or after acute bleeds have slowed to prevent further bleeding from that site. Whilst the value of prophylactic treatment has not been established, it is sometimes considered if the child lives remotely and struggle to access emergency care in a short space of time.

Once a course of ligation or sclerotherapy has been embarked upon repeated sessions are required to ensure obliteration of varices. Repeated courses will be required as there are often multiple varices present and more will continue to develop until the underlying portal hypertension is cured (7).

The risks associated with endoscopic management include:

- Acute or chronic oesophageal ulceration
- Stricture formation
- Perforation of the oesophagus

## Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS is a portocaval shunt performed under radiological guidance. It links the hepatic and portal veins in the liver using a stent (7).

TIPS is used for control of acute variceal bleeding in patients with cirrhosis that is not responsive to all other forms of treatment.

It is used extensively in adults but rarely recommended in children due to the commonly experienced neurological side effects and technical issues associated with paediatric anatomy (9).

## Orthotopic Liver Transplantation

Variceal bleeding is rarely the sole indication for transplant in end stage liver disease. However because a large bleed confers significant mortality and morbidity, variceal bleeding often provides impetus to early transplant (7).

Once transplant has happened the portal hypertension corrects thus reducing the flow through the varices and over time the varices completely disappear. The spleen may take a number of years to shrink and may never return to a normal size depending on the extent of the enlargement pre transplant.

### SHARED CARE NOTE:

**Whilst most bleeds stop spontaneously ALL significant bleeds warrant further investigation and should be discussed with the Starship team as a matter of priority. This will enable prompt transfer to Starship or Christchurch for investigation and management by a paediatric gastroenterologist.**

**Additional parental support will be required when children are diagnosed with varices. Parents/care givers are generally extremely anxious and are taught to have a low threshold for obtaining medical assessment or calling an ambulance.**

**A parent who has seen a varix bleed is likely to be traumatised for some time particularly if the bleed is large.**

**Careful management of nasogastric (NG) tubes becomes even more important in this situation.**

- **Prevention of accidental dislodgement**
- **NG should not be replaced in the community if varices are present.**
- **Gentle placement with plenty of lubricant should occur**

**Emergency management:**

**Is the emergency department aware of this child/ can you alert them to the specific circumstances?**

**Do the family have a clear plan of where to present and who to contact?**

**Are the family members of St John Ambulance?**

**Do you have Octreotide available locally or can you obtain it for emergency use?**

**Do you have a copy of the protocol with doses and instructions available?**

## Ascites

Ascites is a frequently encountered complication of cirrhosis in both children and adults (11).

The pathophysiology of ascites is complex and there are many theories about its cause.

During progression of liver disease a multitude of changes occur in the circulating blood plasma volume, pressure and composition (6).

The presence of portal hypertension (high portal venous pressure) is key to the formation of ascites, decreased serum albumin, peripheral vasodilatation and sodium retention are some of the other changes involved.

All of these play a role but the primary cause of ascites remains a matter for debate (1).

In children with liver disease serum sodium is often low, but extracellular sodium is very high. The overall effect is a high total body sodium level which may be a significant issue.

The localisation of fluid within the peritoneal cavity rather than in peripheral tissues is most likely related to portal hypertension. Increased pressures in the hepatic sinusoids and hepatic venous obstruction stimulate hepatic lymph formation which adds to the ascites (6).

Ascites may appear suddenly or develop slowly over a period of months.

Most children have slow overall development of ascites but may present with acute increases in volumes related to sudden changes in their overall health, e.g. Infections including cholangitis and sudden drops in serum albumin during bleeding.

Rapid onset of ascites is often easily rectified as it is related to specific causes which can generally be treated.

The child should then return at least some of the way to their original state.

Gradually increasing ascites is much harder to control for long periods of time as the cause is not easily treated and is related to progression of liver disease rather than intercurrent illness (6). Children waiting for transplant usually fall into this category.

### Clinical Features:

The child with significant ascites will usually be jaundiced and may be dehydrated in spite of weight gain on the scales.

The abdomen will be distended not only with fluid but also with air from dilated intestines. An enlarged liver and spleen also contribute to distension. Increased abdominal pressures add to the appearance of hernias in the groin and umbilicus. Distended abdominal wall veins may be present. These are often more obvious when ascites is greatest although they are caused by portal hypertension.

Veins radiate from the umbilicus or abdominal surgical scars and will persist even if ascites is reduced.

Gross abdominal distension due to ascites may lead to splinting of the diaphragm and breathlessness.

Respiratory compromise is more common in babies and young children than adults (1).

Pleural effusions are uncommon in children pre transplant but can occur due to defects in the diaphragm. When this does occur it is most likely to be on the right side.

Neck veins may also be distended due to pressure changes throughout the venous system. Peripheral oedema may be associated with ascites and is due to low serum albumin and reduced flow through the vena cava caused by pressure from abdominal fluid.





## Management

The only cure for ascites caused by progressive liver failure and cirrhosis is reversal of the disease process or liver transplant. However there are a number of ways we can manage ascites.

The management of ascites includes salt and fluid restriction, treatment with diuretics and paracentesis.

Salt restriction in adults may entail a severely restricted diet with multiple supplements. In children this extreme restriction is not an option for many reasons.

The adult diet involves:

### Salt restriction:

- No added salt or salt for cooking.
- Limitation or avoidance of a large number of foods including ham, bacon, seasonings, bottled sauces, pastry biscuits crackers cake, dry cereals

### Protein:

- Many high protein foods also contain salt
- Severe limitation of meat, poultry and eggs and milk intake

### Fats:

- Some guidelines also encourage reduced fat intake (due to steatorrhoea)

### Other:

- No lollies or milk chocolate

These restrictions are not practical for babies and young children due to the requirement for growth and for the development of oral skills making oral intake important in the overall care. However if ascites becomes a significant problem diet can be reviewed with the dietitian and changes implemented which are manageable for child and family.

## Diuretics

Spironolactone and Frusemide are commonly prescribed to help reduce ascites formation.

These medications work to induce diuresis and sodium excretion in different ways.

Both medications (especially if used in single large doses) can lead to electrolyte imbalance and in extreme cases encephalopathy and renal failure.

Small regular doses of both forms of diuretics will slow ascites formation and minimise electrolyte imbalance. This option is used for long term management for children.

## Albumin

Albumin is generally administered in the child with an albumin level less than 30. However this is dependent on the child's clinical condition, some will require transfusion at a higher level and other will tolerate slightly lower levels.

For those requiring admission to hospital a combination of Human Albumin 20% IV infusion (usually 5mg/kg over 4 hours) with a single dose of IV Frusemide during the infusion is typically used.

- This works by increasing the serum albumin level which in turns draws the extracellular fluid back from the peritoneal cavity and into the systemic circulation primarily by osmosis.
- The frusemide then causes a diuresis and prevents systemic overload.
- This can have remarkable effects in a very short time span which makes it ideal if a child has mild respiratory distress or other complications which need to be dealt with quickly.

Depending on a number of factors this intervention can benefit the child for several weeks or only a matter of days. Factors influencing this include how advanced the child's liver disease is and the presence of concurrent illnesses such as cholangitis or viral illnesses. This treatment may need to be repeated regularly in a child with end stage liver disease if they continue to accumulate ascites and cannot maintain their serum albumin.

## Paracentesis

Paracentesis is defined as the surgical puncture of a cavity for the removal of fluid.

It is sometimes called "Ascitic Tap"

In this case it is done for the removal of excess fluid from the peritoneal cavity.

It may be used as a diagnostic test (particularly if there are concerns about peritonitis) or to control severe ascites when diuretic therapy is not obtaining the required results and the child has significant respiratory compromise.

It is used in conjunction with Albumin 20% infusions.

A small needle is inserted through the abdominal wall into the peritoneal cavity and ascites is drained through this. Ascitic tap is performed with the assistance of ultrasound guidance either before or during the procedure to ensure the maximum effect is obtained.

Although there have been few studies into paracentesis in children the consensus appears to be that large volume paracentesis (>50ml/kg) is a safe and effective method for managing tense abdominal ascites in children (11).

It provides rapid relief of discomfort and respiratory compromise from a tense abdomen but may last very



short periods only as the underlying liver disease will continue to drive further ascites formation(12).

Complications of Paracentesis include:

- Infection
- Bleeding
- Rapid protein and fluid shifts resulting in renal impairment(12). Albumin infusions in conjunction with paracentesis will help prevent this (7).

It is used with greater caution in children who have advanced liver cirrhosis as their ability to cope with even minor systemic changes is significantly lessened.

Some texts recommend that it is not done in end stage failure due to the high risks and therefore should only be performed after discussion with the Starship team.

#### SHARED CARE NOTE:

**Management of children with liver disease should include regular assessment of abdominal size and tension.**

**Consider measuring the girth with each weight, but ensure that measures are taken in the same place each time.**

**If the child is an inpatient consider placing marks on the abdomen with waterproof pen above and below the tape measure on both sides and use the umbilicus as the centre bottom. This will ensure accuracy.**

**All weight and girth measures should be taken with the child lying flat and naked.**

**Please discuss changes with the Starship team at the earliest opportunity so medical management can be maximised.**

## Spontaneous Bacterial Peritonitis (SBP)

Infection of ascitic fluid may be spontaneous or follow a previous paracentesis (1).

It occurs more frequently in people with decompensated cirrhosis.

The infection is blood- borne and is most often caused by a single pathogen (6).

Factors occurring in liver cirrhosis which predispose a person to spontaneous bacterial peritonitis include

- Increased gut permeability to bacteria.
- Abnormal host defences with intrahepatic shunting and impairment of bactericidal activity in the ascitic fluid.
- Ascitic fluid favours bacterial growth.
- Functional immunosuppression associated with malnutrition and impaired protein (including immunoglobulin) synthesis
- Symptoms children with SBP may present with include;
  - Fever
  - Increased White Blood Cell count
  - Irritability (increased from baseline or sudden)
  - Abdominal pain
  - Hypotension, and shock can occur in more severe cases
  - Increased hepatic encephalopathy (6)

#### SHARED CARE NOTE

**SBP can be severe and life threatening and any suspected episodes need to be discussed as a matter of urgency with the Starship team. Suspension from the active transplant waiting list may be required whilst treatment is initiated and control of the infection is gained.**

## Hepato-Renal Syndrome

Hepato-renal syndrome occurs in patients with chronic liver disease, severe hepatic failure and portal hypertension. It is defined as a progressive renal insufficiency of unknown cause in a patient with severe liver disease and is almost always associated with the presence of ascites (6). This is a functional failure characterised by changes in blood flow within the kidney. The kidney tissue itself is not damaged. Hepato -Renal syndrome development is often precipitated by other events. These include reduction in the intravascular volume due to;

- Over vigorous diuretic therapy
- Paracentesis
- Haemorrhage
- Sepsis
- Diarrhoea

In the mildest stage there is failure to excrete a water load and hyponatraemia.

In the moderate stage the child may have anorexia weakness and fatigue. Blood urea concentration is

increased and hyponatraemia is persistent. Fluid accumulates in spite of normal urinary volume and diuretics.

In later stages nausea, vomiting and thirst are present. The child may be drowsy and it may be extremely difficult for nurses to distinguish this from hepatic encephalopathy.

Hepato-renal failure is progressive and terminal and survival depends on the reversibility of the liver disease (1). Successful liver transplant will reverse the process.

### SHARED CARE NOTE

**It is unlikely you will see Hepato renal syndrome in a child who has well compensated liver disease and has been stable, however the syndrome is best prevented by early recognition of any complications such as fluid and electrolyte imbalance, haemorrhage or infection. Monitoring of renal function and electrolytes as part of regular surveillance bloods is key to early detection of progressive renal insufficiency.**

## Hepatic Encephalopathy

Hepatic encephalopathy refers to a wide variety of neuropsychiatric abnormalities that occur in association with end stage liver disease (6). The pathogenic cause is not fully understood. Unless complications associated with cerebral oedema arise, transplantation leads to reversibility of the encephalopathy.

Studies show changes in several neurotransmitter systems. The changes are complex and no single defect provides the complete answer (1).

There are three factors known to be involved in the development of Hepatic Encephalopathy

- Porto-systemic shunting of blood flow through collaterals (rather than through the liver) allows neurotoxic nitrogenous intestinal metabolites into the circulation.
- Alterations in the blood brain barrier is present and appears to be related to the presence of increased concentrations of ammonia particularly in the later stages of encephalopathy
- Interactions of toxic metabolites in the central nervous system (6).

Ammonia has been the most widely studied factor in the development of hepatic encephalopathy.

Ammonia is produced from the breakdown of amino acids and other organic compounds in the intestine. About half of the ammonia arising from the intestine is synthesised by bacteria. The liver normally converts ammonia to urea and glutamine.

In hepatic encephalopathy blood ammonia levels are elevated in 90% of patients. Brain levels are also increased.

Patients going into hepatic coma are suffering from cerebral intoxication by chemicals which have not been metabolised by the liver.

There are a number of different syndromes of hepatic encephalopathy. Each appears related to the severity of aetiological and precipitating factors in that child.

## Clinical Features

Clinically the picture is complex and there is marked variability in symptoms between one child and the next. The clinical features may also fluctuate in an individual child. For descriptive purposes features of encephalopathy can be separated into changes in:

- Consciousness
- Personality
- Intellect and Speech.

Disturbed consciousness (with sleep disorder):

- The child sleeps excessively during the day and is inappropriately awake at night.
- Reductions in spontaneous movement, apathy, and slowness or absence of response to non-painful stimuli

These are early signs of an evolving encephalopathy and they may be difficult to detect. Especially in young babies who have presented with an intercurrent illness.

- Further deterioration results in reaction to only intense or noxious stimuli.

Coma at first resembles normal sleep, but progresses to complete unresponsiveness.

Rapid changes in conscious state are accompanied by confusion.

Personality changes:

- Are most conspicuous with chronic liver disease.
- Include regression in behaviour
- Irritability
- Verbal or physical aggression
- Loss of concern for those people and events around them.

Intellectual Deterioration:

- From slight impairment of organic function to gross confusion.
- Speech may be slowed or slurred.

- Decreased ability to learn and memory may deteriorate
- Some patients have a sour faecal smell to their breath (Fetor Hepaticus).
- "Flapping tremor" (asterixis) may also be present.
- This occurs in the fingers and wrists.
- Usually absent at rest and most obvious during sustained posture.
- Usually bilateral but can be more marked on one side.
- In coma the tremor disappears.
- This tremor can be caused by other conditions as well as liver failure.

Hepatic encephalopathy may appear spontaneously. It usually occurs in the child with acute liver failure or in the context of end stage chronic liver disease and ascites

In Chronic liver disease encephalopathy is most commonly precipitated by electrolyte and fluid imbalance. This may be caused by:

- Diuretics are the most common precipitant and encephalopathy is induced by a brisk response to a potent diuretic.
- Large paracentesis may also precipitate coma.
- Electrolyte imbalance following removal of large quantities of electrolytes and water. Change in hepatic circulation and hypotension may contribute.
- Diarrhoea
- Vomiting
- Gastro intestinal haemorrhage, usually from oesophageal varices.
- Infections, especially with bacteraemia. Spontaneous bacterial peritonitis. Urinary and chest infections can also contribute.
- Other: A large protein meal or constipation.

- TIPS procedure is known to induce encephalopathy in 20-30% of cases.

### Chronic Encephalopathy

This relates to extensive portal systemic shunting. It is more slowly progressive although its features are similar.

The intellectual prognosis in children with hepatic encephalopathy associated with chronic liver disease is good if a successful liver transplant restores normal liver function.

#### Hepatic Encephalopathy Score

Stage	Asterixis	Clinical Manifestations	EEG Changes
1	Slight	Mild intellectual impairment, disturbed sleep-wake cycle	Minimal
2	Easily elicited	Drowsiness, confusion, coma, inappropriate behaviour, disorientation, mood swings	Usually generalised slowing of rhythm
3	Present if patient co-operative	Drowsy, unresponsive to verbal commands, delirious, hyper-reflexia, +ve Babinski sign	Grossly abnormal slowing
4	Usually absent	Unconscious, decerebrate or decorticate response to pain present (4a) or absent (4b)	Appearance of delta waves, decreased amplitude

*Stage 2 and above requires Paediatric Intensive Care or High Dependency Unit management*

### Management of Hepatic Encephalopathy

Prevention and treatment of Hepatic encephalopathy is directed at:

- Controlling precipitating factors such as GI bleeding, rapid fluid shifts, dehydration and infection.
- Decreasing production and absorption of ammonia and other toxins from the GI tract in particular through inducing rapid removal (6, 13).

Lactulose causes the alteration of enteric bacteria, and the colonic environment to suppress the bacteria species which form ammonia.

- In high doses lactulose will induce faster gut times.
- The aim is to create an acid environment which inhibits the production and absorption of ammonia.

Many antibiotics used to alter the gut bacteria have long term issues in children, e.g. Some can cause deafness. They are used with extreme caution and only for short courses (6).

Avoidance of use of opiates or sedating medications is crucial in the management of encephalopathy.

## Hepato-Pulmonary Syndrome

There are a number of changes to the pulmonary system occurring in association with chronic liver disease and in direct association with portal hypertension (6).

These include:

### Intra pulmonary shunting

- Through microscopic arteriovenous fistulae.

### Ventilation-Perfusion mismatch.

- Ideally all alveoli are equally ventilated and the blood flow through the capillaries to the alveoli is the same. An imbalance between ventilation and perfusion is called a mismatch. Any mismatch leads to impaired gas exchange which can result in hypoxia and respiratory failure(14).
- In children with liver disease pulmonary vaso-dilation is a contributing factor. This occurs in both acute and chronic failure
- Reduced transfer factor- caused by thickened capillary walls.
- Pleural effusions
- Porto-pulmonary shunting - these are thought to have little effect as the shunting is between to systems with high oxygen saturation and the flow through the shunts is small.
- Raised diaphragm, due to abdominal distension.

About a third of patients with decompensated cirrhosis have reduced arterial oxygen saturation and are sometimes cyanosed (1).

Hypoxia may not be present at rest but appear rapidly with low level exercise.

Hypoxia may increase if the child is lying flat and be relieved with elevation of the head of the bed.

Longstanding hypoxia due Hepato pulmonary syndrome may lead to clubbing of the fingers.

Children with Hepato-pulmonary syndrome are more likely to need respiratory support during an intercurrent illness.

Hepato-pulmonary syndrome will reverse within weeks of transplant in most children.

In adult reversal can take several months or longer (1).

## Development

Chronic liver disease affects the development of children.

There are a number of issues that contribute to this, including:

- Poor nutritional state and lowered energy levels for play.
- Abdominal distension affects the centre of balance and makes physical tasks such as rolling over even more challenging.
- Reduced muscle growth and, in advanced stages of disease, muscle wasting.
- Frequent periods of concurrent illness such as colds and cholangitis.
- Frequent hospital visits and stays with periods of activity restriction caused by the presence of IV lines etc.
- Chronic hepatic encephalopathy

In the older child these stays also affect their relationships at school or kindergarten. They may spend long periods away from home and find it difficult to keep up with classmates in terms of school work physical activity and social involvement.



Involvement of the allied health team including Physio, Occupational and Play Therapy can assist families to create opportunities for development within the constraints of the child's current health status.

Play is important to allow children to maintain a normal level of development while they are in hospital.

Hospital stays are stressful times for not only the child, but also other family members and play helps to reduce the stress associated with a hospital admission. Play therapy can also help to support a child through understanding their condition and any procedures they may encounter. Children and their families can be empowered via the use of diversion and distraction techniques taught to the child and their parents.

### SHARED CARE NOTE

**Balancing the need for protection from infection and meeting the social, intellectual and physical developmental needs of the hospitalised child can be challenging.**

**Creating space both physically and within the schedule of medical needs is an important consideration for the child who has frequent or prolonged hospital stays.**

## Blood Tests

The Table below lists the common blood tests used to assess liver function and their normal values.

Test	Normal Values – Babies	Normal Values -Older Children
Bilirubin -Total	0-24	0-24
ALP	80-350	45-250
GGT	0-50	0-50
ALT	<45	<45
AST	0-80	0-80
<b>Measures of synthetic function</b>		
Albumin	38-52	36-50
INR	0.8-1.2	0.8-1.2

*(Adapted from Starship Éclair (clinical reporting system))*

There are some variations in the normal levels related to age.

Tests results should be read in conjunction with the normal range specified by the reporting laboratory as depending on the assay used in testing these levels may change (15).

No single test in isolation provides full information on disease severity or prognosis as there are a number of factors which influence the results. These tests are used in combination alongside clinical assessment and other blood monitoring e.g. Electrolytes and full blood count, to guide towards diagnosis and monitor progression of disease.

Series of blood results demonstrating trends give valuable insight which cannot be obtained from a single set of bloods.

## Bilirubin

Jaundice is caused by a raised bilirubin. Bilirubin is formed from the breakdown of haem.

There are 2 distinct types of jaundice. Each has different causes, clinical features and management.

### Unconjugated hyperbilirubinaemia

Occurs if there is either impaired hepatic bilirubin conjugation or a large load of bilirubin to conjugate, e.g. Sickle Cell disease.

Children with high unconjugated bilirubin will not have bilirubin in their urine.

Conjugated hyperbilirubinaemia occurs if there is hepato-cellular injury or obstruction of bile flow and is always pathologic. In this situation the urine will be dark and contain bilirubin (15, 16).

### Serum Enzyme Tests

These tests give some indication of type of liver injury.

They are valuable in directing the choice of specific serological tests, imaging, or liver biopsy to reach a diagnosis. Some enzymes occur in multiple sites throughout the body.

### ALP- Alkaline Phosphatase

This is a marker normally used to identify cholestasis. The level of ALP will rise during cholestasis and to a lesser extent when liver cells are damaged (15, 16). Bone disease and even recent growth spurts may also lead to elevation of ALP levels

### GGT- Gamma-glutamyltransferase

GGT is a sensitive indicator of cholestasis or biliary disease (16). Levels parallel ALP in cholestasis and may be used to confirm hepato-biliary origin (15). Many factors influence the level of GGT, including medications such as phenytoin. Therefore isolated rises in GGT need to be considered in association with other levels.

## The Transaminases;

### Alanine Transaminase (ALT) and Aspartate Transaminase (AST)

These are the measures of liver cell injury not of liver function. They are not specific to the liver.

Transaminases are important for cell energy production and convert excess amino acids into metabolic fuel.

Normal serum levels are derived from normal cell death. Elevated levels more than 1.5 times normal are significant and indicate cell injury or death. Sustained abnormal levels indicate ongoing injury (16).

ALT is localised in one specific area of the liver and there are negligible quantities in other tissues.

ALT has a half life of 47 hours

AST is present in a wide variety of tissues both internal and external to the liver including;

- Liver
- Cardiac muscle
- Skeletal muscle
- Brain
- Kidney
- Pancreas
- Lungs
- Leukocytes

If there is diagnostic uncertainty, measurement of Creatine Kinase may help to distinguish whether raised transaminase levels are of liver or muscle/heart origin.

AST has a half life of 17 hours.

Serum levels of both transaminases are increased to some extent in almost all liver diseases (15).

Degree of elevation is not disease specific, nor does it define prognosis or extent of liver injury (16).

However falling transaminase levels in the context of acute liver failure may be a marker of loss of hepatocytes due to widespread liver necrosis and is a poor prognostic marker.

## Albumin

Most circulating proteins in plasma are synthesised in the liver and levels indicate synthetic capability of the liver. Albumin accounts for 65% of serum protein and has a half life of about 3 weeks (15).

The long half life of albumin makes it unreliable as an indicator in acute hepatic failure as the reduction in serum levels is slow. Blood concentration depends on the synthesis rate plus the plasma volume.

Low serum albumin levels are often associated with ascites. In general albumin is a good marker of severity of chronic liver disease, but levels can be affected by chronic renal insufficiency, nutritional state, urinary protein losses and gastrointestinal losses.

## Coagulation

### APPT, PR, INR Fibrinogen and PT

Severity and prognosis of liver disease can be assessed using measurement of clotting factors and are used to assess the synthetic function of the liver. These reflect the deficiency of one or more of the liver synthesized clotting factors. Clotting factors have short half lives so become abnormal much more quickly than the serum albumin level (15).

Prolonged times of these tests indicate decreased clotting ability and therefore increased risk of bleeding. 80% of patients with liver disease will have at least one abnormality in their coagulation tests regardless of the cause of liver disease (15).

PT may be raised due to Vit D deficiency when cholestasis and/or synthetic dysfunction are present.

The cause can be distinguished by the administration of Intravenous Vitamin K, which will address deficiency, but will not significantly impact on synthetic problems.



## Section 4 Disorders of the Liver

### Infantile Cholangiopathies

Cholangiopathies means diseases of the biliary system.

Cholestasis (disruption of bile flow) in infancy can have many causes.

These causes are classified broadly into 2 main classifications;

- Extra Hepatic, e.g. Biliary atresia
- Intra-Hepatic, such as neonatal hepatitis and Progressive Familial Intrahepatic Cholestasis (PFIC)

The next section will cover the most common disorders that seen in New Zealand

### Biliary Atresia

Biliary Atresia occurs in 1 in 10,000 live births (1).

Children with Biliary Atresia make up the majority of children who have undergone liver transplant in NZ.

When biliary atresia is present, bile is absent from the extra hepatic biliary system including the gall bladder. The common bile duct or hepatic duct are often involved. The gall bladder may be absent or connected directly with the duodenum.

There are five types of biliary atresia and the abnormality can occur in any part of the biliary system.

Below are the three seen most commonly.

25% of children with biliary atresia will have a syndromic type known as Biliary Atresia Splenic Malformation

Syndrome. This involves anomalies in other organs or systems such as malrotation, dextracardia, situs inversus, polysplenia and interrupted inferior vena cava.

Biliary Atresia affects all races, although rates have been reported as higher in non white infants in some studies (6). This is true for the New Zealand setting as Maori are proportionately over represented and more females than males.

Biliary atresia commences in intra uterine life. It is not the result of failure of the bile ducts to form, but of destruction of these ducts at some point during late gestation or early after birth (6).

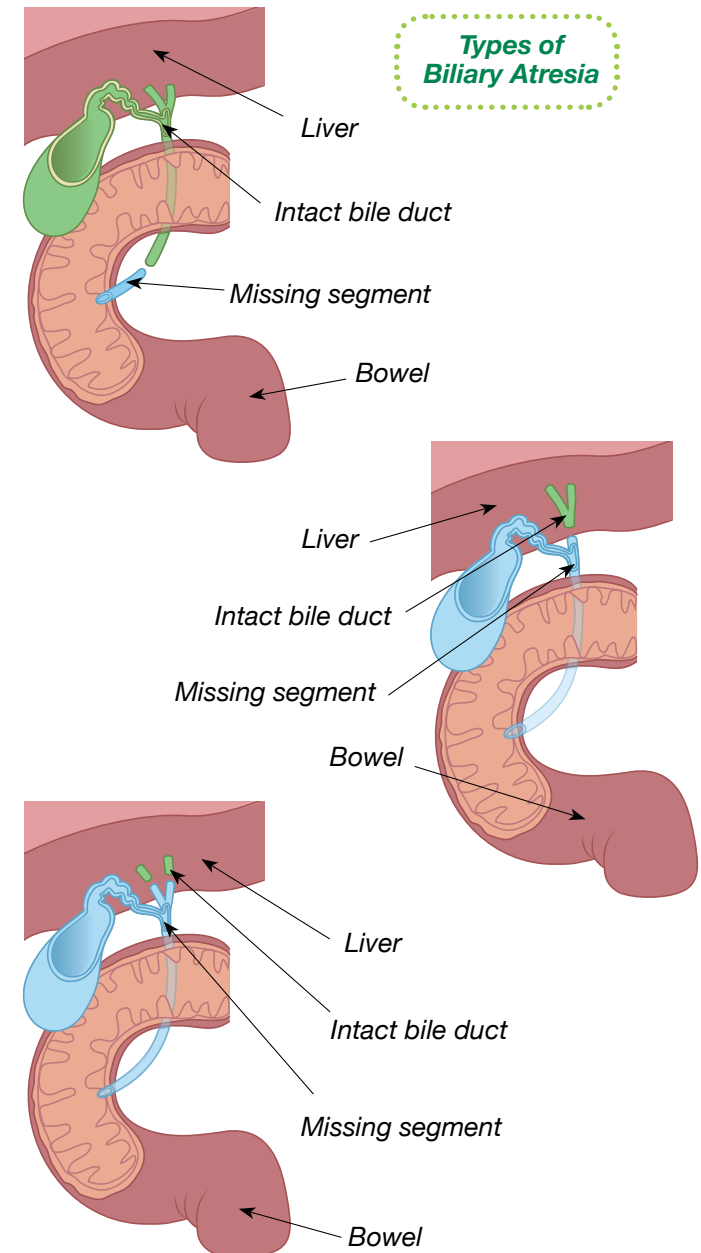
The cause of duct destruction is a topic of significant research and debate.

There are a number of theories, none of which have been proven. These include:

- Infections such as reovirus 3, cytomegalovirus and rubella.
- Ischemic disease related to other abnormalities in that child.
- A sclerosing inflammatory process, occurring in the ducts during the pre or post natal period.

In some children bile ducts are present at birth. In others there are only fibrous strands present where ducts should have been. In babies with ducts present at birth the destructive process is rapid.

Intralobular bile ducts are progressively destroyed and there is degeneration of bile duct epithelial cells followed by a marked inflammatory cell response and fibrosis in ductular tissues. The bile ducts become angulated and distorted and may contain bile plugs and form cysts. Cholestasis (significantly reduced or absent bile flow) is prominent.



## Clinical features

- Jaundice develops in the first week after birth and does not resolve.
- Stools are acholic (lacking bile pigment and are therefore pale)
- The urine is dark.
- In the first 8 weeks of life nutrition is often well maintained but subsequently deteriorates.
- Itching becomes increasingly severe.

## Diagnosis:

Children with liver disease often pose a considerable diagnostic challenge.

Due to

- The relative rarity of each individual condition
- The same symptom may be produced by many causes.
- Symptoms apparently quite unrelated to the liver may be the presenting feature of liver disease. E.g. Cerebral haemorrhage due to vitamin K deficiency impairment of clotting.
- The same disease may present in many different ways.
- There is a poor relationship between the severity of symptoms and the severity of underlying liver disease.
- The absence of pain in most liver disorders.

All of these things lead to the potential for late presentation (17).

In order to diagnose Biliary Atresia a number of steps need to be taken.

- Family history
- Blood and stool examination

- Ultrasound is a valuable tool in the diagnosis of biliary atresia
- Liver biopsy will give definitive results in many cases

When biliary atresia is diagnosed the infant will go on to have a Kasai Porto-enterostomy unless the presentation is extremely late and the child has well established cirrhosis.

Surgery, Kasai Portoenterostomy is the first line of treatment for Biliary Atresia

When biliary atresia is diagnosed the infant will go on to have a Kasai Porto-enterostomy unless the presentation is extremely late and the child has well established cirrhosis.

The single most important factor in the success of the Kasai portoenterostomy is the timeliness of the operation. This relies on prompt recognition of the likely diagnosis and referral to Starship for further diagnostic work-up and surgery if the diagnosis is confirmed.

Any child with jaundice persisting beyond two weeks of age and/or pale stools requires urgent investigation.

The initial investigation should include a total and conjugated bilirubin. A conjugated bilirubin which is greater than 20% of the total bilirubin and greater than 20µmol/ml is suggestive of liver disease and needs further investigation.

Kasai will achieve bile drainage in up to 81% of infants if done at less than 60 days old. By the time the infant is more than 120 days old this number is reduced to 15% (17). A Kasai generating partial bile flow allows growth before liver transplantation becomes necessary.

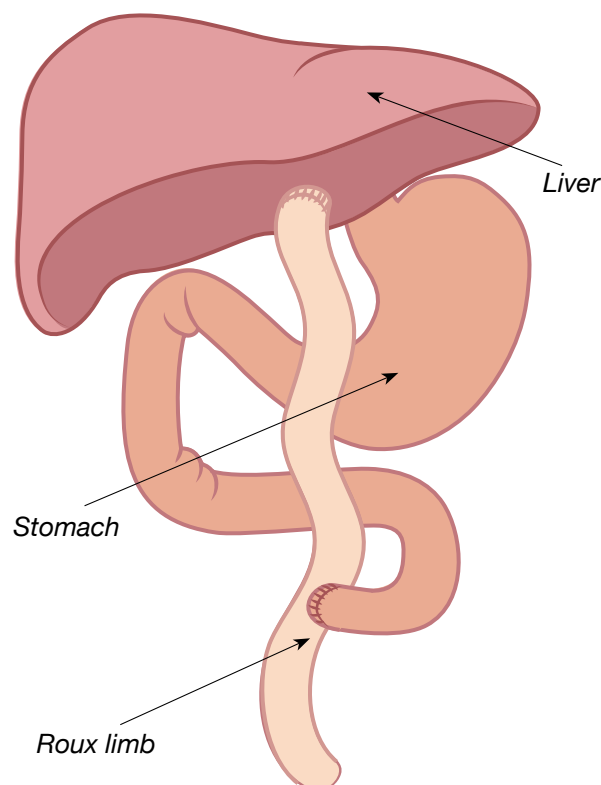
80% of children with Biliary Atresia will ultimately end up requiring transplant (1). Many of these children will require transplant within the first 2 years of life.

## The Kasai Procedure

The left and right hepatic bile duct remnants and / or fibrous tissue are dissected at the porta-hepatis. A roux-en-Y loop of the jejunum is anastomosed sideways to the porta-hepatis. The intrahepatic bile ducts are free to drain directly into this loop of bowel

Care needs to be taken to ensure that surgery at this point does not have a significant effect on the ability to perform liver transplant later (1).

### Anatomy with Roux-en-y Loop



Although the Kasai procedure results in many positive outcomes it also has a number of complications.

## Complications of Kasai Porto-enterostomy

### Cholangitis

Cholangitis is infection within the bile ducts most often caused by bacteria and is the most common post operative complication. It is often called 'ascending cholangitis' which refers to the contamination being caused by the reflux of intestinal contents into the biliary system. It may also be caused by blood-borne infection. In some studies fungal infection has been implicated as a cause and there is still debate as to whether viruses may also cause cholangitis (1).

The only proof that cholangitis is present is by growing the infective agent in a culture of liver tissue taken at biopsy. Liver biopsy poses significant risks in the unwell infant or child. Therefore cholangitis is treated on the basis of symptoms, lack of other diagnosis explaining the symptoms and previous history of the child.

There has been much debate and research into other methods to diagnose cholangitis and as yet no gold standard has been identified (17). The incidence of cholangitis is as high as 40 to 60% in the first year post surgery. This incidence falls over time. The occurrence of cholangitis adversely affects both short and long term liver function and prognosis(17).

- Symptoms of cholangitis are non specific and can include
- Fever (with no obvious focus)
- Increased irritability/ Abdominal pain
- Vomiting (without diarrhoea)
- Rising liver function tests and/ or WCC
- Pale stools

### SHARED CARE NOTE

With each infection the bile ducts and liver may become increasingly damaged.

Prompt identification of possible infection and initiation of appropriate antibiotic treatment will minimise the impact. Early discussion with the Starship team regarding treatment and monitoring is essential to ensure opportunity to treat is maximised.

Frequent or recurring cholangitis may be an indicator for transplant assessment and should be discussed with the Starship team early to ensure treatment opportunities are maximised and assessment is performed at the first opportunity.

Children with Biliary Atresia have progressive liver disease. For some it is rapid and in others it occurs over a number of years. They will develop all of the complications of chronic liver disease and failure over this time.

The shortage of organs for transplant is the biggest single issue effecting outcomes in these children.

The wait for the liver often results in the child being much sicker than would be ideal at the time of transplant.

Without surgical intervention death will usually occur within the first 18 months of life (1).

## Alpha 1 Anti-trypsin Deficiency

Is a genetic deficiency which is the second most common diagnosis after extra-hepatic biliary atresia in infants who require liver transplantation.

Alpha 1 antitrypsin is a protease inhibitor (a digestive enzyme that breaks down protein) and is a major blood protein.

Alpha-1 anti-trypsin (A1AT) is mostly produced in the liver; it comprises 80-90% of serum alpha-1 globulin.

PiMM is the normal expression and occurs in 85% of the population. Serum concentrations of 200-400 mg/dl are normal and increase with pregnancy, infection, acute liver disorders and perinatal diseases(1). In A1AT serum concentrations are usually 20 – 160mg/dl but can increase to near normal during the above stressors.

There are a number of different genetic mutations which cause A1AT. The deficiency state most commonly associated with liver disease is PiZZ.

10-15% of PiZZ children develop liver disease

It is an autosomal recessive disorder so each parent must carry the abnormal Z allele for a child to be PiZZ.

For two carrier parents each pregnancy carries a 1:4 chance of a child being PiZZ.

PiNUL individuals have no alpha-1 anti-trypsin.

A1AT deficiency (both PiZZ and other genotypes) is associated with an increased risk of developing emphysema in early adult life. This risk is greatly increased if the individual is a cigarette smoker, so it is essential that families and children are appropriately counselled (1).

## Pathophysiology

Initiation of the disease is unclear. Biopsy findings are similar to Biliary Atresia as there are fibrosed intra-lobular bile ducts present.

Alpha-1 anti-trypsin is a protease inhibitor and inhibits elastase, collagenase, leucocyte and bacterial

proteases. These are crucial in initiating and perpetuating aspects of inflammatory response as well as complement activation, coagulation and fibrinolysis.

Uninhibited action of those enzymes could cause tissue destruction and inflammation.

## Diagnosis

As with all liver disease in childhood the symptoms may mimic those of other diseases.

- Alpha-1 anti-trypsin phenotyping is performed.
- Liver biopsy is performed and histology checked
- A visual scan of serum protein electrophoretic strips of alpha-1 globulin is completed

Serum levels are unreliable as levels may increase or decrease with associated disease or drug use

## Clinical Features

Children typically present with acute hepatitis before the age of 4 months with conjugated hyperbilirubinaemia. The severity of hepatitis and jaundice varies widely.

Some appear well other than being jaundiced, whilst others may be failing to thrive and vomiting.

Irritability and lethargy also commonly occur. The baby may have jaundice associated with a chest infection.

Low platelet counts, prolonged prothrombin time and/or septicaemia may also be presenting symptoms. 10% present with hepatosplenomegaly, ascites and liver

synthetic dysfunction (6). 40% will present with abnormal liver function tests and may not show any signs of liver disease(1).

Some present later in childhood or adult life with cirrhosis.

## Prognosis

Liver biopsy findings are a reliable guide to prognosis

If a poor prognosis is identified the patient will have fibrosis, oedema of vessels shown with marked cirrhosis in the first 6 months of life (6). In some instances liver disease is so severe that cirrhosis and complications of liver disease develop so rapidly that death may occur by 5 months of age (17).

The majority recover from acute hepatitis but elevated liver functions tests (LFT's) remain for long periods of time and hepatomegaly persists without splenomegaly. LFT's may normalise in the 3-10 years age group (17).

## Treatment

Is mostly supportive with vitamin therapy and increased caloric intake.

The child is nursed in the same way as a child with biliary atresia as both diseases are chronic in nature and present very similar nursing problems.

Liver transplant is offered to those with end stage liver disease.

# Alagille's Syndrome

Alagille's Syndrome is sometimes called syndromic, or syndromic paucity of intra-hepatic bile ducts.

It occurs in 1 in 100,000 live births and is an autosomal dominant inherited disorder; meaning only one parent needs to have the genetic pattern. It is probably caused through a deficit on chromosome 20(1). Whilst it is hereditary its presentation can vary markedly even within families.

## Features

The major features associated with Alagille's syndrome include;

### 1. Cholestasis

### 2. Facial Features

- The child has a triangular shaped face with a prominent forehead and deep set eyes.
- The nose is straight and the chin is pointed. See photos above.

### 3. Ophthalmologic abnormalities

- Posterior embryotoxon is the most common
- The eyes may have other minor developmental anomalies but function is normal.

### 4. Skeletal defects

- Butterfly vertebrae are most common and are identified on x-ray, but again don't affect function.

### 5. Cardiac defects

- The cardiovascular system is affected to varying degrees.

This may include:

- Peripheral pulmonary stenosis (most common),
- Valvular pulmonary stenosis,

- VSD,
- ASD
- Patent ductus arteriosus

These can all occur alone or in combination.

Chronic cholestasis is the presenting complaint in the majority of cases. This usually occurs in the first 3 months. It may resolve again over the next 2 years but may also recur intermittently. Significant portal hypertension is rare in Alagilles. The syndrome can vary, with only 3 or 4 of the clinical features or all 5 systems involved. All children presenting with liver disease associated with Alagille's syndrome will have cholestasis present (1)

Renal abnormalities have been associated with the syndrome and function may deteriorate later in life.

Hyperlipidaemia occurs in these patients and is of long term concern due to impact on cardiovascular risk.

Growth retardation is present in 50% of patients despite the presence of normal levels of growth hormone.

This is thought to be partially related to reduced fat malabsorption (6).

Vascular system involvement is variable and not clearly understood however these children are at greater risk of intracranial bleeding even in the presence of normal liver function (6).

Mortality in childhood from liver disease in this group is low but some may need liver transplant.

## Management

Management of these patients focuses nutritional support (including fat soluble vitamin supplementation), management of pruritus and treatment of associated anomalies. Pruritus in these children is often severe and may significantly impact on quality of life.





## Progressive Familial Intrahepatic Cholestasis (PFIC)

PFIC is a varied group of autosomal recessive disorders leading to defects of bile transport.

Bile contains a number of components including bile acids, organic anions, phospholipids and cholesterol. Each has its own transporter mechanism and a defect in the transporter system leads to various forms of inherited cholestatic liver disease.

PFIC disorders usually present in the first 6-12 months of life with a variety of symptoms depending on type. The disorders are progressive which without treatment, lead to liver failure with death anywhere from early childhood to the second decade of life (6, 18).

There are three clearly identified types of PFIC and each is defined by a different genetic mutation.

### PFIC type 1

Has previously been called Bylers disease or Bylers syndrome.

Usually presents around the age of 3 months (6).

The transporter defect is unclear but is thought to involve bile acid absorption from the intestine. This form of PFIC is not limited to the liver and affects the intestine and pancreas (19).

Symptoms include:

- Intense Pruritus
- Diarrhoea
- Pancreatitis
- Cough
- Wheezing
- Hearing loss

Treatment options:

- External biliary diversion should be considered preferred method of treatment in children who are not cirrhotic.
- Liver transplant is possible but not recommended as first line treatment because the disease is not limited to the liver. Liver transplant can result in intractable diarrhoea and episodes of pancreatitis leading to poor quality of life (20).

### PFIC Type 2

Is caused by an error in the transport of bile acids from the hepatocytes to the bile cannicular surface.

Type 2 usually presents in the neonatal period with progressive cholestasis (6).

Symptoms are limited to those associated with cholestatic liver disease in general with the addition of intense pruritus (19).

Treatment options;

- Symptom management
- Liver transplant

### PFIC Type 3

Is caused by a defect in the transport of lipids across the cannicular membrane.

This form may present in infancy but onset varies greatly and can be as late as 20 years of age and progression of disease is generally slower than in the other types (6)

Symptoms:

- Pruritis is mild to moderate in this type.
- Those associated with cholestatic liver disease

Pruritus associated with the PFIC group can be extreme, is resistant to treatment and can lead to poor quality of life with significant sleep deprivation for both child and parents. Delays in development are also noted in

the literature probably related to the impact of pruritus on sleep and ability to complete tasks easily in the presence of constant distraction. Young babies may not be obviously itchy due to the immaturity of the pathways which convert the recognition of itch to the ability to scratch prior to 6 months (6). These babies are usually irritable and restless when awake and wake frequently from sleep.

## Management

Caring for these children can be extremely challenging for families and support of carers is paramount to long term coping.

Early intervention and initiation of coping strategies such as respite care (within extended families or professional carers) to avoid parental burn out should be considered. Referral to social work and or psychological support services is likely to be of benefit.

### Tips and tricks which may help:

In general allergy and eczema treatments will not work, however some basic principles do provide limited relief, these include

- Keeping the baby or child cool
- Not overheating bedrooms
- Avoid having baby/ child sleeping in the bed with adults.
- Using blankets rather than duvets and limiting number
- Tepid baths during hot days and at night before bed
- Using a fan in the bedroom in summer- not directly on the child.
- Using all in one suits to avoid direct skin contact and minimise skin breaks.
- Mittens when asleep (babies and young children need their hands for development so limit use during awake times)
- Moisturisers help avoid increasing the itch through the presence of dry skin.



## Metabolic Liver Disease.

Is an inherited inability of the liver to metabolise a specific product, which results in damage and tissue pathology that is either hepatic or mostly extra hepatic (21).

There are many different metabolic diseases and each very specific in its effects on the child.

Examples of metabolic liver disease are:

- Wilson's disease - affecting the ability to metabolise copper
- Crigler-Najjar – effecting bilirubin conjugation
- Tyrosinemia- effecting tyrosine metabolism

Familial Hypercholesterolemia- the inability to regulate blood cholesterol levels appropriately.

The extremely low incidence of each of these diseases means that we may see very few patients over a number of years and each will need individual management in close liaison with the Starship Liver and metabolic teams. Therefore they have not been included more fully in this package.

## Acute Liver Failure

Is the clinical syndrome of sudden and severe impairment of liver function in a previously healthy person. The generally accepted definition of acute hepatic failure includes a time frame of developing within 8 weeks of the first symptoms or jaundice (1).

Acute failure is further defined into acute and subacute (or late onset) classifications.

It is important to classify the type as the outcomes vary substantially.

There are a large number of causes of fulminant hepatic failure including:

- Infection
- Drug reactions
- Toxins
- Ischemic (e.g. Surgical shock)
- Metabolic
- Other rare conditions

There is also hepatitis of unknown aetiology. This may also be called hepatitis non-A-E, These patients have the symptoms and blood profiles suggestive of viral hepatitis but no infective agent is identified (6).

## Clinical features

The patient who has been previously healthy usually develops non-specific symptoms, such as nausea and malaise. Jaundice, coagulopathy and other signs of liver impairment follow.

Diagnostic criteria;

Acute onset with no evidence of pre-existing liver disease.

Biochemical and/or clinical evidence of severe liver dysfunction

Hepatic-based coagulopathy with a PT >20s that is unresponsive to treatment with iv vitamin K And/or hepatic encephalopathy.

Hepatic encephalopathy is a hallmark feature of acute liver failure in adults. In children, it may be difficult to identify or occur late. Hence presence of encephalopathy is not an essential diagnostic criterion.

## Disease course

This can happen in a time frame as short as 7 days but is often longer.

Generally the liver size will be decreased once in end stage, whereas in chronic liver failure it enlarges.

Liver biopsy is used to determine how much the liver has been damaged if it is clinically safe to do so.

However this can be extremely high risk due to reduced clotting ability.

If necrosis is present through >50% of the liver then transplant is likely to be the only option for survival (1).

Hepatic encephalopathy is a striking feature of acute liver failure. It is generally rapidly occurring and more severe than that which occurs associated with chronic liver disease. The neuropharmacologic events which result in hepatic encephalopathy are not well understood (6).

The neurological sequence of events of fulminant hepatic failure is: hepatic encephalopathy leading to cerebral oedema with raised intracranial pressure. Clinically these symptoms overlap.

There are 4 grades of encephalopathy; Grade 4 is the most severe. The prognosis for children in grade 1-2 hepatic encephalopathy where the patient is confused and /or drowsy is good in comparison to those with stage 3-4. Fluctuation in severity of encephalopathy does occur making it difficult to assess.

65% of children who reach grade 1-2 encephalopathy may survive.

20- 50% of children who reach grade 3-4 encephalopathy may die without transplant (1, 22).

Prognosis for children developing severe encephalopathy in association with acute failure is much poorer than in

those with chronic liver failure(1). Even with transplant 50% of children with Grade 4 encephalopathy do not fully recover neurologically post transplant

Children with fulminant failure and encephalopathy are a challenge to manage and early referral to Starship is essential. Ward management may only be appropriate for a short number of hours from initial presentation.

They are often extremely irritable and/ or agitated. They may be delusional or have nightmares.

Renal function will fail in 50% of children with acute failure. Electrolyte imbalance is a significant issue in these children.

Due to the rapid deterioration of these children they are often best managed in an intensive care environment preferably a PICU.

There are a number of variables in outcomes of these children. 10 % of children with non a-e will develop bone marrow failure.

The fact that in many children with acute failure no cause is identified, makes it extremely difficult to predict outcomes. Children with acute failure may survive without transplant. There is significant debate in the literature regarding the best prognostic tools to use to determine who should be transplanted and who will recover without.

Children with liver failure are listed on the transplant list and the urgent listing process is followed due to the short time frame available to obtain a liver.

While in hospital they are at high risk of hypoglycaemia and fasting without a protective glucose infusion should be avoided.

### SHARED CARE NOTE

**Early referral to Starship of any child with suspected sudden onset of liver failure is critical to the child's survival.**

**Deterioration requiring intensive care management can occur in a matter of hours from initial presentation.**

**Families and children who have been transplanted due to acute liver failure will require substantial support and ongoing education on return home. They generally have limited experience with the healthcare system and had little time for adjustment to the routines required for ongoing care.**

**The children themselves are likely to have no memory of the events leading up to transplant and some have described confusion and frustration at going from being completely well to suddenly having a chronic medical condition.**

## Section 5 Medications Used In Liver Disease

Children are on multiple medications when they have liver disease.

### Vitamins and Minerals

Vitamin supplementation is essential.

Children with liver disease require a substantial amount of vitamin supplementation.

Multivitamin preparations are generally not suitable due to the high dosage levels required by the child.

Vitamin supplementation will include A, D, E, and K.

Mineral supplementation such as Phosphate and Potassium and Magnesium may be required particularly in relation to prolonged disease states.

Doses are likely to exceed those recommended in the general population.



## Frusemide (Lasix)

Is a potent diuretic. It inhibits sodium and chloride absorption which promotes diuresis.

Onset of diuresis from oral dosing occurs within one hour.

Onset from IV dosage is within 5 mins of dose. This makes it medication of choice when fast clinical action is required.

However frusamide is used with caution in children with significant liver disease due to its potential rapid effect on electrolyte balance.

## Spironolactone (Aldactone)

A diuretic agent.

Causes increased amounts of sodium and water to be excreted whilst potassium is retained.

Its mode of action is particularly suitable for treatment of oedema and ascites.

It takes 2-3 days to have an effect after starting or changing the dose.

## Co-Trimoxazole (Sulphamethoxazole-trimethoprim)

Is used in prophylactic doses to help prevent bacterial infections particularly cholangitis.

It is more commonly used post liver transplant than pre transplant.

## Rifampicin

Is an antibiotic which once absorbed is eliminated primarily in the bile. In this situation it is used for its side effect of reducing itch. Rifampicin is hepatotoxic so should be discussed with the Starship team prior to prescribing.

Rifampicin may produce a reddish coloration of the urine, sweat, sputum, and tears and parents should be made aware of this prior to commencing treatment.

Increased frequency of blood tests may be required.

## Ursodeoxycholic acid

Is a bile acid naturally occurring in human bile. It is thought to decrease cholesterol absorption and facilitate blood flow through the liver.

It is believed to help reduce the inflammatory process within the biliary tree. It can also reduce pruritis although this is variable. Long-term effect on disease progression unproven and it not prescribed commonly as it is not a funded medication and can usually only be obtained through the ADHB hospital pharmacy

## Phenergan

Phenergan is used in the situation for its sedative effects as a means to reduce night time waking caused by itching skin associated with jaundice.

It is important to note that tolerance of the sedative effects builds quickly and it should be used sparingly to maintain its effectiveness.

## Propanolol

Is a beta blocker medication used to treat portal hypertension and reduce the risks of variceal bleeding.

It is important to note that it will mask tachycardic response to bleeding

## An Overview

Orthotopic liver transplantation is where the native liver is removed and replaced with a donor liver in the same anatomical position.

The first liver transplant was performed on a dog in 1955 by Welch.

In 1963 the first successful transplant in man was carried out by Starzl (1).

Continuing developments in immunosuppressive medications, surgical techniques, managing patient haemostasis during surgery, organ preservation (between donor and recipient) along with many other innovations have improved transplant outcomes. Throughout the decades liver transplant has progressed from an experimental surgery with low survival to being considered state of the art treatment in end stage chronic liver disease. Many centres report survival rates of greater than 80% 5 yrs post transplant.(23)

The New Zealand Liver Transplant Unit (NZLTU) was set up in 1997. It is a national service based at Auckland City Hospital. Prior to 1997 New Zealand adults were offered transplant under Ministry of Health contracts in Sydney and Brisbane. Children were offered transplant via contract with the Brisbane Transplant Unit with children and their families continuing to travel to Brisbane for liver transplant until the paediatric contract was awarded to the NZLTU in 2003. The paediatric program is also a national service based at Starship Hospital, with its funding and transplant surgical care being delivered from the NZLTU. The benefits of a shared campus housing both Auckland City Hospital (Adult) and Starship Children's Hospital is apparent in this setting as it allows transplant surgery to occur within the larger adult operating theatres, whilst operative and post operative care utilises the paediatric expertise within Starship.

The NZLTU performs approximately 40 transplants per year in total, with the number of children growing from 5-8 per year in the period 2002 to 2008 to 12 children in 2010. As at November 30 2011 there have been 73 children transplanted within the NZ paediatric program and survival rates are 98.6% at 1 year and 96.1% at 5 years post transplant (Nurse Specialist database, 2011).

Whilst survival rates are excellent and improving this is not an easy option for treatment. It involves a core group of experienced and dedicated Surgical, Medical, Nursing, and Allied Health staff to make it happen.

Liver transplant is one of the most complicated of transplants undertaken and the recovery is often punctuated by life -threatening complications.

The shortage of organ donors means a variety of donor sources and grafting techniques are used to maximise donor availability. In New Zealand children must have a projected > 50% chance of survival 5 years post transplant (measured against available published evidence) in order to be considered suitable for transplant. Transplant is often performed when the patient is sicker than would be ideal for such invasive and prolonged surgery which adds to the potential risks.

There are significant complications that can arise in both the short and long term post transplant period.

The decision to transplant is made only when the patient has evidence of irreversible progressive disease for which there is no acceptable alternative therapy (1).

Transplant is often described by health professionals as the trading of one disease for another i.e. Trading the disease which has lead to liver failure e.g. Biliary Atresia for that of living with a transplanted organ. It requires lifetime commitment to medical assessment and treatment.

For transplant to be considered as an option the patient must go through a rigorous assessment process.

## Section 1 Pre Transplant

### Assessment:

Assessment occurs at the point where the medical team consider that transplant is most likely to be the best option for treatment at the time or in the near future. The decision to assess and list for transplant can be on medical or quality of life grounds.

Assessment includes both extensive medical and psychosocial evaluation and requires at least 2 adults be present if at all possible, along with the child. The assessment process is carried out at Starship, usually over a week long period. The requirement for 2 adults is due to a number of factors

- The commitment to transplant is lifelong. It is important that more than one person understands the child's medical needs to act as day to day support and back up to the primary carer in case of illness etc
- The assessment time is intense for both the family and staff involved and parents/ carers both have the right to access to the information regarding the child and the opportunity to discuss it between sessions and clarify any issues.
- Relationships are assessed and both parents/ primary care givers should contribute to this wherever possible to allow for most appropriate support.

If the child is stable enough to remain an outpatient the assessment is done during daily visits to the Day Stay Unit. It is performed as an inpatient if the child requires inpatient care during this time.

Parents are supplied with a written guide to transplant which covers all areas discussed verbally during assessment in greater detail.

### SHARED CARE NOTE

- From the time of assessment until 3 months post liver transplant the NZLTU contract pays for the travel of the child and one support person (usually the primary carer) between home and Auckland as required for medical/educational reasons. NZLTU also pays for one room at Ronald MacDonald House when the child is required to be in Auckland.
- It is important to address issues regarding parental and sibling travel as early as possible after the diagnosis of chronic liver disease to minimise separation issues and maximise family functioning. If your DHB is unable to fund the second support person or siblings please contact the Starship CNS team immediately so we can assist you to advocate for allocation of additional funding through other sources.

## Medical

The aims of the medical assessment are to

- Confirm diagnosis
- Define dysfunction and disease progression
- Establish what complications are currently present
- Determine what other organs have been affected eg, kidneys
- Identify specific patient risks and to rule out concurrent diagnoses which may cause additional complications or the transplant to fail.
- Identify anatomy to allow surgical planning and appropriate matching of donor to recipient for best outcomes.
- Formal assessment allows opportunity to optimise treatment based on extensive information.

In many children other medical disorders are present which add to the risks, but may not automatically make transplant unfeasible. It may mean the correction of other problems needs to occur first or modification to surgical technique is required.

There are few absolute contra-indications for transplant but do include;

- Un-correctable pulmonary or cardiac disease
- Ongoing infection such as pneumonia, peritonitis and septicaemia.
- Metastatic malignancy – it is important to note that presence of malignancy does not always preclude transplant but there are strict criteria applied relating to size, number location and type when determining eligibility.

In fulminant (acute) failure some of the screening may not be done due to the time constraints imposed by a rapidly failing liver.

## Psychosocial Component

The aims of the psychosocial assessment are to identify

- Vulnerabilities
- Problematic behaviour or social situations.

Social work and the child liaison psychiatry team perform this assessment to allow for early recognition and intervention of potential problems and allow time to address them.

For children who reside outside the Auckland region the input of the shared care team is extremely important. Local nursing, social work, and medical staff can provide significant history and information regarding a family's ability to engage with healthcare providers and deliver the care required in their own environment and over much longer periods of time than the time spent in Auckland. Regardless of location, community nurses provide a valuable insight into the living arrangements of families, quality of housing and family accessibility to health and social resources.

Housing is of particular concern post transplant and ensuring a warm dry home, which is not overcrowded is key to maintaining good health in a child who is immunosuppressed.

The assessment may result in referral to outside agencies to assist with meeting appropriate housing and financial needs, or to provide supports to strengthen the family and allow appropriate provision of care to occur. The team philosophy is to ensure that all children who medically require transplantation will be offered it and that every effort will be made to ensure that social circumstance do not prevent this occurring.



This philosophy has resulted in removal of 2 children into Child Youth and Family (CYFs) care on the basis of medical neglect by the family. Removal of children from their family occurs as a last resort after all other avenues have been exhausted.

The assessment findings are shared with the multidisciplinary team and if the child resides outside the

Auckland region, the shared care team for ongoing management.

## Education component

### Aims to provide families with the information they need to:

- Provide appropriate care for their child whilst waiting for transplant
- Gain understanding of potential complications and how they need to be managed
- Provide insight into the demands they will be facing in the care of their child both pre and post transplant and the importance of long term partnership with their healthcare team.
- Be able to give informed consent for transplant

### Covers the following topics

- Progression of disease and associated complications
- What to do when there are changes in the child's health eg increasing abdominal distension or haematemesis
- Waiting for transplant
- Acute transplant phase (from the day of transplant to 3 months post)
- Long term management and complications
- Nutrition pre and post transplant
- Medications post transplant.

## Waiting for transplant

Once the assessment has been completed the child will be:

- Activated on the waiting list
- Added to the waiting list and suspended- This will only occur if the child is considered medically stable enough to wait longer for transplant, the reasons may be:
  - Need for live immunisations which cannot be given whilst active on the list or post transplant
  - Psychosocial plans need to be implemented or completed
  - Family may need time to sort other family issues in order to be available
- Rejected- This is rare and can be due to the child being;
  - Medically unsuitable
  - Considered too well for transplant at that time

The child's name, blood group, size and weight are entered into a national data base.

Liver transplantation has emphasised the need for an accurate prognosis so that surgery may be performed at the right time.

### Priority on the Waitlist:

Determining priority on the waitlist continues to be a topic of medical and ethical debate and ongoing research in the transplant world.

Donor organs are a valuable and very limited resource and with increasing demand for transplant, waiting times vary substantially and are expected to become longer overall. Managing patients to give them the best opportunity for transplant and transplant survival is challenging.

Numerous strategies have been employed to increase the donor pool and address the reality of death whilst waiting. Death on the waitlist is a real potential, the NZ paediatric liver transplant program has a current death on the waitlist rate of approximately 10%.

Children and Adults are on the same list in NZ and initially separated into ABO blood groups.

From there medical condition is the next consideration. There are a number of factors which can provide a prognostic guide to disease severity and likely survival in the pre transplant period.

In children the Paediatric Endstage Liver Disease (PELD) score is used. However this is used as a starting point along with clinical judgement. There is still a great deal of research happening to validate the tool and debate remains as to which other factors, if any, should be taken into account. However it provides a continuous scale of measurement and prediction of survival without transplant.

The PELD calculator takes into account the child's age, bilirubin level, albumin level, International

Normalised Ratio (INR) and growth (24). Each person is ranked within their blood group according to their PELD score and MELD score for children over the age of 12 and Adults. The higher the number, the more urgency is allocated. However there are a number of other factors including presence of oesophageal varices and quality of life issues, such as severe itching which also impact on the ranking within the group. Time on the waitlist is considered only when 2 or more people have the same medical urgency.

In addition to this the surgeon needs to consider the donor organ being offered and its suitability for each candidate, Size, age of the donor and organ quality come



into play at this point and there are a huge number of variables considered in each decision. The final decision rests with the surgeon after consultation with the paediatric gastroenterologist.

The standard waiting list is a New Zealand only list however we are part of the Australasian organ sharing group.

Each time a donor organ becomes available, it is first offered to the teams within the donor state/ NZ.

If it is not needed, it is offered to the various transplant units in Australia/ NZ on a predetermined rotating basis.

Being a member of this group allows us to access the urgent listing system. This is an Australia/ NZ wide list used in cases of urgent medical need, or limited window of opportunity for transplant. Such situations include fulminant liver failure, time between chemotherapy cycles, or if a child with chronic liver disease has deteriorated to the point that they are ICU and ventilated. This usually allows us to use the first suitable liver that becomes available in Australia or NZ giving a greater catchment area and chances of finding a match. The criteria for urgent listings are very strict and going into transplant while being so sick does increase the risks of transplant significantly.

All decisions involving transplantation must be guided by the Transplantation Society of Australia and

New Zealand -Organ transplant from deceased donors- Consensus Statement on Eligibility Criteria and Allocation Protocol 2011

Organs are allocated on the basis of blood group match. However the NZLTU has recently developed

a protocol for transplanting using ABO incompatible donors in children in certain circumstances.

## Special considerations for children on the waiting list

- Families must be in phone contact at all times and prepared to come to Starship almost immediately if a deceased donor becomes available. Cell phone coverage is crucial to allow families to go about their normal lives whilst remaining accessible.
    - We recommend there is more than one contact number,
    - Cell phones remain fully charged
    - If the phone is prepay, that there is at least \$10 credit at all times so families can return calls to the hospital should the need arise at the time of a donor offer.
    - Arrangement for care of siblings and pets should be considered at time of listing and revised as required.
  - If a family is coming all or part way by car ensuring there is access to a reliable vehicle and sufficient fuel at all times or fuel vouchers have been issued if required.
  - Notification of travel away from the normal place of residence.
    - If families are staying away from home such as for weekends/ holidays, the Starship team needs to be aware, as it may impact on the arrangements which would be required in the event of a donor offer.
    - Travel to areas outside the 6 hour timeframe, without cell phone coverage or outside
- NZ are not appropriate for someone on the active transplant list. If any of these are required early discussion with the Starship CNS service is imperative. Families are made aware that the child will be suspended in these circumstances.
- Notification of intercurrent illness;
    - Intercurrent illness is likely to impact on liver function and increased monitoring/ support may be required

during these periods

- The presence of infection may (but not always) necessitate temporary withdrawal (suspension) from the active list until recovery, families should inform the CNS service of any other illness in the child or siblings at the first opportunity so that management plans can be put in place.

The child will be reactivated as soon as it is safe to proceed with transplant.

### • Immunisations.

- Live immunisations cannot be given whilst a child is actively waiting for transplant.
- All immunisations should be discussed with the SSH team prior to giving. In certain circumstances it may be preferable to suspend the child to achieve vaccination, each case is evaluated individually.
- Immunisations pre transplant are extremely important and where it is medically appropriate the accelerated schedule of immunisations should be completed as far as possible before children are placed on the waitlist.

### • Monitoring

- As a general rule children will require weekly blood tests whilst on the waitlist.
- Liver Function tests, Electrolytes, Urea,, Albumin, Full Blood Count and INR should be taken each time
- Vitamin levels ( A,D E) 3 Monthly

## SHARED CARE NOTE

Where possible bloods should be done early in the week and on the same day each week to allow for results to be assessed and any additional interventions initiated during normal working hours.

The CNS service would appreciate any bloods taken outside greater Auckland being faxed or emailed directly to us.

Children may wait at home providing they are medically stable and can get to Auckland within 6 hours.

Families are not asked to wait in Auckland unless it is essential due to the negative impact associated with geographical isolation from family, usual environment and supports for an indefinite period of time.

We are aware that many families rely on air transport to achieve the time frames required and that commercial flights are not available in many centres overnight. The risks and alternatives available are assessed by the transplant team prior to a child returning home and in some cases we may ask a family to wait in Auckland when they are the highest priority in the blood group or for medical reasons.

The waiting time can be as little as a few days or many months and this is completely unpredictable.

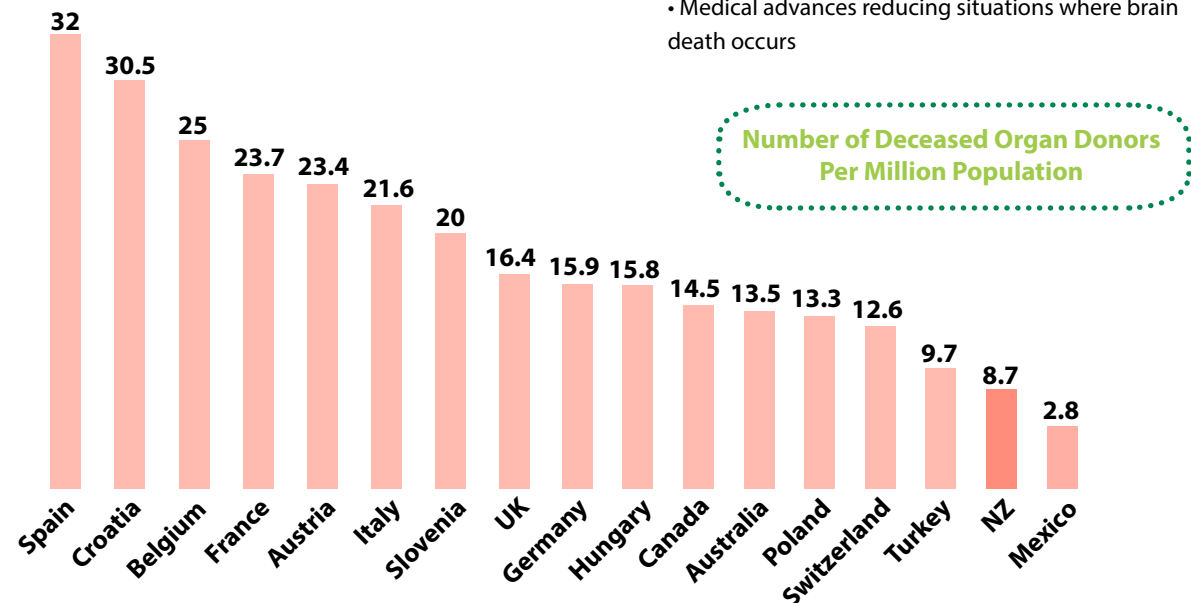
This time is extremely hard on families and maintaining support networks is vital to coping in the longer term.

Many laboratories outside Auckland are able to copy results directly to ADHB Éclair. Parental consent may be required for this to happen. Please consider speaking to your lab and setting this up if possible. This allows us to see cumulative results without the need for manual handling of results by staff at either end. Please ensure all blood results are copied to either the CNS fax (09 307 2809) or the primary Auckland consultant if electronic or results will not be visible within the Auckland electronic system. For South Island centres consider copying results to Christchurch as these results can be accessed at outreach clinics and the CNS service has direct access.

## Donor Sources

Donors can come from three different sources in New Zealand. The traditional donor pool (commonly called deceased donor or previously called cadaveric donor) has been expanded in a number of ways in an attempt to meet the increasing disparity between the number of people requiring an organ and the number of donors. The donation rate in New Zealand is one of the lowest in the world and this occurs for a number of reasons which include but are not limited to:

- Structure of the healthcare system
- Sparsely populated country in comparison to many others
- Geographical challenges
- Cultural considerations
- An "opt in" system rather than an "opt out" one
- Medical advances reducing situations where brain death occurs



## Deceased Donor

This term is used to describe a person who has become a donor after the diagnosis of brain death, that is irreversible loss of all functions of the entire brain, including the brain stem.

Donors must be in an ICU environment with good ventilation and perfusion present at time of donation commencing.

Organs are obtained in the operating theatre in the donor's hospital after cross clamping the aorta.

Life support is ceased directly after cross clamp occurs.

The liver is then flown to Auckland and other organs retrieved are flown to the respective centres for implanting and prepared for placement in the recipient.

Benefits of deceased donor include:

- The ability for split grafts
- Ability to take extra blood vessel and biliary tree to assist in recipient implant. Limitations include
- Inability to plan as forewarning is generally only a few hours to mobilise the team, retrieve and implant the liver.
- Less ability to control and minimise ischemic time due to donor geographical location.
- Unknown factors about the donor- in spite of extensive screening of lifestyle and medical history
- Limited availability- In NZ only 35 livers were obtained from deceased donors on 2010, Whilst the waitlist varies it generally sits between 20-30 at any given time

## Live donor

Live donor transplant is offered by the NZLTU. In order to be considered as a live donor the person must be a family member or be well known to the family and have

an emotional attachment to the parents or child. Altruistic donation is not accepted for live donor liver transplant in NZ.

Benefits include:

- Increases the donor pool- reduces the chance of death whilst waiting
- Allows planned transplant at a time which maximises recipient and family benefits.
- Ability for intense donor scrutiny reducing unknown factors which may impact on patient or graft survival.

Limitations include;

- Risking the life of someone through major surgery they don't need in order to help someone else
- Increased family stress as more than one life is put at risk.
  - Long term implications of being a live donor are not well understood due to the relative young age of live donor programs
- No opportunity for taking extra vessel or bile duct lengths
- Increased risk of some post transplant complications such as biliary strictures
- Magnified impact in the event of recipient death

Ensuring the donor focus is equal and separate to the recipient care focus is critical in the setting of live donor programs

The emphasis must fall to the donor medical team to ensure donor safety is paramount (25). During one study it was reported that up to 60% of parental donors indicated they were willing to donate and die rather than not donate and have their child die (26). Informed and free consent without guilt is almost impossible in this situation.

Separate teams for both donor and recipient, wherever possible, are crucial to limit potential for perceived coercion and maximise opportunity for free and informed consent along with donor privacy.

At the NZLTU donors are assessed by physicians at Auckland City Hospital – these physicians have a mandate to advocate for the donor at all times. Some crossover of surgeons is inevitable due to the small size of the unit. However every attempt is made to ensure unbiased assessment is obtained.

Supporting families as they make decisions regarding live donation is important. Some donors report experiencing a sense of loneliness and isolation as they grapple with weighing up the risks to themselves, their family, and the child recipient as a result of their choice (26). It is important to note that the physical and medical criteria for donation are strict and many potential donors are found not suitable.

Post transplant challenges for the donor include adjusting to the change from being a healthy person to one who has had major surgery. In addition they will have ongoing health monitoring and potential for future concerns which only adds to the perceived need to recover quickly and get back to their previously established role in the family (25).



## Donation after Cardiac Death (DCD)

Sometimes referred to as “Non Beating Heart” donation.

Donation after cardiac death is defined as irreversible cessation of circulatory and respiratory function and was the original way donors were obtained up until the 1960s when brain death criteria were devised (27). However, with the recognition of brain death and the ability to obtain potentially better quality organs, donation after cardiac death was considered obsolete for some decades.

The person still needs to be being cared for in an intensive care setting and the organs are retrieved in the operating theatres in the same way as deceased donors. However life support is withdrawn and the patient is declared dead after a defined period of time post cessation of function. At this point organ retrieval commences. The window of opportunity for success is small relying on the donor heart stopping within an hour of the life support being withdrawn.

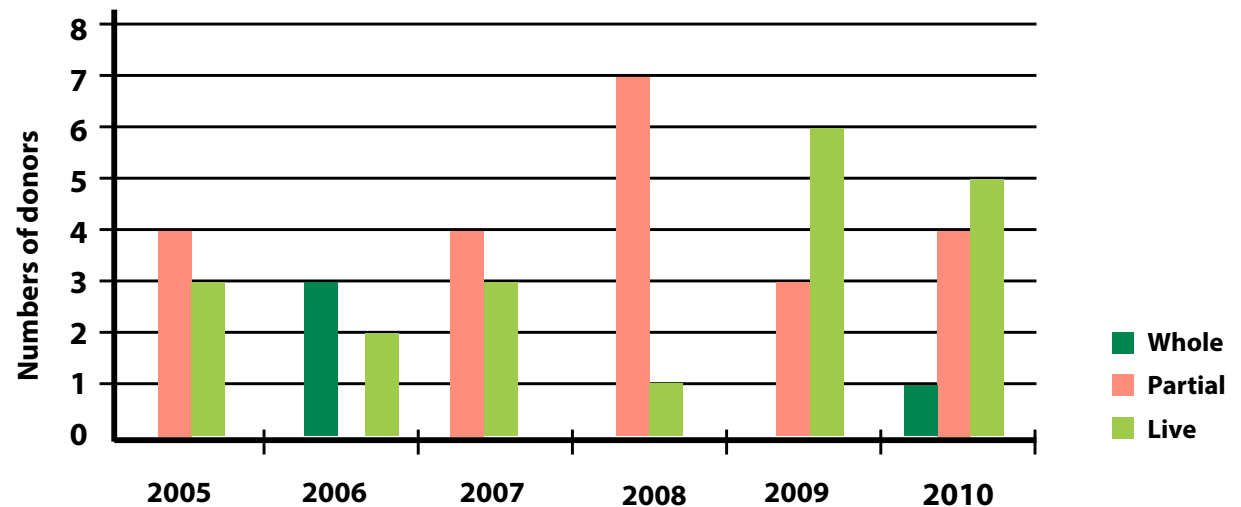
Benefits include:

- Increasing the donor pool

Limitations of include:

- Ischaemic times to the organs are prolonged
  - o Warm ischaemic time (when the organ is not on ice and not perfused with preservation fluid) has significant impact on organ deterioration. This may lead to an increased rate of graft failure and injury to the bile ducts (ischaemic cholangiopathy).
- Cannot be used for splitting or undergo significant modifications due to organ quality considerations which limits DCD use in children.
- If a DCD donor is being considered for a child, parents will be consented specifically for the associated risks.

### Donor Sources New Zealand



*No DCD donors were used for children during the timeframe within the graph*

## “Dummy Runs”

Transplantation is an incredibly resource intensive process and requires 3 separate operations. One at the donor hospital, the second on the back table to prepare the liver for implantation (which most often occurs at the recipient hospital due to resource availability) and the third is the recipient operation.

At any time during the process information may come to light which determines that the liver is completely unsuitable for transplant or not suitable for the intended recipient. This can occur for a myriad of reasons including logistics of retrieval, anatomy variations or findings at the time of retrieval.

Often the recipient family has been called to the hospital and commenced the preparations for transplant before the information is known. This is sometimes referred to as a dummy run and, whilst it occurs rarely, it is incredibly hard on families who may have been waiting for some months for a transplant. Additional support is likely to be required in the post call period.

## The Transplant Surgery

Liver transplant surgery in NZ is only performed in Auckland City Hospital. The surgeons perform liver transplants on children and adult recipients and perform the donor surgery in most cases.

The transplant liver will be placed in the same anatomical position as the native liver (orthotopic).

Whilst it is possible to place a whole or partial new liver as an auxiliary to the native one, this has only occurred in a small number of recipients worldwide (28). This option has been used in the setting of acute liver failure as a bridge to recovery but has not been performed in NZ.

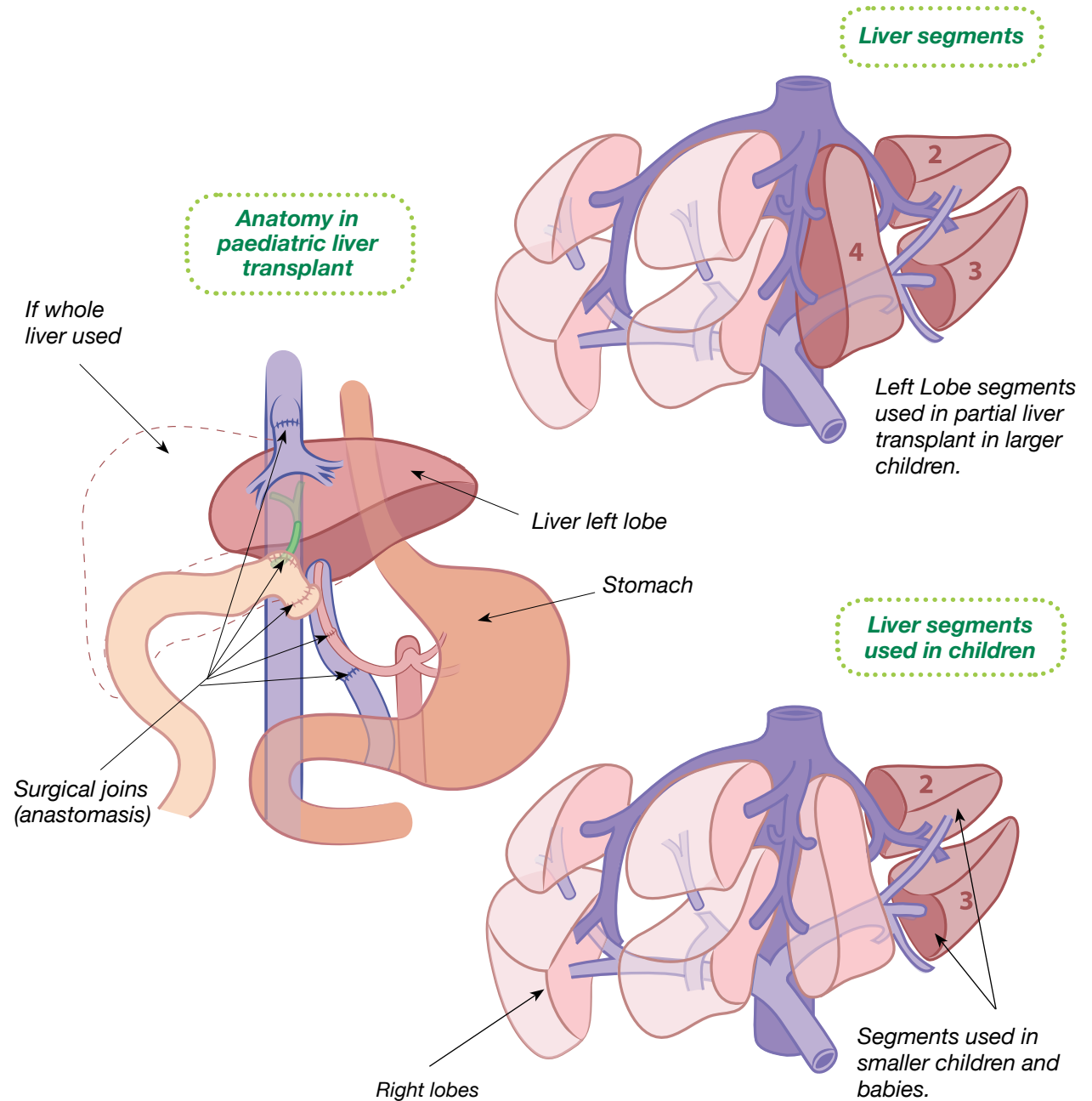
The transplant involves three distinct phases;

Removal of the native liver, placement and connection of the donor liver, and reperfusion of the donor liver.

The surgery takes an average of 6 to 8 hours. This time is often extended and families are kept up to date throughout the procedure via the transplant coordinator or the Starship CNS.

Children can receive a whole liver, a partial liver which has been surgically reduced in size or a split liver. A split liver has been divided to allow transplant of an adult with the right lobe and the child with the smaller left lobe. Live donor livers are considered split livers.

Children can receive segments 2 and 3 or 2, 3 and 4 depending on a number of factors.





## Section 2 Recovery

### The First Three Months

All children return to the Paediatric Intensive Care Unit (PICU) post transplant. They remain heavily sedated and intubated until after the first post transplant ultrasound on the morning of the first day.

Once it is established that the child is medically stable, the liver has good perfusion and no other complications are present the sedation will be weaned with the aim of extubation. In most cases the PICU stay is between 24 and 72 hours in length- however this is dependent on a number of factors including how well the child was going into transplant, duration of surgery, intraoperative complications and the need for further surgical revision in the first few days post operatively.

Children are then moved to the medical specialty ward and remain an inpatient for the next 2-3 weeks.

The key considerations during this inpatient stay are prevention and early recognition of surgical complications such as bleeding, bile leaks and infection.

- Intensive fluid management to avoid fluid overload or dehydration is imperative to the functioning of both the new liver and kidneys
- Pain management
- Nutrition is re-established at the earliest opportunity – often in the PICU via a nasojejun tube
- Establishing appropriate immunosuppression levels to prevent rejection
- Wound and surgical drain management

- Preparation of parents for discharge including re-education

During the first week ultrasounds occur on a daily basis and bloods are twice daily then daily in the mornings pre Tacrolimus dose.

The threshold for instigating further intervention, imaging, liver biopsy or surgical intervention is very low as the liver is at its most fragile as it recovers from the transplant associated ischemia. Small changes in blood flow, oxygenation, rejection or sepsis can have catastrophic consequences if left untreated. In combination with high immunosuppression levels these complications make the child medically fragile.

If the child lives outside the Auckland region then they remain at the Ronald Macdonald house until they are at least three months post transplant.

This is due to the availability of rapid blood result turnaround times, specialist radiological intervention and liver biopsy resources, medical and surgical facilities to address urgent issues which may arise.

If the family live in greater Auckland then they return home with the expectation of a minimum twice weekly visits to SSH and three times weekly bloods gradually spreading out to weekly as stability is achieved.

Families find this time intense and whilst they are celebrating the milestone of receiving a transplant it brings with it a new set of challenges and worries. Families are often exhausted through this period but continue to need to meet intensive medical demands and may be doing so with limited family support if they are not from Auckland.

Infection, rejection and biliary strictures are the three most common complications in the early phase post discharge.

### SHARED CARE NOTE

**Transition to home is a challenging time for families as they move away from the Auckland- based resources they have come to rely on over the last few months and negotiate their way round local facilities and staff. This is particularly the case if a family has spent a large proportion of their waiting time in Auckland or for the family who's child has been transplanted for acute liver failure for whom both the Local and Auckland services are entirely new.**

**Nursing links between SSH and Shared care teams provide significant additional strength and safety for children and families during this time.**

**Common issues which arise during transition to home are**

- **Availability of up to date information from the SSH team particularly for nurses.**
  - **Communication of up to date, accurate and relevant clinical information from the Starship transplant team at time of discharge is an ongoing challenge and the CNS service acknowledges the system is somewhat lacking.**
  - **Identifying the correct people to communicate with can also add to gaps in information transfer. If you are being included in communication which you feel should be directed to others instead of yourselves, or in addition to, please inform us so we can correct the situation.**



- If children have not required admission during the recent weeks then a written summary of care through this time is not automatically generated. Clinic letters are the most informative and likely to be delayed by 1-2 weeks due to dictation systems. The CNS service endeavours to provide a nursing transfer letter or phone call on discharge from Auckland as an adjunct to medical information provided.

- It is important to note that every effort is made to have the shared care team included in every piece of correspondence regarding a child. However the system only allows for the GP to be included as an automated system. Discharge letters in particular are problematic as they are generated by junior medical staff that may be unfamiliar with the implications of the shared care system.

- Obtaining blood samples.

- Please consider the following issues when preparing to manage a newly transplanted child.

- The family will be provided with an Auckland blood sample request to act as a guide for the required bloods- is it possible to create a permanent card to photocopy on each occasion? Reduces time involved and transcription errors.

- Bloods must be taken before the morning Tacrolimus dose.

- Please consider the immunosuppressed

state of the child and minimise contact with potentially infectious people and exposure by avoiding prolonged periods in ward or pathology areas where possible

- All bloods (Except EBV and CMV) are required on every occasion. Many labs have recently stopped reporting AST and Urea unless specifically requested- please check with your local lab prior to collection on the first occasion.

- EBV and CMV bloods are for viral loads (not serology) and will require additional separate tubes as they will need to be sent to the Auckland lab for processing. Processing occurs weekly on a Thursday so if rapid turnaround is required bloods will need to be drawn on Monday or Tuesday to allow for transit time.

- It may be worth considering performing viral loads on a separate day as often there is difficulty in obtaining sufficient samples particularly in younger children.

- Send away blood results are often available by phone well before paper based notification is available

- Collection and collation of blood results is the primary responsibility of the shared care team with the support of SSH where required and management changes should be made in conjunction with the Starship team. The only exclusion to this is Christchurch who have paediatric gastroenterologist Professor Day.

- The CNS service monitors blood results on a weekly basis (Mondays) on newly transplanted patients but we will not be aware between these times if there are concerns unless notified by the family or the shared care team. Please fax or email results or phone us if there are changes.

- Please refrain from faxing results where the current results are highlighted or shaded as it is illegible at our end of the fax.

- Many Labs outside Auckland are able to copy results directly to ADHB éclair. Please consider speaking with your lab and setting this up if at all possible.

## Medications:

Changes to Tacrolimus levels are common in the post transplant period as the child heals, biliary flows settle and the child grows. These changes are likely to result in changes to the Tacrolimus dose. This will be guided by the SSH team and most often occurs after the MDT meeting on a Monday afternoon although can occur at any time.

- If changes occur the CNS team will notify parents directly and then the shared care team via email if available or by phone.

- We do not notify community nurses in the greater Auckland region unless there is a specific reason to do so.

- If a dose change is made it is likely additional bloods will be required in 2-3 days after the change to assess the impact.

## Section 3 Post Transplant Complications

### Growth

In the setting of end stage liver disease faltering growth (previously referred to as failure to thrive) is common and faltering linear growth is a more reliable marker of malnutrition than weight due to organomegaly and fluid retention. Comparisons between groups and individuals can be made using a system of Z scores. Z scores are standardized scores that indicate by how many standard deviations an observation is above or below the age-specific and gender-specific mean (29). The Z score system is considered an excellent descriptor of malnutrition on a population level (30).

Post transplant the aim is to target full adult height however there are a number of factors which impact on achievement of this goal. An individual child's growth potential is predicted by a number of factors including genetic factors (mainly mid parental height), severity of growth failure pre transplant and in some cases, the primary diagnosis or co morbidities.

Pre transplant major factors include the child's age and the height Z score at time of transplant.

Diagnosis leading to transplant (e.g. Alagilles) may also contribute to growth velocity in the post transplant years.

Children transplanted under the age of 2 years demonstrate the greatest catch up growth but they also generally have the greatest growth failure pre transplant (31). There has been data published to suggest that children with Biliary Atresia demonstrate the best catch up growth, but this could be due in some part to the fact

they are often transplanted very young. Children with Alagilles syndrome demonstrate little if any catch up growth (31).

Post transplant growth is also impacted most commonly by the use of corticosteroids as part of the immunosuppression regimen. However the need for re-transplant, graft dysfunction and Post

Transplant Lymphoproliferative disease (PTLD) also play a role when present. Growth hormones which appear to be lower in children pre transplant return to normal levels in the post transplant period but many children will still not obtain their predicted optimal height potential many years after transplant.

Much of the literature suggests linear (height) growth does not accelerate in the same way as weight until the second post transplant year. This is most likely related to the presence of pre transplant malnutrition and the need for catch up weight to occur first, as well as the presence of corticosteroids in the immunosuppression regimen. Whilst catch up growth does occur post transplant height distribution in children after liver transplant is consistently lower than the normal population (32). Older children with established short stature are less likely to experience catch up growth at the same level as those transplanted before the age of two years.

The NZLTU is aware of the need to minimise corticosteroid use and so steroids are weaned rapidly after transplant to a small maintenance dose with the aim of ceasing them completely if the post transplant protocol biopsy establishes that there is no subclinical rejection or inflammation present.

Addition of corticosteroids to the medication regimen for treatment of other illnesses such as asthma should be discussed with the SSH team prior to initiation and the dose and length of the course should be minimised where possible.

### Development

It is well recognised that children with chronic liver disease fall behind normal developmental milestones, particularly gross motor skills. There are significant challenges in measuring neurocognitive function across small populations in multiple age groups and combining the results to achieve a meaningful result.

It is only recently that significant studies have been performed to assess the long-term development, intellectual and functional outcomes in children post liver transplant.

Onset of liver disease in infancy is thought to increase the risk of neurocognitive delay in children with chronic liver disease (29). Recent studies suggest that up to 15-18% of children post liver transplant will have an IQ less than 70 compared with 2% in the general population (29).

Group mean IQ did not change between pre and post transplant (32) once the initial recovery was completed. This makes it likely the presence of chronic liver disease rather than the process of transplant itself that creates this situation. Unfortunately I could not find studies which compared those receiving transplant for acute liver failure compared with chronic liver failure. Changes in IQ were not limited to liver transplant patients but also applied to those who had chronic renal disease pre transplant.

In several small studies up to 26% of children were found to meet criteria for a learning disability.

However the larger study by the Studies of Paediatric Liver Transplantation (SPLIT) registry provided a far larger cohort of patients (638 over 6 years old) and found 17.7% had been diagnosed with a learning disability as opposed to 8% in the general population.

The level of disability is likely to have a number of contributing factors

- Presence of chronic illness/ frequent or long term hospitalisation
- Exposure to Calcineurin inhibitors has been suggested but not yet proven (32)
- Frequent access to the healthcare system may facilitate greater recognition and diagnosis than those who are functioning well at a superficial level and masking underlying disability

Monitoring for cognitive delay and initiation of additional supports at the earliest opportunity is essential to promote highest possible functioning. Liaison between the child's local health care and education providers promotes these opportunities.

## Biliary Strictures

A biliary stricture is a narrowing of the biliary tract caused by inflammation and/ or scar tissue formation. Biliary stricture formation is a well known complication of liver transplant and sometimes described as the "Achilles Heel" of liver transplant, occurring in 11-25% of recipients (33). This is increased in children receiving a partial graft and in the 10 years to 2008 the NZLTU had an overall paediatric biliary stricture rate of 33% (34). They can be anastomotic (at the site of surgical anastomosis), non-anastomotic or a mix of both. The strictures slow or prevent drainage of bile from all or part of the liver and can lead to graft dysfunction and in extreme circumstances graft loss (35).

Incidence of biliary strictures varies by centre and incidence directly correlates with the type of transplant graft used.

The following table demonstrates the incidence reported in the literature by type of graft used at transplant.

Type of Graft	Incidence of Biliary Strictures
All Grafts	11-25%
Reduced size or whole livers	0-16%
Split livers	24%
Live donor	50%

*33% of children transplanted between 1998-2008 in NZ, developed biliary strictures (34). There are two types of strictures;*

## Anastomotic Strictures

Occur at

- The biliary duct to Roux en Y connection or
- The bile duct to bile duct connection in child who does not have Biliary Atresia and receives a whole organ– rare in children

In this case the strictures occur as a direct result of the normal healing process and the development of scar tissue narrowing the duct. The risk of strictures becomes higher the more the duct is modified and in children modification of an adult duct to join to a smaller paediatric or infant duct is common.

Some centres with very high transplant numbers use micro surgeons to perform the biliary anastomosis and have a significantly lower stricture rate; unfortunately this is not feasible in the New Zealand setting.

Anastomotic strictures are more easily treated than other forms and rarely recur post treatment.

## Non anastomotic strictures

Most often occur later post transplant (months or even years). The strictures are related to injury to the biliary tree as a direct result of poor arterial blood flow. Prolonged periods of liver ischaemia related to donor age, organ transport (perfusion injury), surgical technique used (back table surgical modifications) at time of transplant and lack of oxygen from the artery due to post-transplant major events (34).

Major events include severe infection, bleeding, biliary leaks, rejection and thrombosis of the hepatic artery. The biliary tree is particularly susceptible to damage as the rate of cell turnover is high.

These strictures can occur anywhere in the liver and can be isolated to a single duct but often involve multiple

smaller ducts and sometimes occur in conjunction with anastomotic strictures.

They are much more difficult to treat and are more likely to recur.

## Diagnosis

Elevated liver function tests are most often the first indication of biliary trouble although they act as a guide rather than providing a definitive diagnosis.

ALP and GGT are elevated in cholestasis (reduced or absent bile flow) but both can also be influenced by other factors.

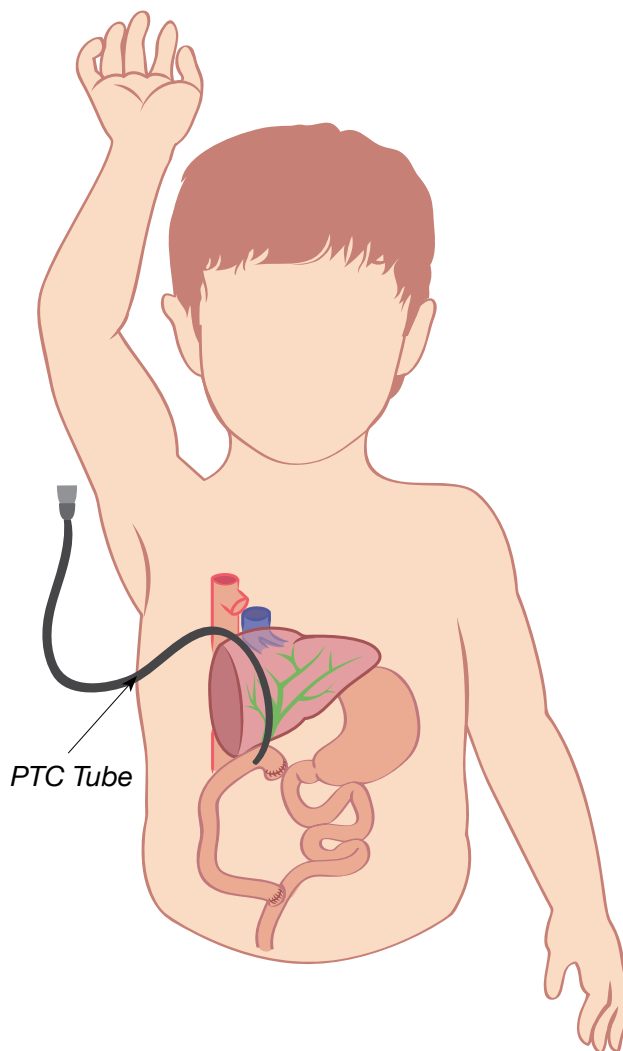
Bilirubin may or may not rise depending on severity of the stricture or the length of time the stricture has been present. A rise in bilirubin above normal limits in the post-transplant setting requires urgent medical assessment.

ALT and AST Liver enzymes may also be elevated as a result of cellular damage caused by the presence of bile. The extent of elevation varies and is not specific for diagnosis prognosis or extent of injury.

Depending on the levels we may require repeat bloods the following day or alternatively liver ultrasound is arranged as a matter of urgency. In most cases this will necessitate a return to SSH even if the child lives outside of Auckland. Ultrasound does not show strictures as such but an experienced liver transplant sonographer can often identify areas of dilated ducts proximal to the stricture.

Percutaneous Transhepatic Cholangiogram PTC is then performed. PTC essentially involves passing a tube through the skin, across the liver and mapping the biliary tree with radio opaque dye as demonstrated in diagram -insert number

## Percutaneous Transhepatic Cholangiogram

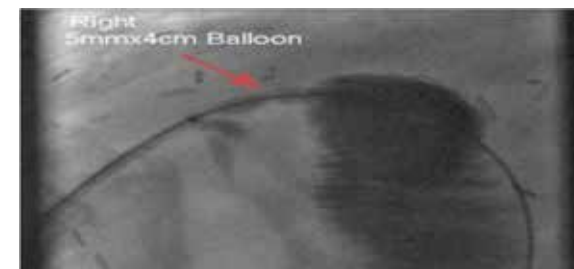


## Treatment

Once the presence and position of a stricture has been verified the radiologist will attempt to dilate the stricture using balloon dilatation.



Site of stricture



Partial inflation of the balloon with the balloon developing a "waist" at the site of the stricture.



Dye flowing freely through Roux loop post dilatation

The PTC tube is passed through the area of stricture and secured in place by a dressing to act as a biliary stent. Occasionally the stent will be sutured at skin level. This stent is left insitu to hold the duct open over a period of time and is changed via repeat cholangiograms every 6 – 8 weeks. Tubes can remain in place for weeks or many months.

Stents will initially be on free drainage into a collection bag. In all circumstances we aim to have the tube clamped prior to discharge. However, in some children this is not possible and the younger the child the more likely they are to have their stent on free drainage either intermittently or continuously due to relative duct size.

In adults and occasionally in older children who have had a duct to duct anastomosis, stenting of biliary duct occurs through a procedure called ERCP (Endoscopic retrograde cholangiopancreatography) and the stent is completely internal. However due to the presence of the Roux-en -Y loop of bowel this is not able to be performed in the majority of children.

Managing stents over a number of months can be challenging particularly in younger children and for those residing outside Auckland. It requires specialist staff, multiple general anaesthetics and frequent visits to SSH.

## Care of the Biliary Stent

Despite numerous attempts to identify current best practice guidelines for nursing care of biliary stents there has not been any published literature identified through literature searching or discussion with other transplant centres via conferences online or email groups.

Therefore significant discussion has occurred and a consensus of local expert opinion has been defined.

The guiding principles for stent care are

- Protect the child and liver
- Protect the tube
- Protect the skin

Biliary stent care should be maintained with the same care and respect as a central venous line (CVL).

Families are taught to manage the stent dressing and flushes using Aseptic Non Touch Technique (ANTT) according to SSH guidelines for CVL care.

We are aware that there is variation in practice nationally particularly in relation to ANTT versus “sterile” technique. Please be guided in your care by local protocol but allow parents to perform cares in the way they have been taught to avoid confusion.

Every family will be sent home with a parent information sheet explaining cares and this can also be used as a guide for staff.

### Clamped Stents:

- Require flushing on a daily basis and this may be once or twice depending on surgical instructions
- Flushes are performed with 5mls of normal saline for injection regardless if stent is on free drainage or clamped.

### Unclamped Stents:

- Regular electrolyte monitoring is required due to loss of bile fluids via the bag.
- Recording of output by parents is also helpful in the initial phases of a new stent
- Replacement of losses may be required and can occur in 2 ways.
  - Orally with an oral rehydration fluid such as pedialyte.
  - Recycling of bile down an NGT, if one is already present for nutrition.

- May require a daily flush to ensure patency if drainage is low or has reduced in volume.
- Ensure the bag is attached to the child in a way that prevents.
  - Kinking of the tubing
  - Accidental dislodgement of both bag and stent
  - Site damage due to weight/ pressure on the exit site.
  - Ensure the bag remains lower than the exit site

## Shared Care considerations

- Equipment availability is often an issue so children should be sent home from SSH with supplies to manage both a clamped and unclamped stent for 7 days.
- Families should also have a copy of the stent care guide which includes equipment required and ordering information for community and shared care nurses.
- The CNS service will forward a copy via email or fax on discharge if the child has not previously had a stent in place. Do not hesitate to contact us should you have different equipment available locally which could be used.
- In the event of increasing LFTs with a stent in place and clamped we are likely to request the family converts to free drainage whilst arrangements are being made for further assessment. It is important families have ready access to the required equipment to do this.
- Please attempt to have appropriate equipment on hand as soon as possible and if there are any issues with delivery of supplies contact the CNS service early so we can identify alternative solutions.
- Children can attend school, kindergarten or crèche with stents in place providing they are well secured.



# Rejection

Rejection is caused by the recipient of an organ mounting cellular and/ or humoral responses to the foreign antigens presented by the donor graft. The Donor liver may induce an episode of rejection at any time post-transplant as it provides a continuous source of foreign antigens being presented to the recipient immune system in a variety of ways (36). However rejection is most common in the first few months post-transplant. Rejection has a number of forms and each is mediated by different components of the immune system.

## Types of rejection

### Hyper Acute Rejection

This form of rejection is extremely rare particularly in liver transplant. However, its effects are potentially devastating.

Hyper acute rejection occurs within minutes or hours of the blood flow being commenced through the transplanted organ.

The immune response is an antibody mediated cytotoxic one. It causes the formed blood elements and clotting factors to be trapped in the microvasculature of the donor organ. This leads to immediate intravascular coagulation and thrombosis causing complete occlusion of blood vessels. Lack of tissue perfusion, necrosis and graft loss rapidly follows. The whole process can occur within the operating room (36). It is most often caused by ABO incompatibility.

### Accelerated Acute Rejection

Accelerated acute rejection is a variation of hyper acute rejection.

It is a cellular immune response and thought to be caused by the recipient being exposed previously to antigens present on the donor organ and leads to rapid formation of memory cells. This form of rejection occurs in the days

and weeks post transplant and will result in the loss of the donor organ (36).

### Acute Rejection

Acute rejection is a cellular immune response resulting in the activation and mobilisation of a variety of immune cells and may be called cellular rejection. It is the most common form of rejection and can occur from less than one week post-transplant onwards. The greatest risk for acute rejection is in the first 3-6 months(36). Literature on the topic reports incidences of acute rejection at between 48 and 65% in the first 12 months post-transplant (37, 38). Risk factors for rejection episodes include younger recipient age, although this is controversial, with some studies reporting better tolerance in infancy.

Older donor age, lack of renal impairment and prolonged cold ischemic times are also common factors. Acute liver failure as the cause of transplant has also been associated with increased episodes of rejection. Whilst acute rejection is most prevalent in the first 12 months it can occur at any time. Vigilant monitoring, early detection and aggressive treatment of acute rejection is very successful and rarely leads to graft loss in the current era. Smith suggests that a significant amount of time spent caring for an organ transplant recipient involves clinical assessment of the patient for episodes of rejection(36). In the CNS service this extends to arranging the logistics for timely administration of immunosuppressive agents to treat that rejection.

Adherence to medication taking is the most common cause of acute rejection episodes in the NZ program particularly within the adolescent age group.

### Chronic Rejection

Chronic rejection has a significant impact on graft and patient survival. Published data suggests that approximately 37% of donor livers are lost late (over 1 year post transplant) due to chronic rejection(39). Chronic rejection is associated with recurrent acute rejection episodes, further strengthening the argument for vigilant

monitoring post transplant.

Chronic rejection is thought to start at the time of transplant but does not manifest itself clinically for months or years. 8-12% of children may have subclinical chronic rejection (40). It can occur at the time of severe or recurrent episodes of rejection or insidiously over a long period of time. Chronic rejection causes significant damage to the arteries impacting on blood flow through the liver and is sometimes referred to as vascular rejection because of this (36). The physiological pathways causing chronic rejection are not well understood, it appears both T and B cells are involved along with non immune processes. It may in part be due to a chronically over primed parts of the immune system trying to counteract the changes caused by immunosuppression.

Risk factors for development of chronic rejection are known to include older donor age and prolonged cold ischemic time at transplant. However immunosuppression side effect such as hypertension, hyperlipidemia and diabetes mellitus all contribute to vascular disease so can therefore act to accelerate the degenerative process (40). Recurrent acute rejection and long term under immunosuppression are well known causes.

Chronic rejection is a much harder to treat. It involves the use of different classes of medications such as monoclonal antibodies and sometimes a change in baseline therapy as well as higher levels which generally slows rather than stops progression. Re transplantation is the only true cure so prevention of chronic rejection is imperative (36).

### Chronic Rejection

Chronic rejection has a significant impact on graft and patient survival. Published data suggests that approximately 37% of donor livers are lost late (over 1 year post transplant) due to chronic rejection(39). Chronic rejection is associated with recurrent acute rejection episodes, further strengthening the argument for vigilant monitoring post transplant.



Chronic rejection is thought to start at the time of transplant but does not manifest itself clinically for months or years. 8-12% of children may have subclinical chronic rejection (40). It can occur at the time of severe or recurrent episodes of rejection or insidiously over a long period of time. Chronic rejection causes significant damage to the arteries impacting on blood flow through the liver and is sometimes referred to as vascular rejection because of this (36). The physiological pathways causing chronic rejection are not well understood, it appears both T and B cells are involved along with non immune processes. It may in part be due to a chronically over primed parts of the immune system trying to counteract the changes caused by immunosuppression.

Risk factors for development of chronic rejection are known to include older donor age and prolonged cold ischemic time at transplant. However immunosuppression side effect such as hypertension, hyperlipidemia and diabetes mellitus all contribute to vascular disease so can therefore act to accelerate the degenerative process (40). Recurrent acute rejection and long term under immunosuppression are well known causes.

Chronic rejection is a much harder to treat. It involves the use of different classes of medications such as monoclonal antibodies and sometimes a change in baseline therapy as well as higher levels which generally slows rather than stops progression. Re transplantation is the only true cure so prevention of chronic rejection is imperative (36).

### Diagnosis of Rejection

Liver function tests are usually the first sign of rejection.

In all forms of rejection ALT and AST will rise in chronic rejection GGT and ALP may also be involved.

As always blood tests alone are only an indicator and the gold standard for diagnosis of rejection and identification of type of rejection is liver biopsy. This is organised as an urgent procedure.

Liver biopsy is performed under general anaesthetic and under ultrasound guidance. Urgent biopsies are done at SSH as turnaround time needs to be minimised and the biopsy needs to be read by someone with significant transplant experience due to difficulties in interpretation. The child will remain an inpatient whilst results are pending and treatment initiated as soon as results are known.

### Treatment of Rejection

High dose IV corticosteroids are first line treatment and for acute rejection this will be a three day course. Treatment for chronic rejection varies depending on the individual circumstances but will be more prolonged and potentially significantly more potent.

### SHARED CARE NOTE

- **Families should expect to stay in Auckland for approximately a week if rejection is diagnosed and longer if chronic rejection is found. This is to ensure treatment has been effective.**
- **Frequency of blood testing will be increased for an indefinite period post a rejection episode and immunosuppression levels are likely to remain higher than baseline for considerable time afterwards.**
- **Turnaround times on blood tests need to be minimised.**
- **If courier runs are being relied on for send away bloods please consider linking blood taking with courier schedules.**
- **Please avoid taking bloods on Fridays as results are likely to be delayed and intervention is harder to achieve on weekends.**

## Tolerance

Tolerance means that the immune system is capable of mounting response to antigens in general but appears to have a blind spot for a specific antigen reducing or even removing the need for immunosuppression post transplant (41). Induction of tolerance is considered the "Holy Grail" of transplant medicine.

Children are particularly at risk of complications associated with immunosuppression due to the longevity of post transplant treatment. Complications such as diabetes, renal impairment, infection and malignancies can significantly impact on the quality of life of transplant recipients.

Minimisation and withdrawal of immunosuppression in the post transplant period are hot topics of discussion and research. Identification of who can stop immunosuppression and not suffer rejection in any form is key to both patient and graft survival.

Many centres worldwide are performing scientific trials and much research is focussed on developing predictive laboratory testing. However at time of writing whilst there is some information indicating some children will not require immunosuppression post transplant there is no means of identifying which children they will be without significant risk. At this time the NZLTU is not participating in any clinical trials regarding tolerance. Families will often ask about lowering or withdrawing immunosuppression and we advise that whilst withdrawal may be an option in the future for some children at this time we aim to manage immunosuppression levels at the lowest therapeutic level possible for each child. It is important to note that each child is individual and direct comparisons between children's doses or levels should not be made in isolation. All changes in immunosuppression management should first be discussed with the SSH team.

## Infection

Infection has been reported as a greater risk to children than acute rejection in recent studies (37).

The balance between preventing rejection and preventing infection is a huge component of post transplant care.

All infections post transplant have the potential to be more prolonged or severe than would be anticipated in the general population and immunosuppressed children are at higher risk of disease complications. Early recognition and assessment of infection, vigilant patient monitoring and early intervention if complications are suspected is crucial to ensure recipient safety.

Common childhood illnesses can influence liver function temporarily and those such as viral gastroenteritis can play havoc with immunosuppression levels so increased monitoring is likely to be required.

## Transplant and Immunisation

Many post transplant children are at higher risk of vaccine preventable diseases. This is due to incomplete immunisation or poor seroconversion to immunisation due to presence of chronic illness.

Non live vaccines can be given safely and every opportunity to improve vaccination status should be taken. However live vaccinations have not been recommended in the immunocompromised population removing the ability for catch up immunisations after transplant (42).

There is a pool of literature and some international experience suggesting that live immunisation in certain circumstances post transplant may be relatively low risk and effective (43, 44). However the number of children included in the studies is very small and fall

into very specific groups so widespread vaccination with live vaccines is not recommended at this time. The NZLTU has begun immunising a small group of post transplant children with live vaccinations but this must be done under direction of the child's primary transplant consultant at SSH.

One way to protect children is to ensure all family members (close contacts) are protected. The immune population provides a barrier to the spread of a disease along with reducing the potential opportunity for exposure at an individual level. The percentage of the overall population who need to be immune to prevent outbreaks varies between diseases (45).

Some Infections cause significant concern in the post transplant setting and these are addressed individually below.

## Human Herpes Viruses

Human Herpes Virus (HHV) group includes a number of viruses common in the general adult population. The group includes, Herpes Simplex Virus, Varicella Zoster Virus, Epstein Barr Virus and Cytomegalovirus (46). A key component of HHVs is their ability to produce lifelong latent infection which reactivates when the right conditions are present, such as in the presence of immunosuppression (46) (47). Studies suggest that 25-30% of post solid organ transplant infections can be attributed to HHV's (47). Latent infection can be passed from donor to recipient via the latent virus within the graft organ (46). This is of particular concern in the paediatric population as most children are naive to EBV and CMV in particular whereas the majority of adults will have been exposed.

### Herpes Simplex Virus (HSV) type 1

Herpes simplex virus antibodies are carried by most adults and cause isolated or recurrent outbreaks of

lesions usually on the face and lips in the general population. Infection can also occur anywhere on the body including in the eyes and throat.

In immunocompromised people the virus can be far more aggressive and cause encephalitis and hepatitis. HSV hepatitis occurs through reactivation of latent virus and having an ABO incompatible live donor liver transplant confers the greatest risk of this complication. HSV hepatitis has a 33% mortality rate (48). Higher prevalence of HSV infection occurs in lower socioeconomic groups.

Virus is shed in saliva during blister formation but may be shed for days or even weeks after. It is spread by direct contact. Various triggers such as sunlight and minor injury may cause virus reactivation but often no obvious triggers are present.

Treatment with antiviral agents such as acyclovir is very effective against HSV and valganciclovir which is used as viral prophylaxis against CMV and EBV is also effective against herpes so infections may occur following withdrawal of valganciclovir at 3 months post transplant (49)

If HSV infection is suspected prompt medical review and vigilant monitoring are required.

### Varicella Zoster Virus (VZV)

VZV is one of our most challenging viruses post transplant due to its high prevalence in our community.

Primary infection with VZV will cause chicken pox and is known to affect more than 90% of the population by the late teen years. Epidemics are common and occur most frequently in late winter and spring (47). Transmission is via the respiratory tract. Chicken pox rash begins on the face and scalp and spreads rapidly to the torso. Vesicles can develop on mucous membranes such as the mouth and urinary tract.

VZV is usually more extensive, severe and prolonged in transplant recipients than the general population (47). VZV may not have typical presentation in the immunosuppressed person so any level of suspicion requires immediate attention. It may have potentially devastating consequences if left untreated. Up to 33 % of cases could become disseminated causing haemorrhagic pneumonia and skin lesions, encephalitis, hepatitis and disseminated intravascular coagulation (DIC).

Secondary infection (Shingles) is caused by reactivation of herpes zoster virus which has lain latent in the dorsal root ganglia of the spinal nerves (50). In immunocompetent individuals the rash remains localised to one area ( Dermatome) and lesions may remain for 2-3 weeks. In the transplant recipient the rash is often more widespread/ disseminated, may go on for many months, and can recur.

The shared care protocol outlines the process for determining direct contact criteria and follow-up action for both contact and presence of active infection.

### **Cytomegalovirus (CMV)**

CMV is the most common opportunistic infection post solid organ transplant (SOT) and a major cause of post transplant morbidity (51). CMV disease can occur as a result of primary infection, reactivation of latent infection or as a superinfection associated with a different virus or a different CMV strain (51).

The highest risk factor for developing CMV disease in the post solid organ transplant period is having a donor/ recipient mismatch. That is, a donor organ which is positive for latent infection (D +) and a virus naive recipient (R-) (46, 47, 51, 52). Some studies suggest that around 33% of recipients will become positive for CMV within the first 12 months post transplant (52).

Other risks include:

- High levels of Tacrolimus or Cyclosporin
- High dose steroids such as those doses used to treat rejection.
- Use of additional specific immunosuppression agents such as anti-thymoglobulin (ATG) and T cell monoclonal antibodies (e.g Rituximab) in the treatment of rejection.

CMV disease can occur in almost any organ system and its effects can range from subclinical viral replication through to disseminated fatal disease. Subclinical replication has been recently associated with decreased graft function and fibrosis (52), along with vanishing bile duct syndrome and accelerated chronic rejection (51).

Symptoms can include:

- Persistent fevers
- Neutropenia
- Thrombocytopenia
- Hepatitis,
- Diarrhoea
- Pneumonia

The greatest impact on the incidence of CMV post solid organ transplant has occurred through the use of prophylactic antiviral agents. These inhibit viral replication. No single regimen (agent or route of administration) has been proven to be superior(47). However it is generally accepted that whilst antiviral medications reduce the rate of infection this is only while the agents are in use (53). Much of the literature reports that prophylaxis only delays onset of infection suggesting that we need to maintain vigilance in screening CMV well beyond the duration of prophylaxis.

Monitoring for CMV is crucial in determining presence of subclinical viral loads and also in measuring response

to changes initiated to address development of CMV. In order to screen for this the CMV viral load is measured on a regular basis. In NZ this is monthly in the first 12 months and more frequently in those with active disease or increasing viral loads or those with unexplained or prolonged illness. The frequency of additional or reduced testing frequency is determined on an individual basis.

Treatment for CMV infection is most commonly with reduction in immunosuppression levels and initiation of a course of antiviral agent such as Valgancyclovir.

### **SHARED CARE NOTE**

- **Viral loads (both EBV and CMV) are processed by the Auckland A plus lab This is the only lab which processes viral loads in NZ.**
- **Each viral load request requires a separate EDTA tube of blood.**
- **Viral loads are generally processed by the lab on a Thursday.**
- **If rapid turnaround of results is required bloods need to be in Auckland by Wednesday PM, which in most instances requires collection to have occurred on the Monday or Tuesday to allow for delivery processes.**
- **Viral load results can be obtained directly from the A plus lab by phone.**
- **Please refer to the shared care protocol for additional information.**

### Epstein Barr Virus EBV

Like the other human herpes viruses EBV is capable of latent infection and infection can occur in the recipient from the donor graft.

Risks for EBV infection and the signs and symptoms of mild EBV disease are similar to those of CMV.

In addition previous or current infection with CMV increases the risk of EBV co- infection.

Events which trigger EBV proliferation are unclear and is thought to involve multiple factors. Whilst high serum viral loads generally create more concern, low loads have been associated with significant disease and some children will become chronic high load carriers for long periods of time with no clinical symptoms (54).

### Post Transplant Lymphoproliferative Disease (PTLD)

PTLD encompasses a rare group of syndromes ranging from benign self limiting forms through to aggressively malignant lymphomas with high rates of mortality (55). Definitions of forms of PTLD in the literature vary widely as it is an illness continuum. However, for ease of general understanding the following system is sometimes used to grade disease from 1-4 (56);

1. Non-specific viral syndrome
2. Mononucleosis (Glandular fever)
3. PTLD
4. EBV-associated malignant lymphoma such as Burkitt's lymphoma.

It is important to note that milder forms of PTLD can evolve into more serious forms. Recent studies suggest that improved treatment outcomes are directly related to early diagnosis and treatment (57)

Treatment for PTLD depends greatly on the severity of disease present. Treatment can range from reducing immunosuppression levels to allow natural disease control through to full chemotherapy in cases of Lymphoma. Due to small numbers of patients worldwide who have had PTLD, the variations in severity and the existence of many varied protocols there is limited evidence to determine the effectiveness of one protocol over another. Decisions regarding treatment are made on a case by case basis and will involve significant liaison between Starship and the local team (57).

#### SHARED CARE NOTE

Additional information can be obtained in the Shared Care Plan:

### Measles

Measles is a highly infectious virus and the most common vaccine preventable disease worldwide (58).

Along with the normal symptoms of rash fevers, conjunctivitis etc, diarrhoea, ear infections and pneumonia are significant complications of the virus. Pneumonia accounts for two thirds of measles related deaths (58). Measles Encephalitis occurs in approximately 1 in 1-2000 infections and is associated with significant morbidity and mortality rates. Children who are immunosuppressed have significantly higher disease severity and a greater risk of complications and than the general population.

Specific information on measles in transplant recipients is not readily available.

Whilst Measles vaccination is included in the standard immunisation schedule in NZ the reality is that the variation in vaccination levels allows regular measles

outbreaks to occur. In 2011 (January 1st to 1st December) 554 cases of measles were confirmed. The majority of these cases occurred in Auckland with 70 children in this region requiring hospitalisation. Eight other DHBs spanning the country also had cases reported and confirmed (58).

Children post liver transplant are at higher risk of measles infection as many will not have had the opportunity to receive complete vaccination due to transplantation occurring at a very young age or may not have mounted a sustained response due to the presence of chronic illness. MMR vaccination like other vaccinations has not been previously recommended for transplant recipients although in certain circumstances the primary transplant consultant may decide vaccination poses less risk to the child than the wild virus and vaccination may occur.

#### SHARED CARE NOTE:

If there is suspicion of measles contact please refer to the Shared Care Plan and notify the Starship team of the contact.

If measles infection is suspected please inform the Starship team as a matter of urgency so appropriate management can be initiated. Management is primarily supportive and involves the administration of immunoglobulin and consideration of reducing immunosuppression

## Bacterial Infections

Bacterial infections are most common in the early post operative period (1-2 months). Bacterial infections are seen in as many as 33-70% of post transplant patients (55, 59). They can be divided into four categories.

Infections related to

- Surgical or technical complications
- Prolonged hospitalisation (Nosocomial)
- The degree of immunosuppression (opportunistic)
- Community acquired infection

Infections often occur in central venous lines, surgical wound, biliary tract, respiratory tract blood stream or urinary tract. The presence of the Roux-en-Y loop of bowel is a significant risk factor for infection and almost all children will have this.

Infections may be caused by commonly encountered bacteria, but can also involve unusual pathogens only seen in the immunosuppressed population

High levels of suspicion and low threshold for initiating further investigations and antibiotic cover is recommended for all transplant recipients.

Specific recommendations are contained in the Shared Care Plan.

## Fungal Infection

The incidence of fungal infection in liver transplant recipients ranges between 4-50% depending on the study. The two most common causative agents of invasive fungal infection are *Candida* and *Aspergillus*(59).

*Candida* infection is substantially higher in liver recipients than any other transplant group and is thought to be due to the surgical disruption and

manipulation of the gut and biliary tree during transplant surgery and if it becomes invasive is associated with a 30% mortality rate(59).

*Aspergillus* is less common but with mortality being reported at 70% for invasive infection is an extremely serious complication.(59)

*Pneumocystis pneumonia* (Previously called *Pneumocystis Carnii* Pneumonia or PCP) is caused by a yeast like fungus and is the most common form of opportunistic pneumonia which occurs in around

10% of recipients without prophylaxis (59).

Most fungal infections occur within the first 100 days post transplant but *Pneumocystis* in particular can occur much later (60).

Risk factors for fungal infection include:

- Re transplant/ re laparotomy
- Prolonged surgery time (more than 11 hours)
- High use of blood product transfusions during surgery
- Prolonged intensive care stays
- Pre transplant use of steroids and antibiotic agents
- Treatment for acute rejection episodes
- Co infection, particularly with bacterial infection associated with prolonged broad spectrum antibiotic use pre transplant
- Renal impairment
- Fungal colonisation pre transplant or in the first few days post transplant (59-61)

Whilst there are a number of agents available to treat fungal infections treatment of invasive disease is complicated. Drug interactions and effects of renal toxicity need to be carefully managed. Prevention is a key

factor in the management of fungal infection.

Cotrimoxazole, the prophylactic management for *Pneumocytis*, is initiated at time of transplant and continues until 12 months.

Nystatin is used for the first three months post transplant in all recipients to prevent *candida* overgrowth.

Other agents are used after discussion with the infectious disease specialists if additional risk factors such as re laparotomy are present.



## Section 4 Healthy Living

Transplant is undertaken in order for children to have the opportunity to live as normal a life as possible and should be encouraged to do so in the majority of situations.

There are some considerations which do need to be taken into account for life but with due consideration we hope the impact will be minimal

### Returning to school or child care post transplant

Parents are often anxious about this and worry about infection.

Children can return to school or kindergarten 3 months post transplant providing the kindergarten is not part of a child care centre.

Children who do attend day care/ child care can return after 6 months. The variation in the return date reflects a number of factors including the age of the children present. Parental ability to keep mildly sick children at home is less in child care settings than kindergartens as they often need to negotiate time off work. Activities within the daycare include food preparation and service creating additional risk.

We recommend parents speak directly to the school principal along with the child's teacher prior to the child returning to school and the topics of discussion should include:

- Notification of infectious disease within the school such as chicken pox or measles
- What to do if others in the class have coughs and colds.

- What to do in case of accident or illness at school.
- Importance of simple hygiene and availability of soap for hand washing.
- Storage of emergency supplies of immunosuppression agents in case of civil defence emergency.
- The SSH CNS service is happy to provide a letter to the school if requested.

### Sport and Swimming

Contact sports such as rugby and martial arts are not recommended for post transplant patients as the liver is often exposed below the rib cage. However, if the liver is concealed or the child demonstrates an active interest in a particular sport, then options for participation should be investigated. All non contact sports should be encouraged as part of a healthy life style.

Swimming creates a particular set of challenges in the post transplant setting due to the risk of infection associated with the water source.

#### Hot pools/ Spa Pools

Swimming in hot pools (natural or manmade) or public spa pools is not recommended at any time post transplant as pathogens such as cryptosporidium may be present in the water. In the immunocompromised liver transplant patient this can be impossible to eradicate from the GI tract and can lead to infection within the liver which leads to significant morbidity long term and potential loss of graft. Private spa pools known to be well maintained and not recently used by someone unwell with an infectious disease such as gastroenteritis may be used in special circumstances after 12 months post transplant. The child and any other in the group must be old enough to follow rules such as not putting their head under and keeping their wet hands away from their mouth etc.

Public swimming pools are not recommended in the first 3–6 months post transplant but can be used after this providing they have not had recent treatment for rejection. Private and known to be well maintained pools are allowed.

Rivers/ lakes and sea are safe from an infection perspective at any time post transplant provided there are no health warnings and are suitable for the general population.

### Other Activities

Many of the transplant families undertake travel to many areas of the world without problems occurring.

Travel plans outside of NZ should be discussed with the medical team prior to bookings being made; Every effort will be made to assist families achieve their travel plans however a number of risks need to be considered, these include:

- What infections are endemic at the proposed destination?
- What additional vaccinations may be required and are they safe to give?
- Does the transplant recipient require additional precautions?
- Medical insurance is essential but can be difficult to obtain for overseas travel.
- Additional supplies of medications and where they will be carried during transit.
- What additional medical supplies should be carried?
- Medical travel letters and where to go if medical help is required.
- How to manage timing of medications through multiple time zones.



There are very few activities which cannot be undertaken by a transplant recipient but some will require a little more thought or planning than may normally be required. Please discuss any concerns with the transplant team before saying no to a family request.

## Diet and Weight

Cardiovascular risk factors are exponentially increased for transplant recipients. Risk factors caused to some degree by immunosuppressant medication include:

- Hypertension
- Dyslipidaemia,
- Impaired glucose tolerance
- Post transplant Diabetes Mellitus (62)

Excessive weight gain is also common after liver transplant with approximately 2/3rds becoming obese

All of these disorders increase the risk of fatty liver disease which can lead to cirrhosis (63).

Medications are tailored to meet individual needs, not only for immunosuppression, but also in relation to the side effects mentioned. Screening and management of weight, a healthy balanced diet and annual review bloods including screening for CVD risk factors from the time of transplant are all important in optimising post transplant outcomes.

## Oral Health

The combination of damage to teeth caused by pre transplant chronic illness and compromised nutrition along with post transplant immunosuppression and other medication regimens adds to additional patient risk in the post transplant period (64).

Dental assessment occurs as part of transplant

assessment and oral health is maximised at this time according to findings. However it remains important throughout post transplant life that professional dental care is maintained and every opportunity to should be taken to promote effective oral hygiene and prompt follow up of oral health issues.

Children who have had prolonged periods of jaundice during tooth development may have staining to milk and adult teeth. This does not pose any significant dental problems but may be unsightly and some families have considered cosmetic dentistry to overcome this.

## Skin Care

Information in the paediatric setting is limited as all large studies have been done in adults. Exposure to immunosuppression, multidrug regimens, and frequent hospitalisation all contribute to a number of skin diseases in post transplant children and young adults (65). Atypical forms of skin diseases, infections, photosensitivity, malignant and premalignant tumours along with acneiform eruptions are all reported in greater incidence amongst transplant recipients.

There is a well established link between chronic immunosuppression and malignancy. The incidence of malignancy increases with time post transplant (i.e. Time of exposure to immunosuppression) and 20% of recipients will have some form of skin malignancy by 10 years post transplant (66) Whilst PTLT remains the most common form of cancer post transplant skin cancers pose considerable risk in the New Zealand environment.

Australia and New Zealand have some of the highest rates of skin cancer in the world. One study in Australia reported approximately half of renal transplant recipients had contracted a non melanoma skin cancer after 20years post transplant (66).

Sun protection strategies recommended for the general population should be actively promoted with post transplant children of all cultures.

Monitoring and low threshold for dermatology examination is recommended.

Prompt treatment of skin infections or other changes is also recommended.

Review of medications may be required should skin disorders become a concern for the recipient as this may lead to non adherence with immunosuppression.



## Section 5 Youth Health and Transition

Professor Susan Sawyer says

"Young people need to be treated as young people first and transplant recipients second"(67).

Adolescence is a time of profound change for any family and when it includes a transplant recipient the issues are be substantially compounded. I will not attempt to cover the topic of adolescent health within this document as it is not an area of transplant specialist expertise.

As of Jan 2012 there is a cohort of 16 patients who have been identified as needing transition to adult care. Processes for supporting transition of liver transplant patients are being established and we expect this service to evolve over time.

However youth health and transition issues should not and cannot be ignored either. This section will highlight some of the additional challenges faced by transplant recipients during adolescent years and their transition to adult healthcare.

Adolescents with chronic disease are just as likely if not more likely than their healthy peers to engage in risk taking behaviours (67). In addition the risks associated with behaviours such as smoking, drinking and drugs are significantly higher in young people with chronic illness (67). This is especially so for liver transplant recipients where complications caused are insidious in nature and they will continue to feel well whilst considerable and sometimes irreversible damage is occurring.

It is anticipated that 80% of children undergoing transplant worldwide will survive to become teenagers

so this population will become a greater part of our day to day work (68).

Teenagers post transplant are often still coming to terms with living with a donated organ. Live donor transplant can increase the feeling of indebtedness experienced by transplant recipients decreasing their ability to move through the adolescent milestones which move them successfully towards independence (69).

Balancing the need for effective immunosuppression within the changing needs and lifestyle expectations of the adolescent transplant patient is critical to ensuring adherence and prevent graft loss (68).

Adolescence is associated with decreased medication adherence with some studies reporting non adherence as high as 71% and medium term graft loss for those in the adolescent group is higher than in any other age group, primarily due to non adherence, and is the most important single reason for organ rejection in long term survivors (70, 71).

Risk factors for non adherence include (72);

- Emotional and behavioural problems
- Learning difficulties
- Lower reported physical quality of life
- Parental emotional distance
- Decreased family cohesiveness
- Single parent families
- Low socioeconomic background

Immunosuppressant medication, like all other aspects of healthcare, needs to be acceptable and convenient for monitoring as well as being free of significant long term side effects (68).

It is important to note that subsequent transplants cannot be considered when non adherence is present and the transplant team are strict on this rule due to donor scarcity and contractual obligations regarding survival expectations.

Sexual related issues such as contraception and pregnancy need to be considered in relation to transplant medications and other risk factors associated with transplant.

Issues around reproductive health are primarily addressed by the primary care provider but collaboration between healthcare professionals is important in the shared care setting.

There is little information in the literature but what there is suggests that puberty is often delayed in transplant patients by 1-2 years and menarche will start late in line with this (73). There does not appear to be any increased incidence of problems with menarche in transplant recipients. Any issues should be dealt with in the same way as with any other adolescent.

It is important to assume that sexual relations will develop alongside that of their non transplant peers and that immunosuppression will increase risks associated with infections and does not reduce fertility in either sex (73). Sexually transmitted infection (STI) can be severe and difficult to eradicate in the immunosuppressed person. Viral infections such as Hepatitis B have significantly higher risk for the transplanted liver. Annual evaluation of immune status and vaccination is recommended if immunity wanes. Human Papilloma Virus (HPV) is a known trigger for cervical cancer and the presence of immunosuppression increases that risk. Vaccination is highly recommended for all transplant patients (73). Barrier methods of protection should be encouraged and prescribed where appropriate.

There are a number of contraception options available to transplant recipients and with careful attention to organ function, immunosuppression levels and other risk factors oral hormonal contraception can be used safely. Pregnancy post transplant is possible and there are many men and women who have become parents to healthy children in this setting. Where possible unplanned pregnancy should be avoided as planning will maximise safety of both mother and baby. If pregnancy occurs, the NZLTU recommends management by the high risk obstetric team based at ADHB.

Alcohol and illegal drugs are not recommended for liver transplant recipients and these need to be screened for and discussed using adolescent health principles.

Throughout the literature one key theme emerged and I believe is embraced in one single statement by Professor Susan Sawyer, an expert in adolescent health and transition: "Young people need to be treated as young people first and transplant recipients second" (67).



## Section 6 Post Transplant Medications:

This section is intended to provide an overview of the medications used and should not replace your pharmacy resources or Shared Care Plan advice.

### Immunosuppressant's

There are many medications which have an immunosuppressant effect. Each works on a different point within the immune system. Some have a wide range of effect and others much more focused on a specific link in the chain of immune response allowing other responses to remain active.

Immunosuppressant medications seen in the New Zealand program include

First line:

Used as multiple or single agent regimens depending on time post transplant and individual patient history

First line includes:

- Tacrolimus
- Steroids -methylprednisolone initially, then prednisone

orally

Renal sparing

Used when renal impairment is present at or after transplant and most often in addition to other agents.

- Mycophenolate Mofetil
- Basiliximab (at time of transplant and repeat dose 4 days later only)
- Cyclosporin
- Sirolimus

### Prednisone

Corticosteroids such as prednisone have some effect on almost every phase of the immune and inflammatory responses. Corticosteroids inhibit antigen presentation which is beneficial in transplant as the transplanted organ will continue to present antigens to the recipient immune system lifelong(41). Corticosteroids are also thought to inhibit cytokine production and proliferation of lymphocytes. Lymphocytes sensitised to the presence of the transplanted organ are kept out of the peripheral circulation reducing their ability to further attack the transplanted organ. Whilst there are significant benefits to using corticosteroids such as prednisone within the immunosuppression regimen, the side effects associated

with high and prolonged doses prevent their use as a sole agent and limit the length of time it is used.

Common side effects seen with corticosteroid use include:

- Sodium and fluid retention
- Impaired glucose tolerance / Diabetes Mellitus
- Hypertension
- Cushing syndrome
- Increased appetite
- Osteoporosis
- Peptic ulcers
- Acnes and/or Hirsutism

Prednisone is used routinely for 12 months following transplant. High doses will be used immediately after the transplant and the dose will be gradually weaned from approximately 3 months post transplant to a lower maintenance dose. Prednisone is usually withdrawn at one year after transplant if the one year biopsy shows no signs of subclinical rejection. It may continue beyond this time if the biopsy shows changes related to rejection, if there have been multiple episodes of rejection in the previous year or if the underlying cause for transplant involves autoimmune disease.

Prednisone should be given in the morning with food but the patient should still be taken if nil by mouth for a procedure .

Both prednisolone liquid and prednisone tablet forms are available in NZ. They are different but considered equivalent in terms of doses.





## Tacrolimus

Currently marketed in NZ as Prograf -generic brands may be available in the future.

Tacrolimus is a Calcineurin Inhibitor (CNI). The development of this class of drugs revolutionised transplant as they are considerably less toxic and far more specific in their action than corticosteroids and other medications previously available (41). There are 2 forms of CNIs available in NZ but tacrolimus is the most frequently prescribed agent. CNI's work by blocking the intracellular T signals responsible for cytokine production. Tacrolimus down regulates cytokine production but it does not stop it completely (41). This helps maintain immune response to infection increasing patient safety (41).

### Important notes:

- Tacrolimus is only available to liver transplant recipients as a capsule.
- Do not use generic medications unless specifically prescribed by the Starship team and do not switch between generic and Prograf brands as patterns of absorption may be different.
- It comes in 3 strengths 0.5mg, 1mg and 5mg
- Administration of tacrolimus must be at 12 hour intervals.
- Initially children are asked to fast 1 hour before and after administration to assist with stable absorption. This may be stopped by the Starship team to meet child and family needs but changes in administration method requires levels to be monitored.
- Tacrolimus doses vary greatly from patient to patient and blood levels need to be monitored.

- Tacrolimus is measured by a trough level pre the morning dose.
- Target levels will vary between patients depending on a number of factors:
  - Time post transplant
  - Episodes of rejection
  - Presence of other immunosuppression agents
  - Individual response
  - Recurrent opportunistic infection
- Tacrolimus is not soluble in water so doses should be prepared using whole capsules where possible.
  - For example; For a 4.5mg dose that need to be dispersed in water it is more accurate to use 4x 1mg caps plus 1x 0.5mg cap dispersed in water than to use 1x 5mg cap in 5 mls and take 4.5 mls.

Side effects of Tacrolimus include (55):

- |                  |                 |
|------------------|-----------------|
| • Hyperglycaemia | • Dyslipidaemia |
| • Nephrotoxicity | • Tremors       |
| • Alopecia       | • Neurotoxicity |
| • Headaches      |                 |

## Medication interactions

Many medications interact with tacrolimus and either raise or lower the blood levels. Tacrolimus may also alter the levels of other medicines. It is critical to ensure that all new medications including over the counter and herbal remedies are checked against the interaction list. Parents have a copy of this list in their parent book. It is also included in the Shared Care Plan.

Common interactions leading to elevated levels leading to possible toxicity;

Macrolide antibiotics -including

- Erythromycin
- Clarithromycin

Quinolones antibiotics-including

- Ciprofloxacin

Nonsteroidal analgesics such as ibuprofen

Antifungals -including

- Amphotericin (IV)
- Fluconazole

Cimetidine,  
Omeprazole

Reduced levels leading to possible rejection:

Anticonvulsants including

- Carbamazepine
- Phenobarbitone
- Phenytoin

Rifamycin antibiotics including

- Rifampicin,
- Rifabutin

Any new medication should be checked carefully against current pharmacologic data to ensure interactions are considered and adjusted for.

### SHARED CARE NOTE

**Families will return home with at least one month's supply and a script to present to their local pharmacy so that further supplies can be obtained. Please ensure families notify their pharmacy of the prescriptions in plenty of time.**

**Tacrolimus does require a special authority for dispensing and a lifetime authority will have been obtained the Starship team prior to discharge from Auckland.**

**Families should initially have a supply of both 0.5mg caps and 1mg caps as small dose changes may require a combination of strengths.**

**Tacrolimus is an expensive medication for pharmacies to hold in stock however we do ask that they always hold a small additional supply in case of emergency.**

**Families should be encouraged to have a minimum 2 weeks supply at home at any time and if the child spends prolonged periods away for the home such as school/ childcare or staying with family there should be an alternative supply in those places in case of emergencies.**

**Families should be taught and reminded about rotating back up stocks so they do not expire.**

**Please discourage parents from keeping Tacrolimus in cars or handbags as these are often exposed to high temperatures and may compromise the medication.**



## Cyclosporin

Cyclosporin was the first CNI developed in the mid 1970s and approved for use in 1983. It is rarely used in New Zealand transplant children as its absorption is variable making it more difficult to maintain stable blood levels. In addition its side effect profile (specifically hirsutism and gum hyperplasia) is less acceptable to patients particularly females.

There are a small number of children who commenced Cyclosporin at time of transplant when it was the only available CNI. They have achieved good immunosuppression with minimal or acceptable side effects and have remained on it in preference to changing to Tacrolimus. Cyclosporin can sometimes be used in cases where Tacrolimus has been poorly tolerated.

Important notes:

- Cyclosporin should be administered strictly 12 hourly in the same way as Tacrolimus.
- Initially children are asked to fast 1 hour before and after administration to assist with stable absorption. This may be stopped by the Starship team to meet child and family needs but changes in administration method needs levels to be monitored.
- Cyclosporin doses vary greatly from patient to patient and blood levels need to be monitored
- Cyclosporin is measured by a trough level pre the morning dose
- Target levels will vary between patients depending on a number of factors;
  - Time post transplant
  - Episodes of rejection

– Presence of other immunosuppression agents

- Cyclosporin is available in tablet and liquid forms.
- Do not use generic medications unless specifically prescribed by the Starship team and do not switch between generic and Neoral brands as profiles may be different.

Side effects of Cyclosporin include (55):

- |                  |                        |
|------------------|------------------------|
| • Headaches      | • Hirsutism            |
| • Tremors        | • Gingival hyperplasia |
| • Hyperglycaemia | • Hypertension         |
| • Nephrotoxicity | • Dyslipidaemia        |

## Mycophenolate Mofetil (MMF)

It is marketed in NZ as CellCept. There are several generic brands, also currently funded but not used by the NZ transplant service due to concerns regarding bioequivalence.

MMF is a potent immunosuppressant and works by preventing proliferation of both T and B cells and inhibits antibody formation.

MMF is used in NZ as part of the renal sparing protocol when children have known renal impairment either at time of transplant or post transplant. The use of MMF generally does not replace Tacrolimus as it is not proven to be equally effective as a single agent and is often poorly tolerated in the larger doses required. However it allows a reduced dose of Tacrolimus reducing renal toxicity. MMF may also be used in patients with problematic acute rejection. In this situation the Tacrolimus dose may not be reduced.

The side effects of MMF are predominantly

gastrointestinal causing diarrhoea nausea and vomiting.

Doses are often started low and once tolerance is established titrated up to therapeutic levels. MMF may also cause bone marrow suppression, so FBC will be monitored after it is commenced.

MMF does not require bloods for therapeutic levels and can be given at the same time as Tacrolimus providing it does not cause diarrhoea. Some patients will take it separately from tacrolimus due to GI and may take it with food to improve GI tolerance. Although it is usually taken twice daily dose may be split to three times daily if diarrhoea is a problem.

## Others

### Immunosuppressant's

Basiliximab, Sirolimus and Azathioprine are all immunosuppressant agents which are used in special circumstances. Basiliximab is an induction agent used at the time of transplant surgery. Sirolimus can be used in place of Tacrolimus and Cyclosporin and there are a few patients in New Zealand on this agent.

The field of immunosuppression agents continues to grow and new forms such as extended release

tacrolimus and other new agents may be used in transplant patients as required. Individual discussion and education will occur at the time of discharge back to the shared care teams as necessary.

## Medications

Antimicrobial medications including antibiotic, antifungal and antiviral agents are all used in the first 3 months post transplant to help counteract the increased risk of infection. The current preferred agents are described in the shared care plan and are commonly used in a number of settings.

## Section 7 Psychosocial Aspects

### Cultural considerations

New Zealand is becoming progressively more multicultural and the challenges of nursing across cultures is no different in the transplant setting. Families need to engage with the healthcare team and remain engaged over a number of years, so early recognition of family structure, supports and cultural needs is imperative. Changes in family coping or major stressors need to be identified and effective strategies need to be put in place to ensure ongoing adherence can be achieved and the child can make it safely into adulthood with their transplanted organ in good health.

Engaging cultural support services in an ongoing way can have enormous benefits to family coping and engagement.

### A Social Work Perspective

Written by Paediatric Social Workers Robyn Agnew and Haylee Riddell

Social work is an integrated part of the multidisciplinary clinical team managing children and families' pre and post liver transplant.

Paediatric social work recognises the needs and the best interests of the child as paramount. Social workers support the parents to meet this need.

Conversely where the parents are demonstrating that they are not able to prioritise the needs of their child, social workers complete further assessment and if necessary make a referral to Child, Youth and Family

(CYFS). This is completed in consultation with the MDT.

A key component of the social work role is to complete a pre transplant psychosocial assessment.

This assessment takes place prior to the patient being listed for organ transplant, and is usually a joint assessment with Consult Liaison. The purpose of the assessment is to determine whether the family have the willingness, strengths and capacity to manage the transplant process including the rigorous medical regime that follows a transplant.

### Key domains explored include:

#### Family

- Culture of the family: We will involve Kaiatawhai (ADHB Maori Health Service) for Maori families and the ADHB Pacific Island Family Support Service for Pasifika families. We will engage interpreters for families when English is a second language.
- Religious beliefs: These can be supportive to transplant and conversely create challenges that some families have to resolve.
- Family perspective on disease and transplant process. As above these can be mediated by cultural beliefs of antipathy to transplant.
- Family dynamics: Any sound relationship can be challenged by the demands of the pre transplant process and the process of caring for a seriously ill child over time.
- Family structure: This must be explored in order to understand how the family functions.
- Mental health diagnoses. This is not a barrier to transplant. We work alongside the Consult

Liaison Team (the Starship inpatient psychological

services) to identify what support the family needs. Sometimes psychiatric services will be required other times more general support from Social Work.

#### Social Situation

- Financial: Parents may need to leave employment to care for the child over time. This will have an impact on family finances. Living costs apply in Auckland whilst the family attends Starship even though their local DHB supports accommodation at the RMDH.
- Housing: There are costs in maintaining their usual home. The family need to have a healthy home (dry, warm) for the child to be safely discharged to.
- Education: A general overview of the child's education to date is gained to support continued education at the Northern Health School at Starship.
- Formal Supports: Documentation completed for: Registration at Ministry of Health for travel and accommodation; Carer Support; Child Disability Allowance.

#### Risk Assessment

We need to have robust plans to manage families over time and the following areas of risk to any child need to be explored.

- Child protection: Any history of Child Youth and Family involvement needs to be further assessed to ascertain any current concerns.
- Family Violence. Any history is predictive of further events unless a successful intervention has occurred. If there has been an incident in the previous 12 months it is assumed that further assessment is required.
- Drugs and Alcohol use: The hospital has Policy of no drug and alcohol use on the premises.

This is a problem for some families. We can link to community alcohol and drug support services. We need functioning support from parents for their child, to assist the child with the transplant process.

## Key Themes for Transplant Families

- Longevity of care prior to transplant:
  - The impact of ongoing medical crisis including life and death situations.
  - Emotional rollercoaster experienced by the family whilst waiting for an organ.
  - Exhaustion/sleep deprivation/development of depressive symptoms in the supporting family.
  - Logistical issues can be a nightmare for families living outside of Auckland. The families are accommodated at Ronald McDonald House but they still have to maintain a couple relationship and relationship with the family left at home, whilst providing one on one caring for the child in hospital.
  - A universal issue for families regardless of where they are domiciled is the maintenance of the family unit i.e. Sibling relationships, parents maintaining relationships with their other children, couple maintenance.
  - Family geographically separated from their support community. Although the hospital tries to provide supports for the family, it is impossible to replicate what the family has in their home environment. As a result of this the family can experience strong emotions at times relating to their feelings of dislocation and disempowerment.
  - Depending on the families previous experience in the course of this illness or other illnesses feelings of mistrust of the MDT can arise. This can inhibit relationships with the team. A lot of time needs to be

spent engaging trust and maintaining it.

- Pre transplant care requirements:
  - Training parents to manage their seriously ill child – social workers provide non medical support to encourage parental adherence with the medical regime. We provide liaison and advocacy for the parents with the medical team.
- When to involve social workers.
  - At any time during an admission.
  - Any time there is concern for a child's safety or wellbeing. In particular in relation to transplant the ability of the parents to provide consistency of care in the pre transplant period.
  - Regular MDT meetings allow the free exchange of information that will throw light on issues that any part of the MDT may have in managing the often competing needs of the child and family.
  - This works both ways i.e. The social worker may pick up a current issue or another discipline may do so as well. Often these issues can be sorted quite quickly. However the MDT should be the sounding board for emerging problems. If several different disciplines are experiencing difficulties then free discussion of issues can occur in the MDT and joint plans can be quickly initiated.

## Tips, Tricks and Warning Signs

- Be on the alert for parental sleep deprivation – If a concerted ward plan is put in place to manage the parents need for sleep this can avoid major emotional blow outs on the ward. Sleep deprivation can coincide with a medical crisis in the care of the child and if this happens it is a potent cocktail creating major emotional problems for the ward to manage.
- Post transplant period can be just as difficult

emotionally for parents and the child to manage while stability is being achieved by the medical team. Parents often expend so much energy in the pre transplant period waiting for the organ that when the transplant occurs they are quite often not prepared for the ongoing instability and complications which can occur in the post transplant phase. By this time they are exhausted and need support usually of the extended family.

## Frequently Heard

- “I’m sitting here watching my child die, what are you going to do about it?”
- “I didn’t realise it would be harder after transplant than before”
- “I’m sick of all of this”
- “I can’t handle this” (In relation to watching their child undergo painful procedures).

Finally, it is a great privilege to be so closely involved in all aspects of family life, seeing families at their absolute best and when they are in crisis. It is a team effort to manage, contain and support the emotional rollercoaster that is the life and death nature of liver transplant work.

### SHARED CARE NOTE:

**The social work service is an essential part of the transplant team and develop a significant knowledge of each family while they are in Auckland. Social Workers do not take responsibility for ongoing management of these families once they return home, but they are more than willing to share their insights and support their local colleagues in the same way the CNS service supports shared care nurses.**

# References

1. Sherlock Sheila, Dooley James. Diseases of the Liver and Biliary System. 10th ed. London: Blackwell Science Ltd; 1997.
2. Chandra R. K. The Liver and Biliary System in Infants and Children. Edinburgh: Churchill Livingstone; 1979.
3. Baker A, Stevenson R, Dhawan A, Goncalves I, Socha P, Sokal E. Guidelines for nutritional care for infants with cholestatic liver disease before liver transplantation. *Pediatric Transplantation*. 2007;11(8):825-34.
4. Mohammad S AEM. Approach to Optimizing Growth, Rehabilitation and Neurodevelopmental Outcomes in Children After Solid-organ Transplantation. *Pediatric Clinics of North America*. 2010;57:539-57.
5. Herbison K YR. Nutrition for kids with liver disease. [Presentation]. In press 2009.
6. Suchy FJ, Sokol RJ, Balistreri WF, editors. *Liver Diseases in Children*. New York: Cambridge University Press; 2007.
7. Wright I. Esophageal Varices: Treatment and Implications. *Gastroenterology Nursing* 1998;21(1):2-5.
8. Molleston JP. Variceal Bleeding in Children. *Journal of Pediatric Gastroenterology & Nutrition*. 2003;37(5):538-45.
9. Shneider B, Emre S, Groszmann R, Karani J, McKiernan P, Sarin S, et al. Expert pediatric opinion on the Report of the Baveno IV Consensus Workshop on Methodology of Diagnosis and Therapy in Portal Hypertension. *Pediatric Transplantation*. 2006;10(8):893-907.
10. Zargar SA, Javid G, Khan BA, Yattoo GN, Shah AH, Gulzar GM, et al. Endoscopic ligation compared with sclerotherapy for bleeding esophageal varices in children with extrahepatic portal venous obstruction. *Hepatology*. 2002;36(3):666-72.
11. Kramer RE, Sokol RJ, Yerushalmi B, Liu E, MacKenzie T, Hoffenberg EJ, et al. Large-Volume Paracentesis in the Management of Ascites in Children. *Journal of Pediatric Gastroenterology & Nutrition*. 2001;33(3):245-9.
12. Saravanan R, Cramp M E. Investigation and treatment of Ascites Clinical medicine. 2002;2(4):310-3.
13. Debray D, Yousef N, Durand P. New management options for end-stage chronic liver disease and acute liver failure: potential for pediatric patients. *Paediatric Drugs*. 2006;8(1):1-13.
14. Maskell G. Paediatric Respiratory Assessment Learning Package. 2001.
15. Deepak G V, Hugo R R. Abnormal Findings on Liver Function Tests. *Postgraduate Medicine*. 2000;107(2).
16. Shepherd Ross. Evaluation and Management of Elevated Liver Transaminases. [Presentation]. In press 2011.
17. Tanner S. *Current Reviews in Paediatrics*. 1st ed. Melbourne: Churchill Livingstone; 1989.
18. Halaweish I, Chwals WJ. Long-term outcome after partial external biliary diversion for progressive familial intrahepatic cholestasis. *Journal Of Pediatric Surgery*. 2010;45(5):934-7.
19. Alissa FT, Jaffe R, Shneider BL. Update on Progressive Familial Intrahepatic Cholestasis. *Journal of Pediatric Gastroenterology & Nutrition*. 2008;46(3):241-52.
20. Ganesh R, Suresh N, Sathiyasekaran M, Ramachandran P. Partial internal biliary diversion: A solution for intractable pruritus in progressive familial intrahepatic cholestasis type 1. *Saudi Journal of Gastroenterology*. 2011;17(3):212-4.
21. Allen K, Soriano H E. Liver Cell Transplant; the road to clinical application. *Journal of Laboratory and Clinical Medicine*. 2001;138(5):298-312.
22. Cochran JBDO, Losek JDMD. Acute Liver Failure in Children. *Pediatric Emergency Care*. 2007;23(2):129-35.
23. United Network for Organ Sharing. UNOS Survival Data. 2011 [30/9/2011]; Available from: <http://optn.transplant.hrsa.gov/data/default.asp>.
24. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, et al. MELD and PELD: Application of survival models to liver allocation. *Liver Transplantation*. 2001;7(7):567-80.
25. Forsberg A, Nilsson M, Krantz M, Olausson M. The essence of living parental liver donation – donors' lived experiences of donation to their children. *Pediatric Transplantation*. 2004;8(4):372-80.
26. Emre S. Living-donor liver transplantation in children. *Pediatric Transplantation*. 2002;6(1):43-6.
27. Steinbrook R. Organ Donation after Cardiac Death. *New England Journal of Medicine*. 2007;357(3):209-13.
28. Faraj WMD, Dar FF, Bartlett AMD, Melendez HVMDP, Marangoni GMD, Mukherji DM, et al. Auxiliary Liver Transplantation for Acute Liver Failure in Children.

- Annals Of Surgery. 2010;251(2):351-6.
29. Alonso EM. Growth and developmental considerations in pediatric liver transplantation. *Liver Transplantation: Official Publication Of The American Association For The Study Of Liver Diseases And The International Liver Transplantation Society*. 2008;14(5):585-91.
  30. World Health Organisation. WHO Global Database on Child Growth and Malnutrition. World Health Organisation; 2011 [cited 2011 28/11/2011]; Available from: <http://www.who.int/nutgrowthdb/about/introduction/en/index4.html>.
  31. Fine RN. Growth following solid-organ transplantation. *Pediatric Transplantation*. 2002;6(1):47-52.
  32. Alonso EM, Sorensen LG. Cognitive development following pediatric solid organ transplantation. *Current Opinion In Organ Transplantation*. 2009;14(5):522-5.
  33. Sharma S, Gurakar A, Jabbour N. Biliary strictures following liver transplantation: Past, present and preventive strategies. *Liver Transplantation*. 2008;14(6):759-69.
  34. Gunawansa N, McCall JL, Holden A, Plank L, SR M. Biliary complications following orthotopic liver transplantation: a 10-year audit. *Hepato Pancreato Biliary Journal*. 2011;13(6):391-9.
  35. Reichert PR, Renz JF, Rosenthal P, Bacchetti P, Lim RC, Roberts JP, et al. Biliary complications of reduced-organ liver transplantation. *Liver Transplantation and Surgery*. 1998;4(5):343-9.
  36. Smith Susan. Immunologic Aspects of Organ Transplantation 2002: Available from: <http://www.medscape.com/viewarticle/436533>.
  37. Martin SR, Atkison P, Anand R, Lindblad AS, The SRG. Studies of Pediatric Liver Transplantation 2002: Patient and graft survival and rejection in pediatric recipients of a first liver transplant in the United States and Canada. *Pediatric Transplantation*. 2004;8(3):273-83.
  38. Turmelle YP, Nadler ML, Anderson CD, Doyle MB, Lowell JA, Shepherd RW. Towards minimizing immunosuppression in pediatric liver transplant recipients. *Pediatric Transplantation*. 2009;13(5):553-9.
  39. Hind JM, Kelly DA. Pediatric liver transplantation: Review of the literature 2006-2007. *Pediatr Transpl*. 2009;13(1):14-24.
  40. Denmetris A J, Duquesnoy R J, Fung J, Murase N, Nalesnik M, Randhawa P, et al. Pathophysiology of Chronic Allograft Rejection 2000: Available from: <http://www.medscape.org/viewarticle/418503>.
  41. Smith Susan. Immunosuppressive Therapies in Organ Transplantation. 2002: Available from: <http://www.medscape.com/viewarticle/437182>.
  42. Ministry Of Health. Immunisation Handbook 2006. Wellington: Ministry of Health; 2006.
  43. Khan S, Erlichman J, Rand EB. Live virus immunization after orthotopic liver transplantation. *Pediatric Transplantation*. 2006;10(1):78-82.
  44. Chaves T, Lopes MH, De Souza V, Santos S, Pereira L, Reis A, et al. Seroprevalence of antibodies against varicella-zoster virus and response to the varicella vaccine in pediatric renal transplant patients. *Pediatric Transplantation*. 2005;9(2):192-6.
  45. Fine PEM. Herd Immunity: History Theory Practice. *Epidemiologic Reviews*. 1993;15(2):256- 302.
  46. Razonable RR, Brown RA, Humar A, Covington E, Alecock E, Paya CV. Herpesvirus infections in solid organ transplant patients at high risk of primary cytomegalovirus disease. *Journal of Infectious Diseases*. 2005;192(8):1331-9.
  47. Slifkin M, Doron S, Snyderman DR. Viral prophylaxis in organ transplant patients. *Drugs*. 2004;64(24):2763-92.
  48. Hori T, Ogura Y, Okamoto S, Nakajima A, Kami K, Iwasaki J, et al. Herpes simplex virus hepatitis after pediatric liver transplantation. *Transplant Infectious Disease: An Official Journal Of The Transplantation Society*. 2010;12(4):353-7.
  49. Ljungman P. Prophylaxis against herpesvirus infections in transplant recipients. *Drugs*. 2001;61(2):187-96.
  50. Tan H, Goh C. Viral infections affecting the skin in organ transplant recipients: epidemiology and current management strategies. *American Journal of Clinical Dermatology*. 2006;7(1):13-29.
  51. Campbell AL, Herold BC. Strategies for the prevention of cytomegalovirus infection and disease in pediatric liver transplantation recipients. *Pediatric Transplantation*. 2004;8(6):619-27.
  52. da Cunha-Bang C, Sørensen SS, Iversen M, Sengeløv H, Hillingsø JG, Rasmussen A, et al. Factors associated with the development of cytomegalovirus infection following solid organ transplantation. *Scandinavian Journal of Infectious Diseases*. 2011;43(5):360-5.
  53. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients (Review) [database on the Internet]. John Wiley and Sons Ltd. 2010. Available from: <http://>



- www.thecochranelibrary.com/.
54. Green M, Soltys K, Rowe DT, Webber SA, Mazareigos G. Chronic high Epstein-Barr viral load carriage in pediatric liver transplant recipients. *Pediatric Transplantation*. 2009;13(3):319-23.
  55. Cupples Sandra A, Ohler Linda. *Transplant Nursing Secrets*. Scheetz Linda J, editor. Philadelphia: Hanley and Belfus Inc; 2003.
  56. Green M, Michaels MG, Webber SA, Rowe D, Reyes J. The management of Epstein-Barr virus associated post-transplant lymphoproliferative disorders in pediatric solid-organ transplant recipients. *Pediatric Transplantation*. 1999;3(4):271-81.
  57. Kerkar N, Morotti RA, Madan RP, Shneider B, Herold BC, Dugan C, et al. The changing face of post-transplant lymphoproliferative disease in the era of molecular EBV monitoring. *Pediatric Transplantation*. 2010;14(4):504-11.
  58. Immunisation Advisory Centre. Health Professionals on Line Resource Centre- Measles. University of Auckland; 2004 [January 7 2012]; Available from: <http://www.immune.org.nz/?t=753>.
  59. Lapointe- Rudow Dianne, Ohler Linda, Shafer Teresa. *A Clinicians Guide to Donation and Transplantation*. Lanexa, KS: Applied Measurement Professionals Inc 2006.
  60. Teisseyre J, Kaliciński P, Markiewicz-Kijewska M, Szymczak M, Ismail H, Drewniak T, et al. Aspergillosis in children after liver transplantation: Single center experience. *Pediatric Transplantation*. 2007;11(8):868-75.
  61. Verma A, Wade JJ, Cheeseman P, Samaroo B, Rela M, Heaton ND, et al. Risk factors for fungal infection in paediatric liver transplant recipients. *Pediatric Transplantation*. 2005;9(2):220-5.
  62. LaRosa C, Jorge Baluarte H, Meyers KEC. Outcomes in pediatric solid-organ transplantation. *Pediatric Transplantation*. 2011;15(2):128-41.
  63. Nobili V, Dhawan A. Are children after liver transplant more prone to non-alcoholic fatty liver disease? *Pediatric Transplantation*. 2008;12(6):611-3.
  64. Shiboski CH, Kawada P, Golinveaux M, Tornabene A, Krishnan S, Mathias R, et al. Oral disease burden and utilization of dental care patterns among pediatric solid organ transplant recipients. *Journal Of Public Health Dentistry*. 2009 2009 Winter;69(1):48-55.
  65. Dornelles da Silva Manzoni AP, Kruse RL, Troian C, Cunha VS, Cestari TF. Skin changes in pediatric transplant patients. *Pediatric Transplantation*. 2006;10(2):210-4.
  66. Tredger JM, Brown NW, Dhawan A. Immunosuppression in pediatric solid organ transplantation: Opportunities, risks, and management. *Pediatric Transplantation*. 2006;10(8):879-92.
  67. Kennedy Aa, Sawyer Sabc. Transition from pediatric to adult services: are we getting it right? *Current Opinion in Pediatrics*. 2008;20(4):403-9.
  68. Kelly DA. Optimal immunosuppression in teenagers. *Pediatric Transplantation*. 2002;6(6):480-7.
  69. Aujoulat I, Schwering KL, Reding R. Living-related donation: a challenge to adolescent transplant recipients who transit from parental care to self-managed care. *Child: Care, Health and Development*. 2011:no-no.
  70. McDonagh JEab, Kaufman Mab. Transition from pediatric to adult care after solid organ transplantation. *Current Opinion In Organ Transplantation*. 2009;14(5):526-32.
  71. Burdelski MM. Pediatric liver transplantation review of the literature 2007–2008. *Pediatric Transplantation*. 2009;13(8):948-54.
  72. Stuber ML, Shemesh E, Seacord D, Washington J, Hellemann G, McDiarmid S. Evaluating non-adherence to immunosuppressant medications in pediatric liver transplant recipients. *Pediatric Transplantation*. 2008;12(3):284-8.
  73. Sucato GS, Murray PJ. Gynecologic health care for the adolescent solid organ transplant recipient. *Pediatric Transplantation*. 2005;9(3):346-56.





The  
**Kids**  
Foundation  
key immune deficiency support

