Pediatric Acute Liver Failure: Observations from the PALF Study

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Disclosure Slide

In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

Pediatric Acute Liver Failure

- Is rare, probably ~200 cases/year in US and accounts for 10-13% of all pediatric liver transplants
- Is a dynamic clinical syndrome
- Etiologies differ by age and country of origin
- Management is largely supportive, but mulitfacited
- Outcomes vary between and among etiologies and presentations

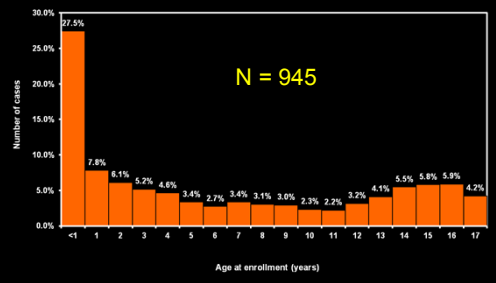
Pediatric Acute Liver Failure (PALF) Study Group

- PALF Study Group (NIH/NIDDK 1 UO1 DK 072146-01)
  - Began in December 1999; Independently funded 2005-2015
  - Multi-center, multi-national study with up to 21 sites; Now 12 sites
    - United States = 11
    - Canada (Toronto)= 1
  - Data
    - Clinical and Laboratory data, plus serum, daily until outcome
    - End points: death, transplant, discharge
    - Biological samples: DNA, liver tissue when taken for clinical purposes
- Treatment trial
  - N-acetylcysteine for non-acetaminophen ALF (Hepatology 2013)
- Core and Ancillary studies

Entry Criteria for the PALF Study

- No evidence of chronic liver disease
- Evidence of acute liver injury
- Coagulopathy unresponsive to Vitamin K
  - PT ≥ 15-19 sec. or INR ≥ 1.5-1.9 with encephalopathy
  - PT ≥ 20 sec. or INR ≥ 2.0 with/without encephalopathy

Age at Study Enrollment

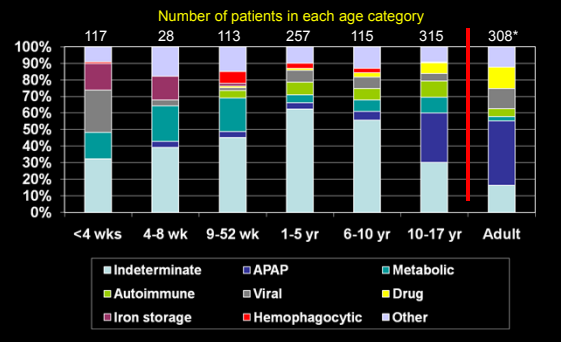


PALF Demographics (N = 945)

Age < 2 years	334 (35%)
Male	475 (50%)
Caucasian	675 (71%)
Hispanic ethnicity	183 (19%)
Coma grade at presentation	
0	441 (49%)
1 – 2	333 (37 %)
3 – 4	120 (13%)
Entry criteria	
INR ≥ 2.0 or PT ≥ 20 seconds	805 (85%)

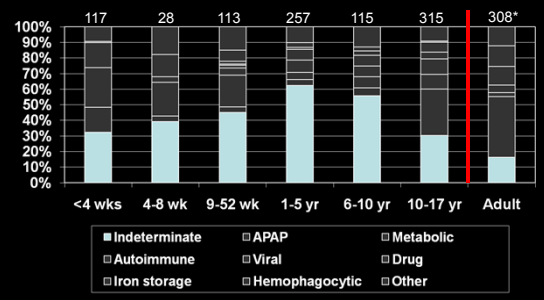
What causes acute liver failure in children?

Etiology of PALF (N = 945)

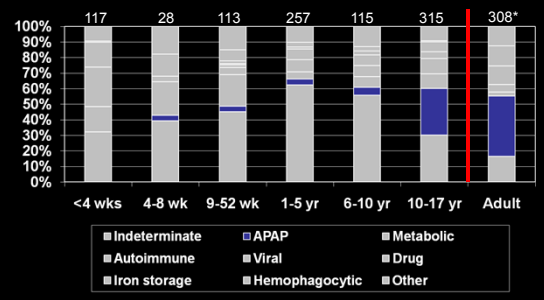


* Lee, WM Sem Liv Dis. 2003;23:217

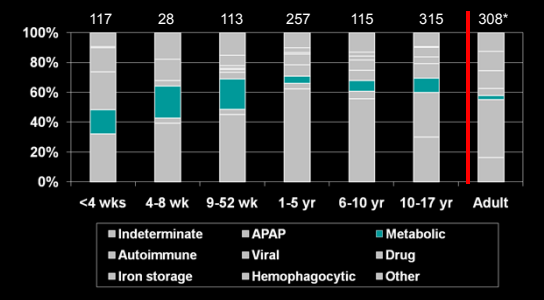
Indeterminate = 418/945 (44.2%)



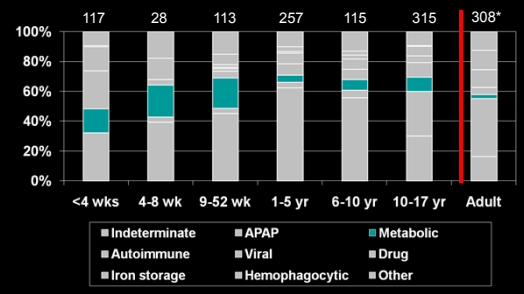
Acetaminophen = 115 (12.2%)



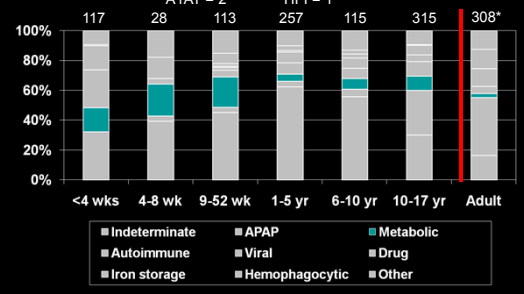
Metabolic Disease = 98 (10.4%)



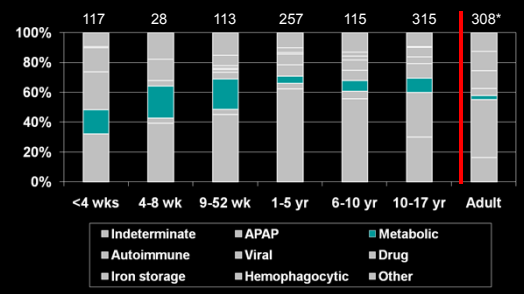
< 6 months of age
Galactosemia = 13
Nieman-Pick C = 4
Glycosylation defect = 1



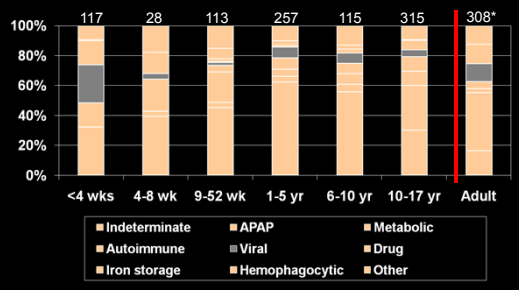
7 months to 4 years old
Mitochondrial = 22
Tyrosinemia = 9
Urea cycle = 1
A1AT = 2
HFI = 1



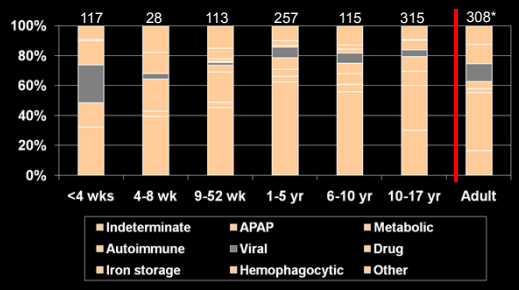
5 years and older
Wilson Disease = 35
Mitochondrial = 1
Reye's syndrome = 1



Viral disease = 73/945 (7.8%)

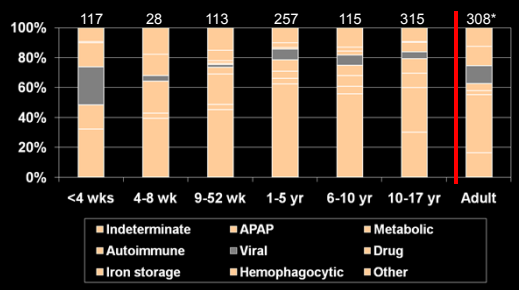


< 7 months of age
Herpes viurs = 25
Enterovirus = 5

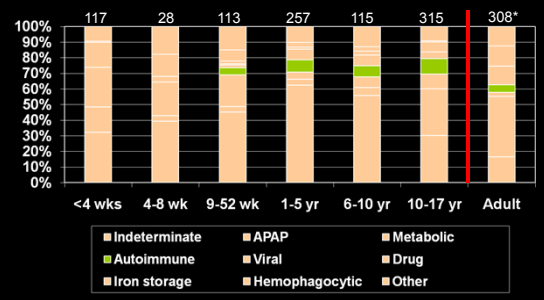


≥ 7 months of age

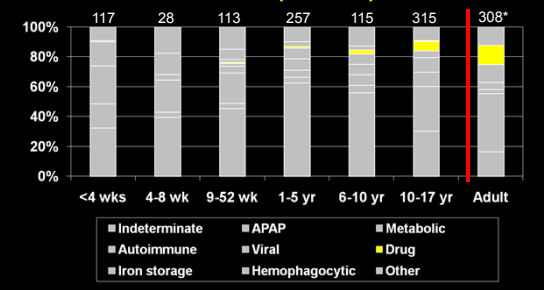
- EBV = 8
- HAV = 5
- HBV = 3
- HEV = 2
- Adenovirus = 5
- Enterovirus = 1
- Influenza/Para = 4
- Parvovirus = 1



Immune marker positive hepatitis 64/945 (6.8%)



Non-APAP Drug Induced 27/945 (2.9%)

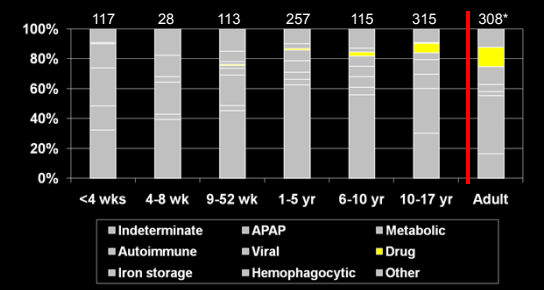


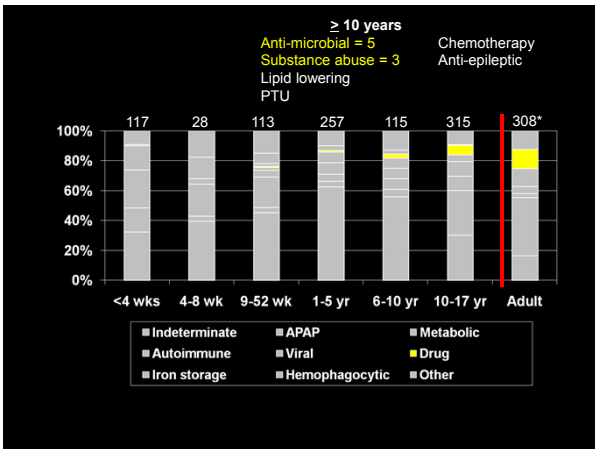
< 10 years

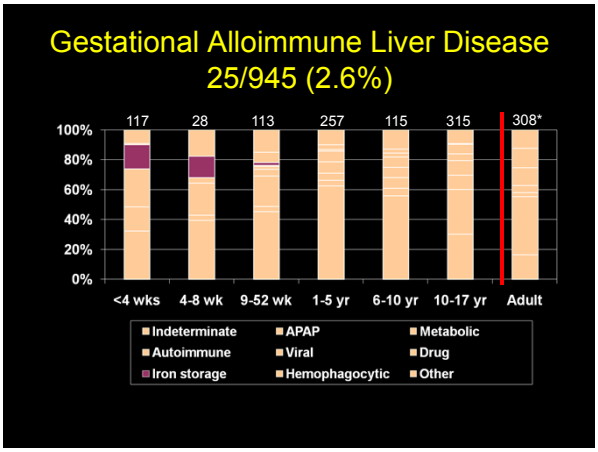
Anti-epileptic = 5

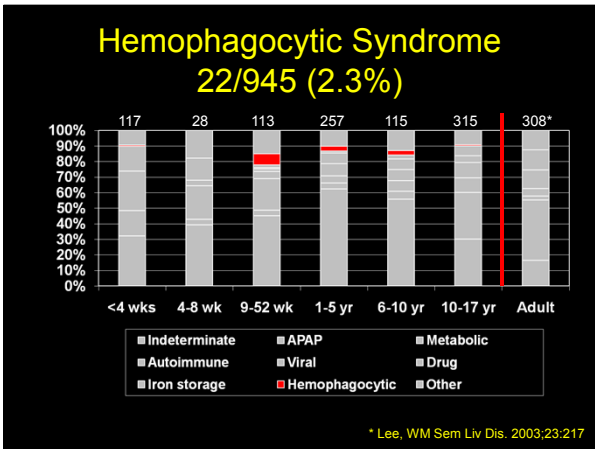
- Dilantin
- Valproic Acid

Chemotherapy =2




≥ 10 years
Anti-microbial = 5
Substance abuse = 3
Lipid lowering
PTU
Chemotherapy
Anti-epileptic
117
28
113
257
115
315
308*
100%
80%
60%
40%
20%
0%
<4 wks
4-8 wk
9-52 wk
1-5 yr
6-10 yr
10-17 yr
Adult
Indeterminate
APAP
Metabolic
Autoimmune
Viral
Drug
Iron storage
Hemophagocytic
Other


Gestational Alloimmune Liver Disease
25/945 (2.6%)
117
28
113
257
115
315
308*
100%
80%
60%
40%
20%
0%
<4 wks
4-8 wk
9-52 wk
1-5 yr
6-10 yr
10-17 yr
Adult
Indeterminate
APAP
Metabolic
Autoimmune
Viral
Drug
Iron storage
Hemophagocytic
Other


Hemophagocytic Syndrome
22/945 (2.3%)
117
28
113
257
115
315
308*
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
<4 wks
4-8 wk
9-52 wk
1-5 yr
6-10 yr
10-17 yr
Adult
Indeterminate
APAP
Metabolic
Autoimmune
Viral
Drug
Iron storage
Hemophagocytic
Other
* Lee, WM Sem Liv Dis. 2003;23:217

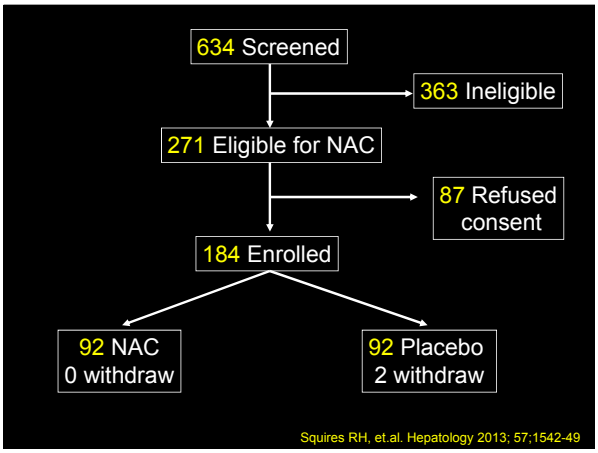
N-acetylcyctine (NAC)

- APAP hepatotoxicity
  - Replenishes mitochondrial and cytosolic glutathione stores
  - Increased mean arterial pressure, oxygen consumption, oxygen delivery, and oxygen extraction ratio.
- NAC for Multi-Organ System Dysfunction and ARDS
  - Improved pulmonary compliance and oxygen consumption
  - The physiological overlap between ALF and MODS syndromes suggests these non-specific beneficial effects of NAC might well apply to ALF.
- NAC in Non-APAP induced ALF in children
  - NAC has a good safety profile, is inexpensive, readily accessible, and approved for IV use in patients with APAP overdose
  - NAC had not been studied prospectively to assess safety and efficacy in non-APAP ALF children; but has been used empirically in pediatric transplant centers in the United Kingdom and North America

Pediatric NAC Study Design

- Double-masked, placebo controlled trial, utilizing a minimization scheme to maintain balance between treatment groups by
  - Age: less than 2 years vs. at least 2 years
  - Coma score: 0-I vs. II-IV
- Participants with non-APAP PALF received a continuous intravenous infusion of NAC (150 mg/kg/d) in D5W vs. D5W for up to 7 days
- We used available literature to estimate that a sample size of 184 patients (92 in each arm) would provide 80% power using a two-sided log-rank test

Squires RH, et.al. Hepatology 2013; 57;1542-49



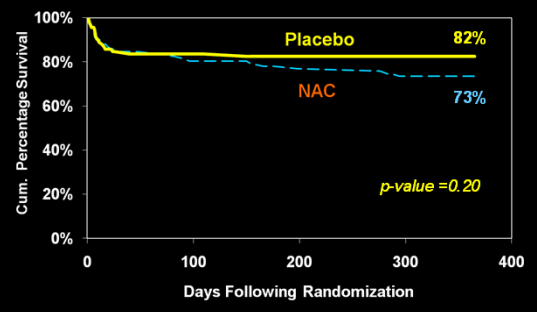
Squires RH, et.al. Hepatology 2013; 57;1542-49

Baseline Characteristics

	NAC N = 92	Placebo N = 92	p-value
Male, N (%)	47 (51)	54 (59)	.29
Not Hispanic or Latino, N (%)	75 (82)	66 (72)	.12
Caucasian	68 (77)	64 (71)	.86
Age (years)			
Median (25%, 75%)	3.7 (0.8, 10.5)	4.5 (1.0, 9.5)	.53
<2, N (%)	33 (35.9)	29 (31.5)	.53
Coma grade at randomization, N (%)			.62
0-1	65 (70.7)	68 (73.9)	
2-4	27 (29.3)	24 (26.1)	
Days to enrollment			
Initial admission to NAC enrollment			.47
Median (25%, 75%)	3 (1, 7)	3 (1,5)	

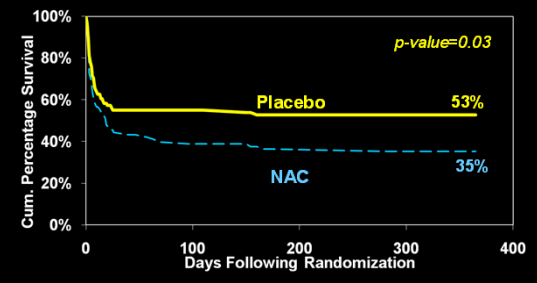
Squires RH, et.al. Hepatology 2013; 57;1542-49

Results
Primary Outcome: 1 Year Survival



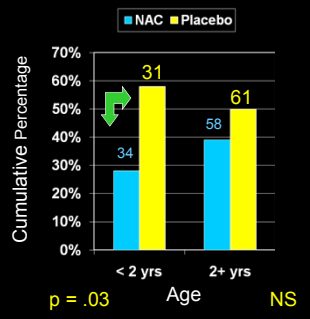
Squires RH, et.al. Hepatology 2013; 57;1542-49

Secondary Outcome: Survival with Native Liver



Squires RH, et.al. Hepatology 2013; 57;1542-49

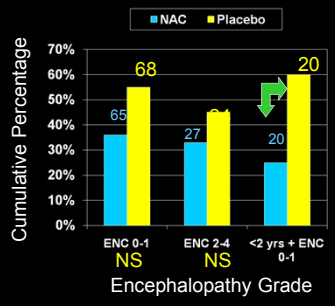
Percent survival with native liver: Age at Randomization



p = .03 NS

Squires RH, et.al. Hepatology 2013; 57;1542-49

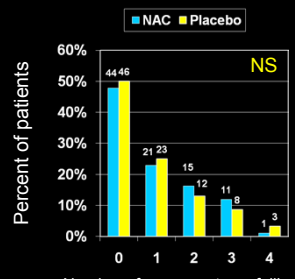
Percent survival with native liver: Encephalopathy Grade at Randomization



p = .049

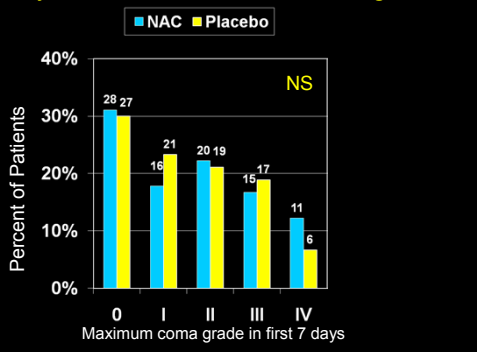
Squires RH, et.al. Hepatology 2013; 57;1542-49

Secondary outcome: Number of organ systems failing



Squires RH, et.al. Hepatology 2013; 57;1542-49

Secondary outcome: Maximum coma grade



Squires RH, et.al. Hepatology 2013; 57;1542-49

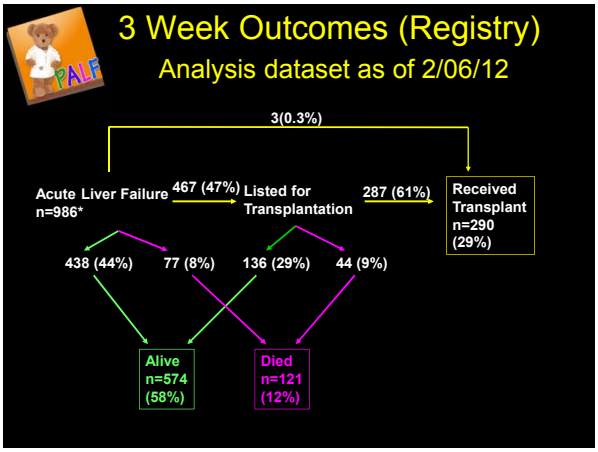
Summary

- NAC did not significantly improve 1 year survival in children with non-APAP acute liver failure
- Survival with the native liver was significantly lower with NAC, particularly among children < 2 years old
- In contrast to findings in adults, children with minimal ENC (stage 0-I) did not benefit from NAC

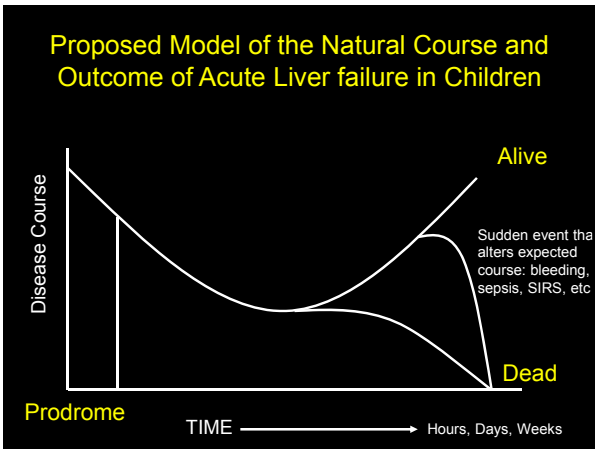
Conclusions

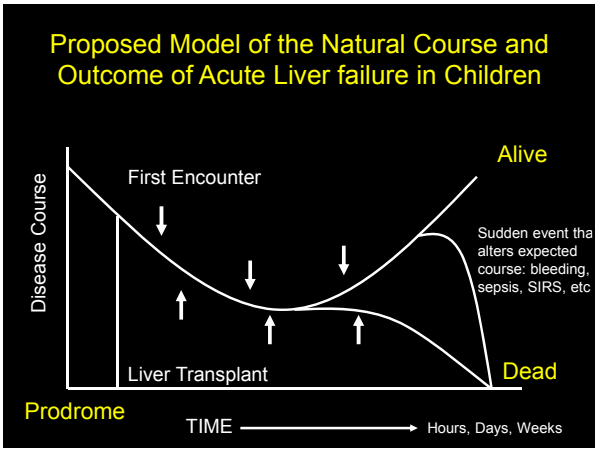
- These results do not support the broad use of NAC in non-APAP pediatric acute liver failure
- This study emphasizes the importance of conducting prospective pediatric drug trials, regardless of results in adults

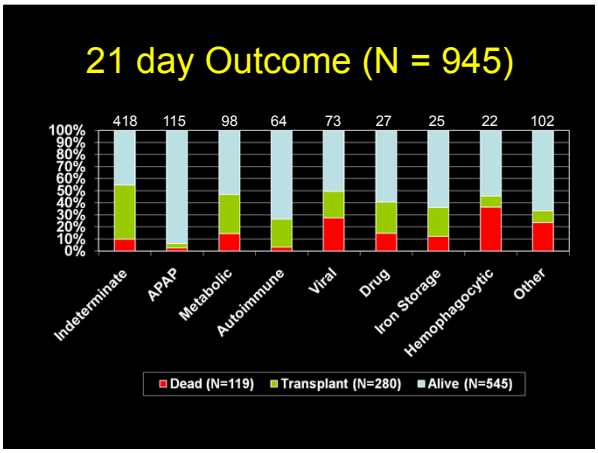
What about outcome in PALF?



Are there tools we might use to assist in predicting outcome?


Proposed Model of the Natural Course and Outcome of Acute Liver failure in Children
Disease Course
Alive
Sudden event tha
alters expected
course: bleeding,
sepsis, SIRS, etc
Dead
Prodrome
TIME
Hours, Days, Weeks


Proposed Model of the Natural Course and Outcome of Acute Liver failure in Children
Disease Course
First Encounter
Alive
Sudden event tha
alters expected
course: bleeding,
sepsis, SIRS, etc
Liver Transplant
Dead
Prodrome
TIME
Hours, Days, Weeks

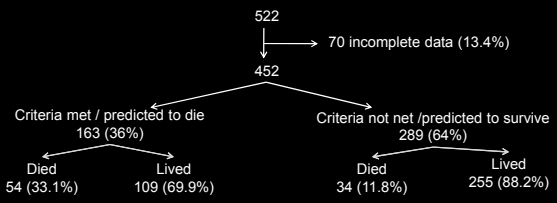

21 day Outcome (N = 945)
418
115
98
64
73
27
25
22
102
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Indeterminate
APAP
Metabolic
Autoimmune
Viral
Drug
Iron Storage
Hemophagocytic
Other
Dead (N=119)
Transplant (N=280)
Alive (N=545)

Kings College Hospital Criteria

- Non-acetaminophen
  - Prothrombin time >100 s (INR > 6.5) OR
  - Any 3 of the following (irrespective of grade of encephalopathy):
    - Age <10 or >40 years
    - Etiology: non-A/non-B hepatitis, drug-induced
    - Duration of jaundice to encephalopathy >7 days
    - Prothrombin time >50 (INR > 3.5)
    - Serum bilirubin >300 µmol/L (17.6 mg/dl)
- Acetaminophen

O' Grady JG, et al Gastroenterology 1989;97:439

Applying KCHC to 522 non-APAP PALF patients not transplanted ("Natural History")



Sundaram V, et.al J. Pediatrics 2013;162:319-23

Outcomes for KCHC applied to non-APAP PALF cohort (N = 522)

KCHC parameter	Total (N)	Met criteria (N)	Death (N)	PPV (%)	NPV (%)	Sensitivity (%)
Met KCH criteria	452	163	54	33	88	61
KCHC components						
INR > 6.5	521	28	8	29	80	7
INR > 3.5	521	118	45	38	84	41
Age < 10 yrs	522	390	85	22	81	77
Etiology Non A-B	522	515	110	21	100	100
Jaundice⟶ ENC >7d	390	22	7	32	86	12
Bilirubin > 17.6 mg/dl	502	100	26	26	80	25

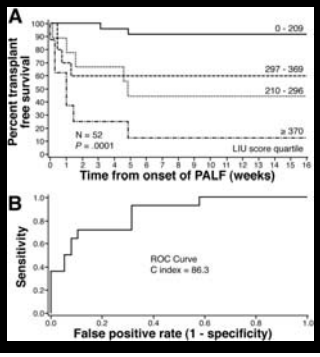
Sundaram V, et.al J. Pediatrics 2013;162:319-23

Pediatric Liver Injury Unit (LIU) Score

- Denver; 81 children; 1993-2003
- Peak LIU
  - 3.584 x peak total bilirubin (mg/dL) +
  - 1.809 x peak PT (sec) or INR +
  - 0.307 x peak ammonia (μmol/L)
- Admission LIU
  - 6.9 x admission bilirubin +
  - 4.0 x admission PT or INR

Liu E. J Hepatol 2006;44:134
Lu, B Clin Gastro Hep 2008;6:1140

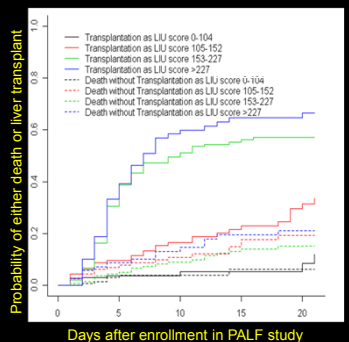
Validation of Liver Injury Unit (LIU) Score using INR



- Survival without liver transplant is stratified by quartiles
- Liver transplant and death were combined into a single outcome
- A low risk of death or liver transplant LIU < 209
- High risk of death or liver transplant LIU ≥ 370
- A "C index" > 85 is considered predictive.

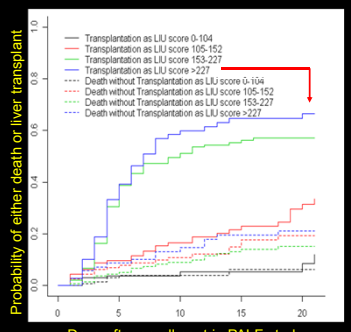
Lu, B Clin Gastro Hep 2008;6:1140

Probability of Death or Transplant by quartile of peak LIU score (n=454)



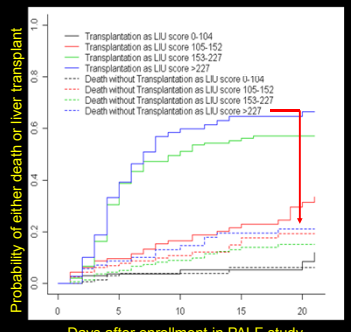
Lu BR, et.al J Pediatr 2013:162:1010

Probability of Death or Transplant by quartile of peak LIU score (n=454)



Lu BR. et.al J Pediatr 2013:162:1010

Probability of Death or Transplant by quartile of peak LIU score (n=454)

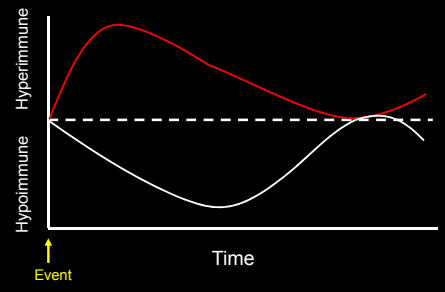


Lu BR. et.al J Pediatr 2013:162:1010

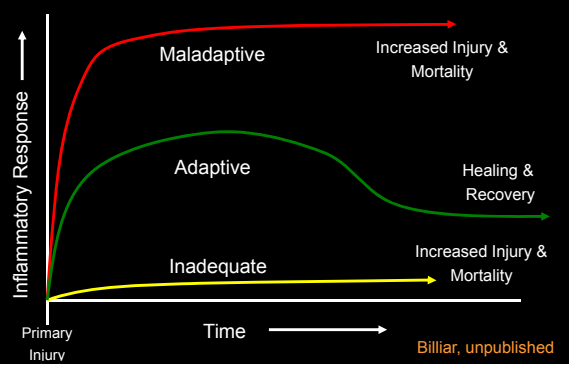
The liver is an immunological organ

- The liver is a "tolerant" organ
  - Indentify and contain pathogens with a tempered immune response
- Innate immune response
- T-cell mediated protection
- Adaptive immune response
- Redundant cellular functions
  - NK cells participate in both innate and adaptive immune response (Nature 2009:457:557-561)
  - Hepatocytes may serve as
    - Antigen presenting cells (Hepatology 2003;37:1079-85)
    - Cytotoxic cells (Hepatology 2008;47:1691-1701)

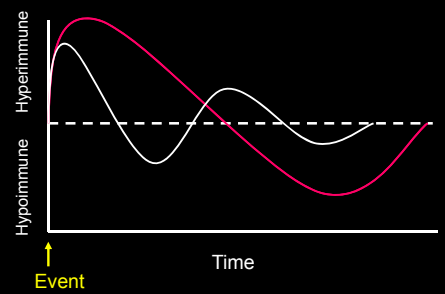
Synchronous Activation of Hyper- and Hypo-immune Responses



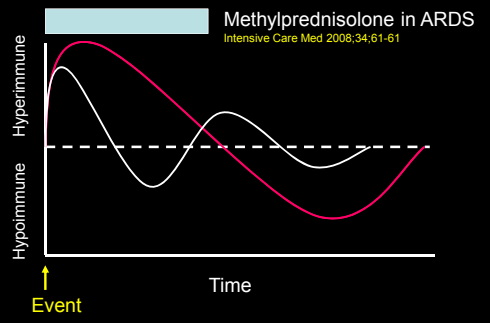
The intensity, duration and type of the initial immuno-inflammatory response determines outcome



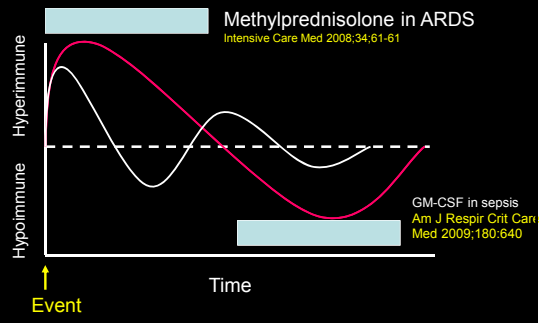
Theoretical therapeutic windows for different interventions



Theoretical therapeutic windows for different interventions



Theoretical therapeutic windows for different interventions



Patient outcome by sIL-2Rα level (n = 75)

sIL-2Rα (n)	LT (%)	Death (%)	Survival
Normal (37)	7 (19)	0 (0)	30 (81)
> ULN – 2 X ULN (15)	4 (27)	1 (7)	10 (67)
≥ 2X ULN -- < 5000 IU/mL (8)	2 (25)	1 (13)	5 (63)
≥ 5000 IU/mL (15)	8 (53)	2 (13)	5 (33)

sIL-2Rα = soluble interleukin 2 receptor alpha
ULN = upper limit of age specific normal

Bucuvalas J, et.al. JPGN 2013;56:311

Preliminary cytokine analysis in PALF

The Dataset:
- 48 patients
- At least 3 samples per patient
- 212 total samples

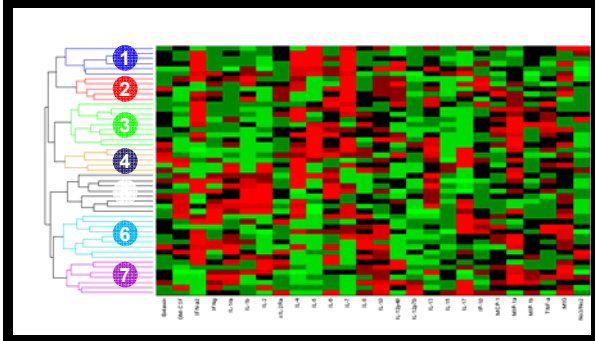
	N (%)
Age at enrollment (years)	
Median	8.7
25%, 75%	1.3, 15.3
Male	24 (50.0)
Diagnosis	
APAP toxicity	7 (14.6)
Autoimmune hepatitis	5 (10.4)
Viral infection	2 (4.2)
Indeterminate	26 (54.2)
Other diagnoses*	8 (16.7)
Coma grade at enrollment	
Missing	2
0-I	36 (78.3)
II-IV	10 (21.7)
21-day outcome	
Alive without transplantation	27 (56.3)
Transplantation	15 (31.3)
Died without transplantation	6 (12.5)

Azhar N, et.al Hepatology 2012;56(Supp):957A

Classification of Markers	Individual Markers Used In Analysis
Pro inflammatory	TNF-α, IL-1β, IL-2, IL-6, INF-γ, MIP-2, eotaxin
Anti-inflammatory	IL-4, IL-10, INF-γ, IL-6, IL-1ra
T-helper cell (TH-1) response	INF-γ, IL-12
TH-2 response	IL-4, IL-5, IL-13
Macrophage activation	IL-12, TNF-α, IL-8
Lymphocyte activation	sIL-2α
NK-cell	IL-4, IL-15, MIP-1α
CD 4+ cell	INF-γ
Monocyte deactivation	IL-10
White cell activation	GM-CSF
Apoptosis	IL-2, IL-6, TNF-α, IL-1β
Anti-apoptotic	IL-7, IL-15
Innate immune response	IL-17, IL-8
Multi-organ failure	MIP-1β, IL-10, IL-6
Chemo-attractant	MIP-1α, MIP-1β, IL-12p40, IL-8, MIG, MCP-1, IP-10

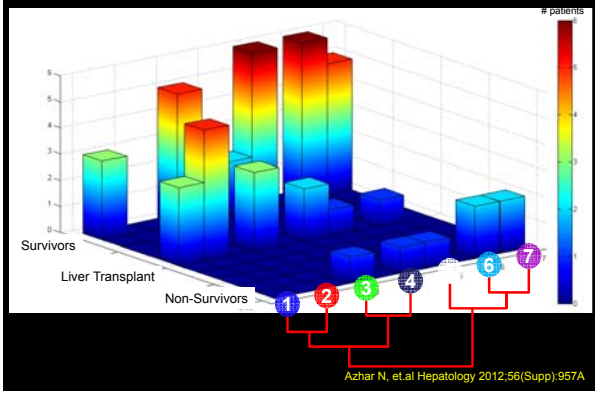
Azhar N, et.al Hepatology 2012;56(Supp):957A

Patient-Specific Principal Component Analysis Followed by Hierarchical Clustering



Azhar N, et.al Hepatology 2012;56(Supp):957A

Distribution of Outcomes Among the 7 Clusters



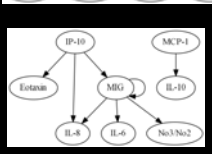
Azhar N, et.al Hepatology 2012;56(Supp):957A

Dynamic Bayesian Network Analysis Segregates PALF Outcomes

A

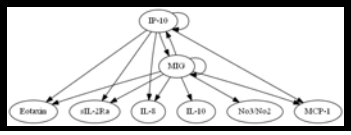
SPONTANEC
SURVIVORS

B



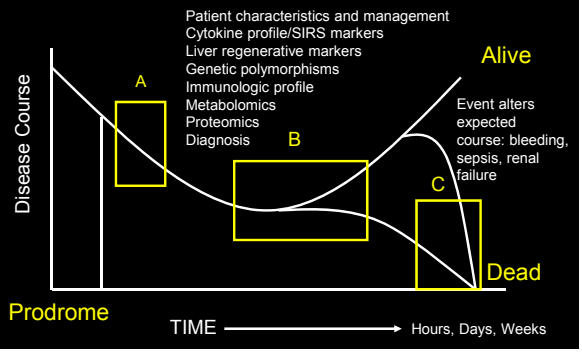
NON-SURVIV

C

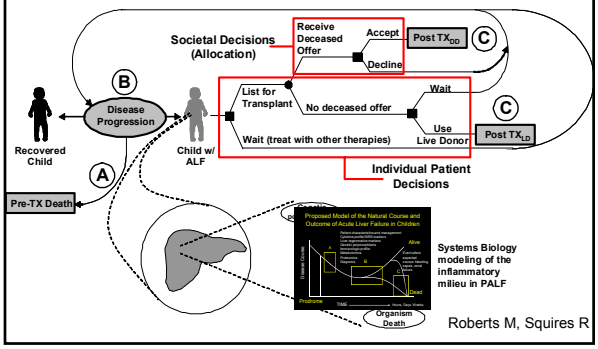


LIVER
TRANSPLAN

Proposed Model of the Natural Course and Outcome of Acute Liver Failure in Children



Integration of Transplant Decisions



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