THE PAEDIATRIC LIVER EMERGENCY

DR MARISA BERETTA AND DR FRAN VAN DE SCHYFF

Disclosures

- No disclosures
- No affiliation with pharmaceutical companies

WITS DONALD GORDON MEDICAL CENTRE

- Non-profit foundation
- Salaried team
- Private-State collaboration

20 2002 2022

We celebrate 20 years of Wits University Donald Gordon

Paediatric Gastroenterologists	Paediatric Intensivists	Transplant Surgeons	Transplant Co-ordinators
•Dr Marisa Beretta •Dr Sarah Berkenfeld •Dr Vusani Mudau •CMJAH: Dr Priya Wallabh	•Dr Despina Demopoulos •Dr Marelize Reynders •Dr Linda Doedens	•Prof Jerome Loveland •Prof Russel Britz •Dr Francisa Van De Schyff •Dr Bernd Strobele •Dr Sharan Rambaran	•Sr Mary Duncan •On Call : rotation of 2 •Procurement : Marelize

Allied Health	Psychologists	Social Worker	Unit Manager
•Tammy (Physio) •Ali and Lindsey (Dieticians) •Karyn (Speech therapist) •Carmen (OT)	•Dr Tina Sideras •Dr Lydia Cilliers •Dr Kallie Naidoo •Dr Nombuso Masinga	•Mbali Msimeki	•Carla Wilmans •CMJAH: Anja Meyer

THE PAEDIATRIC LIVER EMERGENCY

- A diagnostic emergency : the infant with liver disease
- PALF: Paediatric Acute Liver Failure
- Variceal bleeding
- Metabolic Encephalopathy

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PALF

- Rapid onset, severe disease that progresses quickly
- Accounts for 12.5 % of all transplants and an important cause of mortality
- Management challenges

I. Determining aetiology
II. Supportive Management
III. Timely transfer

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DEFINITION

TABLE 1. PALFSG study entry criteria—all three components required

Acute onset of liver disease without evidence of chronic liver disease
Biochemical evidence of severe liver injury
Coagulopathy not corrected by vitamin K
- Prothrombin time (PT) ≥15 s or INR ≥1.5 with evidence of hepatic encephalopathy or
- PT ≥20 s or INR >2 with or without encephalopathy

INR = international normalized ratio; PALFSG = Pediatric Acute Liver Failure Study Group.

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FEATURES OF CLD

TABLE 3. Physical examination findings suggestive of preexisting or chronic liver disease

Organ system	Physical examination findings
General or Constitutional	Growth failure
	Dysmorphic features
Abdominal	Hepatosplenomegaly suggestive of portal hypertension
	Ascites
Musculoskeletal	Digital clubbing
	Rachitic rosary
Skin	Xanthomas
	Abdominal varices or spider angiomas
	Peripheral edema

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DEFINITION OF ENCEPHALOPATHY IN CHILDREN

JPGN • Volume 74, Number 1, January 2022 *North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition*

TABLE 6. Assessment of encephalopathy

For young children (age < 4 y): modified from (13)

Grade	Mental status	Reflexes	Neurological signs	EEG changes
Early (Stage 1 and 2)	Inconsolable crying, sleep reversal, inattention to task	Unreliable/normal or hyperreflexic	Difficult to test. Reponses may be delayed, and attention span shortened	Normal or mild slowing
Mid (Stage 3)	Somnolence, stupor, combativeness	Unreliable—can be decreased, absent, or increased	Difficult to test. Progressive decrease in response to external stimuli	Mild or moderate background abnormality with slowing
Late (Stage 4)	Comatose, arouses with painful stimuli or no response	Unreliable—can be decreased, absent, or increased	Decerebrate or decorticate	Severe attenuation or slowing

For children (age > 4 y): modified from (51,52)

Stage	Mood and mental status	Reflexes	Neurological signs	EEG changes
Stage 1, prodromal	Mood swing: euphoria/ depression; mild confusion; slowness of mentation and affect; untidiness; slurred speech; disordered sleep	Normal or hyperreflexic	Tremor, apraxia, impaired handwriting	Normal or diffuse slowing
Stage 2	Accentuation of Stage 1; lethargy; moderate confusion; inappropriate behavior; inability to maintain sphincter control	Hyperreflexic	Ataxia, dysarthria	Abnormal, generalized slowing
Stage 3, stupor	Marked confusion; sleepy but arousable; incoherent speech	Hyperreflexic	Rigidity	Abnormal, generalized slowing
Stage 4, coma	May or may not respond to painful stimuli	Usually absent	Decerebrate or decorticate	Abnormal, very slow

EEG = electroencephalography.

COAGULOPATHY & ENCEPHALOPATHY

- Balanced loss of pro and anti-coagulants
- Represents a loss of hepatic synthestic function rather than a bleeding tendency
- Risk of thrombosis > risk of bleeding
- Only 5% have a clinically significant bleed, < 1% intra-cranial
- Overtransfusion can increase the risk of both bleeding and thrombsosis

- Encephalopathy does not relate to coagulopathy
- In PALSFG: 25% with Grade 3 and 4 only had a MILD coagulopathy (INR < 2)
- HIGHEST rate of mortality

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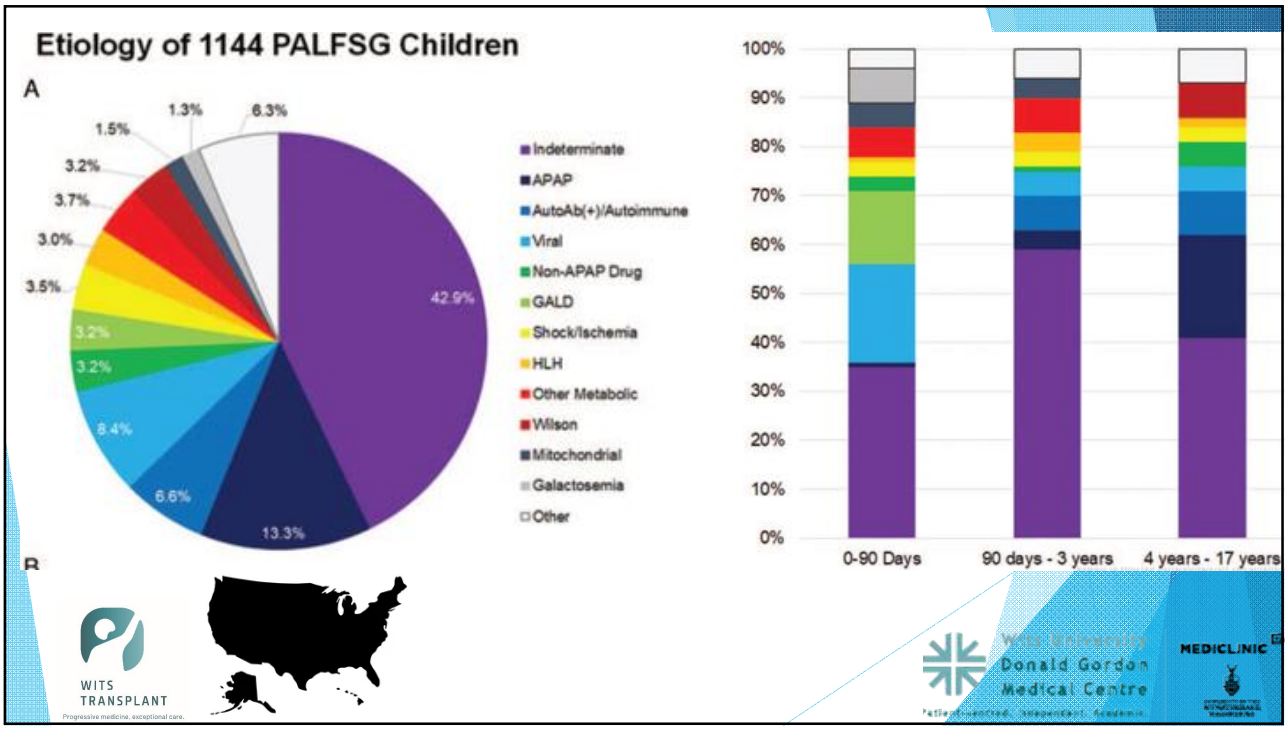

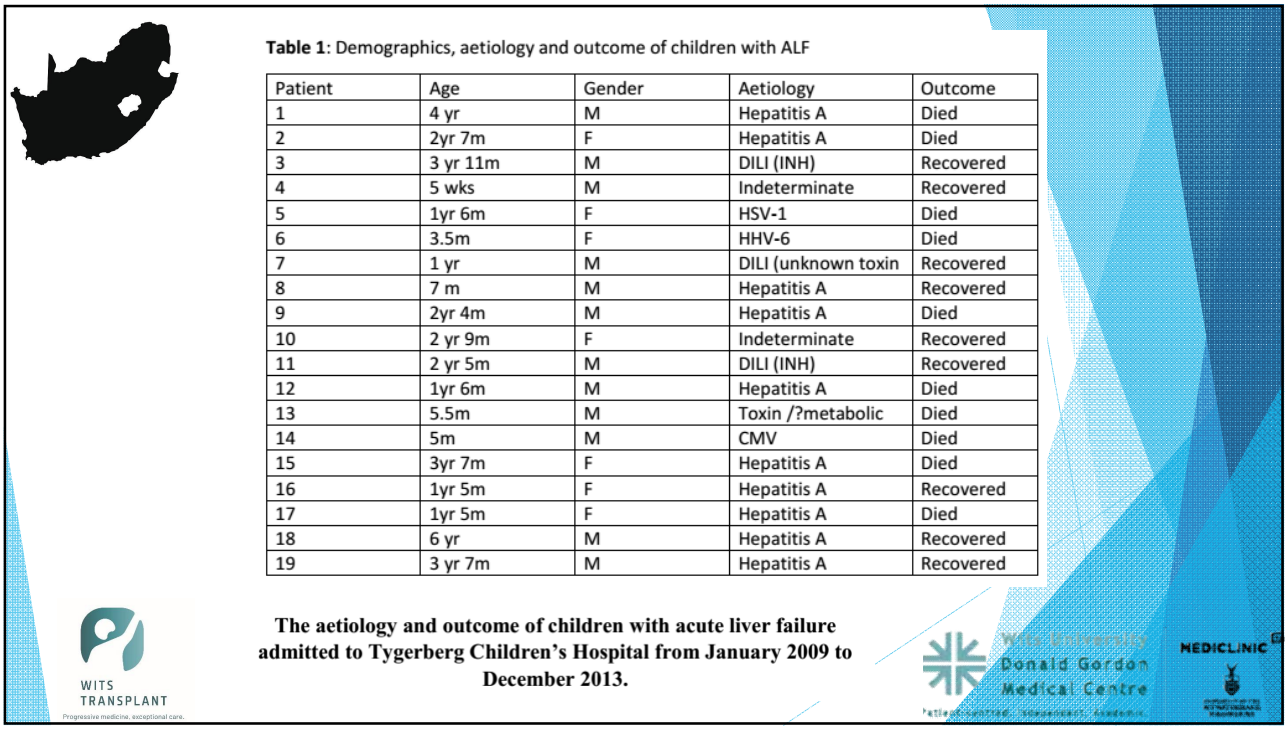

Table 1: Demographics, aetiology and outcome of children with ALF

Patient	Age	Gender	Aetiology	Outcome
1	4 yr	M	Hepatitis A	Died
2	2yr 7m	F	Hepatitis A	Died
3	3 yr 11m	M	DILI (INH)	Recovered
4	5 wks	M	Indeterminate	Recovered
5	1yr 6m	F	HSV-1	Died
6	3.5m	F	HHV-6	Died
7	1 yr	M	DILI (unknown toxin	Recovered
8	7 m	M	Hepatitis A	Recovered
9	2yr 4m	M	Hepatitis A	Died
10	2 yr 9m	F	Indeterminate	Recovered
11	2 yr 5m	M	DILI (INH)	Recovered
12	1yr 6m	M	Hepatitis A	Died
13	5.5m	M	Toxin /?metabolic	Died
14	5m	M	CMV	Died
15	3yr 7m	F	Hepatitis A	Died
16	1yr 5m	F	Hepatitis A	Recovered
17	1yr 5m	F	Hepatitis A	Died
18	6 yr	M	Hepatitis A	Recovered
19	3 yr 7m	M	Hepatitis A	Recovered

The aetiology and outcome of children with acute liver failure admitted to Tygerberg Children's Hospital from January 2009 to December 2013.

TABLE 1 Demographic, clinical, and biochemical characteristics of children undergoing transplantation for acute liver failure at WDGMC between 2005 and 2019

Category	(n = 27) n (%)
Demographics	
Age (y): median (IQR); (range)	3.7 (2.3 to 9.0); (0.6 to 15.5)
Weight (kg): median (IQR)	15.6 (13.5 to 26.3)
Weight-for-age Z-Score: median (IQR) (n = 26)	−0.2 (−0.8 to 0.7)
Sex: F; M	13 (48); 14 (52)
Population Group (self-reported)	
Black	15 (56)
Mixed race	8 (30)
Indian	2 (7)
White	2 (7)
Healthcare sector	
Private	9 (33)
Public (referral source by Province):	18 (67)
Gauteng	12 (67)
Kwazulu-Natal	2 (11)
Western Cape	2 (11)
North West	1 (5.5)
Unknown	1 (5.5)
Etiology of Acute Liver Failure	
Viral	16 (59)
Hepatitis A	11 (69)
Enterovirus	2 (13)
Adenovirus	1 (6)
Parvovirus	1 (6)
Ebstein-Barr	1 (6)
Wilsons (acute)	5 (18)
Amanita phalloides mushroom	1 (4)
Paracetamol	1 (4)
Lymphoma	1 (4)
Indeterminate	3 (11)
PELD/MELD: median (IQR) (n = 25)	37 (30 to 40)
KCC criteria fulfilled	27 (100)
ABO blood type matching	
Identical	12 (44)
Compatible	10 (37)
Incompatible	5 (19)
Graft type	
Living donor: left lateral segment	15 (56)
Deceased donor	12 (44)
Whole graft	4/12
Split graft – left lateral segment	7/12
adult co-recipient	5/7
pediatric co-recipient	1/7

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Table 3. Evaluation for aetiology in paediatric acute liver failure.

Aetiology	Investigations
Drugs/ toxins*	Serum paracetamol level, urine screen for toxins/drugs
Autoimmune liver disease	Serum total IgG, anti-smooth muscle antibody, anti-liver kidney microsomal antibody, anti-nuclear antibody, anti-liver cytosol antibody, antibody to soluble liver antigen, liver biopsy[$]
Viral infections	Serum PCR for herpes simplex virus, serology for acute EBV infection, EBV PCR, adenovirus PCR, parvovirus PCR, enterovirus PCR, cytomegalovirus PCR, HBV DNA PCR, HBsAg, IgM anti-HBcAb, IgM anti-HAV, anti-HEV antibody
Haematological disorders – haemophagocytic lymphohistiocytosis, congenital leukaemia, lymphomatous infiltration	Full blood count, blood film, lactate dehydrogenase, serum triglycerides, serum ferritin, serum fibrinogen, soluble CD25, granzyme B, bone marrow aspiration and trephine biopsy, NK cell activity, perforin mutations
Metabolic and genetic work-up	Red blood cell – galactose-1-phosphate uridyl transferase Urine – succinyl-acetone, organic acids, plasma amino acids Serum – lactate, pyruvate Genetic analysis for mitochondrial genetics and Wilson's disease: serum caeruloplasmin, 24-hour urine copper, serum carnitine and acyl carnitine profile, urine ketones **Genetics for mutations suggesting NBAS deficiency, E3 deficiency, Wolcott-Rallison syndrome, CALFAN syndrome (*SCYL1* mutations), *TRMU* mutations, *MARS*, *LARS*, *RINT1*, *PCK1* mutations, fatty acid oxidation disorders[33–41] Whole-exome sequencing for indeterminate aetiology group
Vascular	Ultrasound with Doppler of hepatic veins
Gestational alloimmune disease	Buccal mucosal biopsy, serum ferritin, transferrin saturation, MRI abdomen for iron deposition in the viscera.

EBV, Epstein-Barr virus; NK, natural killer.
*Tools to measure serum paracetamol adducts are not widely available.
[$]Role of liver biopsy is controversial.
**Disorders causing recurrent acute liver failure.

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FULMINANT LIVER FAILURE

DOB:

	DATE	RESULT
GENERAL		
Total bilirubin		
Direct bilirubin		
Total protein		
Albumin		
Alk Phos		
GGT		
ALT		
AST		
LD		
Sodium		
Potassium		
Chloride		
CO2		
Urea		
Creatinine		
Calcium		
Magnesium		
phosphorus		
Hb		
Hct		
WCC		
Platelets		
AFP		
HIV		
TPHA		
Cholesterol		
Triglycerides		
Serum iron		
Ferritin		
% Sat		
Transferrin		
Lactate		
LIVER FUNCTION		
PT/PTT		
INR		
Glucose		
Ammonia		
Fibrinogen		
Factor V levels		
VIRAL		
Hepatitis A IgG		
Hepatitis A IgM		
Hepatitis B sAg		
Hepatitis B sAb and titre		
Hepatitis cAb		
HSV PCR		
Parvovirus PCR		
Enterovirus PCR		
CMV VL		
EBV VL		
HHV 6		
Respiratory multiplex PCR		
TOXIN		
Paracetemol		
Toxin screen		
AUTOIMMUNE		
Total IgG		
ANA		
Anti SM		
Anti LKM		
Anti mitochondrial		
Anti dsDNA		
METABOLIC / GENETIC		
ALL		
Alpha 1 antitrypsin		
INFANTS		
Urine succinylacetone		
GALT		
Urine organic acids		
Plasma amino acids		
Plasma organic acids		
VLCFA		
Plasma Carnitine		
Acyl carnitine profile		
MPV 17		
	Pre and post hypoglycemic event for FA oxidation	
	PRE	POST
Glucose		
Lactate		
Urine ketones		
Pyruvate		
CHILDREN		
Serum copper		

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Table 4. Disorders causing paediatric acute liver failure for which there are aetiology-specific treatment options.

Aetiology	Treatment
Tyrosinemia type 1	Nitisinone
Paracetamol toxicity	N-acetyl cysteine
Haemophagocytic lymphohistiocytosis	Immunosuppression protocols
HSV infection	Acyclovir
Drug-induced liver injury	Withdrawal of offending drug
Galactosemia	Galactose-free formula
Fatty acid oxidation disorders	Dextrose infusion
NBAS deficiency	Dextrose/lipid infusion
Gestational alloimmune liver disease	Double volume exchange transfusion and intravenous immunoglobulin administration
Acute HBV	Anti HBV antivirals
Acute Budd-Chiari syndrome	Hepatic venoplasty and stenting

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INDETERMINANT (I-PALF)

- 43-49% of PALF
- Hypotheses:
  - Undiagnosed metabolic/ genetic
  - Drug-induced
  - Unknown or undetected viral
  - Disorders of immune dysregulation
- CD 8 intense infiltrate on biopsy
- Poor native liver survival

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COURSE

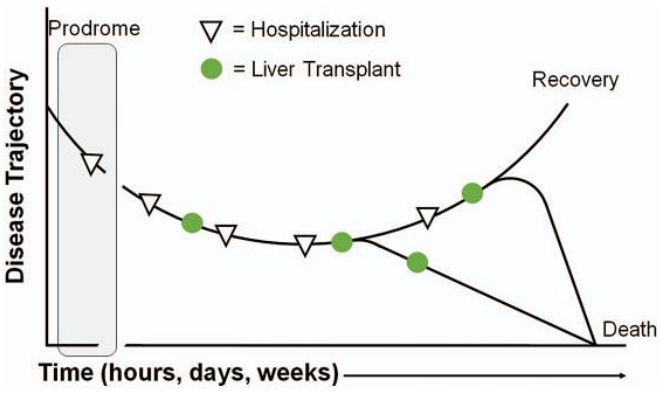

FIGURE 1. The clinical trajectory of a child with acute liver failure is dynamic. Liver transplantation interrupts the natural history of acute liver failure.

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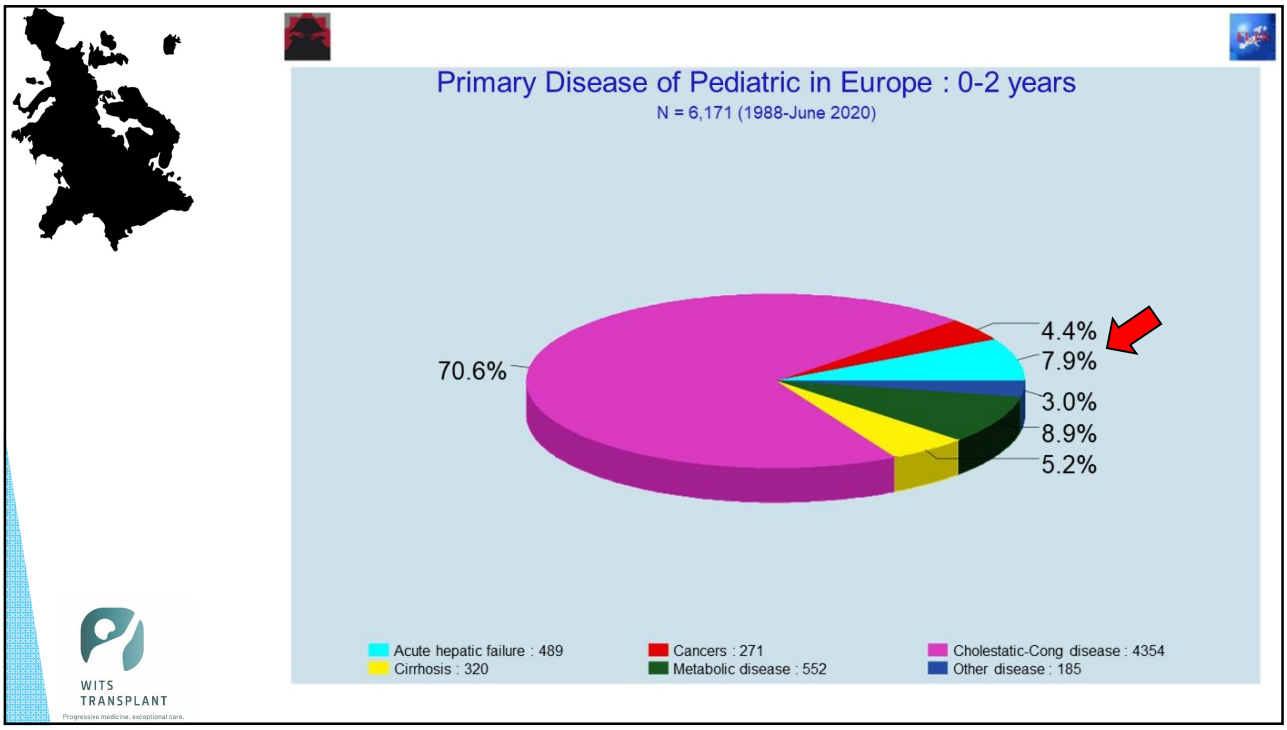
Primary Disease of Pediatric in Europe : 0-2 years
N = 6,171 (1988-June 2020)
70.6%
4.4%
7.9%
3.0%
8.9%
5.2%
Acute hepatic failure : 489
Cirrhosis : 320
Cancers : 271
Metabolic disease : 552
Cholestatic-Cong disease : 4354
Other disease : 185
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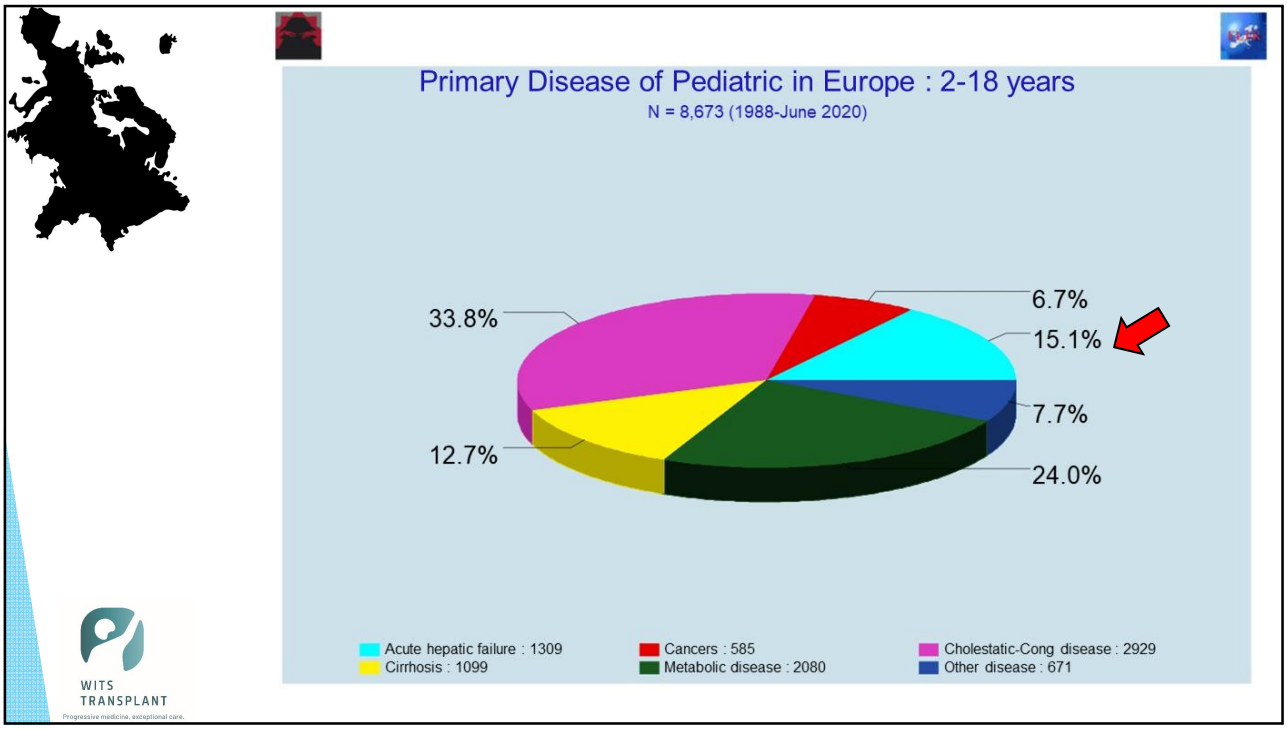
Primary Disease of Pediatric in Europe : 2-18 years
N = 8,673 (1988-June 2020)
33.8%
12.7%
6.7%
15.1%
7.7%
24.0%
Acute hepatic failure : 1309
Cirrhosis : 1099
Cancers : 585
Metabolic disease : 2080
Cholestatic-Cong disease : 2929
Other disease : 671
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Characteristic	2008-10 N	2008-10 Percent	2018-20 N	2018-20 Percent
Diagnosis				
Acute liver failure	190	10.9%	125	7.7%
Cholestatic biliary atresia	572	32.8%	537	33.2%
Other cholestatic	225	12.9%	212	13.1%
Hepatoblastoma	105	6.0%	114	7.1%
Metabolic	204	11.7%	279	17.3%
Other/unknown	449	25.7%	349	21.6%
Blood type				
A	598	34.3%	551	34.1%
B	243	13.9%	198	12.3%
AB	54	3.1%	48	3.0%
O	850	48.7%	819	50.7%
Medical condition				
Hospitalized in ICU	445	25.5%	281	17.4%
Hospitalized, not ICU	309	17.7%	278	17.2%
Not hospitalized	991	56.8%	1057	65.4%
Medical urgency				
Status 1A	264	15.1%	173	10.7%
Status 1B	221	12.7%	359	22.2%
MELD/PELD ≥ 30	481	27.6%	707	43.8%
MELD/PELD 15-29	526	30.1%	209	12.9%
MELD/PELD < 15	249	14.3%	163	10.1%
Unknown	4	0.2%	5	0.3%
Any MELD/PELD exception	521	29.9%	757	46.8%
All recipients	1745	100.0%	1616	100.0%

Table LI 19 Clinical characteristics of pediatric liver transplant recipients, 2008-2010 and 2018-2020. Pediatric liver transplant recipients, including re-transplants. Pediatric candidates aged 12 to 17 years can be assigned MELD or PELD scores.

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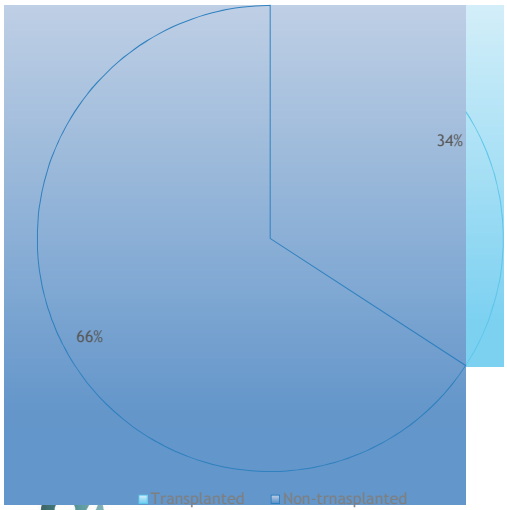
PALF



Indicators of severity	
Hepatic Encephalopathy grade (n = 26)	
0 to 2; 3 to 4	4 (15); 22 (85)
On Acute dialysis	5 (19)
Hemodynamically unstable (n = 21)	11 (52)
Mechanical ventilation (n = 25)	21 (84)

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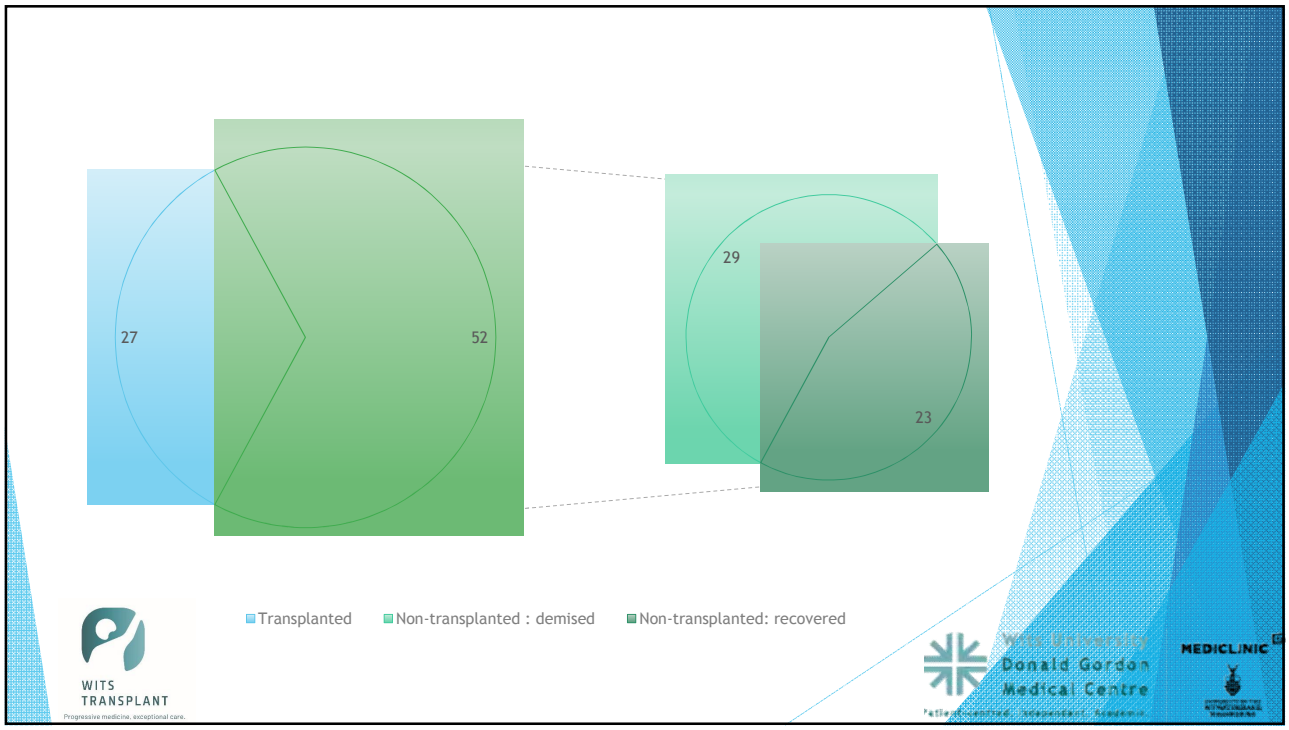
27
52
29
23
Transplanted
Non-transplanted : demised
Non-transplanted: recovered
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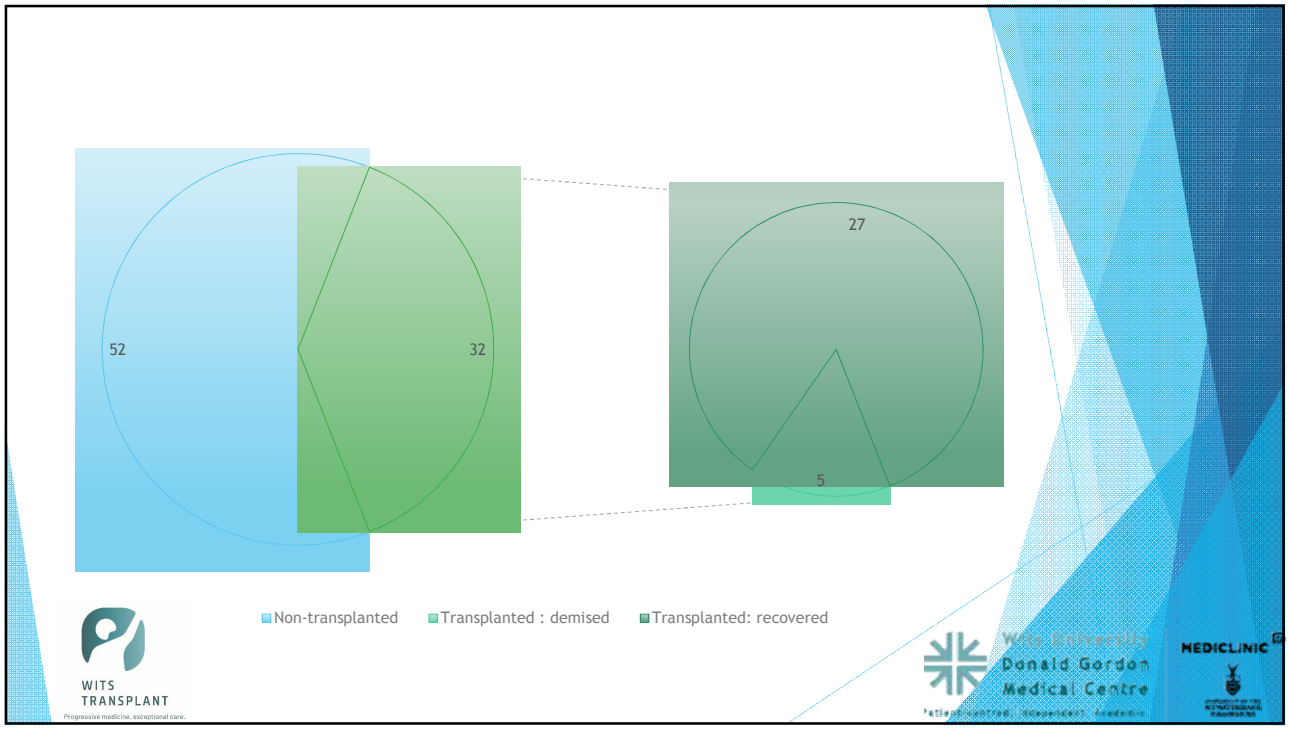
52
32
27
5
Non-transplanted
Transplanted : demised
Transplanted: recovered
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OUTCOME AND COSTS OF HEPATITIS A IN CAPE TOWN

Paediatric patients

Evidence of acute liver injury	All patients (N = 239)	Uncomplicated hepatitis (n = 211, 88.3%)	Complicated hepatitis A (n = 27, 12.8%)	Deceased (n = 1, 0.4%)
INR 1.50–1.99	9 (3.8%)	8 (3.8%)	1 (3.7%)	0 (0.0%)
INR ≥ 2.0	4 (1.7%)	0 (0.0%)	3 (11.1%)	1 (100.0%)
ALT > 40 U/L	239 (100.0%)	211 (100.0%)	27 (100.0%)	1 (100.0%)
AST > 40 U/L	238 (99.6%)	211 (100.0%)	26 (96.3%)	1 (100.0%)
ALP > 128 U/L	233 (97.5%)	207 (98.1%)	25 (92.6%)	1 (100.0%)
Total bilirubin > 21 U/L	232 (97.1%)	206 (97.6%)	25 (92.6%)	1 (100.0%)

All variables are presented as N (%)

ALT alanine aminotransferase, *AST* alanine aminotransferase, *U/L* units per liter

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ADMISSION DAYS PER STAY

Paediatric patients

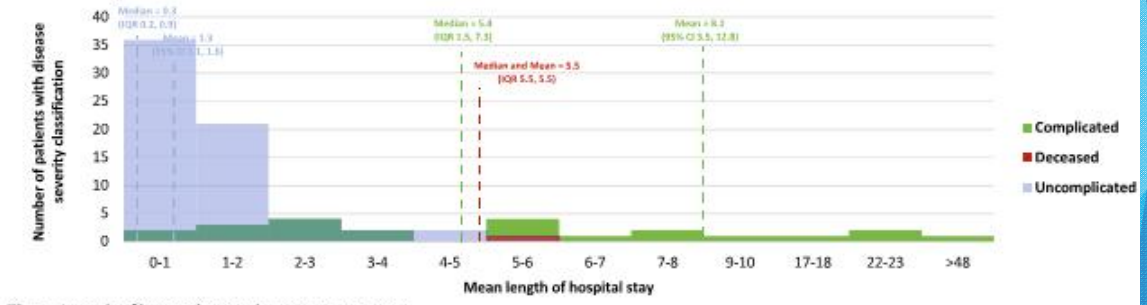

Fig. 2 Length of hospitalization by patient outcome

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Table 4 Cost per patient day equivalent at included facilities in USD

Overhead line item	Groote Schuur Hospital serving adult patients	Red Cross Children's War Memorial Hospital serving paediatric patients
Compensation of employees	$119,892,542.40	$9,548,135.59
Employee benefits	$556,000.00	$175,457.63
Goods and services	$27,203,728.81	$9,441,423.73
Machinery and equipment	$1,715,050.85	$878,983.05
Software and intangible equipment	$16,949.15	$0.00
Total overhead costs	$149,384,271.20	$20,044,000.00
Total patient days	599,931	122,439
Overhead cost per patient day equivalent*	$249.00	$163.71

*To obtain the cost per patient day equivalent, the total overhead costs were divided by the total patient days per facility

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TRANSFER OF THE PATIENT

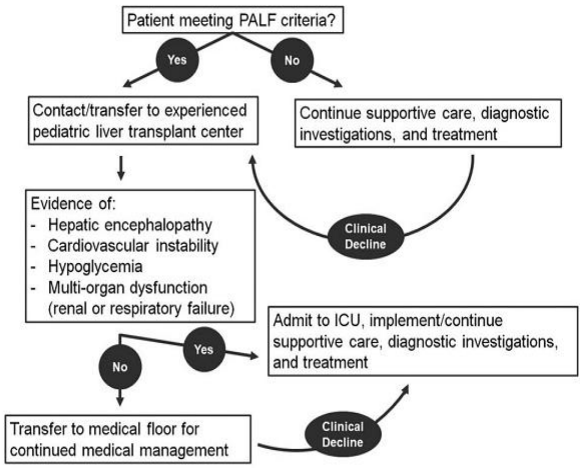

FIGURE 2. A general management algorithm for patients meeting PALF study entry criteria. PALF = pediatric acute liver failure.

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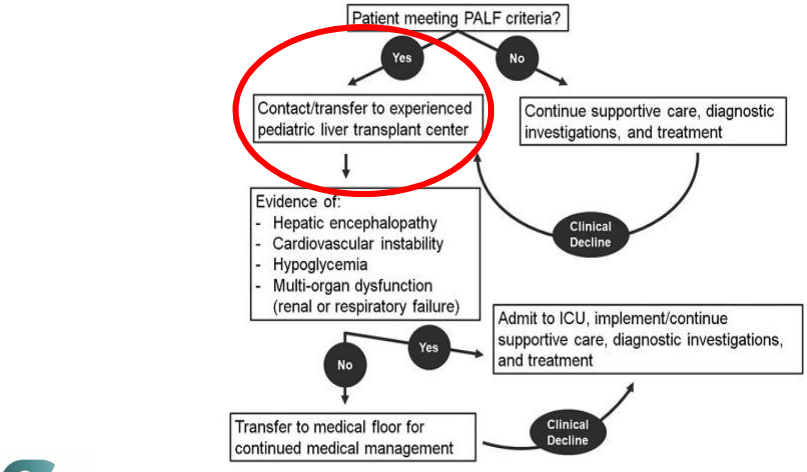
TRANSFER OF THE PATIENT



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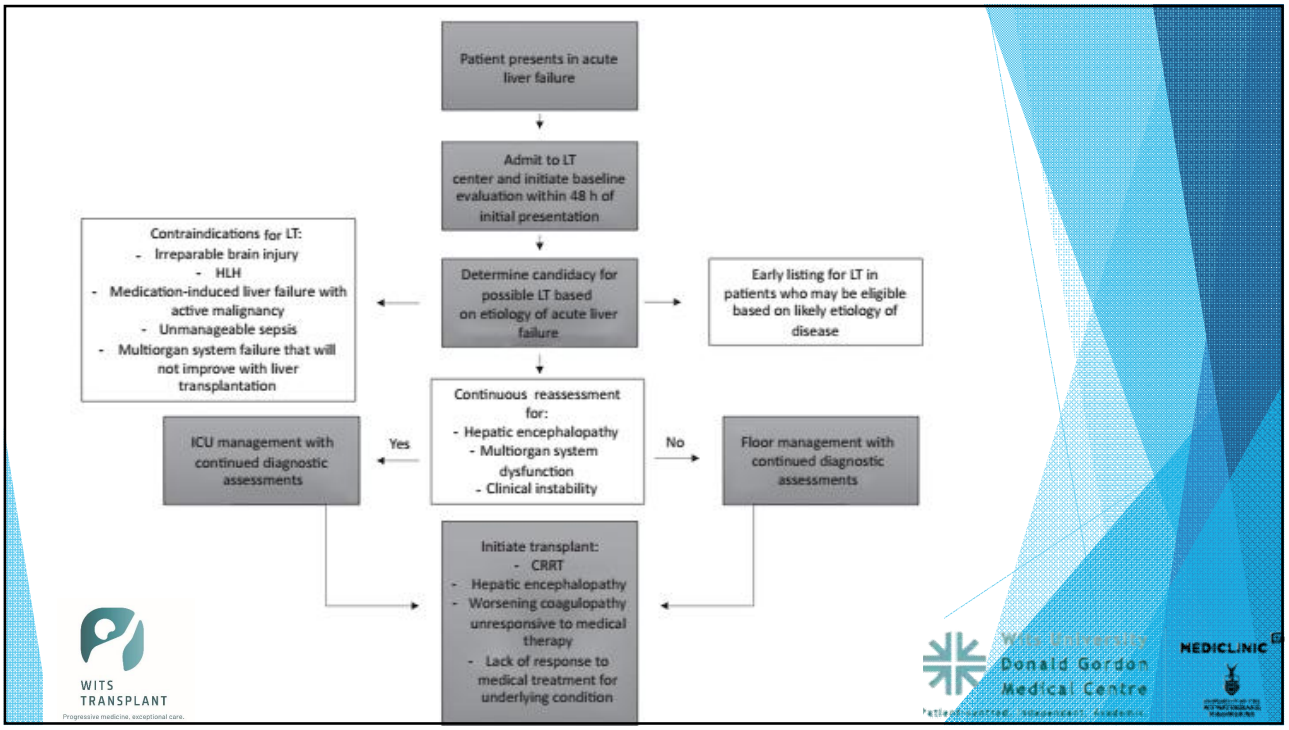

WHEN TO TRANSFER

- Should be admitted to a paediatric liver transplant centre as early in the disease course as possible
- Rapidly progressive and unpredictable
- Better outcomes in those transferred BEFORE hepatic encephalopathy evolved
- Centres favour listing during work up and ongoing intensive care treatment within the first 24 – 48 hours
- Time to listing on the PALFSG study after enrolment = 1 day

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THE NEED FOR IMMINENT TRANSFER

	20/4 20:35	21/4 04:26	21/4 18:00	22/4 02:43	22/4 18:29	
ALT IU/L	688	509	289	232	111	
ASTIU/L	1622	119	552	416	202	
INR	> 10	> 10	> 10	> 10	> 10	
AMMONIA		123		226	166	

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CLINICAL EVENTS

	20/4 20:	4 04:26	21/4 18:00	22/4 02	2/4 18:29
ALT IU/L	688		289	232	11
AST IU/L	1622		552	416	02

ENCEPHALOPATHY & VENTILATION

↑ INTRACRANIAL PRESSURE

CRITICALLY ILL + AUTONOMIC INSTQABILITY

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TIMELINE

ARRIVAL 20/04 20:00 → DECOMPENSATION 20/04 - 22/02 → TRANSPLANT 22/04 22:30

TIME TO TRANSPLANT = 48 HRS

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CONTACTING THE TRANSPLANT UNIT

Wits Donald Gordon

- On call phone: 067 413 5449 (Dr Beretta / Dr Berkenfeld / Dr Mudau)
- Dr Beretta: 082 565 3216
- Paediatric transplant ward: 011 356 6494
  - Leave name and contact details and state contact reason is for a patient in acute liver failure

Charlotte Maxeke

- Dr Wallabh: 073 233 3155

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SPECIFIC THERAPIES

- Wilsons: Single pass albumin dialysis and plasmaphoresis to remove copper
- AIH: Steroids (41.4% response) ; role in I-PALF not established
- Role of plasma exchange : not established
- Role of N acetyl-cysteine in non-acetaminophen liver failure: controversial; no survival advantage demonstrated
- High volume haemofiltration: HE > 2 +/- haemodynamic instability ; improved MAP, serum creatinine and HE grade but survival outcomes unknown
- CVVHD + plasma exchange: decrease in catacholamine index
- Extracorporeal liver support: not recommended on available evidence

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PALF

- Rapid onset, severe disease that progresses quickly
- Accounts for 12.5 % of all transplants and an important cause of mortality
- Management challenges

I. Determining aetiology

II. Supportive Management

III. Timely transfer

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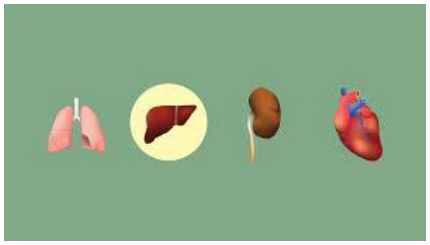
Supportive management

- Treat extrahepatic dysfunction
- Supporting life until liver regeneration or transplantation
- Promotes liver regeneration



- Systemic support of:
  - Airway and respiratory system
  - Fluid, electrolyte and metabolic status
  - Renal system
  - Cardiovascular system
  - Neurological function
  - Coagulation
  - Secondary infection prevention
  - Nutrition
  - Cause specific treatment

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Airway and respiratory support

- At risk of ARDS and TRALI
- Monitoring:
  - SpO2, pO2, pCO2 and pH
- Mechanical ventilation with airway protection
  - Grade III/IV encephalopathy
  - Agitation with lower encephalopathy grades
- Lung protective ventilation
  - TV 6-8 ml/kg
  - Low PEEP
- If paralysis required:
  - Atracurium preferred: not dependent on hepatic elimination
- Prevent aspiration: nurse head up
- Avoid dyssynchrony on the ventilator: keep sedated

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Fluid, electrolyte and metabolic management Common derangements

- Sodium derangements
- Hypokalemia, hypophosphatemia, hypocalcemia
- Hypoglycemia
- Metabolic acidosis
- Acute kidney injury:
  - Intrarenal vasoconstriction, decreased renal perfusion
  - Drug toxicity, hypovolemia, sepsis
  - Typically recovers as hepatic function improve

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Fluid, electrolyte and metabolic goals and management

Euvolemia:

Over-hydration> pulmonary and peripheral oedema, ascites, cerebral oedema

Under-hydration>HRS, ATN, worsening encephalopathy, hypotension

Protect cerebral perfusion

80% maintenance

Beware rapid fluid boluses

Normoglycemia:

Dextrose infusion via central access

Electrolyte replacement:

Phospate

Sodium: maintenace at 2-3 mEq/kg/day. Avoid sustained hypernatremia in attempt to reduce ICP

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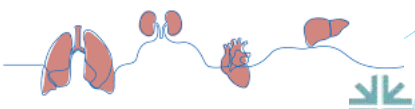
Renal support

- Acute kidney injury very common
- CVVHD:
  - Controls metabolic acidosis and fluid overload
  - Decreases inotrope requirements
  - Decreases ammonia levels in children, less evidence for it in adult population
- Beware hypocalcemia and acidosis on regional citrate CRRT

- Initiate CRRT early if:
  - Oliguric
  - Fluid overload
  - Hyponatremia (<130 mEq/L)
  - Hyperkalemia
  - Metabolic acidosis
  - Hyperammonemia >150 umol/L



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Cardiovascular support

- Hyperdynamic circulation common: peripheral vasodilation, decreased SVR, low MAP
- Monitoring:
  - PR, BP, IAP, UO, CRT, temperature
  - Mixed venous oxygen saturation, SVV, PVV in patients on inotropes
- Support:
  - Once fluid replete: Noradrenalin inotrope of choice, low dose vasopressin (1-2 units/h) considered if NE requirements escalate
  - Escalating inotrope requirements may indicate need for hepatectomy: toxic liver
- Pitfalls:
  - Relative adrenal insufficiency if inotrope unresponsive.

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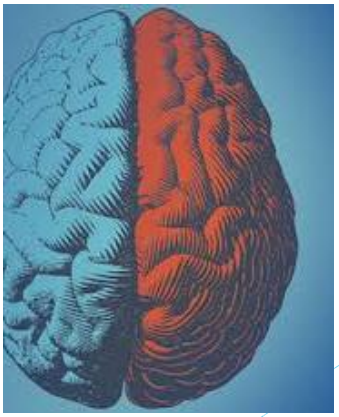
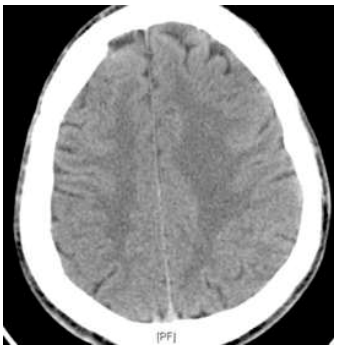
Neurological monitoring

- Hepatic encephalopathy and raised ICP common
- Hyperammonaemia increases intracellular osmolarity in astrocytes and cerebral oedema
- Monitoring:
  - GCS/AVPU/HE staging
  - Features of raised ICP – bradycardia, dystonia and hypertension, pupillary abnormalities, focal neurological deficits, seizures
  - Glucose levels
  - Ammonia levels: Free flowing blood sample, quickly placed on ice to avoid falsely elevated results



Neurological monitoring

- Invasive ICP monitoring:
  - Limited evidence of overall benefit: 7% bleeding complications
- Reverse jugular venous oxygen saturation:
  - Intermittent, indirect measure, prone to jugular venous thrombosis
- Transcranial doppler
  - Operator dependent
  - Measures pulsatility index, mean blood flow velocity and arterial pressure
- Cross-sectional imaging for intracranial bleed:
  - Any sign of neurological deterioration and in grade 3 or 4 HE



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Neurological support: prevention and management of raised ICP

- Head end elevation to 30 degrees
- Sedation, minimise stimulation
  - Avoid benzodiazepines
  - Morphine/Fentanyl preferred
- Avoid fluid overload
- Sodium between 145-150 mEq/L
- Early CRRT
- Evidence for prophylactic anticonvulsants poor
- Urea cycle disorders: ammonia scavengers
- Lactulose and Rifaximine use: little supporting evidence in acute setting
- Spurt ICP:
  - 3% saline
  - 0.5-1 g/kg (20%) mannitol (contraindicated in AKI, beware serum osmolality>320 mEq
  - Transient hyperventilation
  - Moderate hypothermia: best avoid fever
  - Indomethacin: causes bleeding and renal dysfunction
- Hepatectomy?

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Coagulopathy management

- NB: DO NOT CORRECT INR UNLESS ACTIVELY BLEEDING
  - Balanced coagulopathy: procoagulant proteins (factors V, VII, X, fibrinogen) and anticoagulant proteins (antithrombin, protein C, S) are reduced
  - Often pro-coagulant, may bleed with concomitant sepsis
  - Factor V levels and INR used as prognostic indicators and signs of liver recovery
- Vit K given
- Only transfuse platelets if <10 or <50 if an invasive procedure is planned
- Stress ulcer prevention – proton pump inhibitor
- At risk of TRALI

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Secondary infection

- Increased risk of sepsis: immunosuppressed, bacterial translocation
- Monitor:
  - Fever
  - SIRS : non-specific
  - CRP: unreliable as a marker of sepsis
  - Daily surveillance cultures
- Prophylactic broad-spectrum antibiotics and antifungals
- Selective gut decontamination not recommended

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Nutritional support

- High metabolic demand
- Enteral feed whenever possible
- Protein at 1g/kg/day
- TPN may provide maximal calories with minimal volume

Cause specific therapies

Table 4. Disorders causing paediatric acute liver failure for which there are aetiology-specific treatment options.

Aetiology	Treatment
Tyrosinemia type 1	Nitisinone
Paracetamol toxicity	N-acetyl cysteine
Haemophagocytic lymphohistiocytosis	Immunosuppression protocols
HSV infection	Acyclovir
Drug-induced liver injury	Withdrawal of offending drug
Galactosemia	Galactose-free formula
Fatty acid oxidation disorders	Dextrose infusion
NBAS deficiency	Dextrose/lipid infusion
Gestational alloimmune liver disease	Double volume exchange transfusion and intravenous immunoglobulin administration
Acute HBV	Anti HBV antivirals
Acute Budd-Chiari syndrome	Hepatic venoplasty and stenting

King's College Hospital Criteria	
Non-PCM	**PCM**
• Any grade HE and INR ≥ 6.5	• Arterial pH < 7.3 (after adequate fluid resuscitation)
OR any three of the following:	OR combination of the following:
• INR > 3.5 • SBR ≥ 300 µmol/L • Age < 10 or > 40 years • Unfavorable cause (DILI, indeterminate)	• HE ≥ III • Creatinine ≥ 300 µmol/L • INR > 6.5 • Lactate > 3.0

Clichy-Villejuif Criteria
Presence of HE AND Factor V level; < 20% of normal in patients < 30 years old OR < 30% of normal in patients > 30 years old

Listing for liver transplantation

- Each patient is assessed for mortality risk without transplantation
- Modern management has decreased mortality of PALF from 72% to 14%
- Multi-point assessment over time critical
- Validated prognostic markers:
  - Degree of liver dysfunction (INR, Factor V levels, Bilirubin levels)
  - Extrahepatic dysfunction (Creatinine)
  - SIRS
  - Age (<10 years, over 40 years)
  - Aetiology (non-Paracetemol, no- Hep A. Acute Wilsons, GALD, HSV do particularly poorly)
- Factors which may preclude patient from LT:
  - Pre-existing advanced or progressive neurological impairment
  - Mitochondrial disorders
  - Active extrahepatic malignancy
  - HLH

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Kings College Criteria

Acetaminophen	Non-acetaminophen
- Lactate > 3.5 Or - pH<7.3 or lactate>3 Or - Grade III or IV HE and INR >6.5 and creatinine>300 mmol/L	- INR>6.5 with HE Or - Any 3 of 5 with HE ○ Age <10 or >40 yrs ○ Bilirubin>300 mmol/L ○ INR>3.5 ○ Duration of jaundice to HE>7days ○ Etiology: toxicity due to drugs or undetermined causes

Clichy criteria

- HE grade III or more and factor V concentration <20% in patients aged under 30 years
- HE grade III or more and factor V concentration <30% in patients aged more than 30 years

ALF: Role of liver transplantation

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ROLE OF TRANSPLANT

- Before transplant, mortality was 70 – 95%
- After introduction of LT: 11% @ 21 day outcome
- Patient survival and waitlist mortality > at centres performing > 50 technical variant graft transplants
- Living donor liver transplantation confers additional advantages
  - Decreased cold ischaemia time and therefore graft function
  - Improved graft quality
  - Higher long term survival (72% vs 40% in deceased donor)
  - Reduced waitlist mortality

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Outcomes of liver transplantation for acute liver failure

- 70% one year survival (vs. 85% for other causes)
- After one year survival is as for any other cause
- Refer early for Status 1 listing
- South Africa has access to a living donor liver transplant unit! Call Wits Donald Gordon Medical Center

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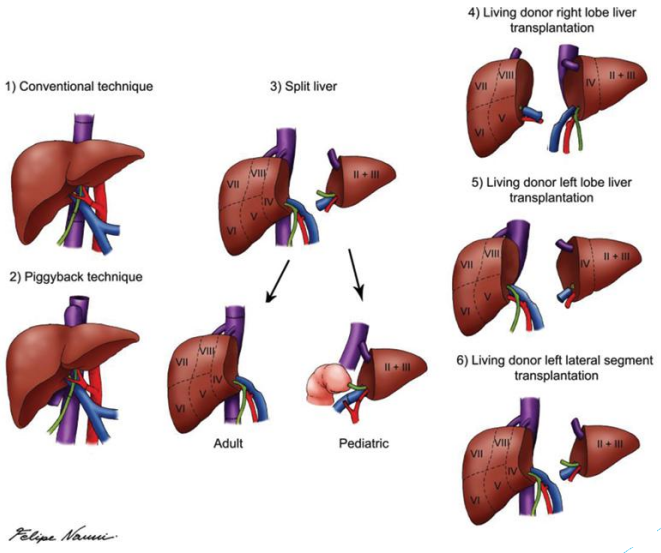
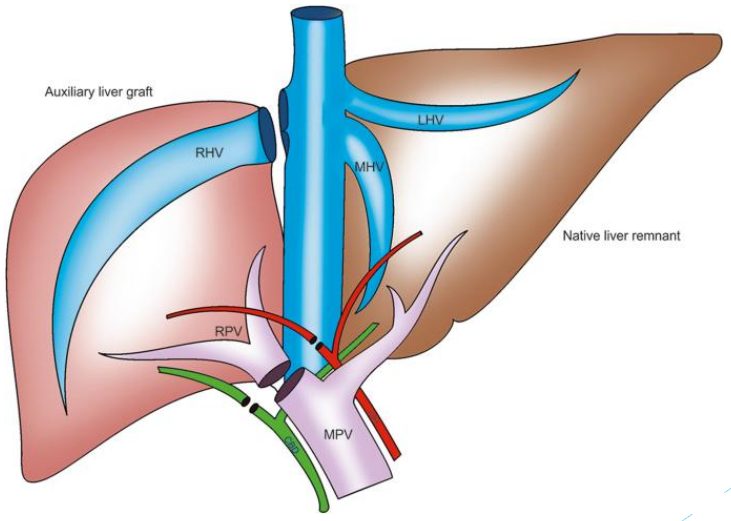
Liver grafts in the paediatric patient

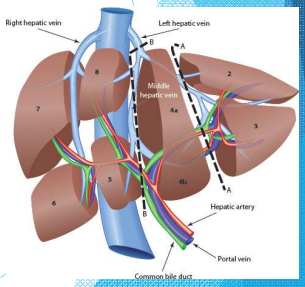


Auxiliary liver transplantation



The patient qualifies for liver transplantation: what now?

- Median waiting times for LT vary among centres:
  - Cadaveric donor pool dismally small in South Africa, paediatric donor pool even more so
  - Most children rely on reduction of an adult graft, mortality and morbidity risk
  - Living donation lifeline
- Once listed: monitor for exclusion criteria and futility:
  - Progressive sepsis despite treatment
  - Invasive fungal infections
  - Escalating inotrope requirements
  - Evidence of brain death
  - ARDS



Liver support therapies: alternatives to liver transplantation

Extracorporeal liver support systems:

- Detoxification: filtering of lipid bound toxins
  - Albumin dialysis
  - Plasma exchange
- Detoxification and synthetic function
  - Bioartificial liver support systems (BAL; human hepatoblastoma cells)
  - Extracorporeal liver assist device (ELAD; human-based cells)
  - HepatAssist (porcine cell-based)
  - Molecular absorbent recirculating system (MARS)

Little evidence for benefit above CRRT

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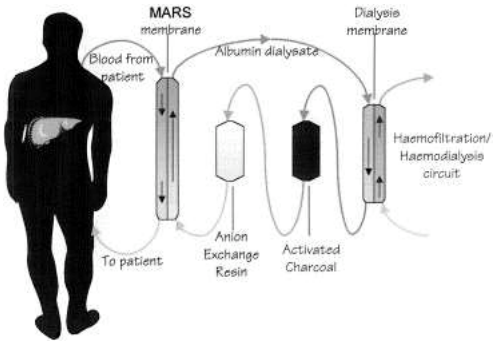
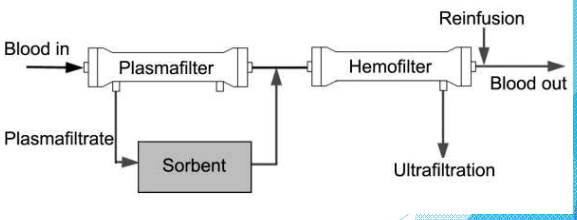
Extracorporeal Blood Purification Therapies

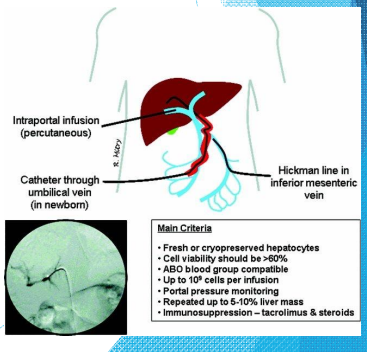
- MARS: MARS (Molecular adsorption and Recirculation System)
- CPFA (Coupled Plasma Filtration and Adsorption)

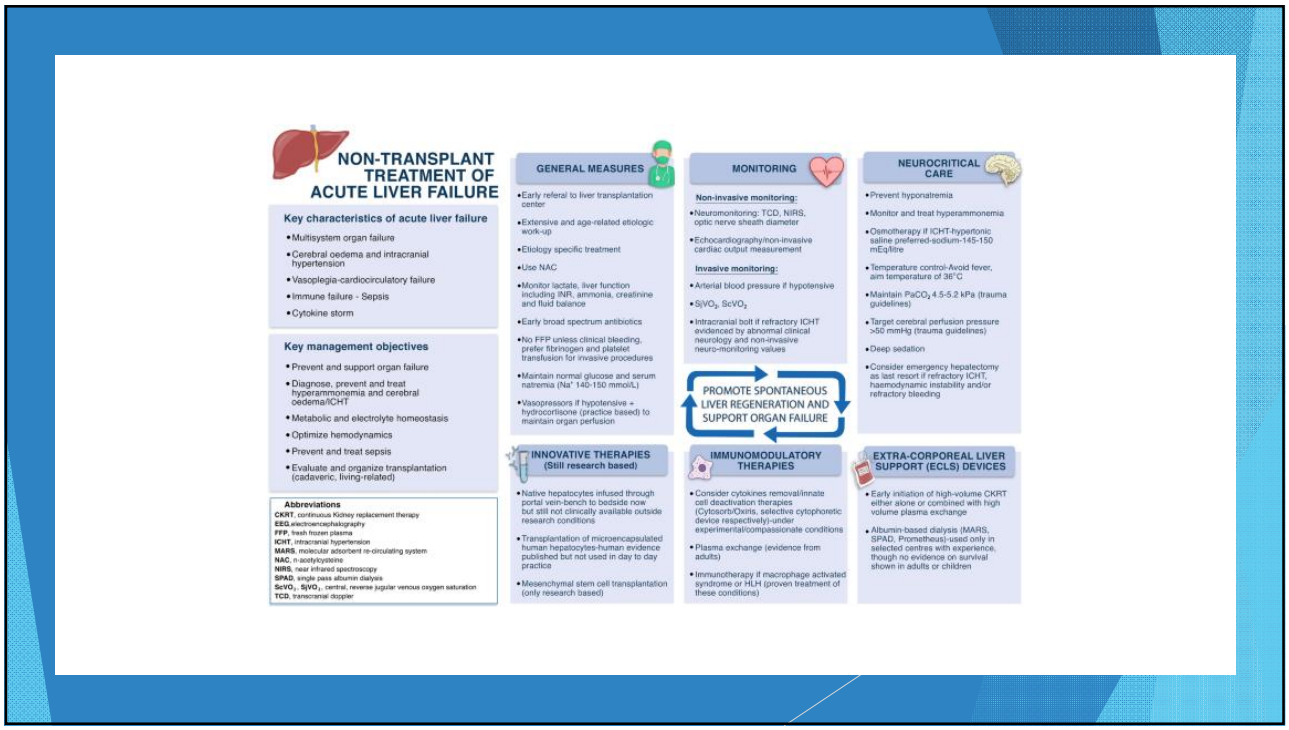




Liver cell transplantation

- Under investigation
- Hepatocytes infused into portal system, peritoneal cavity, spleen
- Source of cells:
  - Hepatoblastoma: malignancy risk
  - Porcine cells: xenotrophic viruses
- Large cell volume required:
  - Most lost on initial infusion
- Does not address any portal hypertension in chronic setting
- Hepatocytes embolisation risk





THE PAEDIATRIC LIVER EMERGENCY

- A diagnostic emergency : the infant with liver disease
  - PALF: Paediatric Acute Liver Failure
  - Variceal bleeding
  - Metabolic Encephalopathy

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LIVER DISEASE IN THE INFANT

- THIS IS AN EMERGENCY!
- Largest population attended to by paediatric hepatologists
- May not look acutely ill, may even be thriving
- Diagnosis can prevent life-threatening complications and can be time-sensitive
  - Haemophagocytic lymphohistiocytosis
  - Metabolic disorders
  - Herpes Simplex
  - Gestational alloimmune disease
  - Biliary Atresia

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I FEEL I MUST BRING TO YOU ATTENTION, MY DEAR FELLOW …

THAT YOU PATIENT IS MOST TERRIFYINGLY YELLOW

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DEFINTION OF THE JAUNDICED INFANT

- 60% of term and 80% of pre-term infants present with jaundice = physiological + unconjugated
- Prolonged jaundice = jaundice for > 2 weeks in a term and > 3 weeks in a pre-term infant
  - TRIGGER INVESTIGATION
- Pale stools and yellow diaper staining are other signs BUT
  - 37% OF DOCTORS AND NURSES AND 66% OF PARENTS CANNOT PROPERLY IDENTIFY PALE STOOLS
  - MUST USE A STOOL CARD FOR COMPARISON

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MAIN CAUSES OF CHRONIC CHOLESTASIS IN CHILDREN

«SURGICAL» CHOLESTASIS	«MEDICAL» CHOLESTASIS
- Biliary atresia - Choledochal cyst	- Disorders related to bile acid transport or synthesis (e.g., PFIC) - Proteic and glucidic metabolism (e.g., tyrosinemia type I, galactosemia) - Genetic syndromes (e.g. Alagille syndrome) - Mitochondrial and endocrine disease - Hepatic infections - Parenteral nutrition – associated cholestasis (PNAC)

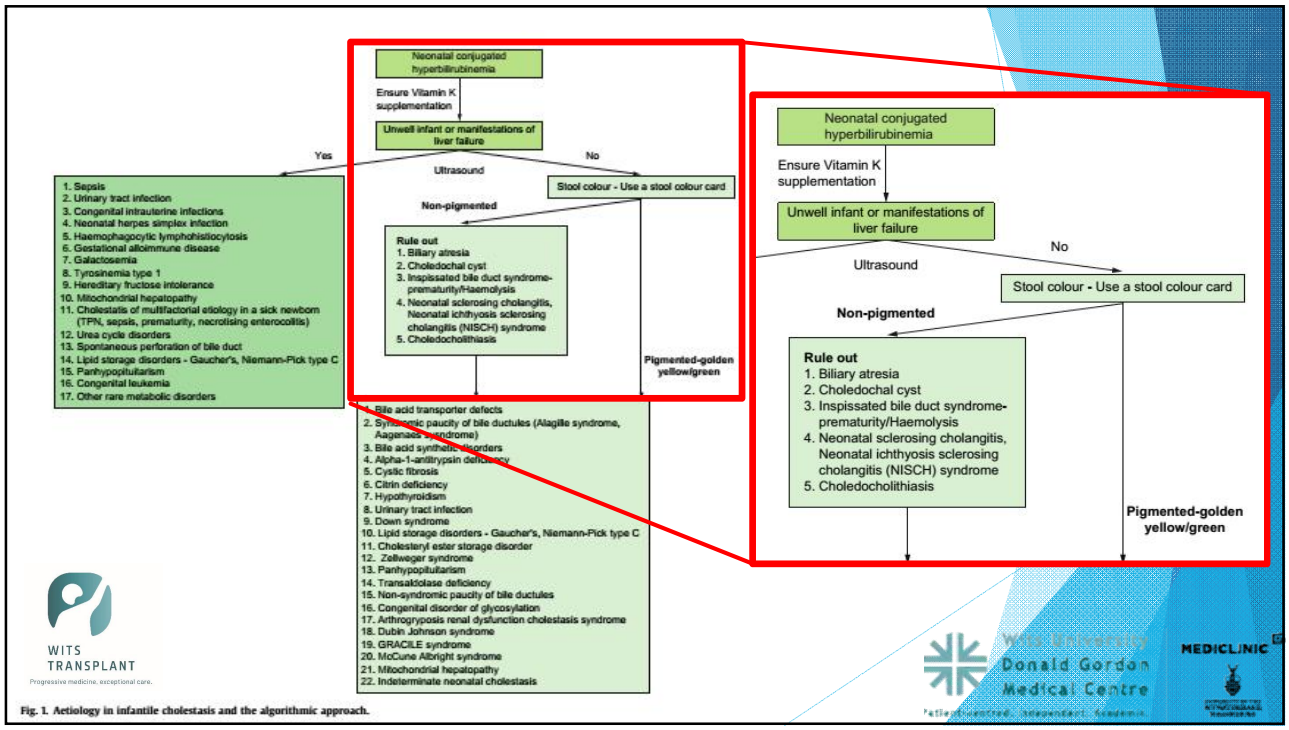
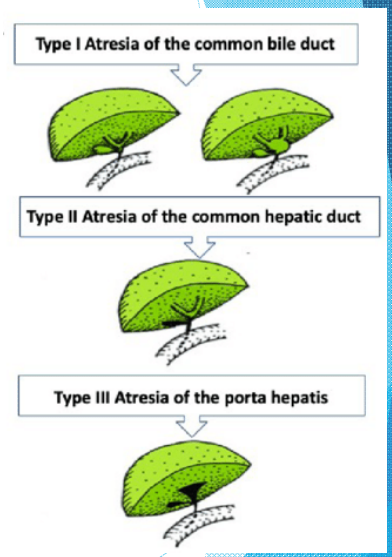


Fig. 1. Aetiology in infantile cholestasis and the algorithmic approach.

BILIARY ATRESIA

- Progressive fibrosing cholangiopathy resulting in the ongoing destruction of the bile ducts
- Accounts for about 25% of neonatal cholestasis
- Diagnosed via on-table cholangiogram or liver biopsy NOT on abdominal US or HIDA scan
- Poor native liver survival if diagnosed beyond the age of 2/12
- For the best results, Kasai portoenterostomy should be performed in under 30 days (70% native liver survival vs 0% in >120 days)



- PALE STOOL + JAUNDICED INFANT = REFERRAL TO PEADATRIC GASTROENTEROLOGIST

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INVESTIGATIONS

- HIDA scan only if stools are ambiguous and liver biopsy is trying to be avoided
- LIVER BIOPSY IS CENTRAL: RAPID AND ACCURATE
  - 88-96.8% accuracy rates
- Ultrasound is useful in the diagnosis of choledocal cysts which may be further investigated with MRCP

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- Ultrasound – Cyst at the porta, triangular cord sign, small irregular gallbladder, polysplenia/asplenia, situs inversus
- Liver biopsy – Expanded portal tract with fibrosis and inflammation, bile ductular reaction, bile plugs
- Operative cholangiogram to confirm the diagnosis

Table 2. Disease-specific investigations for infants with liver disease.

Disorder	Investigations
Sepsis, urinary tract infection	Blood culture, urine culture.
Congenital intrauterine infections	Review of maternal serology, history of infection during pregnancy, In the neonate – urine CMV PCR, Guthrie card blood spot DNA, VDRL serology test, toxoplasma serology, Rubella serology
Neonatal herpes simplex infection	Serum HSV PCR
Hemophagocytic lymphohistiocytosis	Full blood count, serum triglycerides, ferritin, fibrinogen, soluble CD25, bone marrow aspiration and trephine biopsy, perforin expression, Natural killer cell degranulation and cytotoxicity, perforin mutations, SAP and XIAP expression
Gestational alloimmune disease	Buccal mucosal biopsy for salivary gland iron staining, MRI abdomen, serum ferritin, total iron binding capacity
Galactosemia	RBC galactose-1-phosphate uridyl transferase levels before any RBC transfusion
Tyrosinemia type 1	Urine succinyl acetone, mutational analysis
Hereditary fructose intolerance, arthrogryposis renal dysfunction cholestasis syndrome, Dubin-Johnson syndrome, GRACILE syndrome, McCune Albright syndrome, citrin deficiency, Down syndrome, trans-aldolase deficiency, ciliopathies	Genetic testing
Mitochondrial hepatopathy	Serum lactate, pyruvate, genetic testing
Ornithine transcarbamylase deficiency	Serum ammonia, plasma and urine amino acids, genetic testing
Spontaneous rupture of bile duct	Hepatobiliary radioisotope scan
Lipid storage disorders - Gaucher's, Niemann-Pick type A, B, C	White cell enzymes, skin biopsy for fibroblast culture and filipin staining, genetics, eye examination, bone marrow aspiration and biopsy
Panhypopituitarism, hypothyroidism	Random serum cortisol, If low short synacthen test, thyroid function test, MRI brain, genetic mutations
[illegible]	[illegible]
Biliary atresia	Ultrasound – Cyst at the porta, triangular cord sign, small irregular gallbladder, polysplenia/asplenia, situs inversus Liver biopsy – Expanded portal tract with fibrosis and inflammation, bile ductular reaction, bile plugs Operative cholangiogram to confirm the diagnosis
Choledochal cyst, choledocholithiasis	Ultrasound, MRCP
Neonatal sclerosing cholangitis, NISCH syndrome	Liver biopsy, genetic studies
Bile acid transporter defects	GGT, genetics, liver immunohistochemistry
Syndromic paucity of bile ducts (Alagille syndrome)	Echocardiography, eye examination, vertebral radiography, liver biopsy and genetics
Bile acid synthetic disorders	GGT, serum bile acid, urine bile acid profile, genetics
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin level and phenotype
Cystic fibrosis	Immunoreactive trypsinogen, genetics
Cholesteryl ester storage disease	Serum cholesterol, triglycerides, lysosomal acid lipase levels, genetics
Zellweger syndrome	Very long-chain fatty acid, genetics
Congenital disorder of glycosylation	Transferrin electrophoresis, genetics

CMV, cytomegalovirus; GGT, gamma glutamyltransferase; HSV, herpes simplex virus; MRCP, magnetic [illegible] cholangiopancreatography; NISCH, neonatal sclerosing cholangitis hypotrichosis; RBC, red blood cell; VDRL, Venereal Research Disease Laboratory.

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TABLE 4. Targeted investigations of the persistently cholestatic infant

Tier 1: Aim to evaluate after cholestasis has been established in order to both identify treatable disorder as well as to define the severity of the liver involvement
- Blood—CBC + differential, INR, AST, ALT, AP, GGTP, TB, DB (or conjugated bilirubin), albumin and glucose. Check α-1-antitryspin phenotype (Pi typing) and level, TSH, T4 if newborn screen results not readily available
- Urine—urinalysis, culture, reducing substances (rule out galactosemia)
- Consider bacterial cultures of blood, urine and other fluids especially if infant is clinically ill.
- Verify results of treatable disorders (such as galactosemia and hypothyroidism) from newborn screen
- Obtain fasting ultrasound

Tier 2: Aim to complete a targeted evaluation in concert with pediatric gastroenterologist/hepatologist
- General—TSH and T4 values, serum bile acids, cortisol
- Consideration of specific etiologies
  - Metabolic—serum ammonia, lactate level, cholesterol, red blood cell galactose-1-phosphate uridyltransferase, urine for succinylacetone and organic acids. Consider urine for bile salt species profiling
  - ID—direct nucleic acid testing via PCR for CMV, HSV, listeria
  - Genetics—in discussion with pediatric gastroenterologist/hepatologist, with a low threshold for gene panels or exome sequencing
- Sweat chloride analysis (serum immunoreactive trypsinogen level or CFTR genetic testing) as appropriate
- Imaging
  - CXR—lung and heart disease
  - Spine—spinal abnormalities (such as butterfly vertebrae)
  - Echocardiogram—evaluating for cardiac anomalies seen in Alagille syndrome
  - Cholangiogram
- Liver biopsy (timing and approach will vary according to institution and expertise)
- Consideration for consultations
  - Ophthalmology
  - Metabolic/Genetic (consider when to involve, especially when there is consideration for gene panels or whole exome sequencing)
  - Cardiology/ECHO (if murmur present or has hypoxia, poor cardiac function)
  - General pediatric surgery
  - Nutrition/dietician

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CBC = complete blood count; CFTR = cystic fibrosis trans-membrane receptor; DB = conjugated (direct) bilirubin; ECHO = echocardiogram; GGTP = gamma-glutamyl transferase; HSV = herpes simplex virus; ID = infectious diseases; INR = international normalized ratio; PCR = polymerase chain reaction; TB = total bilirubin; TSH = thyroid-stimulating hormone.

TABLE 4. Targeted investigations of the persistently cholestatic infant

Tier 1: Aim to evaluate after cholestasis has been established in order to both identify treatable disorder as well as to define the severity of the liver involvement
Blood—CBC + differential, INR, AST, ALT, AP, GGTP, TB, DB (or conjugated bilirubin), albumin and glucose. Check α-1-antitryspin phenotype (Pi typing) and level, TSH, T4 if newborn screen results not readily available
Urine—urinalysis, culture, reducing substances (rule out galactosemia)
Consider bacterial cultures of blood, urine and other fluids especially if infant is clinically ill.
Verify results of treatable disorders (such as galactosemia and hypothyroidism) from newborn screen
Obtain fasting ultrasound
Tier 2: Aim to complete a targeted evaluation in concert with pediatric gastroenterologist/hepatologist

TABLE 3. Physical findings in children with neonatal cholestasis

Assessment of general health	Ill appearance may indicate infection or metabolic disease, infants with biliary atresia typically appear well
General appearance	Dysmorphic features: Alagille syndrome in the neonate rarely exhibits characteristic facial appearance with a broad nasal bridge, triangular facies, and deep-set eyes. Typical facial features may appear at around 6 months of age, but are often nonspecific (69)
Vision/slit lamp examination	
Hearing	Congenital infection, storage disease, septo-optic dysplasia, posterior embryotoxon, cataracts
Congenital infections, PFIC1, TJP2, mitochondrial	
Cardiac examination: murmur, signs of heart failure	Congenital heart disease: Alagille syndrome, biliary atresia splenic malformation syndrome
Abdominal examination	Presence of ascites; abdominal wall veins, liver size and consistency, spleen size and consistency (or absence thereof), abdominal masses, umbilical hernia
Stool examination (crucial—the primary physician should make every effort to view stool pigment)	Acholic or hypopigmented stools suggest cholestasis or biliary obstruction
Neurologic	Note overall vigor and tone

PFIC = progressive familial intrahepatic cholestasis; TJP = tight-junction protein.

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EXAMINATION & INVESTIGATION

1st TIER

- Clinically ill / well
- Dysmorphic features
- Cardiac lesions on cardiac examination
- Ascites; liver and spleen size + consistency and abdominal masses on abdominal examination
- Tone and vigour on neurological examination

- FBC and diff, INR, LFT and glucose
- a-1-antitrypsin phenotype (Pi typing) and level, TSH, T4
- Urine –urinalysis, culture, reducing substances
- Consider bacterial cultures of blood, urine and other fluids especially if infant is clinically ill
- Fasting ultrasound

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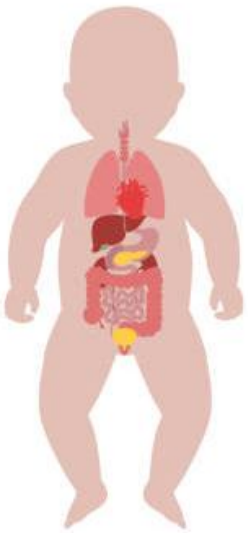
Facial dysmorphism	Down syndrome, Zellweger syndrome, ARC syndrome, Smith Lemli Opitz syndrome, Alagille syndrome (difficult to appreciate in neonates)
Abnormalities in eye examination	*Cataract* - Congenital rubella, galactosemia, Zellweger syndrome, Wolman disease *Posterior embryotoxon and Drusen* – Alagille syndrome *Cherry-red spot* – Gaucher's and Niemann-Pick disease *Septo-optic dysplasia* - Hypopituitarism
Skin changes	*Icthyosis, hypotrichosis* – Neonatal sclerosing cholangitis *Cutaneous laxity* – ARC syndrome, transaldolase deficiency Lymphoedema – Aagenaes syndrome
Congenital cardiovascular defects	*Pulmonary and peripheral pulmonary stenosis, tetrology of Fallot* - Alagille syndrome *Atrial and ventricular Septal Defects, preduodenal portal vein, absent Inferior vena cava* – Biliary atresia
Skeletal abnormalities	*Vertebral anomalies* – Alagille syndrome *Patellar stippling on X-ray* – Zellweger syndrome
Neuromuscular involvement	*Hypotonia* – Down syndrome, Zellweger syndrome, Wolman syndrome, congenital disorders of glycosylation, mitochondrial disorders, Gaucher and Niemann-Pick disease *Seizures* – Congenital intrauterine infections, disseminated herpes infection, hypoglycaemia due to any cause of liver failure, galactosemia, fructosemia *Arthrogrypopsis* – ARC syndrome
Massive splenomegaly	Gaucher's and Niemann-Pick's disease
Ascites	Ascites without liver failure – Spontaneous rupture of bile duct Ascites with liver dysfunction – Any cause of neonatal liver failure
Genital abnormalities	*Micropenis* - Septo-optic dysplasia *Ambigous genitalia* - Smith-Lemli-Opitz syndrome
Renal anomalies	*Cysts* – ciliopathies *Dysplasia* – ARC syndrome



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2nd TIER

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Table 2. Disease-specific investigations for infants with liver disease.

Disorder	Investigations
Sepsis, urinary tract infection	Blood culture, urine culture.
Congenital intrauterine infections	Review of maternal serology, history of infection during pregnancy, In the neonate – urine CMV PCR, Guthrie card blood spot DNA, VDRL serology test, toxoplasma serology, Rubella serology
Neonatal herpes simplex infection	Serum HSV PCR
Hemophagocytic lymphohistiocytosis	Full blood count, serum triglycerides, ferritin, fibrinogen, soluble CD25, bone marrow aspiration and trephine biopsy, perforin expression, Natural killer cell degranulation and cytotoxicity, perforin mutations, SAP and XIAP expression
Gestational alloimmune disease	Buccal mucosal biopsy for salivary gland iron staining, MRI abdomen, serum ferritin, total iron binding capacity
Galactosemia	RBC galactose-1-phosphate uridyl transferase levels before any RBC transfusion
Tyrosinemia type 1	Urine succinyl acetone, mutational analysis
Hereditary fructose intolerance, arthrogryposis renal dysfunction cholestasis syndrome, Dubin-Johnson syndrome, GRACILE syndrome, McCune Albright syndrome, citrin deficiency, Down syndrome, trans-aldolase deficiency, ciliopathies	Genetic testing
Mitochondrial hepatopathy	Serum lactate, pyruvate, genetic testing
Ornithine transcarbamylase deficiency	Serum ammonia, plasma and urine amino acids, genetic testing
Spontaneous rupture of bile duct	Hepatobiliary radioisotope scan
Lipid storage disorders - Gaucher's, Niemann-Pick type A, B, C	White cell enzymes, skin biopsy for fibroblast culture and filipin staining, genetics, eye examination, bone marrow aspiration and biopsy
Panhypopituitarism, hypothyroidism	Random serum cortisol, If low short synacthen test, thyroid function test, MRI brain, genetic mutations
Congenital leukaemia	Full blood count, bone marrow aspiration, biopsy, flow cytometry
Biliary atresia	Ultrasound – Cyst at the porta, triangular cord sign, small irregular gallbladder, polysplenia/asplenia, situs inversus Liver biopsy – Expanded portal tract with fibrosis and inflammation, bile ductular reaction, bile plugs Operative cholangiogram to confirm the diagnosis
Choledochal cyst, choledocholithiasis	Ultrasound, MRCP
Neonatal sclerosing cholangitis, NISCH syndrome	Liver biopsy, genetic studies
Bile acid transporter defects	GGT, genetics, liver immunohistochemistry
Syndromic paucity of bile ducts (Alagille syndrome)	Echocardiography, eye examination, vertebral radiography, liver biopsy and genetics
Bile acid synthetic disorders	GGT, serum bile acid, urine bile acid profile, genetics
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin level and phenotype
Cystic fibrosis	Immunoreactive trypsinogen, genetics
Cholesteryl ester storage disease	Serum cholesterol, triglycerides, lysosomal acid lipase level, genetics
Zellweger syndrome	Very long-chain fatty acid, genetics
Congenital disorder of glycosylation	Transferrin electrophoresis, genetics

CMV, cytomegalovirus; GGT, gamma glutamyltransferase; HSV, herpes simplex virus; MRCP, magnetic resonance cholangiopancreatography; NISCH, neonatal ichthyosis sclerosing cholangitis hypotrichosis; RBC, red blood cell; VDRL, Venereal Research Disease Laboratory.

2nd TIER

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GOOD NEWS …. TIER 2

Tier 2 = Targeted evaluation **in concert with a paediatric gastroenterologist / hepatologist**

CALL YOUR HEPATOLOGIST

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TABLE 4. Targeted investigations of the persistently cholestatic infant

Tier 1: Aim to evaluate after cholestasis has been established in order to both identify treatable disorder as well as to define the severity of the liver involvement
- Blood—CBC + differential, INR, AST, ALT, AP, GGTP, TB, DB (or conjugated bilirubin), albumin and glucose. Check α-1-antitryspin phenotype (Pi typing) and level, TSH, T4 if newborn screen results not readily available
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- Consider bacterial cultures of blood, urine and other fluids especially if infant is clinically ill.
- Verify results of treatable disorders (such as galactosemia and hypothyroidism) from newborn screen
- Obtain fasting ultrasound

Tier 2: Aim to complete a targeted evaluation in concert with pediatric gastroenterologist/hepatologist
- General—TSH and T4 values, serum bile acids, cortisol
- Consideration of specific etiologies
  - Metabolic—serum ammonia, lactate level, cholesterol, red blood cell galactose-phosphate uridyltransferase, urine for succinylacetone and bile acids. Consider urine for bile salt species profiling
  - Infectious—broad spectrum nucleic acid testing via PCR for CMV, HSV, listeria [illegible]
  - Genetics—in discussion with pediatric gastroenterologist/hepatologist, with a low threshold for gene panels or exome sequencing
  - Sweat chloride analysis (serum immunoreactive trypsinogen level or CFTR genetic testing) as appropriate
- Imaging
  - CXR—lung and heart disease
  - Spine—spinal abnormalities (such as butterfly vertebrae)
  - Echocardiogram—evaluating for cardiac anomalies seen in Alagille syndrome
  - Cholangiogram
- Liver biopsy (timing and approach will vary according to institution and expertise)
- Consideration for consultations
  - Ophthalmology
  - Metabolic/Genetic (consider when to involve, especially when there is consideration for gene panels or whole exome sequencing)
  - Cardiology/ECHO (if murmur present or has hypoxia, poor cardiac function)
  - General pediatric surgery
  - Nutrition/dietician

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CBC = complete blood count; CFTR = cystic fibrosis trans-membrane receptor; DB = conjugated (direct) bilirubin; ECHO = echocardiogram; GGTP = gamma-glutamyl transferase; HSV = herpes simplex virus; ID = infectious diseases; INR = international normalized ratio; PCR = polymerase chain reaction; TB = total bilirubin; TSH = thyroid-stimulating hormone.

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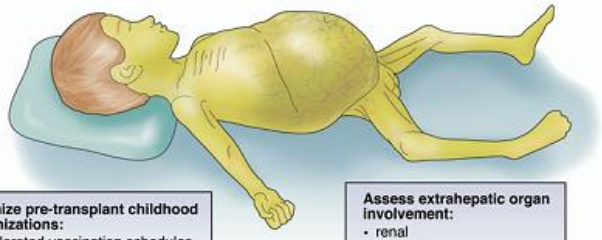
Management

Optimize nutritional status:
- protein/caloric intake
- feeding tolerance
- vitamin/micronutrient status

Manage complications of cirrhosis:
- ascites
- variceal bleeding
- encephalopathy
- spontaneous bacterial peritonitis



Maximize pre-transplant childhood immunizations:
- accelerated vaccination schedules
- live-virus vaccine precautions

Assess extrahepatic organ involvement:
- renal
- cardiac
- hematologic
- skeletal

Integration of the services of a dedicated pediatric multidisciplinary health care team:
- pediatricians and pediatric surgeons
- nurses
- dieticians
- social work
- psychology
- financial services
- home health care
- pediatric hospital setting

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NUTRITIONAL ASSESSMENT OF CHILDREN WITH CHOLESTASIS

ANTHROPOMETRIC MEASUREMENTS	BIOCHEMICAL MARKERS (in association with other parameters)	INSTRUMENTAL INVESTIGATIONS
- Length (children <2 years) - Height (children >2 years) - Mid upper arm circumference - Triceps skin fold	- Serum protein levels - Albumin - Prealbumin - Transferrin - Retinol-binding protein - etc	- Dual-energy X-ray Absorptiometry - Bioelectrical impedance - Indirect calorimetry

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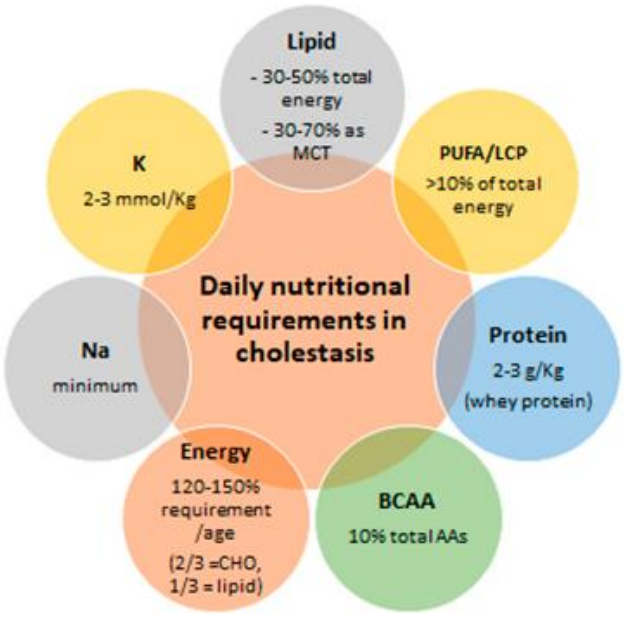
Figure 4. Nutritional assessment of pediatric chronic cholestatic liver diseases.



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MEDICATION

Pruritus

- Ursodeoxycholic acid 15-20mg/kg/day
- Bile acid binding resins 250-500mg/kg/day
- Phenobarbitol 3-10mg/kg/da
- Rifampicin 10mg/kg/day
- Antihistamines
- Naltrexone 1-2mg/kg/day

Ascites

- Furosemide 1-2mg/kg/day
- Spironolactone 2-6mg/kg/day
- Albumin 1g/kg 20%

Variceal bleeding

- Octreotide 1-5ug/kg/hr

Cholangitis prophylaxis

- TMP/sulfamethoxazole 2-5mg/kg/day

Vitamin Supplementation

- **A** 5000 – 25 000U/day
- **D** 500 – 1000iu/kg/day
- **E** 25-200iu/kg/day
- **K** 2.5mg x 2 per week up to 10mg daily

Of note ….

- ALL children with cholestatic jaundice should be managed with a paediatric hepatologist
- Ascites is a complication of chronic liver disease representing decompensation and warrants expedited referral
- Suspected upper gastrointestinal bleeding should be referred to a facility with a paediatric gastroenterologist or paediatric surgeon with access to endoscopy

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CONTACTING THE TRANSPLANT UNIT

Wits Donald Gordon

- **On call phone: 067 413 5449 (Dr Beretta / Dr Berkenfeld / Dr Mudau)**
- **Dr Beretta: 082 565 3216 / rees.beretta@gmail.com**
- **Paediatric transplant ward: 011 356 6494**
  - Leave name and contact details and state contact reason is for a patient in acute liver failure

Charlotte Maxeke

- **Dr Wallabh: 073 233 3155**

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THANK YOU

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