the children's hospital at Westmead

LIVER TRANSPLANTATION - CHW

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Children requiring liver transplantation have complex medical needs.
- Thorough medical assessment is performed before the decision to place on the liver transplant waiting list.
- Thorough post-transplant medical and nursing care is critical to ensure good outcomes.
- Careful attention to fluid balance, central venous pressure and biochemical and haematological parameters in the intensive care post-transplant is paramount.
- Early loss of the hepatic arterial doppler ultrasound trace should be immediately communicated to the liver transplant team.
- Appropriate nutritional support is an important part of success in liver transplantation.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
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CHANGE SUMMARY

- Addition of section 1.4
- Number of Units of blood products amended from 10 to 5 (Section 3)
- Other information added:
  - HLA (p8),
  - boxed area (p10),
  - Addition of 'blood tests' to section 4.1,
  - Basiliximab p13,
  - changes in the 'other medications' section p14,
  - Pages 17 – 18: addition of sections Sudden Intra-Abdominal Haemorrhage, Sepsis, Primary Graft Non-Function and Hepatic Artery Thrombosis.
  - Page 25 – more information about viral infections.

READ ACKNOWLEDGEMENT

- Medical and Nursing staff caring for Liver transplant patients should read and acknowledge this document.

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1 Introduction

1.1 Transplant Indications

Patients requiring liver transplantation have the following features: [1-5]

- irreversible, progressive or end-stage liver disease
- acute hepatic failure
- an inborn error of metabolism that only liver transplantation can correct
- absence of contraindications to transplant (see below)
- ability of the patient and their family to understand and accept the inherent risks and potential outcomes of liver transplantation.

1.2 Absolute Contraindications

Include: [6]

- serious infection outside the hepatobiliary system
- irreversible, severe and/or progressive brain injury
- irreversible cardiac, renal or pulmonary disease*
- primary malignant disease outside the hepatobiliary system
- metastatic hepatobiliary malignancy

(* With certain diseases, combined organ transplants may be possible, e.g. in hyperoxaluria type I, combined liver and kidney transplantation; in cystic fibrosis, heart-lung-liver transplant.)

1.3 Relative Contraindications

(dependent on the specific clinical situation) Include:

- intrahepatic or biliary sepsis.
- portal vein thrombosis / occlusion (may exclude live donation).
- infection with HIV (now a relative contraindication in adult patients)
- portal venous or hepatic vascular anomalies which may make transplantation impossible.
- hepatopulmonary syndrome with severe hypoxaemia from intrapulmonary A-V shunting, and portopulmonary syndrome with severe pulmonary hypertension.
- Immunodeficiency (in specific circumstances children with liver disease due to immunodeficiency may be considered for liver followed by bone marrow transplantation)

1.4 ABO Incompatible Liver Transplantation

Children are usually transplanted with organs from ABO compatible donors. In uncommon situations, such as urgent liver transplantation, an organ from an ABO incompatible (ABOi) donor may be used. These transplants have historically higher risks of rejection, as well as vascular and biliary complications. More recent evidence suggests that ABOi liver transplants can be successfully performed in infants under 12 to 18 months of age, due to the relative "immaturity" of the immune system at that age which is reflected in low or absent levels of naturally occurring anti-A and B antibodies. [7]

Measures reported to prevent the complications of ABOi transplantation include plasmapharesis, splenectomy and the use of rituximab, an anti-CD20 monoclonal antibody which selectively eliminates B cells [8]. Several children at CHW have successfully received ABOi liver transplants using Rituximab alone, without the need for either plasmapharesis or splenectomy.

The following approach to ABOi at CHW is as follows, organised by the Liver Transplant team:

- measurement of anti-donor blood group antibody titres (anti-haemolysin) in the recipient, both pre- and post-transplant
- consider giving rituximab (375 mg/m^2) pre-transplant, although this is not usually required in infants < 12-18 months old
- Possible additional use of Basiliximab (Interleukin-2 receptor antibody) at Day 0 and day 4
- monitoring of anti-donor haemolysin titres post-transplant
- immunosuppression with tacrolimus, corticosteroids, mycophenolate mefotil

2 Initial Inpatient Evaluation of the Paediatric Liver Transplant Candidate

Children undergo assessment for suitability for liver transplantation as both an inpatient and an outpatient. Assessment includes numerous blood tests, imaging and consultation with various specialists involved in the care of liver transplant patients. Additional tests and consultations may be indicated for individual patients.

The transplant work-up is arranged and coordinated by the Liver Transplant CNC. Any issues regarding investigations or bookings should be directed to the CNC.

2.1 Blood Tests

1. Serum FBC, UEC, CMP, LFT, CPK
2. thyroid function tests (TFT)
3. Coagulation profile
4. Infectious serologies:

i. Hepatitis A IgG (if positive for total HAV then HAV IgM will be done to check for acute infection)

ii. Hepatitis B surface Ag, Hep B surface Ab, core Ab

- if surface Ag positive check e Ag, e Ab and HBV PCR; also check Hep D IgM and IgG

iii. Hepatitis E IgG

iv. Hepatitis C ab

v. EBV nuclear antigen IgG and EBV viral capsid antigen IgG; EBV viral capsid antigen IgM

vi. CMV IgG; CMV IgM

vii. herpes simplex IgG; herpes varicella zoster IgG; human herpes virus-6 IgG;

viii. serology for childhood vaccinations (done according to the patient's age):

- rubella IgG; measles IgG; mumps IgG;

ix. assess vaccination status for pneumococcus, meningococcus, polio, Haemophilus influenzae b, Diphtheria, Tetanus and Pertussis via history and "blue book"

5. HIV-1 and HIV-2 antibody (requires consent)
6. Blood group and red cell antibody screen

HLA typing and leucocyte antibody screen (Sent to Red Cross, Sydney – arrange with Blood Bank at CHW).

This entails quite a lot of blood for small infants and may need to be discussed on a case by case basis with the Red Cross Blood Service (pH 92342345, 92342322, 92342360: ask for either Gina Melick, Senior Scientist or Rebecca Gavin).

i. HLA (in ACD tube):
   1. If < 8 years: 5 mL
   2. If > 8 years: 30 mL

ii. Blood group = 0.5 mL

iii. Cross match = 1.5 mL

iv. Antibody screen = 5 mL (clotted tube)

7. serum alpha feto protein
8. serum cholesterol, triglycerides and bile acids (fasting if possible)
9. serum zinc, folate, RBC folate
10. serum vitamins A, 25 (OH) Vit D, E, C, B12
11. ammonia
12. amylase, lipase
13. lactate

14. Baseline thrombophilia screen (if portal vein thrombosis present, or being retransplanted for hepatic artery thrombosis)
15. Serum immunoglobulins A, G, M

2.2 Other Tests

1. Microurine; urinary analysis; protein:creatinine ratio
2. Chest X-ray
3. Doppler ultrasound of portal vein, hepatic artery and liver; if required by surgeon, further anatomical delineation (CT or MRAV). Alagille syndrome patients should undergo abdominal angio CT
4. ECG, echocardiogram (requires Cardiology consultation)
5. Pulse oximetry overnight (arterial blood gases if oximetry is abnormal)
6. Cystatin C (formal GFR if abnormal or pre-existing kidney disease).
7. Bone Mineral Density (Dexa) Scan (if > 4 years age)
8. MRI brain scan (discuss with consultant – e.g. for Wilson's Disease, Alagille syndrome)
9. Baseline audiology
10. Mantoux test
11. Consider lung function tests, sputum analysis (especially if patient has cystic fibrosis)
12. MRSA and *Staphylococcus aureus* screening swabs of nose and throat – will need repeating every 3 months while waiting for transplant. Especially important for those infants treated for pruritus with long-term Rifampicin.
13. Metabolic liver disease testing – as discussed with metabolic service
14. Baseline developmental assessment (Occupational Therapy)

2.3 Consultations

Please arrange formal consults for the following:

1. Paediatric Liver Transplant Surgeon On-Call (Drs Shun, Thomas, Karpelowsky, Lawrence, Alexander)
2. The Hepatology CNC will show families the Paediatric Intensive Care Unit. In specific circumstances formal PICU consultation may be required.
3. Anaesthetics – contact Anaesthetic Department and inform the on-call Liver Transplant Anaesthetist
4. Department of Psychological Medicine
5. Cardiologist (for clinical assessment and baseline echo)
6. Liver Transplant Social Worker
7. Occupational Therapist

8. Dietitian
9. Dentist
10. Liver Transplant Co-ordinator and Transplant Surgeon based at Royal Prince Alfred Hospital (Australian National Liver Transplant Unit) – CNC will arrange this.

2.4 Consent

All children undergoing Liver Transplantation and their parents are fully informed about the process and the risks. They have undergone an extensive educational exercise. A fully comprehensive Liver Transplantation Consent form is signed prior to listing and this is filed in the child's medical record. A copy is kept in a file on Clancy ward in the NUM's office.

Consent should be obtained by the liver transplant surgeon, or if unavailable one of the transplant physicians. The child's parents also have a copy of this. If living related donation is being considered the family will receive extensive counselling and information booklets outlining this procedure.

After 12 months consent will lapse and further consent signing is necessary.

In addition there should be a "long term" consent taken for receiving blood products as necessary.

2.5 Immunisations [6,9]

Children awaiting liver transplantation should have all their routine immunizations up to date.

Live virus vaccines:

1. Measles, mumps and rubella (MMR) vaccine can be given from 9 months of age, assuming they have negative measles serology. The presence of measles antibody in infants usually reflects maternal transmission and indicates that vaccination is not feasible at that time.
2. Varicella can be given from around 9 months of age (if no previous chicken pox or evidence of immunity to varicella).
3. Pneumococcal and meningococcal vaccination, as well as Hepatitis A and B, should also be undertaken.

   Specific immunisation guidelines are available for pre and post liver transplant patients. Consultation with an immunisation specialist can be sought if necessary. Rotavirus vaccine should also be considered pre-transplant.

2.6 Liver Transplant (Clancy) Ward and Paediatric Intensive Care

During the assessment family members will become familiar with the hospital, and in particular Clancy Ward and the nursing staff involved with the care of liver transplant patients. The child and their family will also visit the Paediatric Intensive Care Unit.

3 Pre-Operative Protocol

The Liver Transplant Coordinator (based at the Australian National Liver Transplant Unit at Royal Prince Alfred Hospital) is responsible for managing the following logistics of the liver transplant at CHW:

- Informing the surgeon, Anaesthetist, on-call Gastroenterologist, AHNM (After Hours Nurse Manager), Intensive Care, Blood Bank, Clancy Ward and the family of the planned transplant procedure
- In working hours the Coordinator also contacts the Operating Theatre; out of hours this is done by the AHNM.
- The donor blood group is faxed by the Coordinator to the Operating Room "attention to anaesthetist".
- The timing of transplant is decided by consultation between the donor surgical team, the recipient (CHW) surgeon, the Transplant Coordinator and discussed with the Anaesthetic team.
- The child will be admitted to Clancy Ward.

1. The patient will be admitted to the ward, put on nil by mouth and height and weight measured.
2. Hibiclens bath and shampoo attended ("MRSA and *Staphyloccus aureus* Screening" swabs from nose and throat taken prior to bath)
3. IV line inserted as soon as possible and maintenance IV fluids commenced. The leg or foot should be preferentially used; sites on the hand or especially the cubital fossa should be saved if possible for use by the anaesthetists at operation.
4. Obtain previous inpatient and outpatient files. Ward clerk on Clancy ward to print off 10 pages of patient identification labels to go to operating room with the patient.
5. **Chest X-ray**.
6. **Blood Tests**:
    i. **Blood Bank** - On Blood Crossmatch form request :
        - 5 units packed RBC
        - 1 unit platelets
        - 5 units fresh frozen plasma (FFP)
    ii. **If a retransplant or the child is 50 kg or more in weight:** (10mL clotted blood sample required)
        - 10 units of RBC
        - 10 units of platelets
        - 10 units FFP
    iii. **Haematology**

- Full Blood Count
- Coagulation Screen

iv. Biochemistry

- UEC, LFT, CMP, BSL

v. Serology

- Repeat CMV IgG, EBV IgG

7. **Microbiology**:
   - **i.** Urine for microscopy and culture
   - **ii.** MRSA and *Staphyloccus aureus* Screening swabs from nose and throat (label as such) - prior to having bath
   - **iii.** Culture from any infected lesion for M, C & S
8. **Medications:** Pre-medication (will be ordered by Anaesthetist)
9. Enema (Microlax) may be given preoperatively to help reduce any colonic distension
10. Generic hospital consent form for "Liver Transplantation". A specific Liver Transplant Consent form is signed by the parents, child or carers at time of listing. This signed consent form will be filed in the patients' medical record notes and a copy is kept on Clancy ward. The parents are also given a copy.
11. Notification of the following hospital personnel should be done by the Liver Transplant Team; out of hours the on-call gastroenterologist in conjunction with the sub-speciality registrar, Clancy ward nursing staff and the AHNM can notify:
    - **i.** biochemistry technician –on call
    - **ii.** haematology technician on call
    - **iii.** Clancy Ward pharmacist (8:30-5pm) or pharmacy re need for intravenous ganciclovir (need patients weight and renal function)
    - **iv.** PICU
    - **v.** radiology re need for post-operative doppler ultrasound in PICU (and daily am Doppler ultrasounds for first 5-7 days post-op)

4 Post-Operative Intensive Care

4.1 Paediatric Intensive Care Unit

The child usually returns to PICU with:

1. Naso-tracheal tube
2. Indwelling urinary catheter
3. Naso-gastric tube

4. Triple-lumen central venous catheter (with accurate CVP measurement)
5. At least one arterial line
6. Two to four peripheral intravenous lines, as required
7. Variable number of abdominal drains
8. **Temporarily closed ("gusseted") abdomen in small children, using VAC dressing (delayed closure 3-4 days later)**

Blood Tests

1. Because of the risk of early haemorrhage, cross-match 3-5 units of packed cells immediately on return to PICU.
2. The following blood tests should be done immediately on arrival to the PICU, then every 12 hours (9a.m., 9 p.m.) for the first 72 hours, then daily:
   - UEC, glucose, CMP
   - LFT
   - ammonia
   - FBC, haematocrit
   - PT, INR, APTT, Fibrinogen (daily unless Haemorrhage)
   - Protein C and S, Antithrombin III
3. Daily (0900 hours):
   - amylase, lipase
   - total protein and albumin
   - tacrolimus trough level (prior to morning dose)
   - Anti Xa should be performed once patient has commenced Heparin, ideally twice daily coinciding with thromboelastogram (TEG)
   - Protein C, S and Antithrombin 3 levels for the first 5 days post op and longer if directed by the transplant team.
   - Thromboelastography (TEG) – ideally performed concurrently with above blood tests, each morning. TEG's should be done until patient is no longer on a heparin infusion, as decided by the Transplant Team.

4. Specific Monitoring
   - **i.** Urinalysis every shift
   - **ii.** Dextrostix q4h
   - **iii.** Weigh daily, provided the abdominal wall is closed
   - **iv.** Haemodynamics – pulse, BP, CVP, urine output, RR, temperature
     - measure and record all fluid losses, beware third spacing of fluid, replacement is usually required (see later section on fluid management).

4.2 Drug Treatment (Initial)

Immunosuppression

1. **Tacrolimus:** To be started after urine output is established. To be given by NG tube twice daily (9AM, 9PM). After the dose is given, the NG tube is to be clamped for one hour. Dose depends on child's weight.

The initial Tacrolimus dose is *0.075 mg/kg per dose given every 12 hours.*

In bigger/older children, the Tacrolimus dosage should not exceed 2mg BD; this should be reviewed by the Gastroenterology Team and discussed with the PICU team.

Subsequent dosing will depend on trough serum levels. A tacrolimus level is to be taken at 9AM each day, immediately prior to receiving the dose. The target 12-hour trough serum level is 12-15microgram/mL [10]. The dose of tacrolimus should be decided each afternoon by the attending transplant team.[11-13]

2. **Methylprednisolone** (IV): (a dose of 10mg/kg is given just before reperfusion in the operating room)
   - 2 mg/kg once daily for the first 3 days
   - 1.5 mg/kg for the next 3 days
   - 1 mg/kg daily

   When oral intake is established the dose is changed to oral prednisolone, and is monitored by the transplant team.

Other immunosuppressants such as **basiliximab** (infusion Day 0 and Day 4) are given in specific situations as decided by the transplant team [15-16]. Basiliximab (Simulect) is an Interleukin2-receptor (IL2) monoclonal antibody which allows for the delayed introduction of calcineurin inhibitors which are nephrotoxic. This can be used for patients with pre-transplant renal impairment.

Basiliximab is given Day 0 (after reperfusion, though should be withheld to another time within the first 24 hours post-transplant if there is significant blood loss, where its efficacy is significantly diminished) and Day 4.

The dose of basiliximab is:

- 10 mg IV if weight less than 35 kg
- 20 mg IV if weight 35 kg or more

Other Medications

1. **Tazocin (piperacillin + tazobactam): 100mg/kg/dose every 8 hours (maximum 4g/dose). Dose refers to piperacillin component**
2. **Analgesia, sedation and muscle relatation as per PICU Policy**
3. **Gastric acid suppression: Omeprazole:** 1mg/kg daily IV (max 40mg/dose)
4. **Nystatin**: 100,000 units every 6 hours (into mouth, not N-G tube)

5. CMV prophylaxis: given to patients who are CMV positive (to prevent reactivation), or if the donor is CMV positive (to prevent infection of naive recipient).[14-21]
    i. Ganciclovir - 5 mg/kg given intravenously over one hour once daily for 14 days.
        - If platelets < 50 and/or WCC < 3.0 discuss with Transplant Team re withholding dose of ganciclovir
        - if ganciclovir is unable to be given due to leucopaenia or thrombocytopaenia (see Section 7), one dose of CMV hyperimmune globulin is given in ICU within 48 hours of the transplant
    ii. Plan to change to oral valganciclovir when oral intake is established (dose usually calculated using the formula 7 x BSA x eGFR = ONCE daily dose in mg (max 900mg daily)[24)]
    When calculating the dose, a maximum eGFR value of 75 mL/min/1.73m^2 should be used even if the calculated Bedside Schwartz eGFR exceeds this value.
6. **Antifungal cover** (usually fluconazole) is not routine unless cultures have been positive, or if transplantation is for acute hepatic failure. Fluconazole and other anti-fungals inhibit the metabolism of tacrolimus and can result in very high trough levels so close monitoring is required.
7. **Antihypertensive agents**. Early therapy in PICU includes intravenous Sodium Nitroprusside ("SNIP"), oral amlodipine, clonidine and prn nifedipine.

4.3 Fluid Balance and Intravenous Fluids

1. Children with liver disease "third space" fluid (particularly as ascites) which is often compounded post transplantation by muscle relaxation and mechanical ventilation. When the abdomen is left open temporarily post-transplant ("gusseted") fluid losses can be difficult to quantify.

It is vital that intravascular volumes be maintained to ensure patency of often small vascular anastomoses, especially the hepatic artery.

Assessment of post-liver transplant fluid status is complex, and should include the following measures of ideal intravascular volume:

- central venous pressure (CVP) maintained at around **8 mmHg**
- haematocrit in range of **25-30** (haemoglobin 80 – 100)
- urine output of at least 1 mL/kg/hr
- serum sodium of 135 – 145 mmol/L

When fluid replacement or volume expansion is needed fresh frozen plasma (FFP) is preferred, though other options include normal saline or 4 % NSA. Losses are usually initially replacedmL for mL.

- Ascitic losses can be measured for electrolyte and albumin content to "quantify" what replacements are needed.

- Hartmanns solution can also be used if bicarbonate losses via ascitic fluid are thought to be significant (lactate in Hartmanns converted to 2 molecules of bicarbonate).

Ideally FFP should be used to replace ascitic drain losses, which contain important anti-coagulant factors such as protein C and S, and anti-thrombin III. In addition, anti-thrombin III is replaced by anti-thrombin III concentrate as detailed below.[25]

Anti-Coagulant Replacement with AT III and FFP:

- **Anti-Thrombin:**
  - Anti-Thrombin (AT) Concentrate is given daily **regardless of level for the first 3 days.** Ring CHW Blood Bank (52284) and order the AT3 specifying how much is required for the three days.
  - The first dose of Antithrombin III is usually given in theatre prior to coming to ICU. PLEASE CHECK IF THIS HAS BEEN GIVEN
    - 0 – 30 kg : 1 vial of AT concentrate (1000 Units)
    - 30 – 60 kg : 2 vials of AT concentrate (2000 Units)
    - > 60kg : 3 vials of AT concentrate
  - After the first 3 days, AT Concentrate should be given if the AT level falls below 50%, until the patient is able to maintain their own AT level above 50% once synthetic function of the grafted liver has returned.
- **Protein C and S**
  - **FFP should be used as mL/mL replacement of drain losses**, which will supply Protein C and S
    - If the drain losses are **less than 20mL/kg, then 20mL/kg of FFP** should be given daily (often as 10 ml/kg aliquots) for the first 3 days regardless of Protein C and S Levels
    - After Day 3, Protein C and S levels should be maintained above 50% with 20 ml/kg of FFP daily until the patient is able to maintain this level without support.
- All patients are to be given Vitamin K (10 mg) postoperatively
- Aspirin is usually started once oral feeds have been established (day 5-7) and heparin has run for a sufficiently long period to prevent hepatic artery thrombosis. Once aspirin has commenced heparin will continue for 24- 48 hours, allowing for some overlap.

Please discuss with Liver Transplant Team prior to giving ANY BLOOD PRODUCTS, especially PACKED RED BLOOD CELLS, as overcorrection of mild anaemia post-transplantation can contribute to hepatic artery thrombosis or portal vein thrombosis.

- **Aim to keep haematocrit 25-30. If haematocrit rises above 35 then increased hydration or sometimes partial exchange (replacing blood with 4% NSA) may be required.**
- **Conversely, if the INR rapidly normalises post-transplant then a heparin infusion may be required as per the Transplant Team and the Hospital protocol. Typically the heparin infusion is commenced once the INR is ≤ 1.5 and is run at 10 Units/kg/hour without heparin loading.**
- **platelets to be given only if haemorrhage is a problem, or if platelet count is less than 20,000**

Heparin should be immediately ceased if there is bleeding or a suspicion of bleeding.

Immediately take bloods:

- FBC, PT, INR, APTT, Fibrinogen, Anti Xa (if on Heparin)
- Cross Match 2 units of Packed cells
- Contact surgeons and consider correction of Thrombocytopenia and/or coagulopathy

2. Monitor electrolytes and correct appropriately, especially **POTASSIUM, PHOSPHATE AND MAGNESIUM** levels. Magnesium levels can fall precipitously due to renal tubular wasting from tacrolimus therapy, and should be corrected to prevent seizures.
3. Enteral nutrition is begun as soon as possible post transplant, as decided by the surgical transplant team. If not tolerated then total parenteral nutrition will usually be begun at 24 or 48 hours post-operatively, depending on the child's condition.

4.4 Other Tests

1. **Doppler ultrasound of the liver:**
   i. Within first 4 hours of returning to PICU from OR (either primary transplant or after delayed abdominal wall closure)
   ii. Then daily for next 5-7 days
   iii. If reversed portal venous flow is noted, this represents an ominous sign and the Transplant Surgeon/Team should be immediately notified
2. **Chest X-ray:** On admission to PICU, after 12 hours, then daily while endotracheal tube is in place.
3. **Cultures:** From Day 2, then second daily until three lots of negative results:
   - bacterial cultures of sputum, urine, abdominal drains and bile
   - viral cultures if indicated
   - MRSA Screening swabs of nose, groin and rectum
   - ensure that all drain tips are cultured upon removal
4. **DISIDA scan:** On Days 1 and 5

4.5 Drug Treatment (Later)

After the initial few days, once oral fluids are allowed:

1. For pain relief, morphine or fentanyl infusion as required, or oral therapy as per the Pain Team who should be consulted. Paracetamol can be used if the liver function is good (10 mg/kg per dose, with a max of 4 doses per day).
2. Tacrolimus is given orally rather than by NG tube.
3. Methylprednisolone can be changed to the oral preparation, prednisolone.
4. Aspirin is given once daily when feeds are established, as prophylaxis against hepatic artery thrombosis. [26-29] Dose 5 mg/kg/day up to maximum 50 mg (half 100 mg tablet) daily [30].
5. Bactrim (as prophylaxis against pneumocystis Jiroveci). Daily dose given Monday, Wednesday and Friday. 5mg/kg/dose (dose based on trimethoprim content) ONCE a day on Monday/Wednesday/Friday of each week. Maximum dose 160mg (TMP content). [31, 32]) If unable to take Bactrim then use atovaquone (see CHW drug formulary)
6. Nystatin, 100,000 Units (1mL) qid po.
7. If there is fluid retention and a low serum albumin, IV albumin (1g/kg over 4 hours) can be given, (usually with furosemide 1mg/kg) to keep serum albumin > 30mg/L.
8. Magnesium supplementation is often required either as oral (magnesium chloride solution: 1mmol/mL, or magnesium tablets: Magmin 1.5mmol/tablet or ZMA+ capsules 4.1mmol/capsule) or, if less than 0.5mmol/L an IV infusion of magnesium sulphate starting at 0.1mmol/kg/dose.

4.6 Allied Health Referral and Intervention

1. Early referral to multidisciplinary allied health (Occupational Therapy, Physiotherapy, Social Work, Child Life Therapy, Music Therapy) for PICU intervention regarding positioning and handling, pressure care management, seating and equipment, early mobilisation and psychosocial support.
2. Physiotherapy review in PICU to manage any secondary cardiorespiratory complications such as lung collapse or consolidation, enhance secretion clearance and optimise positioning and mobility.

5 Early Post-Operative Problems (1st Week Post Transplant)

5.1 Acute Collapse / Deterioration:

Consider the following differential diagnoses:

- **graft failure (consider acute hepatic artery thrombosis, acute portal vein thrombosis, primary non-function)**

- **septic shock (consider gut perforation)**
- **intra-abdominal haemorrhage**
- **acute pancreatitis**
- **CNS: intracerebral bleed; unrecognized seizures (especially if muscle relaxed); tacrolimus toxicity**

Sudden Intra-Abdominal Haemorrhage

Acute decompensation, such as with "collapse" or severe hypotension (with or without massive haemorrhage through intra-abdominal drains) signals haemorrhage requiring resuscitation and urgent laparotomy. If on a heparin infusion stop the infusion and send blood for anti Xa and heparin levels. If possible arrange an urgent TEG.

Sepsis

- The transplanted patient is vulnerable to bacterial, fungal and viral infection. [33-35]
- Tazocin (piperacillin + tazobactam) is administered prophylactically intra-operatively, and for the first 48 hours post-operatively. Other antibiotic agents are given at the discretion of the attending team according to patient requirements.
- The major early problems are with enteric organisms causing peri-hepatic infection, cholangitis and liver abscesses, but lung infection may occur in the intubated patient and urine infection in the catheterised patient.
- If candida is found in peritoneal fluid drains, one should suspect enteric perforation or leak. Gram negative sepsis may suggest hepatic infarction from hepatic artery thrombosis (see below).
- The central venous lines placed preoperatively (usually in the neck veins) can be an infection risk and should be assessed daily, with removal wherever possible by 5-7 days post-transplant.

Primary Graft Non-Function

If the graft functions well, there is good bile flow with decreasing serum bilirubin. Serum transaminases may rise for the first 48 hours, but should then fall.

Rarely, there is primary failure of the graft to function despite a patent hepatic artery on doppler ultrasound. This will be apparent from failure of bile flow, acidosis with rising lactate, coagulopathy, hypoglycaemia, rising serum bilirubin and raised blood ammonia in the first 48 hours. A DISIDA scan may help to demonstrate poor hepatic tracer extraction reflecting non-viable liver tissue.

This requires immediate re-transplantation. [36, 37]

Hepatic Artery Thrombosis

Hepatic artery thrombosis is one of the most serious complications of liver transplantation and is the most common reason for re-transplantation in children, accounting for 40% of re-transplants. [38-40]. If diagnosed within 24 hours of occurrence, urgent angiogram or operative thrombectomy may be successful. Diagnosis is suggested by a sudden unexpected rise in

the white cell count, or by the absence of hepatic arterial flow on doppler ultrasound. Clinically it can present in a variety of ways:

1. acute severe liver failure due to massive hepatic necrosis, often with Gram negative sepsis.

   Treatment: Urgent re-transplantation.

2. gram negative sepsis due to hepatic infection and abscess formation.

   Treatment: Antibiotics, possible resection of infarcted/infected hepatic tissue. May require re-transplantation.

3. early bile duct necrosis with biliary leak, leading to biliary peritonitis or fistula, often with biliary sepsis. Later complications are biliary strictures which may require percutaneous dilatation.(41)

   Treatment: Percutaneous drainage (interventional radiology) or early revision of biliary-enteric anastomosis; subsequent biliary strictures require dilatation via percutaneous transhepatic cholangiogram (PTC), and possible future re-transplantation.

Post-Operative Fluid Problems

- During the first 24 hours post-transplant and through the first week or more, losses through abdominal drains, "third-spacing" of fluid in the intestine or as ascites or pleural effusion, results in large requirements for IV fluid replacement.
- Most patients develop a sympathetic right pleural effusion post-operatively, related to irritation or paralysis of the right hemidiaphragm, plus ascites. If the pleural effusion is interfering with respiration and delaying weaning from the ventilator then drainage via an intercostal catheter is required.
- Accurate fluid balance post liver transplant is crucial. Measure and record all fluid losses, and if possible perform daily weighs. Losses from abdominal drains should usually be replaced mL for mL, with attention to CVP and urine output. Aim for CVP of 8, depending on urine output. The fluid lost can be assessed for its electrolyte and albumin content so that appropriate fluids can be used for replacement (usually normal saline and/or 4% albumin). Monitor blood values such as serum sodium, urea, creatinine, haemoglobin and haematocrit to assess for intravascular depletion.

Hypertension

Systemic hypertension occurs during the first week in nearly all patients, contributing factors being fluid overload, pain, corticosteroids and tacrolimus. In the initial phase, in the absence of fluid overload, IV therapy should be used in conjunction with the PICU and/or Renal Teams. Oral agents are used when the oral route is available. The Renal Team can be consulted for problems with hypertension. (42)

Graft Rejection

In up to 70% of patients, usually after day 5, there will be evidence of rejection, signalled by a secondary rise in serum bilirubin and hepatic enzymes. Sometimes there are symptoms such as fever, anorexia, malaise and abdominal pain. A liver biopsy will be performed to confirm

rejection, as other complications such as infection with CMV can mimic rejection. Rejection is treated initially with daily pulses of IV methylprednisolone as follows:

- 20 mg/kg Day 1 (max 1 g)
- 10 mg/kg Day 2 (max 500 mg)
- 5 mg/kg Day 3 (max 250 mg)
- then prednisolone 1 mg/kg/day.

In addition, the dose of tacrolimus is optimized. Depending on the response to this therapy, consideration is given to introducing mycophenolate mofetil (MMF) [43].

If response is poor the patient may require more potent anti-T cell therapy; OKT3 has now been replaced by ATG (antithymocyte globulin).

Convulsions

- Convulsions may occur during the first post-operative week.
- Causes include toxic tacrolimus levels, hypoglycaemia, hypomagnesaemia, hypocalcaemia, hypertension, intracerebral bleed, and infectious causes.
- Urgent cerebral imaging should be undertaken.
- Acute treatment with an appropriate benzodiazepine is usually effective and long-term anti-convulsant therapy is mostly not required. Short-term treatment is with clonazepam rather than anticonvulsants that induce cytochrome P450, however the Neurology team should be consulted early.(46)
- Antifungal therapy should be considered.(47)

Bradycardia

A curious phenomenon we have observed in some children about 2 to 5 days post-transplant is sinus bradycardia. The cause is unknown, but in the past was related to the intravenous preparation of cyclosporin. It is usually benign, however if elevated blood pressure is also present raised intracranial pressure (e.g. due to intracerebral bleed) should be considered. The thyroid function should also be checked.

6 Post-Operative Care

6.1 After Transfer to Medical Ward (Clancy)

Specific Nursing Care

1. **Protected isolation:** the risk of nosocomial infection is high, so all contacts (medical, nursing, paramedical, family) should be free of intercurrent illnesses when visiting. Hand washing before and after seeing the patients is mandatory. Medical students are not to see the patient unless accompanying the transplant team rounds.
2. **Visiting** restricted to immediate family (siblings, only if free of contact with infection)

3. **Pressure area care:** turn every four hours (if patient is not mobile), nurse on preventative pressure area apparatus
4. **Hygiene:** Daily sponge - may shower or bath when wounds are healed and sutures and clips removed. Oral hygiene requires special attention to maintain mucosal integrity and prevent infection.

Allied Health Care

5. **Physiotherapy:** The physiotherapist should be consulted to see all patients in regards to mobility. Patients may sit out of bed and ambulation is encouraged. When condition permits, patients may walk outside but should wear a mask (or be taken in a covered stroller) and avoid areas where groups of people congregate.
6. **Occupational Therapy:** The Occupational Therapist is consulted to see all post-transplant children in regards to positioning and handling; equipment prescription; graded participation and engagement in activity; developmental support; and discharge planning.
7. **Child Life Therapist:** Child Life Therapists is consulted to provide procedural support, and to assist with engaging participation in developmentally appropriate activity.
8. **Music Therapist**: Music Therapy is consulted to provide music-based psychosocial intervention, and to assist with engaging participation in developmentally appropriate activity.
9. **Family and psychological support:** Parents usually "live-in" at the hospital. This is a high stress time for families and support is given by the team CNC, social worker, psychologist and psychiatrist. A weekly meeting with the ward staff and all team members reviews all the issues facing patients and their families.

Intravenous Access

The child may have a central venous catheter (CVC) placed at the time of the transplant or soon after. Ideally any CVC should be removed as soon as it is not needed, as there is a high incidence of line sepsis in post liver transplant patients. A peripheral venous cannula is kept in-situ as required.

Observations

1. T.P.R. second hourly initially (blood cultures are to be taken for temp $\geq$38.0°C)
2. B.P. at least 4/24 initially
3. Weight daily
4. Urinalysis daily
5. Fluid Balance - strict record of all input and output
6. blood sugar levels as required (especially for small babies re-establishing feeds)

6.2 Dressings and Wound Care

1. Abdominal drainage tubes, urinary catheters and central lines are ideally removed prior to transfer from Intensive Care. All decisions about indwelling devices should be made in conjunction with the transplant surgical and medical teams.
2. Abdominal drain sites are cleaned with an antiseptic solution (e.g. Betadine) and covered with a dry dressing. These sites may drain considerable volumes of fluid for several days and a collecting bag may be applied following consultation with the Surgeon. If used, the bag must be emptied regularly to prevent backflow of drainage fluid into the peritoneal cavity. Consider fluid replacement as required.
3. Incisions. The original dressing placed by the surgeon is left on until directed to be removed.
4. Wound closure is achieved with PDS (absorbable suture) and staples. These are removed at the surgeon's discretion, by replacing all clips and sutures with steri-strips by post-op day 14. The steri-strips are allowed to come off naturally post transplant. The wound should be covered with Tegaderm.

Abdominal Wound:	- alternate clips at	Day	12
	- remaining clips at	Day	13
	- sutures at	Day	14

5. CVC wound is dressed in accordance with CVAD Practice Guideline.

6.3 Nutrition

Successful liver transplantation requires aggressive nutritional rehabilitation, both pre and post-transplant. The Dietitian should be closely involved in the nutritional care of these children.

Total Parental Nutrition (TPN) may be used early post-transplant if enteral feeding is not possible. As the patient is graded onto enteral feeds TPN is ceased. Supplementation may be required with high energy foods and fluids if intake is poor. Nasogastric feeding may be necessary.

6.4 Medications

1. **Immunosuppressive therapy:** Standard drugs are prednisone (once daily) and tacrolimus (twice daily).
2. **Aspirin:** This is given daily for the first six months post-operatively as prophylaxis against hepatic artery thrombosis [26-29]: 5 mg/kg/day up to maximum of 50 mg daily
3. **Nystatin:** 100,000 Units q.i.d., as prophylaxis against thrush.
4. **Analgesia:** Following cessation of opioid infusion, if the liver function is good paracetamol can be given for pain. The Pain team provides advice and daily review. Non-steroidal anti-inflammatory drugs should be avoided due to their risk of causing stomach irritation and ulceration.

5. **Antibiotics:** Bactrim is given three times per week as prophylaxis against pneumocystis jiroveci, usually for 12 months post-transplant [31, 32]. Atovaquone is used as an alternative if Bactrim is not tolerated. Other antibiotics are used as required for infective complications.
6. **Antihypertensives:** Hypertension commonly persists early post-transplant and requires ongoing treatment. Renal consultation can provide advice.
7. **Vitamins and minerals:** The jaundiced patient will still require supplements of vitamins A, D, E and K. Serum levels of vitamin A, E and 25-OH Vit D can be measured, while the INR can reflect vitamin K deficiency. Vitamin C levels can be measured and supplemented as necessary. Magnesium levels may be low due to the effects of tacrolimus causing loss via the kidneys, and should be supplemented. In addition zinc levels can be measured and replaced.
8. **CMV prophylaxis:** CMV prophylaxis is provided for patients who are CMV negative who receive a CMV positive liver, or for those patients who are CMV positive pre-transplant. Prophylaxis is given for 6 months post-transplant, initially with intravenous ganciclovir and then oral valganciclovir. Monitoring can be performed via CMV PCR, which can be quantitated as required. **CMV immunoglobulin is usually given as prophylaxis only when ganciclovir/valganciclovir is unable to be used because of early post-transplant leucopaenia/thrombocytopaenia** (See attached protocol) [20-23]

6.5 Blood Tests

Blood tests are performed frequently for the first 3 - 4 weeks post-transplant. Then they are performed as clinically indicated. The usual tests are liver function tests, tacrolimus level, FBC, UEC and CMP.

6.6 Visitors

Visitors should be kept to a minimum in the post-transplant period, because of risk of transmissible disease. Initially, visitors should be restricted to immediate family. Anyone with an infectious illness, suspected or proven, should stay away.

6.7 Discharge

Discharge may occur as early as 2-3 weeks after transplant. Planning for discharge includes ensuring parents are appropriately educated in giving medications, attending to requirements from the appliance centre, providing community links for ongoing therapy support, and providing parents with an information booklet. Many patients require longer hospitalisation because of complications, or for recuperation. Following discharge frequent follow up occurs in the Liver Transplant Clinic, held every Tuesday morning.

6.8 Interstate Patients

A number of children and their families come from interstate (especially WA, ACT and SA) for their transplants. The families generally live in the long stay units in the hospital. Once it is clear that the child is recovering from the transplant operation and that any complications have been sorted out, the patient is referred back to their home state for ongoing care.

7 CMV Protocol

Protocol for the intravenous administration of CMV Immunoglobulin-VF as prophylaxis against cytomegalovirus infection after liver transplantation

CMV Immunoglobulin needs to be directly ordered through the Red Cross Blood Bank, Clarence Street.

Children who are CMV negative receiving a liver from a CMV positive donor, and children who are themselves CMV positive pre-transplant are given ganciclovir as primary CMV prophylaxis.

In circumstances where ganciclovir is unable to be used early post operatively because of thrombocytopaenia or leucopaenia, CMV immunoglobulin may be used for additional protection.

The dosage is based on empirical recommendations of 25,000 units per kg (Units/kg). The product comes as a vial containing 1,500,000 units of CMV immunoglobulin. Doses are usually given day 1 post liver transplant and then every 2 weeks for the first 4 -6 weeks.

The risks associated with CMV immunoglobulin include infection (since it is made from human plasma) and potential analphylaxis, especially if the child has been shown to be IgA deficient (unless anti-IgA antibodies not present). Therefore the following administration should occur:

- if product is turbid or contains sediment it should be returned to blood bank
- infuse undiluted
- initial rate of infusion is to be 5mL/hr, gradually increasing to the desired amount after one hour if there are no side effects
- patient to be on a cardiac monitor
- side effects may include stomach pain, headache, chest tightness and shortness of breath, facial flushing, pallor, hypotension and anaphylactic shock
- pulse and temperature are to be recorded every 15 minutes for the first hour. If the pulse and temperature remain normal, they are then to be recorded every half hour until the end of the infusion.
- if the temperature rises to $\geq$38.0°C, the infusion is to be ceased and medical review arranged. When the temperature returns to normal the infusion can be recommenced at the rate of 5mL/hr and remain at that rate until the end of the infusion.

8 Post-Transplant Follow Up

8.1 Post-Transplant Monitoring and Follow Up

After discharge patients are seen for follow up in the liver transplant clinic. Initially this occurs weekly, and usually by around 3 months post-transplant the frequency of visits is reduced depending on the clinical situation. Over time patients who are stable are seen at least every 3 months for review and blood testing.

Standard clinic review includes:

- history, physical examination, measure height and weight, blood pressure
- blood tests: LFT, UEC, CMP, FBC, trough tacrolimus level, fasting cholesterol and triglycerides, BSL
- review of EBV and CMV status (see later)
- assessment as required by dietetics, social worker, occupational therapist, psychologist, psychiatrist

Immunosuppression Post-transplant

Patients will require life-long immunosuppression to prevent rejection of their new liver. The following strategies are used as a guide, however at all times the clinical scenario needs to be taken into account.

- **tacrolimus** is the mainstay of the immunosuppression regime. Target trough levels vary with time post-transplant and clinical situation. Generally the aim is for levels of:
  - 1st post-transplant month : 12 nanog/mL
  - 2nd post-transplant month: 10 nanog/mL
  - 3rd post-transplant month: 8 nanog/mL
  - From 3 – 6 months post-transplant the level is kept between 5 – 8 ng/mL
  - From 6 -12 months post-transplant aim for around 5 ng/mL
  - After 12 months the level can be kept between 3 – 5 ng/mL
- **prednisolone** is usually slowly weaned from 1 mg/kg at 2 weeks post-transplant, with the aim of either stopping at 4 – 6 months post-transplant or leaving on long term low dose therapy. This will vary with the clinical scenario
- **mycophenolate mofetil (MMF)** is usually introduced after an episode of rejection as an adjunctive immunosuppressant to tacrolimus. The dose range is 20 – 40 mg/kg/day divided into two doses. Main side effects of MMF are myelosuppression and gastrointestinal upset
- **sirolimus** is used infrequently, it's role has still not been well defined for children post-liver transplant[48]. Reported benefits include its non-nephrotoxic side effects and use in EBV induced post-transplant lymphoproliferative disease.

Rejection Post-Transplant

Rejection can occur at any time post-liver transplant. The risk is highest in the first 3 – 6 months after transplantation, though after 6 months there is an estimated 10% risk of rejection at any point in time. Rejection is typically heralded by a rise in the liver enzymes, especially the transaminases, and may be asymptomatic. If symptoms occur they may be non-specific, such as malaise, lethargy, fever, RUQ pain. Jaundice can occur but is less common and suggests that the process of rejection is more severe and may have been present for some time.

Ideally the diagnosis of rejection should be confirmed by a liver biopsy. Biopsies are usually performed by interventional radiology under ultrasound guidance given that most children have split grafts. Infection, particularly CMV, adenovirus or HHV6, can mimic rejection and should therefore be excluded before embarking on high dose anti-rejection immunosuppressant therapy. Since biliary strictures may also present in a similar fashion, imaging via ultrasound (+/- percutaneous cholangiogram) should be undertaken. Other entities such as post-transplant autoimmune hepatitis can also be excluded via liver biopsy and autoantibodies.

The treatment of **acute cellular rejection** is based on an increase in immunosuppression. Usually this entails high dose pulsed intravenous methylprednisolone over 3 days:

- **day 1: 20 mg/kg** (max 1g)
- **day 2: 10 mg/kg** (max 500 mg)
- **day 3: 5 mg/kg** (max 250 mg)
- **followed by oral prednisolone 1 mg/kg**.

Sometimes pulses are not used but the oral dose of prednisolone is maximized and the response via LFT monitored.

The tacrolimus level is also typically optimized to around 8 - 10 microgram/mL.

MMF may be added in as an adjunctive immunosuppressant, dose range 20 – 40 mg/kg/day in two divided doses.

On rare occasions ATG (antithymocyte globulin) is used for severe resistant rejection.

Where **Chronic Rejection** is suspected or confirmed (ideally via biopsy), the most efficacious treatment is optimizing tacrolimus levels to at least 8 microgram/mL. Steroids are not beneficial in chronic rejection. Other drugs such as MMF or sirolimus have unproven roles in chronic rejection but can be considered.

Antibody mediated rejection (AMR) is increasingly recognized post liver transplant. Investigations include checking for Donor Specific Antibodies. Treatments include plasmapheresis and intravenous immunoglobulin.

Infection Post Liver Transplant

Serious life threatening infections can occur at any time post liver transplantation, and may not necessarily be associated with high fevers. Therefore any child post liver transplant who is unwell should be suspected to be "septic" until proven otherwise. The risk is greatest in the early transplant period when recovering from surgery and more heavily immunosuppressed, however may occur at any time.

Bacterial infections include cholangitis; central line sepsis; spontaneous bacterial peritonitis, particularly if ascites is present; systemic sepsis from any pathogen, especially gut organisms such as gram negatives and enterococcus. Treatment should be broad based and aggressively directed at potential pathogens. If central lines are suspected or proven to be infected they are usually removed and the tip cultured.

Viral infections are also common post liver transplantation.

- CMV infection can be devastating to the immunosuppressed child, and at risk patients (either donor or recipient CMV positive) receive 6 months of prophylaxis with ganciclovir (intravenous, 5 mg/kg daily) or valganciclovir (oral calculated using formula 7 x BSA x eGFR = dose in mg given ONCE a day (maximum 900mg/ day).
    - ***When calculating the dose, a maximum eGFR value of 75 mL/min/1.73m^2 should be used even if the calculated Bedside Schwartz eGFR exceeds this value.***
- After the 6 month prophylaxis period patients should be screened with 3 monthly quantitative CMV PCR.
- Other viral infections such as EBV may occur, especially in infants who are EBV naïve who receive an EBV positive liver. The EBV viral load will be measured and assessed longitudinally, usually at 3 monthly intervals. The optimal management of this virus post-transplant is contentious, though may require minimisation and/or cessation of immunosuppression. EBV may precipitate post transplant lymphoproliferative disease, so abdominal US should be done to assess for lymphadenopathy .
- Contact with viruses such as varicella should be discussed with the transplant team as zoster immunoglobulin (ZIG) may be required. If chicken pox develops then acyclovir, either intravenous or oral, is required.
- Ideally vaccination against measles, mumps and rubella (all live vaccines) should be done wherever possible pre-transplant, however if immunity is uncertain and exposure occurs then the transplant team should be notified.

Fungal infections can also be devastating in immunosuppressed patients and should always be considered, investigated for and treated empirically if clinically necessary. The presence of **yeast in any abdominal drain or swab is highly suggestive of an intestinal leak**.

Opportunistic infections occur in post-transplant children and should be considered based on the clinical situation. Our current practice is to prophylaxis with Bactrim for 12 months post-transplant against pneumocystis jiroveci.

Other Standard Post-Transplant Medications

The medications used post-transplant are as follows (excluding immunosuppressants and CMV prophylaxis listed above):

- Nilstat - stopped 3 months post-transplant
- Aspirin – stopped 6 months post-transplant
- Bactrim – stopped 12 months post-transplant
- Magnesium supplementation – continued as necessary, monitor serum levels

Post-transplant Vaccinations

From 6-12 months post transplant, non-live vaccinations can be given, including "catch up" vaccinations. Annual influenza vaccination is recommended.

Anniversary (Transplant "Birthday") Review

The following guidelines have been established to monitor all health aspects of children post liver transplantation. The best way of ensuring these tests are done is to organize for them to occur at the time of the transplant anniversary.

- autoantibodies (ANA, SMA, LKMA) + immunoglobulins (yearly) [49]
- Donor Specific Antibodies (DSA) are usually done at same time as liver biopsies, either protocol or when clinically indicated
- serology for varicella IgG, Hep A IgG, Hep B s ab, CMV IgG, EBV IgG (yearly) **THESE TESTS ARE PERFORMED DEPENDING ON PRE-TRANSPLANT SEROLOGIES AND VACCINATIONS DONE POST-TRANSPLANT; THEY MAY NOT NEED TO BE DONE EACH YEAR BUT ON AN INDIVIDUAL BASIS**
- doppler ultrasound of liver, abdomen (yearly)
- cystatin C to monitor renal function post transplant
- dexa bone mineral density scan – every 3 - 4 years
- review immunization status, check for relevant immunity, and immunise as clinically indicated.
- hearing tests
- "protocol" liver biopsies are now performed, currently at 2, 5 and 10 years post-transplant [49]
    - If biopsy (or clinical scenario) raises possibility of hepatic venous outflow obstruction then Hepatic Venogram will be performed by Interventional Radiology
- Dental review should be considered as required
- Occupational therapist review for repeat developmental assessment when delay shown on baseline assessment. Assessment completed 12 months from date of initial baseline assessment.(yearly or as required)
- Psychiatry / psychological review (yearly or as required)

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