

Acute Liver Failure in Children

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ALF in children is a devastating condition

- In pre-transplant era, 28% spontaneous survival, 4% with Stage IV coma (Kings, 1980)
- Overall survival improved to 63% with early referral to a liver transplant center, but spontaneous survival remained at 28% (Paris, 1990)
- Poor prognostic factors: cerebral edema, ascites, rising bilirubin with falling ALT, prolonged PT not responding to FFP, and delay onset of encephalopathy (UCLA 1997)
- Spontaneous survival improved to 58% with improved ICU care and a change in definition to include patients with coagulopathy ($PT \geq 20$ sec) without coma

Etiology Single Site Experience

Etiology	London 69-77	UCLA 85-93	Bicêtre 87-91	Denver 93-01	Brisbane 85-00	B'gham 91-00	India 97-00	Total (%)
Define	King's	King's	King's	Coag	Coag	Coag +		
Indeter	26	36	8	12	12	36	4	134 (36)
APAP	3	7	1	9		14		34(9)
Viral		11	15	6	2	17	63	114(30)
Metabolic		5	4	12	3	22*		46(12)
Med/Toxin	2	3	5		4	5		19 (5)
Heme/Onc			1	8				9 (2)
Autoimm			1			3		4 (1)
Shock				8	1			9(2)
Other		2		2				4(1)
Total	31	66	35	57	22	97	67	375

Pediatric Acute Liver Failure (PALF) Study Group

- PALF Study Group (NIH/NIDDK 1 UO1 DK 072146-01)
 - Multi-center, multi-national study
 - United States = 17
 - Canada (Toronto)= 1
 - United Kingdom (London, Birmingham) = 2
 - Data
 - Clinical and Laboratory data, plus serum, daily for 7 days
 - End points: death, transplant, discharge
 - Biological samples: DNA, bile, liver tissue, fibroblasts, urine
- Treatment trial
 - N-acetylcysteine for non-acetaminophen ALF
- Core Ancillary studies
 - Acetaminophen adducts
 - Fatty acid oxidation defects in PALF
 - NK cell dysfunction in PALF

Pediatric ALF Registry Principal Investigators and Sites

Norberto Rodriguez-Dallas
Karen Murray-Seattle
Phil Rosenthal-San Francisco
Nanda Kerkar-New York (Mt. Sinai)
Rob Squires-Pittsburgh
Estella Alonso-Chicago (Northwestern)
Jim Lopez-Ann Arbor
Mike Narkewicz-Denver
Maureen Jonas-Boston (Harvard)
Girish Subbarao-Indianapolis

John Bucuvalas-Cincinnati
David Rudnick-St. Louis (Wash U)
Kathy Schwarz-Baltimore
Steve Lobritto-New York (Columbia)
Liz Rand-Philadelphia (CHOP)
Saul Karpen-Houston (Baylor)
Rene Romero-Atlanta (Emory)
Vicky Ng-Toronto, Canada
Anil Dhawan-London, UK (Kings)
Deirdre Kelly-Birmingham, UK

NIH-NIDDK

Pat Robuck, PhD, MPH
Edward Doo, MD
Jay Hoofnagle, MD

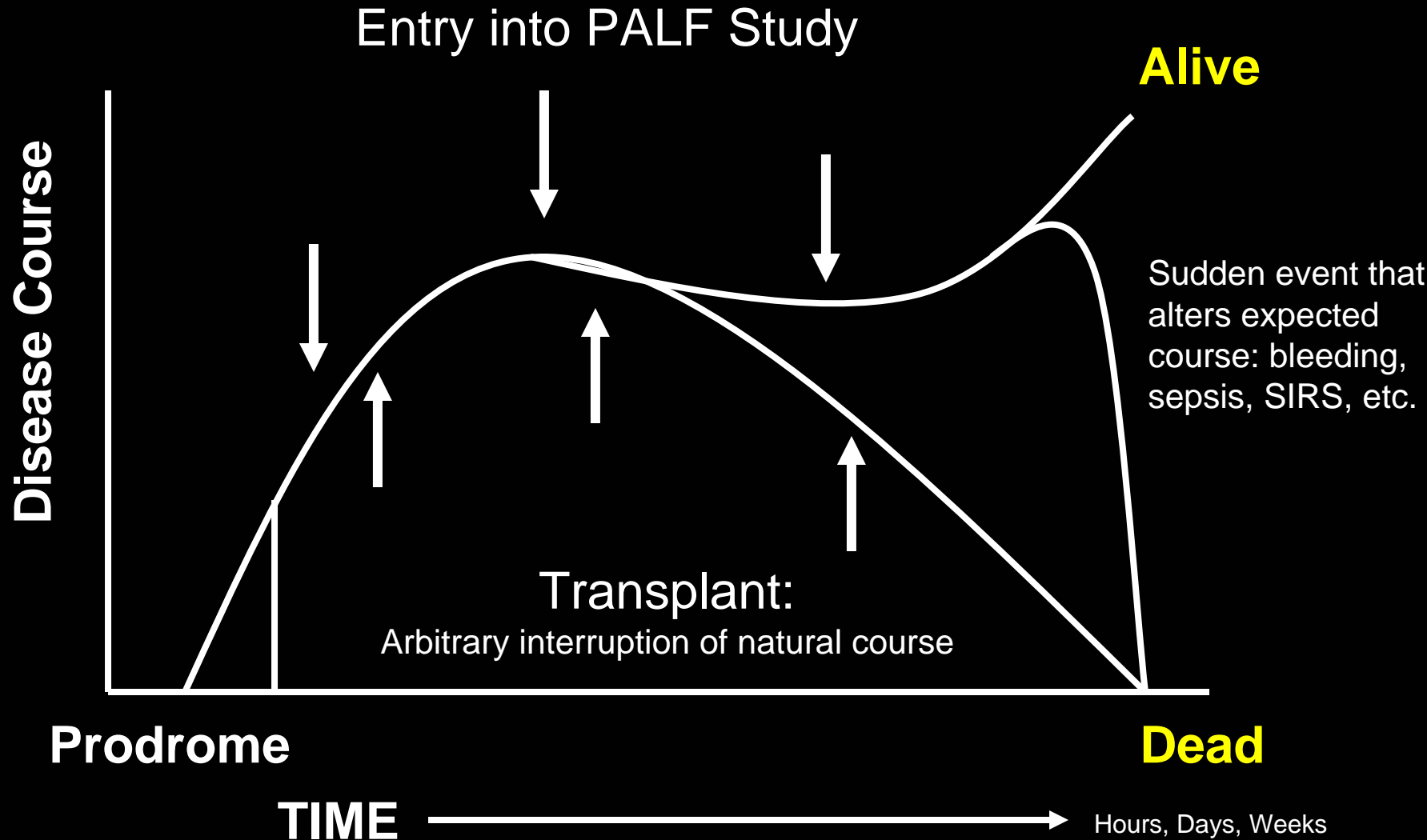
Ongoing Projects

- **Core Projects**
 - Fatty Acid Oxidation Study—Shneider
 - NK cell study—Yazigi/Bucuvalas
 - Acetaminophen Adduct Study—James/Alonso
- **Descriptive Studies**
 - Pattern of diagnostic evaluation—Narkewicz
 - Autoimmune hepatitis—Narkewicz
 - Characterize evaluation of infectious causes of PALF—Schwarz
 - Characterize children who died vs. those who lived—Shneider
- **Ancillary Studies that require bio-samples or more data**
 - Novel human hepatitis viruses—Presti/Rudnick
 - Serum LIGHT analysis—Anders/Schwarz
 - CLiC Mitochondrial Hepatopathy—Holmes/Sokol/Narkewicz
 - Aminoacid analysis to predict liver regeneration—Rudnick
 - ALF in very young infants—Sundaram/Alonso

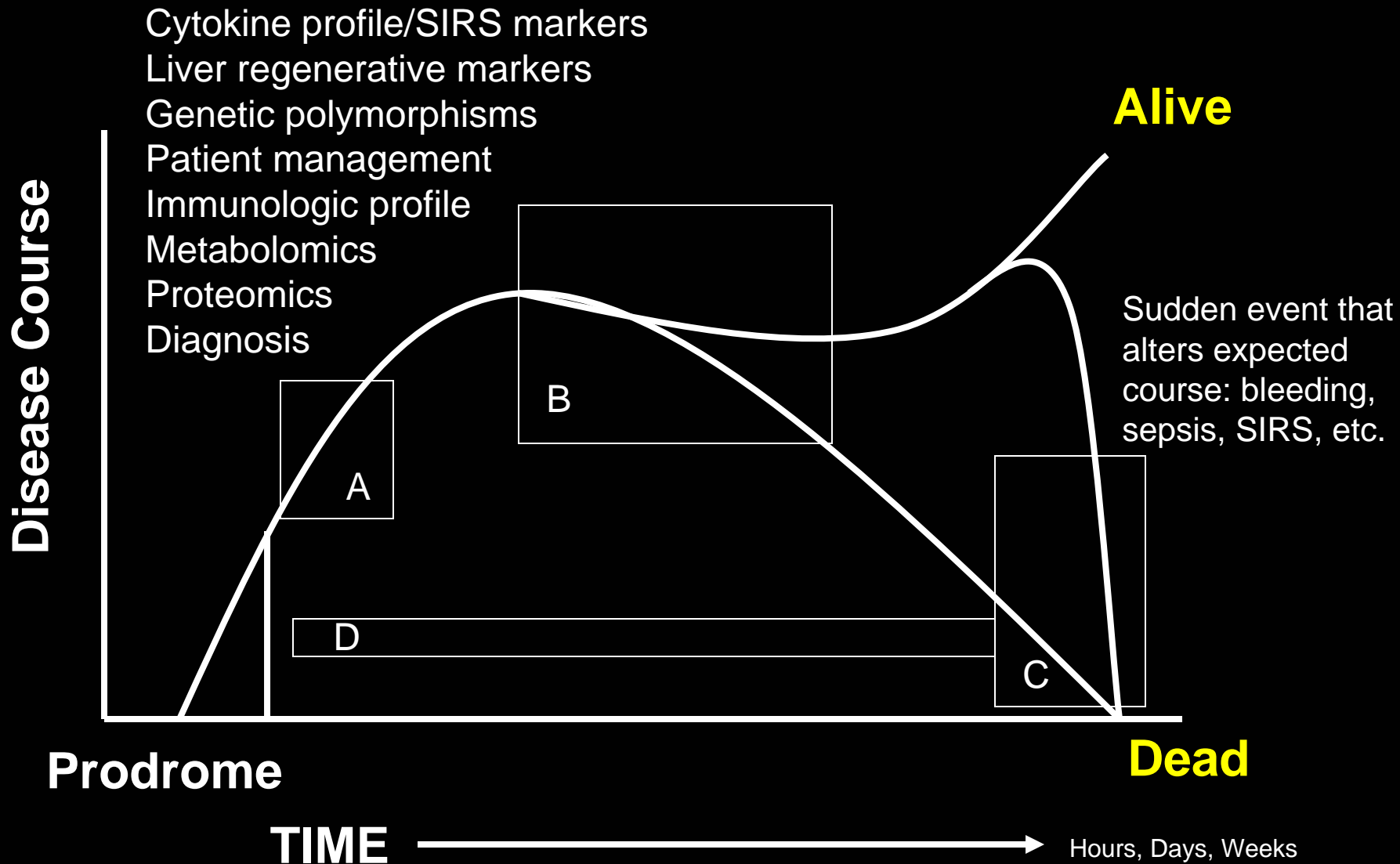
Collaborative Partners

- **Fatty Acid Oxidation Study**
 - Arnie Strauss, MD—Cincinnati
 - Piero Rinaldo, PhD—Mayo Clinic
 - Jerry Vockley, MD, PhD—Pittsburgh
- **NK cell Study**
 - Nada Yazigi, MD—Cincinnati
 - Alexandra Filipovich, PhD--Cincinnati
- **Acetaminophen Adducts**
 - Laura James, MD—Little Rock
- **Discovery of Novel Human Viruses**
 - Rachel Presti, MD, PhD—Washington University
 - Greg Storch, MD—Washington University
 - Herbert Virgin, MD, PhD—Washington University
 - David Wang, PhD—Washington University
- **Pathogenesis and Correlation of serum LIGHT in ALF**
 - Robert Anders, MD, PhD—Johns Hopkins
- **Mitochondrial Hepatopathy—CLiC Collaboration (nearing approval)**
 - Ron Holmes, MD—Denver
 - Ron Sokol, MD—Denver

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



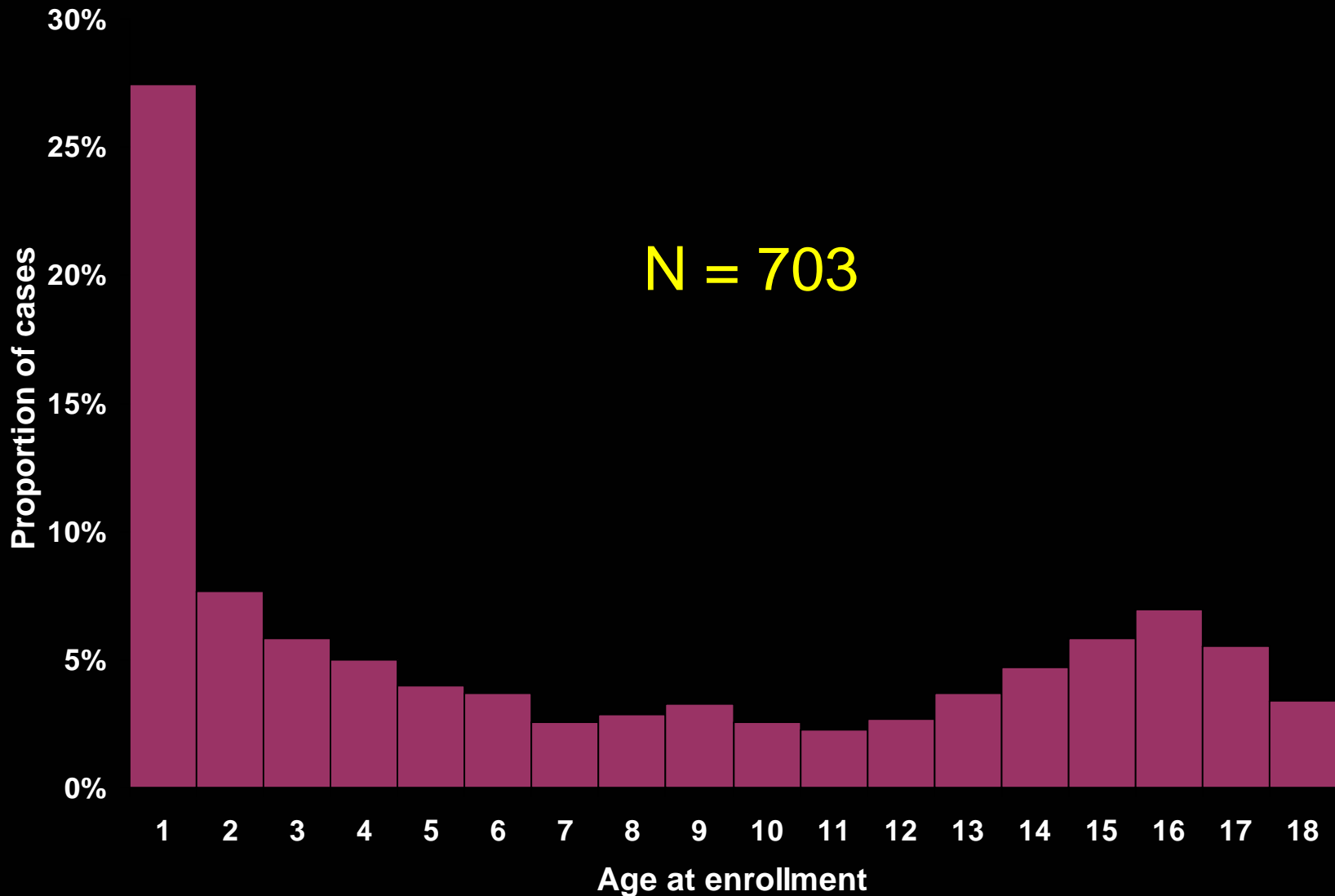
Proposed Model of the Natural Course and Outcome of Acute Liver failure in Children



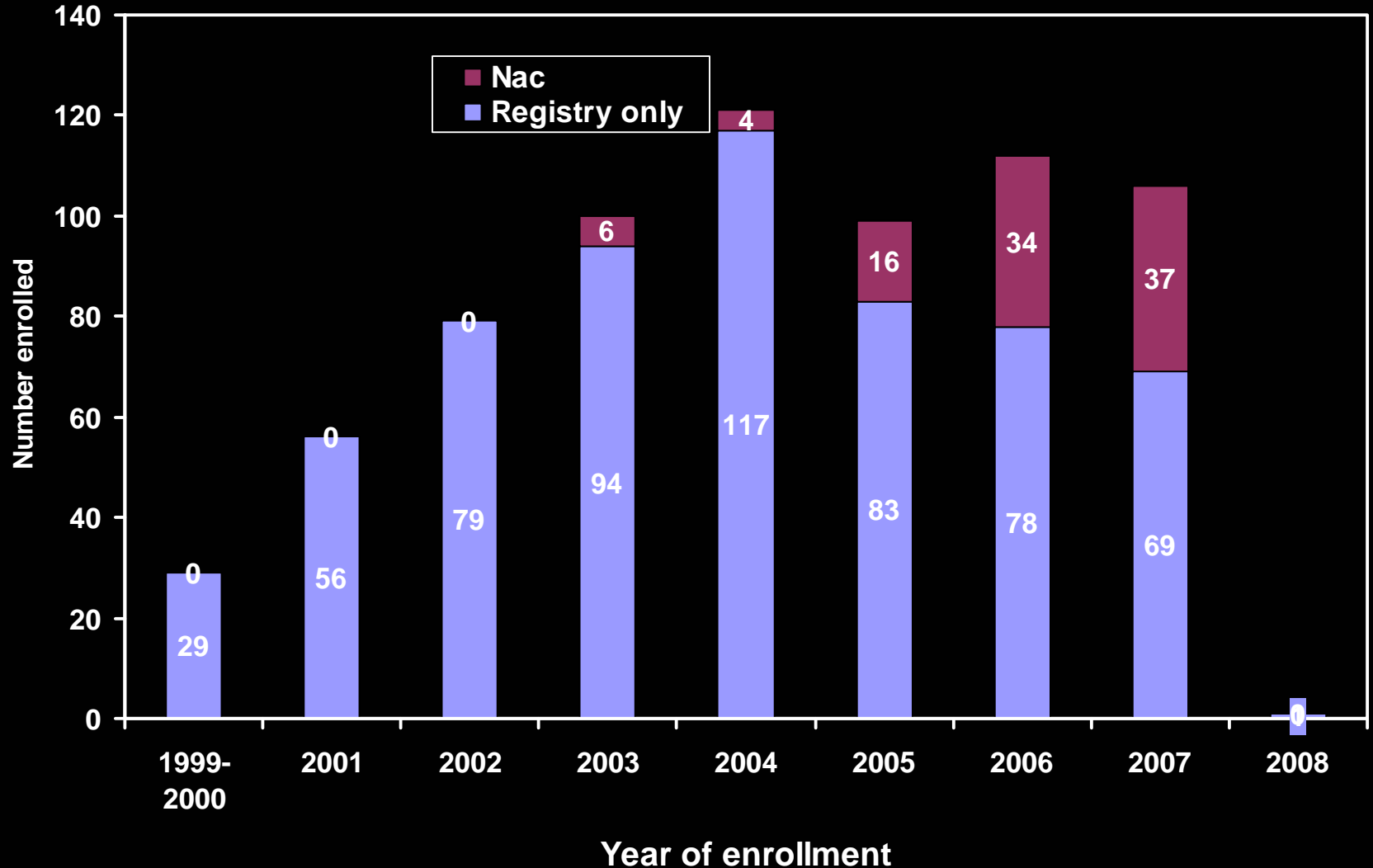
STAGES OF HEPATIC ENCEPHALOPATHY

Stage	Clinical	Reflexes	Neurological Signs	EEG Changes
0	None	Normal	None	Normal
I	<u>Infant/child</u> : inconsolable crying, inattention to task Child is not acting like self to parents	Normal or hyperreflexic	Difficult or impossible to test adequately	
	<u>Adult</u> : confused, mood changes, altered sleep habits, forgetful	Normal	Tremor, apraxia, impaired hand writing	Normal or diffuse slowing to theta rhythm, triphasic waves
II	<u>Infant/child</u> : inconsolable crying, inattention to task Child is not acting like self to parents	Normal or hyperreflexic	Difficult or impossible to test adequately	
	<u>Adult</u> : Drowsy, inappropriate behavior, decreased inhibitions	Hyperreflexic	Dysarthria, ataxia	Abnormal, generalized slowing, triphasic waves
III	<u>Infant/child</u> : Somnolence, stupor, combativeness	Hyperreflexic	Difficult or impossible to test adequately	
	<u>Adult</u> : Stuporous, obeys simple commands	Hyperreflexic, (+) Babinski	Rigidity	Abnormal, generalized slowing, triphasic waves
IV	<u>Infant/child</u> : Comatose, arouses with painful stimuli (IVa) or no response (IVb)	Absent	Decerebrate or decorticate	
	<u>Adult</u> : Comatose, arouses with painful stimuli (IVa) or not (IVb)	Absent	Decerebrate or decorticate	Abnormal, very slow, delta activity

Age at Study Enrollment

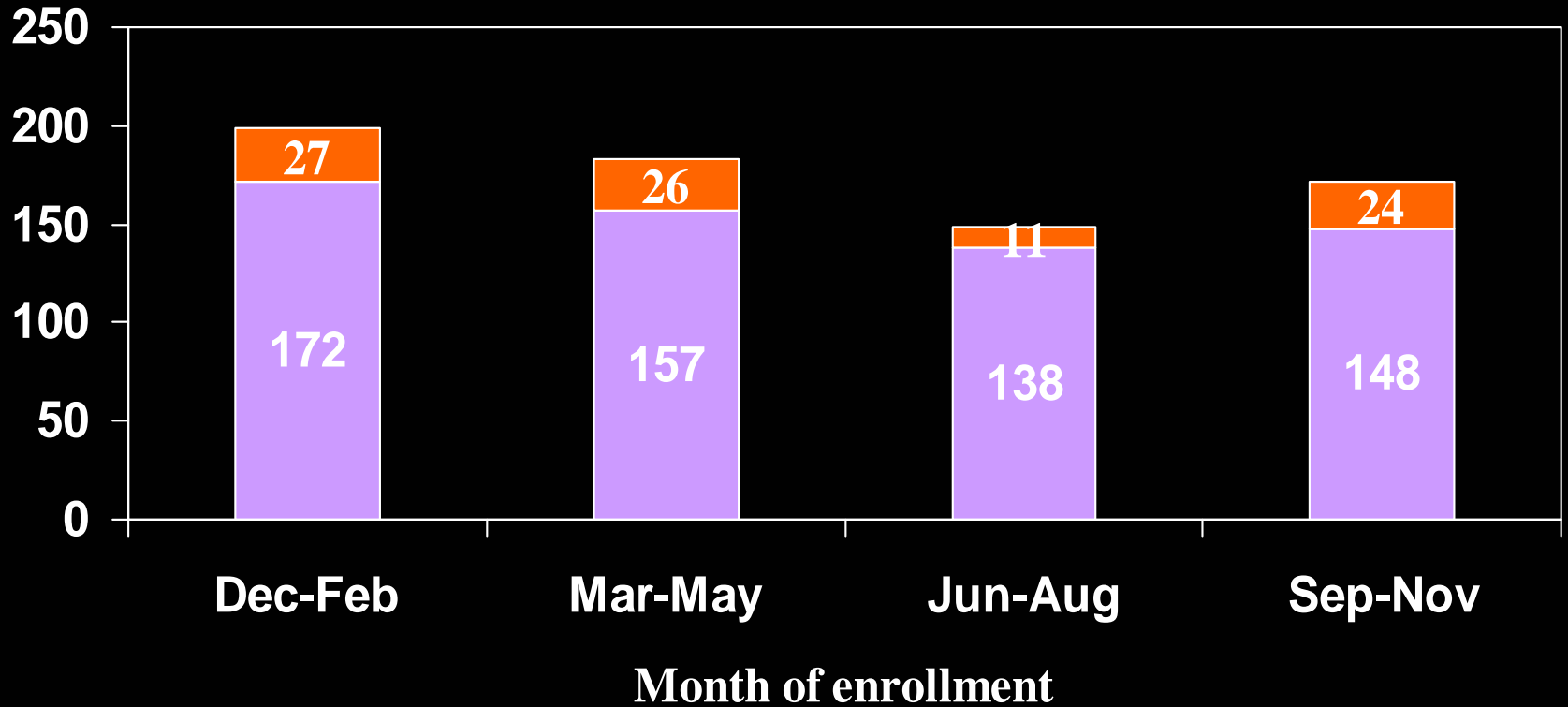


Pediatric ALF Patient Enrollment

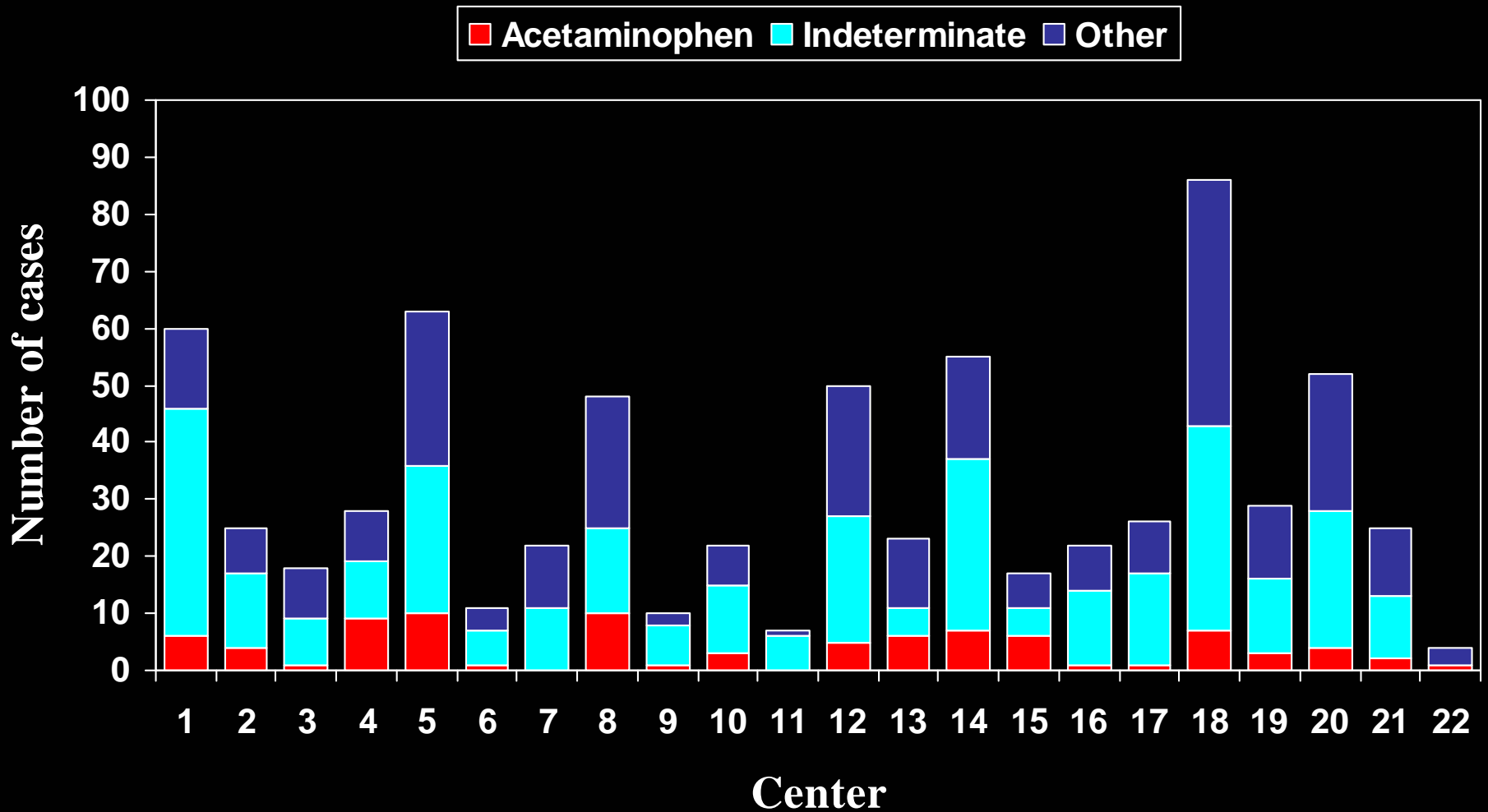


Seasonal Variation

Number



Diagnosis by Center



Pediatric ALF: Demographics

Demographic characteristic (total n=653)		Diagnostic category		
		APAP n (%)	Indeterminate n (%)	All others n (%)
		88 (12.5)	329 (46.8)	286(40.7)
Gender	Female (n=347)	70 (20.2)	149 (42.9)	128 (36.9)
	Male (n=356)	18 (5.1)	180 (50.6)	158 (44.4)
Age	< 3 (n=288)	9 (3.1)	145 (50.4)	134 (46.5)
	≥ 3 (n=415)	79 (19.0)	184 (44.3)	152 (36.6)

Pediatric ALF: Demographics

Demographic characteristic (total n=548)		Diagnostic category		
		APAP n (%)	Indeterminate n (%)	All others n (%)
		88 (12.5)	329 (46.8)	286 (40.7)
Race*	White (n=448)	67 (13.8)	217 (44.8)	200 (41.3)
	Af Amer (n=88)	8 (9.1)	52 (59.1)	28 (31.8)
	Asian (n=56)	7 (12.5)	26 (46.4)	23 (41.1)
	Other (n=74)**	6 (8.1)	33 (44.6)	35 (47.3)
Hispanic (n=131)		10 (7.6)	67 (51.2)	54 (41.2)
Non-Hispanic (n=572)		78 (13.6)	262 (45.8)	232 (40.6)

*Race was not specified for 1 participant

**Other includes Native American race, Other race, and those with more than one race.

Clinical Characteristics

Clinical feature, n	Diagnostic category			
	Non-APAP		APAP	
	<3 years n (%)	≥3 years n (%)	<3 years n (%)	≥3 years n (%)
Total	279	336	9	79
Ascites, 161	86 (30.8)	70 (20.8)	2 (22.2)	3 (3.8)
Seizures, 50	20 (7.2)	29 (8.6)	0 (0)	1 (1.3)
Respirator, 263	123 (44.1)	124 (36.9)	3 (33.3)	13 (16.5)
Pressor Support, 161	80 (28.7)	72 (21.4)	2 (22.2)	7 (8.9)
Hemofiltration, 76	26 (9.3)	47 (14.0)	0 (0)	3 (3.8)
Transfusion (RBC's), 283	170 (60.9)	102 (30.4)	3 (33.3)	8 (10.1)
Fresh frozen plasma, 410	188 (67.4)	194 (57.7)	4 (44.4)	24 (30.4)

ALF in Infants

9 weeks

Final Diagnosis	< 4 weeks,	4-8 weeks,	- <1 year
Indeterminate	30 (37.0)	10 (41.7)	40 (45.5)
APAP	0 (0)	1 (4.2)	4 (4.6)
Metabolic	11 (13.6)	6 (25.0)	17 (19.3)
Autoimmune	0 (0)	0 (0)	5 (5.7)
Viral Hepatitis	19 (23.5)	0 (0)	3 (3.4)
Shock/Ischemia	3 (3.7)	2 (8.3)	5 (5.7)
Drug-induced	0 (0)	0 (0)	1 (1.1)
Neonatal iron storage dis.	10 (12.4)	3 (12.5)	2 (2.3)
Veno-occlusive disease	0 (0)	0 (0)	3 (3.4)
Hemophagocytic Syndrome	1 (1.2)	0 (0)	5 (5.7)
Budd-Chiari	0 (0)	0 (0)	0 (0)
Other diagnosis	6 (7.4)	2 (8.3)	2 (2.3)
Multiple diagnosis	1 (1.2)	0 (0)	1 (1.1)
Total	81	24	88

ALF in Adolescents

Final Diagnosis	1 - 5 years	6-10 weeks,	> 10 years
Indeterminate	123 (66.9)	48 (60.8)	78 (31.6)
APAP	8 (4.4)	3 (3.8)	72 (29.2)
Metabolic	8 (4.4)	6 (7.6)	20 (8.1)
Autoimmune	12 (6.5)	5 (6.3)	26 (10.5)
Viral Hepatitis	9 (4.9)	2 (2.5)	12 (4.9)
Shock/Ischemia	4 (2.2)	5 (6.3)	7 (2.8)
Drug-induced	2 (1.1)	3 (3.8)	17 (6.9)
Neonatal iron storage dis.	0 (0.0)	0 (0.0)	0 (0.0)
Veno-occlusive disease	1 (0.5)	1 (1.3)	4 (1.6)
Hemophagocytic Syndrome	4 (2.2)	0 (0)	1 (0.4)
Budd-Chiari	0 (0)	1 (1.3)	2 (0.8)
Other diagnosis	9 (4.9)	2 (2.5)	4 (1.6)
Multiple diagnosis	4 (2.2)	3 (3.8)	4 (1.6)
Total	184	79	247

Viral Hepatitis of Children with ALF

PALF Data (n = 45)

- Herpes simplex 16
- EBV 8
- Hepatitis A 5
- Adenovirus 3
- Enterovirus 4
- Paramyxovirus 2
- Hepatitis B 2
- CMV 2
- Influenza A 1
- Hepatitis C 1
- Hepatitis E 1

Literature

- Hepatitis B, E, D
- HHV-6
- Parvo B19
- GBV-C

Metabolic Causes of ALF

PALF Study (n = 68)

- Wilson's disease 23
- Tyrosinemia 8
- Resp chain deficit 7
- Mitochondrial 7
- Urea cycle defect 2
- Galactosemia 4
- OTC deficiency 1
- Fatty acid oxidation 2
- Neimann-Pick C 1
- Fructose intolerance 1
- Alpha-1 antitrypsin 2
- LCHAD 1
- Reye syndrome 1
- Other 8

From the Literature

- Transaldolase def
- Mitochondrial DNA depletion

Drug-induced Hepatitis in children with ALF

Agent (PALF Study)	n (%)
Acetaminophen	1 (4)
Anesthetic	1 (4)
Bactrim	1 (4)
Chemo drugs with additional in	1 (4)
Cylert	1 (4)
Cytoxan/Dilantin	1 (4)
Dilantin	2 (9)
INH	2 (9)
Iron	2 (9)
Methamphetamine	1 (4)
Methotrexate	1 (4)
Minocycline	1 (4)
Pravastatin	1 (4)
PTU	1 (4)
Tripleptal	1 (4)
Valproate	3 (13)
Ectasy idiosyncratic reaction	1 (4)
Not specified	1 (4)
Total	23 (100)

Other Drugs from the Literature

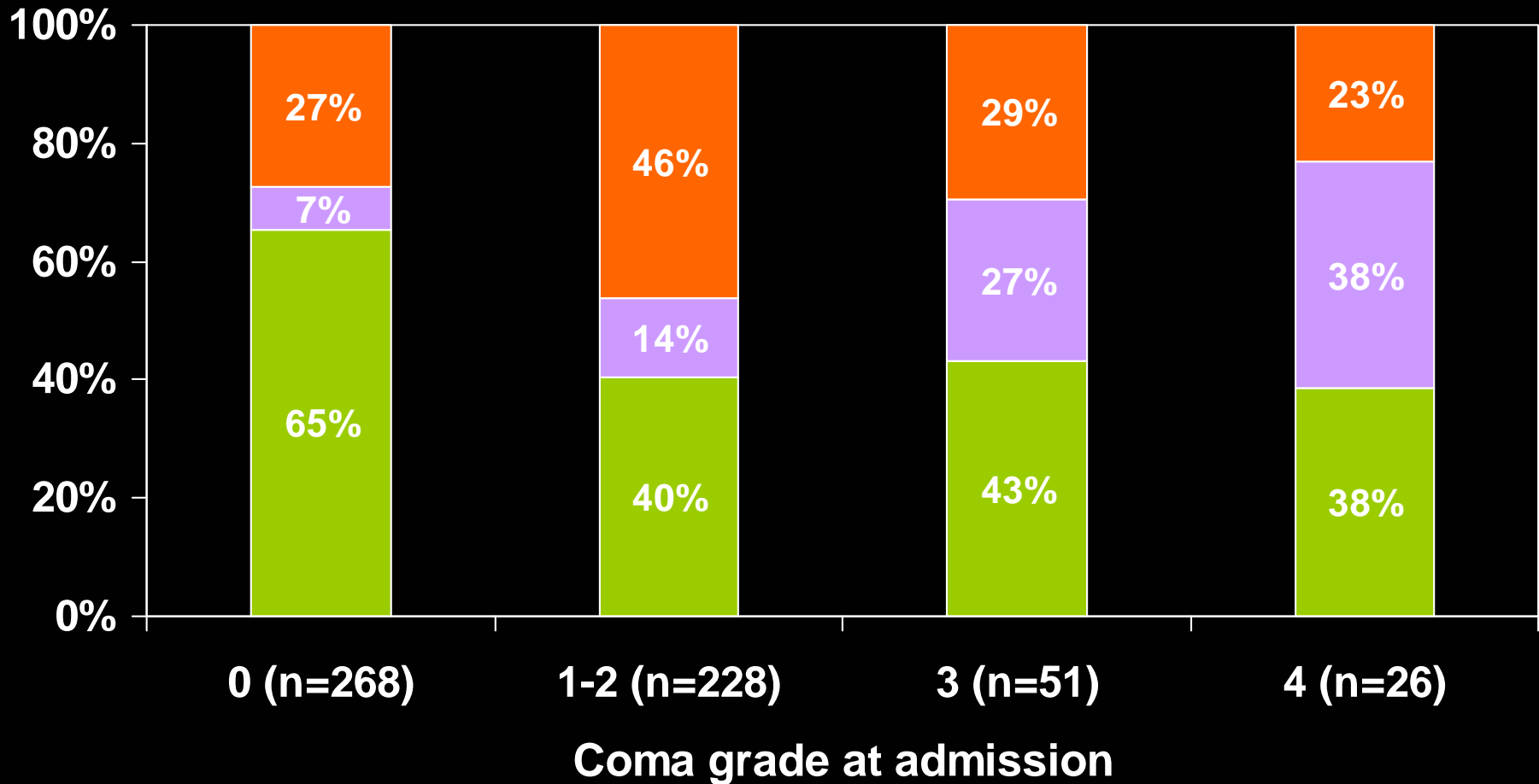
- Carbamazepine
- Non-steroidal anti-inflammatory
- Tetracycline
- Halothane
- Methyldopa
- Phosphorus

21 Day Outcomes

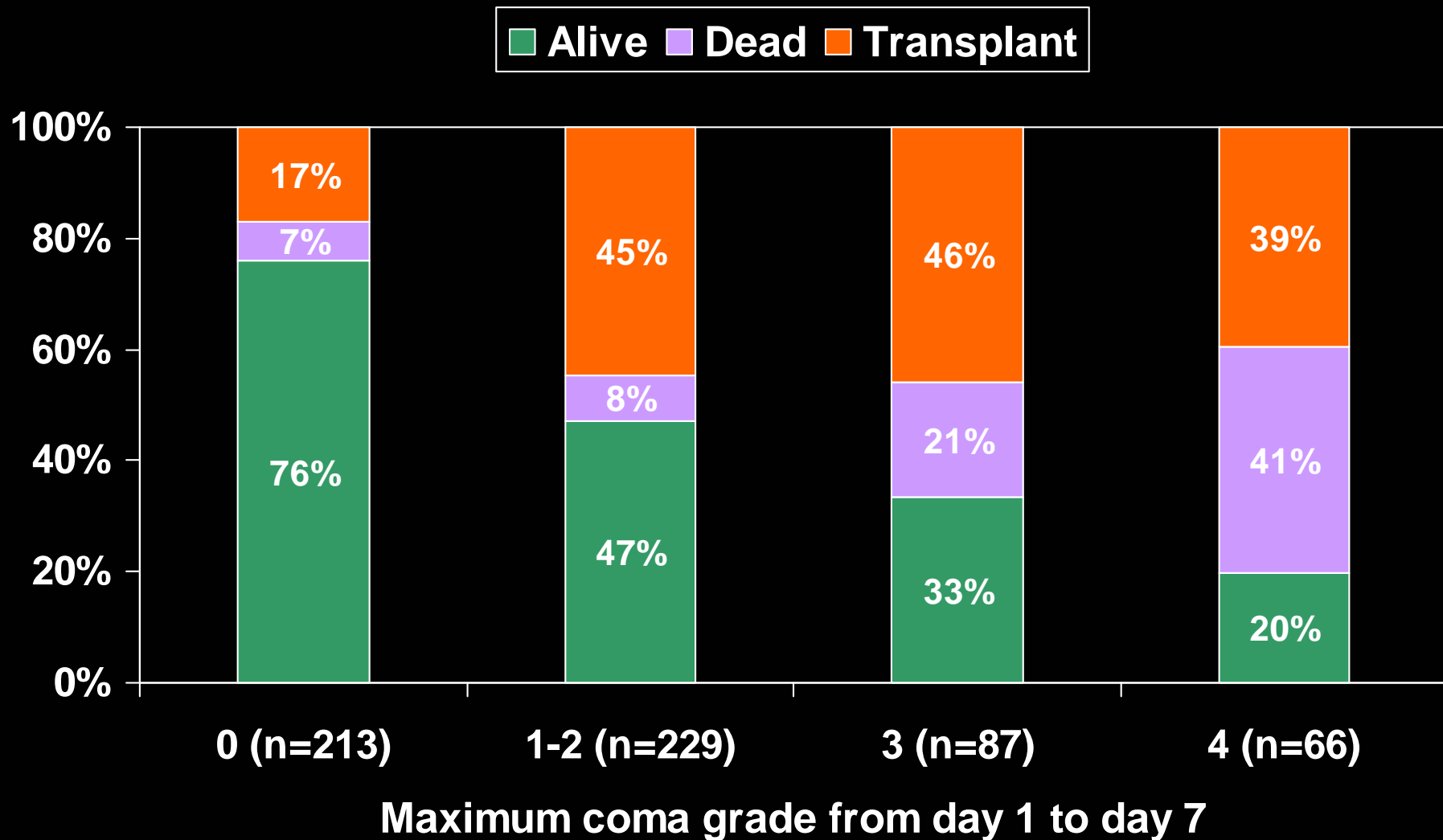
Final diagnosis, n	Outcome		
	Dead n (%)	Transplant n (%)	Alive n (%)
Indeterminate, 329	31 (9.4)	146 (44.4)	152 (46.2)
APAP, 88	3 (3.4)	5 (5.7)	80 (90.9)
Metabolic, 68	10 (14.7)	22 (32.4)	36 (52.9)
Autoimmune, 48	2 (4.2)	15 (31.3)	31 (64.6)
Viral Hepatitis, 45	14 (31.1)	10 (22.2)	21 (46.7)
Shock/Ischemia, 26	7 (26.9)	1 (3.9)	18 (69.2)
Drug-induced, 23	4 (17.4)	6 (26.1)	13 (56.5)
Neonatal iron storage disease, 15	2 (13.3)	4 (26.7)	9 (60.0)
Veno-occlusive disease, 9	5 (55.6)	1 (11.1)	3 (33.3)
Hemophagocytic Syndrome, 11	3 (27.3)	1 (9.1)	7 (63.6)
Budd-Chiari, 3	0	1 (33.3)	2 (66.7)
Multiple, 13	4 (30.8)	1 (7.7)	8 (61.5)
Other diagnosis, 21	3 (14.3)	0 (0.0)	18 (85.7)
Total, 703	88 (12.5)	215 (30.6)	400 (56.9)

21 Day Outcomes by Admission Coma Grade for the Non-APAP Group

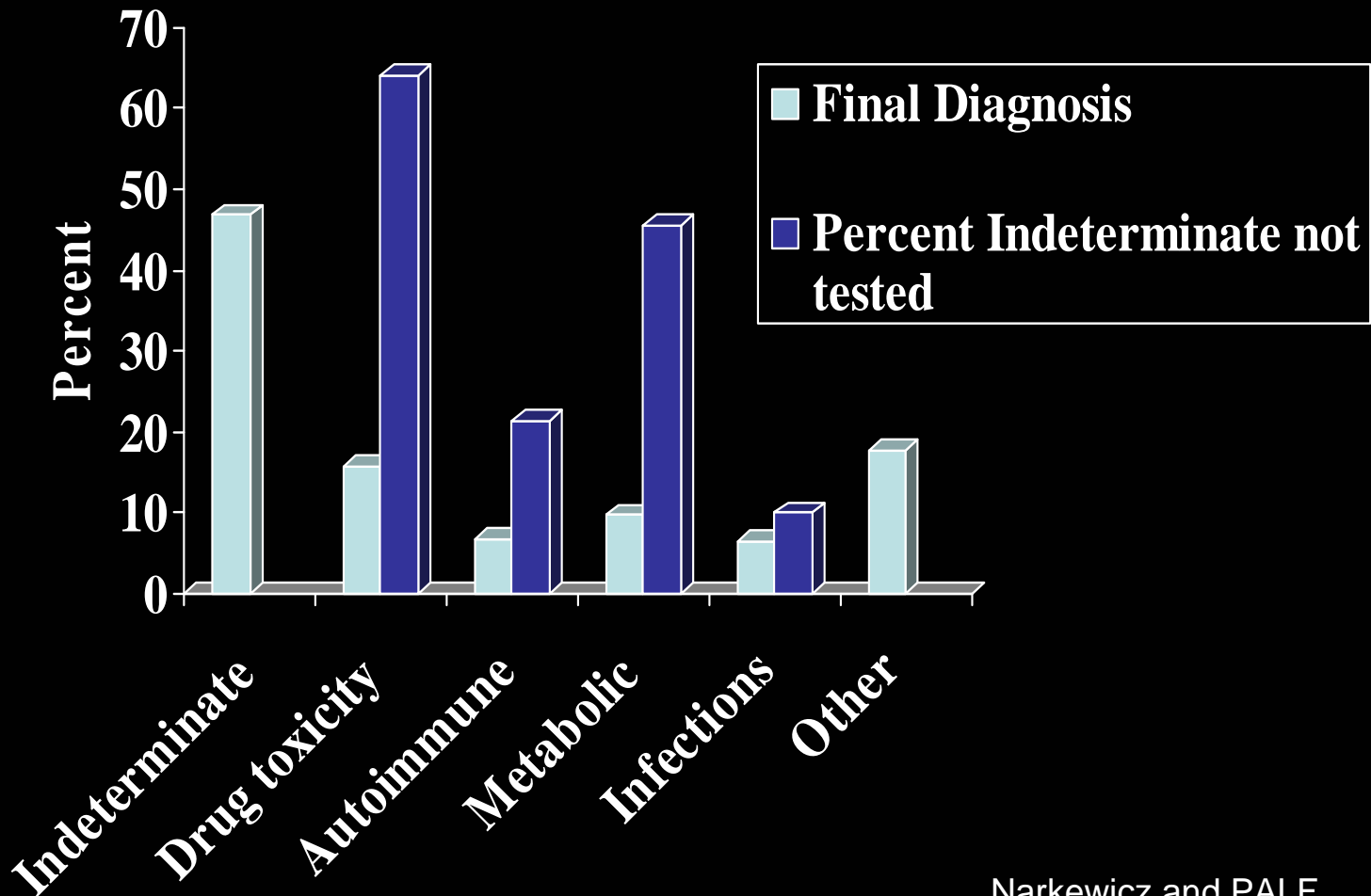
■ Alive ■ Dead ■ Transplant



21 Day Outcomes by Peak Coma Grade for the Non-APAP Group



Common Causes identified in PALF and diagnostic testing



Medical Management of ALF: Diagnosis Established

Infection

- Herpes Family
- Enterovirus
- Parvovirus

Acyclovir

Pleconaril \pm IVIG

IVIG (?)

Drug and toxin

- Medication induced
- Acetaminophen
- *Amanita phalloides*

Remove the offending drug

n-acetylcysteine

silibinin, penicillin, prednisone

Metabolic disease

- Neonatal iron storage
- Tyrosinemia type 1
- Wilson's disease
- Galactosemia

anti-oxidant cocktail

NTBC

Chelation therapy

Remove lactose

Immune dysregulation

- Hemophagocytic syndrome
- Autoimmune hepatitis

VP-16, corticosteroids

corticosteroids

INFECTIOUS DIS.**DRUGS / TOXINS****CARDIOVASCULAR****METABOLIC/IMMUNE****Infant ≤ 1yr**

Herpes Simplex*

APAP misadventure*

Hypoplastic Left Heart

Galactosemia

Echovirus

Asphyxia

Tyrosinemia

Adenovirus

Myocarditis

Neonatal hemachromatosis

EBV

Fructose Intolerance

CMV

Fatty Acid Defects*

Hepatitis B

Mitochondrial Defects*

Parvovirus

Hemophagocytic Synd

Measles

Neiman Pick Type C

HHV-6

NK cell dysfunction*

Enterovirus*

Child

Hep A,B,C,D,E

Valproic Acid

Heart Surgery

Fatty acid oxidation defects

Leptospirosis

INH

Cardiomyopathy

Leukemia

EBV

Halothane

Budd-Chiari

Autoimmune disease*

CMV

Acetaminophen*

Myocarditis

Hemophagocytic syndrome

Phosphorus

NK cell dysfunction

Acetosalicylic acid

Wilson disease*

Vitamin A acute

Adolescent

Hep A*,B,C,D,E

Mushroom poisoning

Budd-Chiari

Wilson disease*

Yellow fever

Acetaminophen*

Congest. heart failure

Fatty liver of pregnancy

Dengue Fever

MAO Inhibitor

Heat stroke

Autoimmune disease*

Lassa Fever

FIAU

Shock

Protoporphyrria

Other

Bacillus cereus toxin

Fatty acid oxidation defects

Tetracycline

Ethanol

Ecstasy

Diagnostic Prioritization

- **In the child < 8 weeks**

- Infection

- Herpes, enterovirus, adenovirus, CMV, EBV

- Metabolic disease

- Galactosemia, tyrosinemia, fatty acid oxidation, mitochondrial/respiratory chain defects

- Newborn screen results may be helpful, but specific tests to rule out a metabolic defect should be performed if clinically relevant

- **Older children**

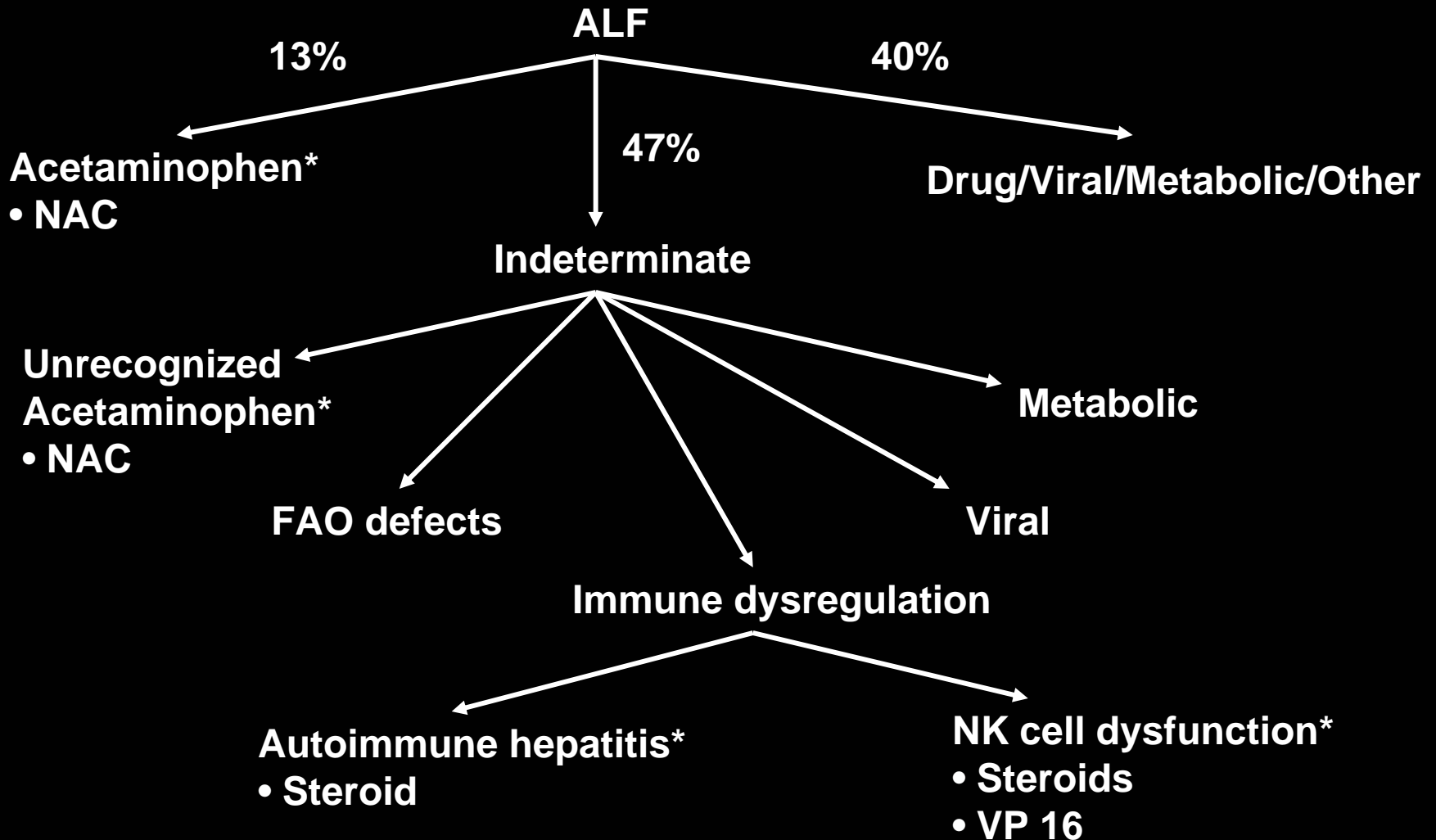
- Autoimmune disease, even in the young child

- Other infections in addition to Hepatitis A, B, or C

- Metabolic diseases in addition to Wilson's disease (e.g. FAO)

- Obtain a good drug history

Etiologic Evolution of ALF in Children



* = groups may respond to therapy

Conclusions

- Prioritize diagnostic studies to identify treatable conditions
- The etiology of ALF is different between children and adult and also differs within pediatric age groups
- Indeterminate causes offers a real opportunity for study
- 24% of children who never develop clinical encephalopathy died or required liver transplant
- Multi-center registries such as The NIH Sponsored Pediatric Acute Liver Failure Study Group
 - will enhance our understanding of ALF in children
 - refine prognostic indicators
 - provide an opportunity to improve the diagnosis and management
 - study treatment options and devices