

Paediatric Acute Liver Failure

Where it differs from adults



Tim De Maayer

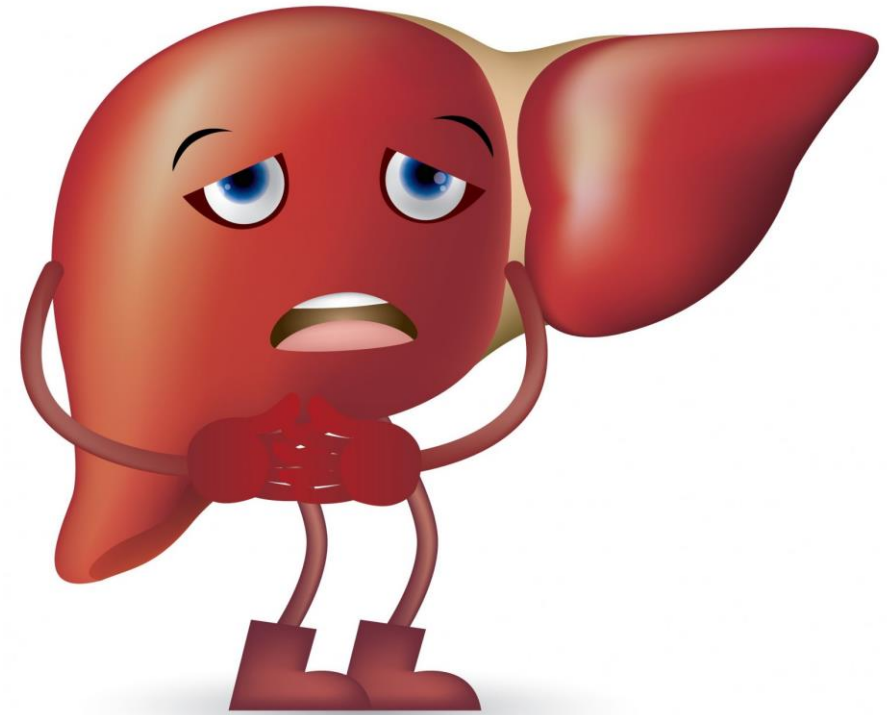




Not just small adults

Content

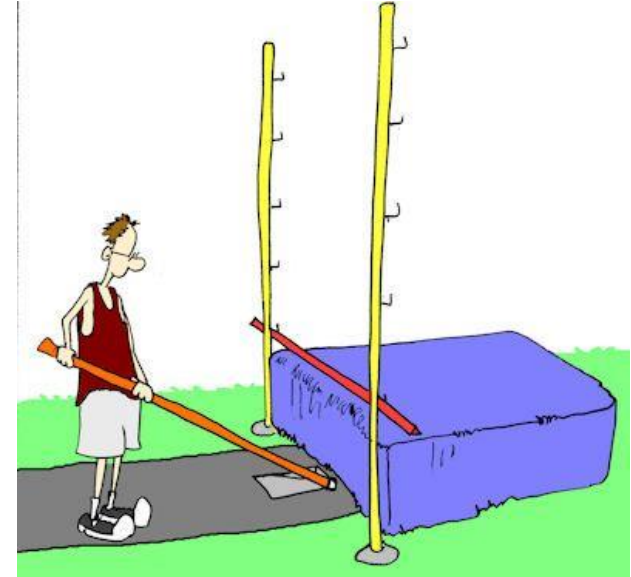
- Definitions
- Encephalopathy
- Aetiology & diagnostic testing
- Medical Management
- Outcome prediction scores



No disclosures

The PALF study group

- Study entry criteria:
 - Evidence of acute liver injury
 - Liver induced coagulopathy:
 - INR $>$ 2.0 if no encephalopathy
 - INR $>$ 1.5 with encephalopathy
 - Absence of chronic liver disease



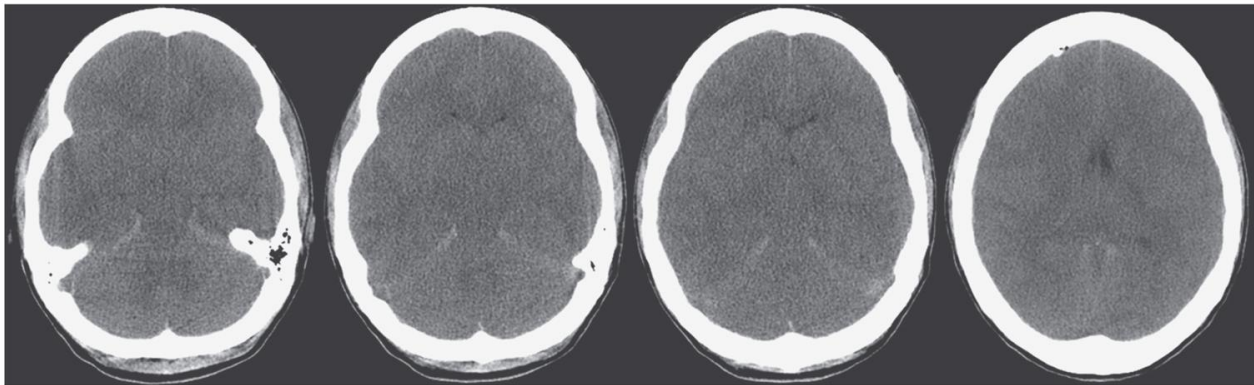
R Squires

Hepatic encephalopathy in children

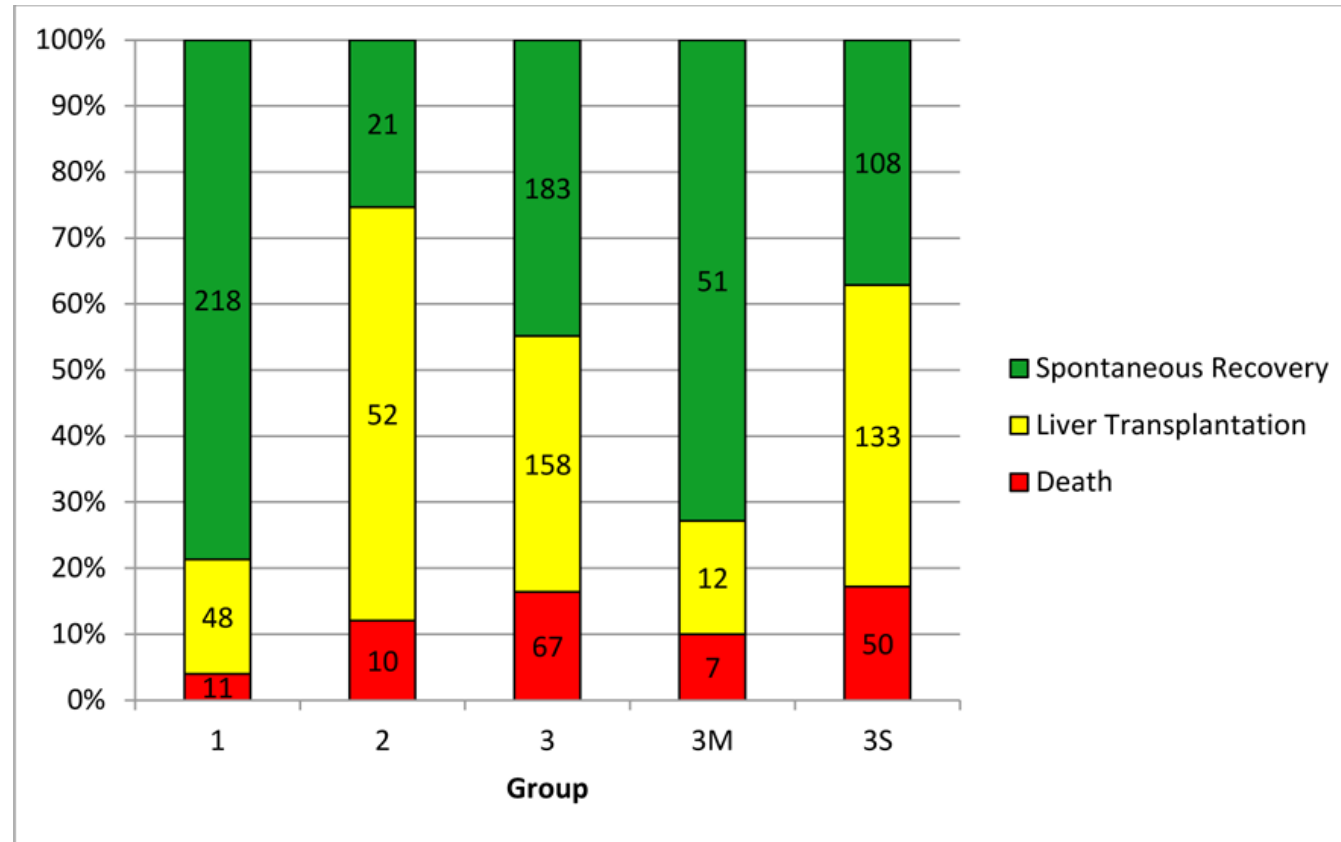
- Not always clinically apparent
- Non-specific
- Often a late/pre-terminal sign

The Whittington scale for encephalopathy in children <3y

Stage	Clinical	Asterixis/Reflexes	Neurological Signs
Early (I and II)	Inconsolable crying, sleep reversal , inattention to task	Unreliable/normal or hyperreflexic	Untestable
Mid (III)	Somnolence, stupor, combativeness	Unreliable/ hyperreflexic	Most likely untestable
Late (IV)	Comatose, arouses with painful stimuli (IVa), or no response (IVb)	Absent	Decerebrate or decorticate



21 day outcomes of PALF by encephalopathy



1 No HE
2 Developed HE
3 HE at enrolment
3M INR < 2
3S INR > 2

In 59% of early LTx patients, peak encephalopathy was mild (grade I or II)



Aetiology and diagnostic testing

Neonatal/infant specific diagnoses

Herpes Simplex virus

- Most common cause of neonatal PALF.
- Intrapartum transmission
- ↑↑ transaminases
- Vesicles not always present

GALD

- Maternal antibody to foetal liver
- Recurs in subsequent pregnancies
- Presents in utero / first few days of life
- Treated with gamma globulins

Specific diagnoses

HLH

- Abnormal immune activation
- Primary or secondary
- Fever, HSM and cytopenia
- Raised ferritin & triglycerides
- Haemophagocytosis
- Rx: immune suppression

Specific diagnoses

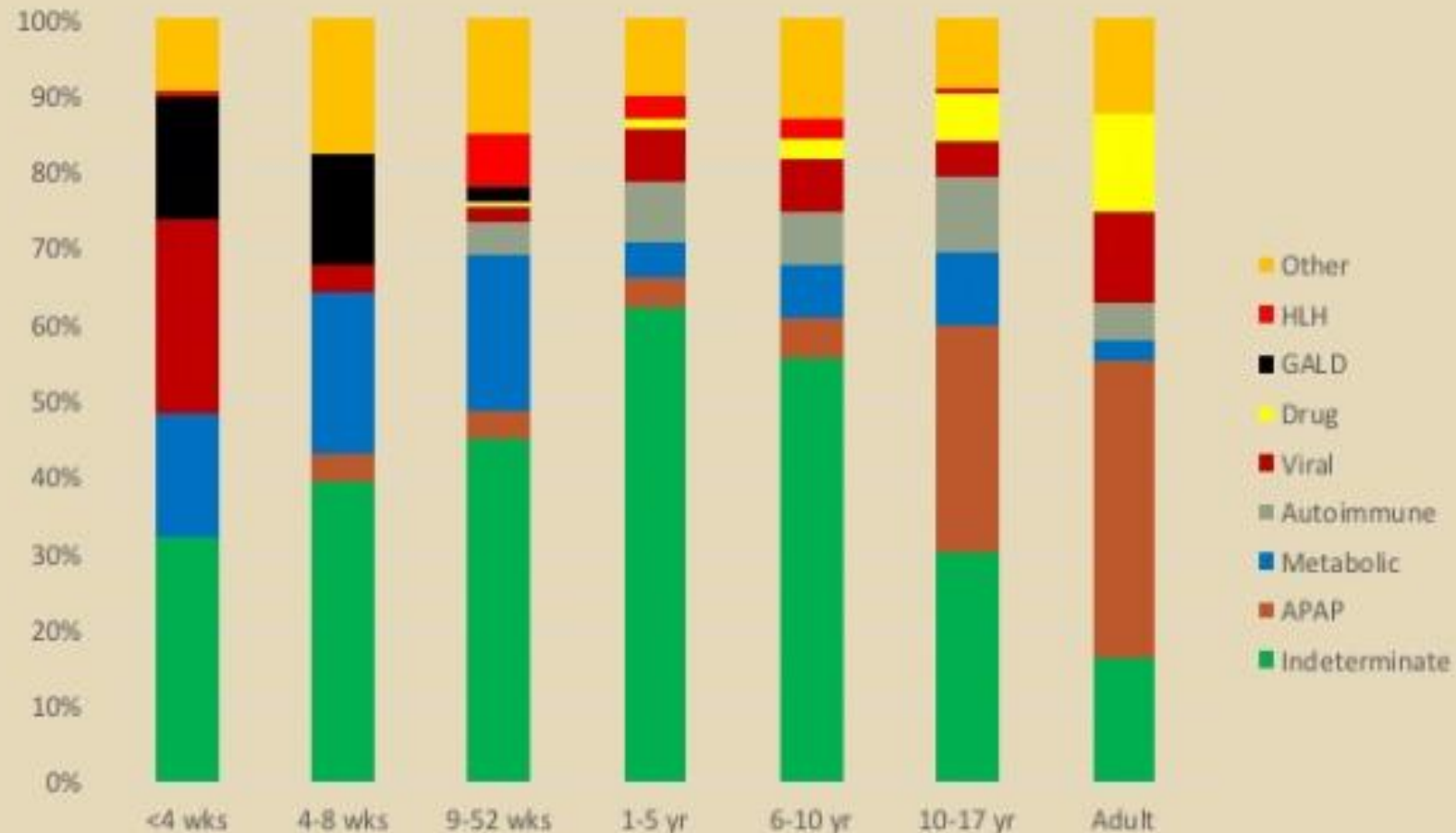
Tyrosinaemia

- FAH deficiency
- ↑↑INR, ↑SBR, ↑transaminases
- High HCC risk
- Rx: Nitisinone, low tyrosine diet
- Tx if treatment fails

Mitochondrial neuro-hepatopathies

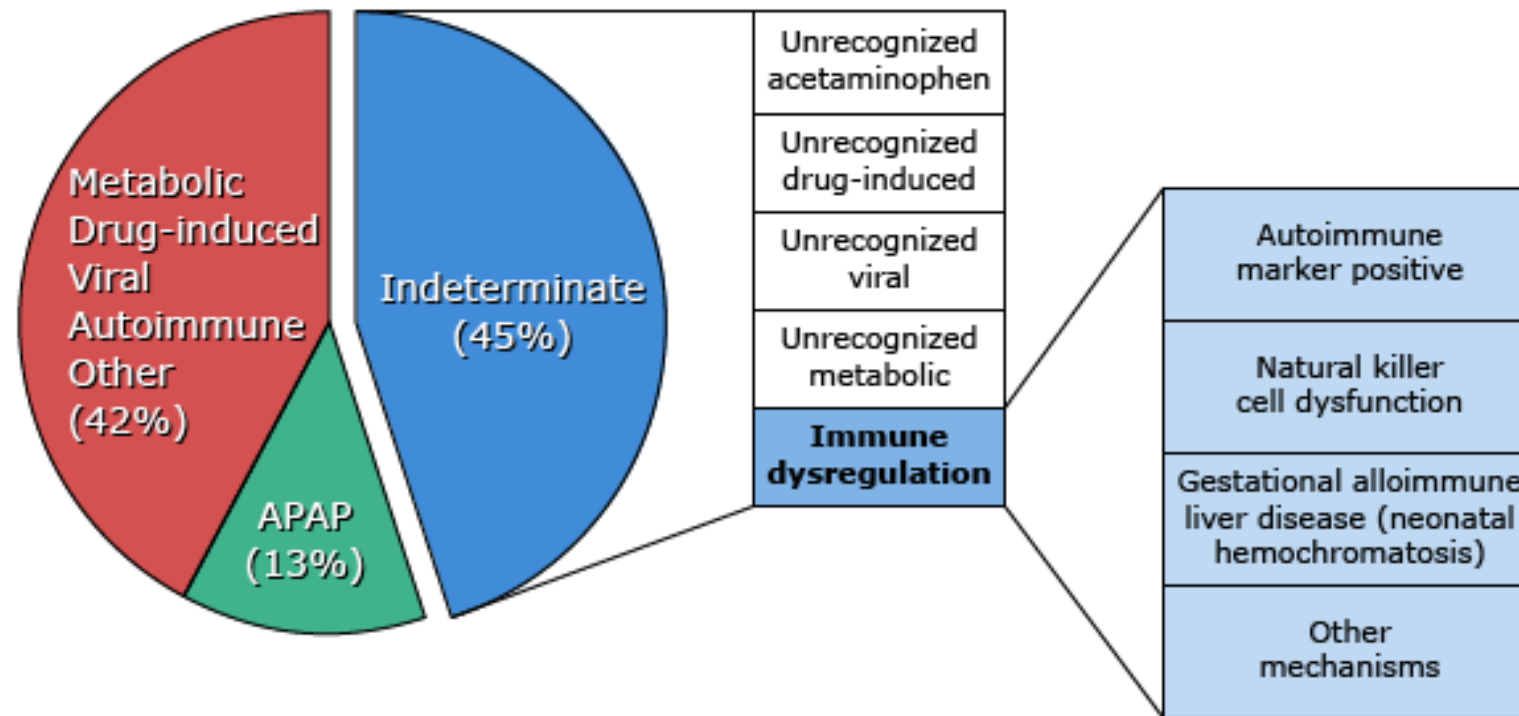
- Defect in electron transport chain
- Impaired ATP generation, fat oxidation
- Elevated lactate, microvesicular steatosis
- Novel MPV17 mutation in black South Africans

Aetiology varies by age (N= 985)



Squires, PALF study group

Categories of idiopathic pediatric acute liver failure



The etiology of pediatric acute liver failure (PALF) is identified in approximately 55 percent of cases, leaving an indeterminate cause in 45 percent. Indeterminate cases are likely composed of a number separate conditions including immune dysregulation, with the latter condition having a variety of manifestations.

%; percent; APAP: acetaminophen (paracetamol).

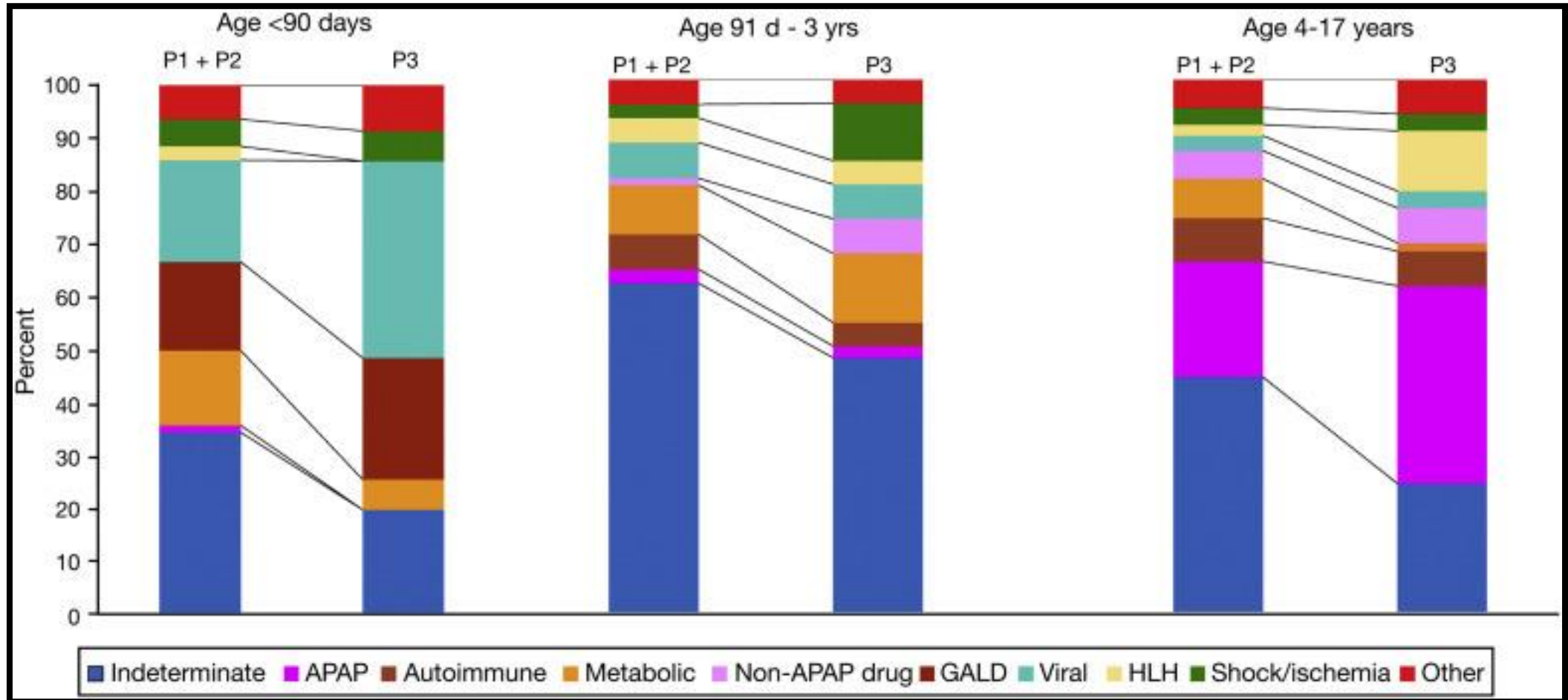
Modified with permission from: Squires RH, Alonso EM. Acute liver failure in children. In: Suchy FJ, Sokol RJ, Balistreri WF, Eds. *Liver Disease in Children*, 4th Ed. Cambridge University Press, New York, 2012. Copyright © 2012 Cambridge University Press.

Age specific diagnostic testing algorithms

- PALF study phase 1 & 2:
 - Neonates <91d old:
 - HSV, GALD, Metabolic (galactosaemia & respiratory chain disorders) most common
 - No EBV
 - No AIH
 - >3 months:
 - AIH, drugs (incl paracetamol)
 - Wilson's only from 4y onwards

Recommended tests	Indication	Recommended age of diagnostic testing			
		<3 mo	3 mo to 3 y	3 mo to 18 y	4–18 y
Blood and urine tests					
Herpes blood PCR	Systemic herpes infection	X		X	
Serum amino acid profile	Urea cycle; other metabolic defects	X		X	
Ferritin	GALD screen	X			
Lactate, pyruvate	Mitochondrial screen	X		X	
Plasma acylcarnitine profile	FAO defects	X		X	
Urine succinylacetone					
Enterovirus blood PCR	Optional diagnostic screening				
Acetaminophen level	Blood culture		X		
Hepatitis A virus IgM	Viral testing for adenovirus, enterovirus, HHV-6, parvovirus, influenza			X	
Hepatitis B surface antigen	Hepatitis E IgM			X	
EBV VCA IgM or PCR	Soluble IL2R, ferritin, triglyceride level			X	
Antinuclear antibody	Liver copper, Wilson gene mutation analysis			X	
Anti-smooth muscle ab	MRI for extrahepatic iron deposition			X	
Liver kidney microsomal ab	Urine orotic acid			X	
IgG	Autoimmune disease screen			X	
Ceruloplasmin	Wilson disease screen				X
24-hour urine copper	Wilson disease screen				X
Historical information					
Drug history	APAP other drug or HDS exposure	X		X	
Confirm newborn screen results	Galactosemia and tyrosinemia	X			
Confirm maternal hepatitis B serology	Hepatitis B in newborn	X			
Procedures					
Abdominal ultrasound with Doppler	Vascular anomalies	X		X	
Echocardiogram	Cardiac dysfunction	X		X	

Age specific testing improves diagnostic yield



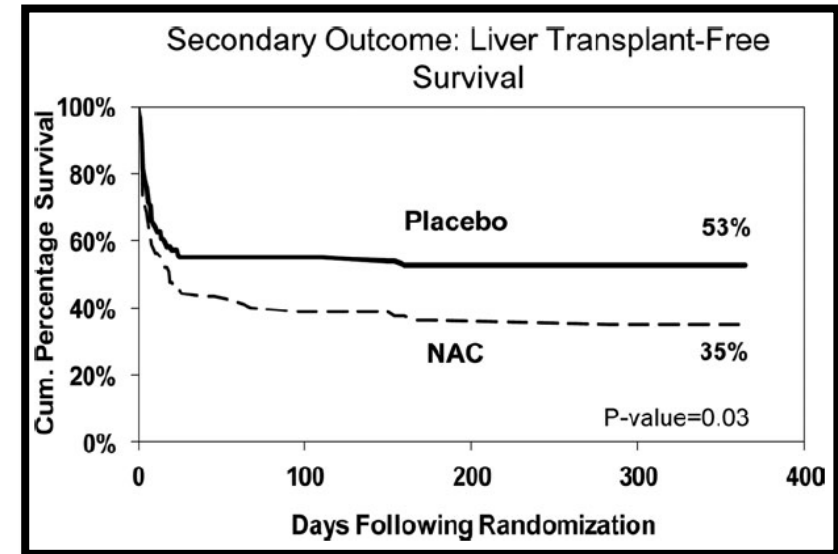
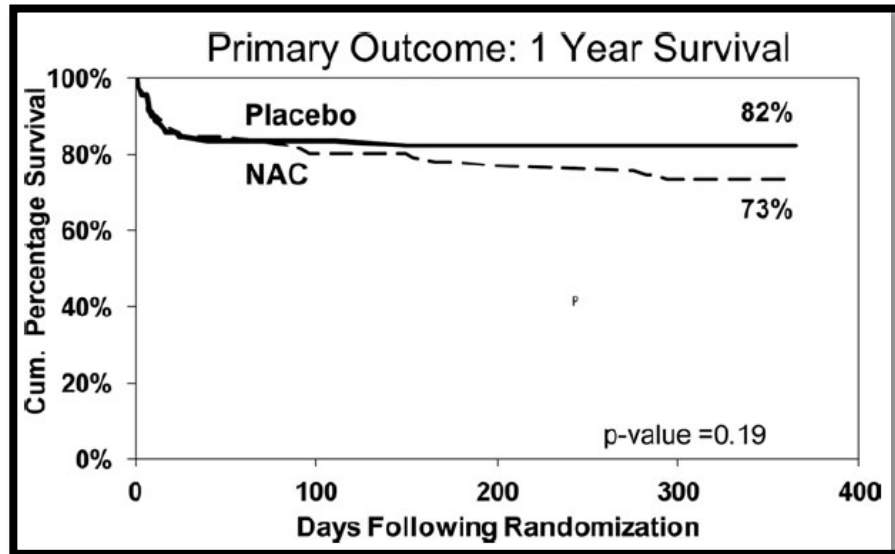


Medical management



Intravenous N-acetylcysteine in Pediatric Patients With Nonacetaminophen Acute Liver Failure: A Placebo-Controlled Clinical Trial

Robert H. Squires,¹ Anil Dhawan,² Estella Alonso,³ Michael R. Narkewicz,⁴ Benjamin L. Shneider,¹
Norberto Rodriguez-Baez,⁵ Dominic Dell Olio,⁶ Saul Karpen,^{7*} John Bucuvalas,⁸ Steven Lobritto,⁹
Elizabeth Rand,¹⁰ Philip Rosenthal,¹¹ Simon Horslen,¹² Vicky Ng,¹³ Girish Subbarao,¹⁴ Nanda Kerkar,¹⁵
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Patricia R. Robuck,²¹ Sharon Lawlor,²² Steven H. Belle²² for the Pediatric Acute Liver Failure Study Group



Predicting
outcomes



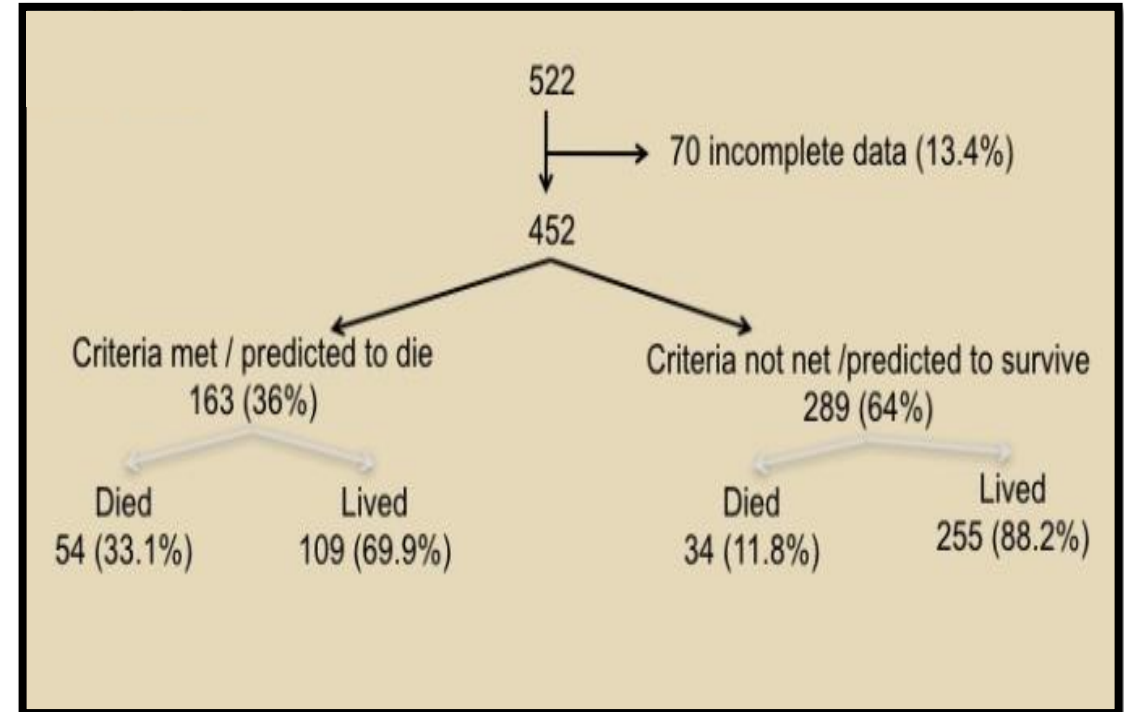
King's College Hospital criteria for liver transplantation in acute liver failure

Acetaminophen-induced disease
Arterial pH <7.3 (irrespective of the grade of encephalopathy)
OR
Grade III or IV encephalopathy AND
Prothrombin time >100 seconds AND
Serum creatinine >3.4mg/dL (301 μmol/L)
All other causes of acute liver failure
Prothrombin time >100 seconds (irrespective of the grade of encephalopathy)
OR
Any three of the following variables (irrespective of the grade of encephalopathy)
1. Age <10 years or >40 years
2. Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
3. Duration of jaundice before onset of encephalopathy >7 days
4. Prothrombin time >50 seconds
5. Serum bilirubin >18 mg/dL (308 μmol/L)

Data from: O'Grady JG, Alexander GJM, Hayllar KM, et al. *Gastroenterology* 1989; 97:439.

King's College Hospital Criteria for Non-Acetaminophen Induced Acute Liver Failure in an International Cohort of Children

Vinay Sundaram, MD¹, Benjamin L. Shneider, MD², Anil Dhawan, MD³, Vicky L. Ng, MD⁴, Kyungah Im, MS⁵, Steven Belle, PhD⁵, and Robert H. Squires, MD²

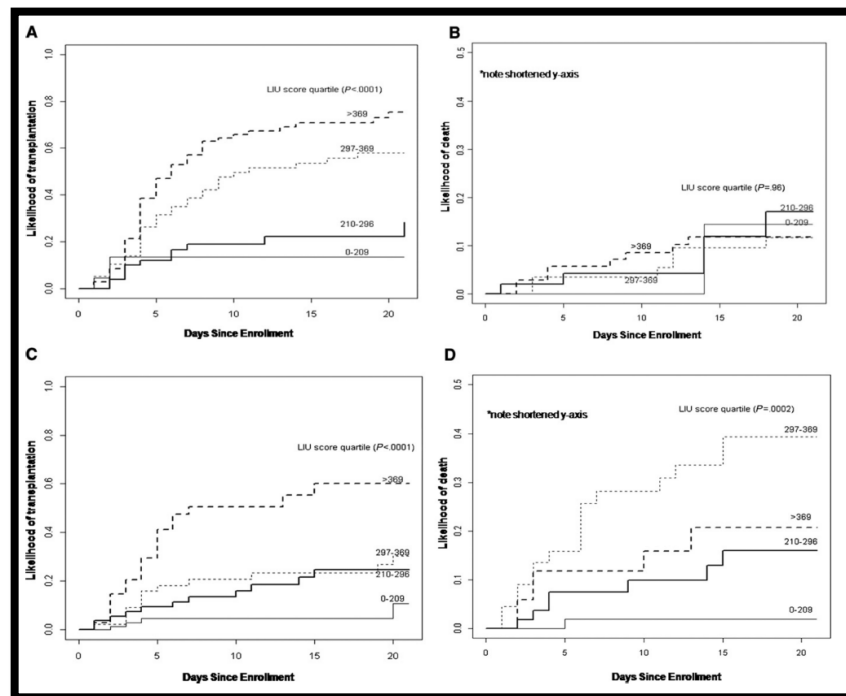


LIU, Clichy, PELD/MELD, ...

Evaluation of the Liver Injury Unit Scoring System to Predict Survival in a Multinational Study of Pediatric Acute Liver Failure

Brandy R. Lu, MD¹, Song Zhang, MS², Michael R. Narkewicz, MD^{1,3}, Steven H. Belle, MD², Robert H. Squires, MD⁴, Ronald J. Sokol, MD^{1,3}, and on behalf of the Pediatric Acute Liver Failure (PALF) Study Group*

$$\text{LIU} = (3.507 \times \text{peak total bilirubin}) + (45.51 \times \text{peak INR}) + (0.254 \times \text{peak ammonia})$$



- Small numbers of deaths in Tx era
- Death & Tx groups combined
- Don't account for dynamic nature of PALF
- Don't help individual patients

The future


Hepatic Encephalopathy in Children with Acute Liver Failure – Utility of Serum Neuromarkers

Toney, Nicole A., MPH^{*}; Bell, Michael J., MD^{*}; Belle, Steven H., PhD[†]; Hardison, Regina M., MS[†]; Rodriguez-Baez, Norberto, MD[‡]; Loomes, Kathleen M., MD[§]; Vodovotz, Yoram, PhD[¶]; Zamora, Ruben, PhD[¶]; Squires, Robert H., MD^{||} for the Pediatric Acute Liver Failure Study Group

Journal of Pediatric Gastroenterology and Nutrition: April 15, 2019 - Volume Publish Ahead of Print - Issue - p
doi: 10.1097/MPG.0000000000002351
Original Article: Hepatology: PDF Only

Data-Driven Modeling for Precision Medicine in Pediatric Acute Liver Failure

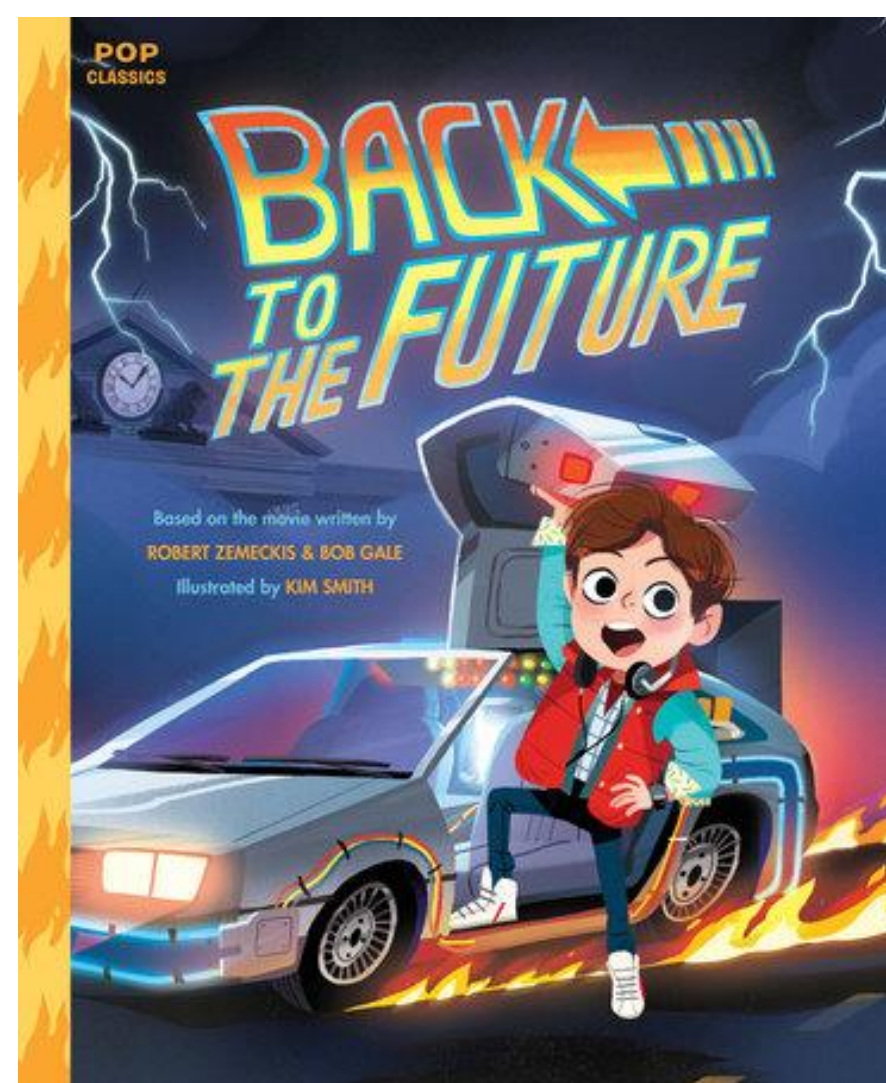
Authors Authors and affiliations

Ruben Zamora, Yoram Vodovotz , Qi Mi, Derek Barclay, Jinling Yin, Simon Horslen, David Rudnick, Kathleen M Loomes, Robert H Squires

Analysis of Serum Inflammatory Mediators Identifies Unique Dynamic Networks Associated with Death and Spontaneous Survival in Pediatric Acute Liver Failure

Nabil Azhar , Cordelia Ziraldo , Derek Barclay, David A. Rudnick, Robert H. Squires, Yoram Vodovotz , for the Pediatric Acute Liver Failure Study Group

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Thank you WDGMC

