Acetaminophen-Related Acute Liver Failure: ALFSG Update 2009

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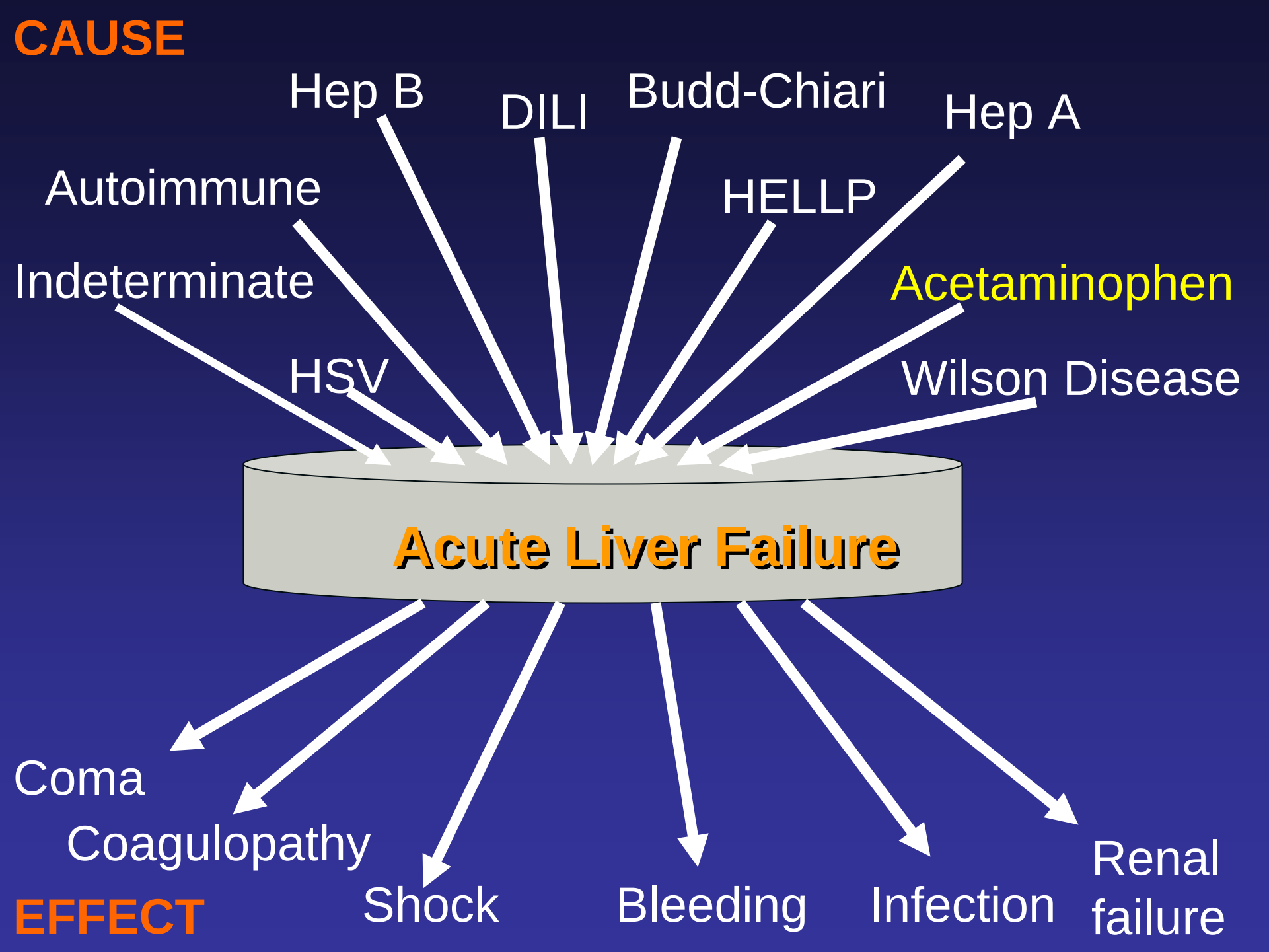
FDA Advisory Committee Meeting

Acute Liver Failure

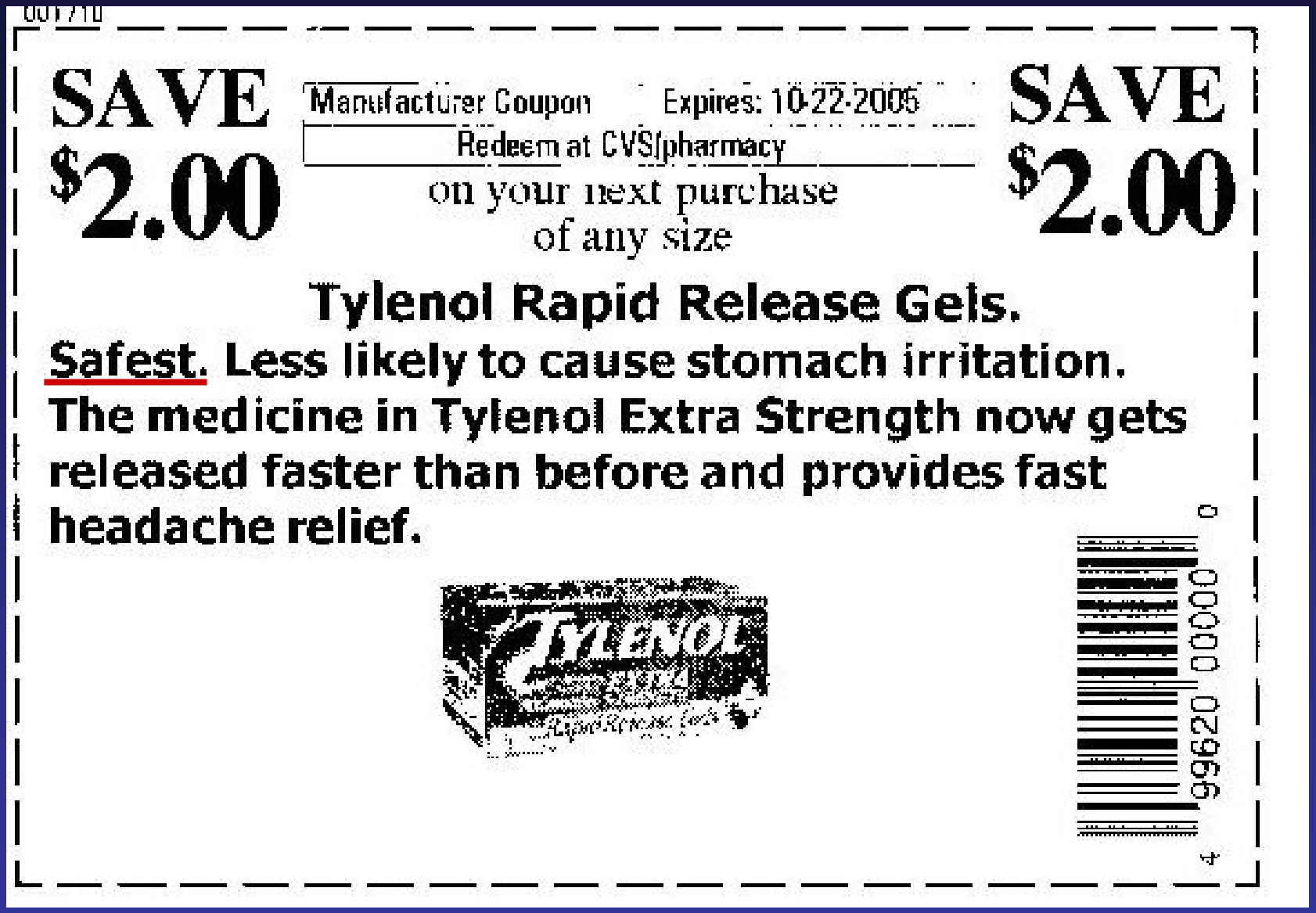
Fulminant Hepatic Failure

- Most severe form of liver injury
- Devastating: survival <10% in earlier era
- UNOS Status 1
- Fascinating
- Frustrating
- Hard to treat
- Rare
- Difficult to study


CAUSE
Hep B
DILI
Budd-Chiari
Hep A
Autoimmune
HELLP
Indeterminate
Acetaminophen
HSV
Wilson Disease
Acute Liver Failure
Coma
Coagulopathy
Shock
Bleeding
Infection
Renal failure
EFFECT

Executive Summary: Acute Liver Failure due to APAP

- Most common form of ALF in Western world
- Outweighs all other drugs combined
- Several hundred deaths annually in US
- Considered safe!
- Unintentional cases exceed suicidal ALF
- Many more cases that don’t reach ALF stage
- Reasons for unintentional cases are complex: narcotic use, alcohol, illicit drugs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Safest. Less likely to cause stomach irritation.
The medicine in Tylenol Extra Strength now gets
released faster than before and provides fast
headache relief.
TYLENOL
99620 00000 0
4

The Hierarchy of APAP ALF

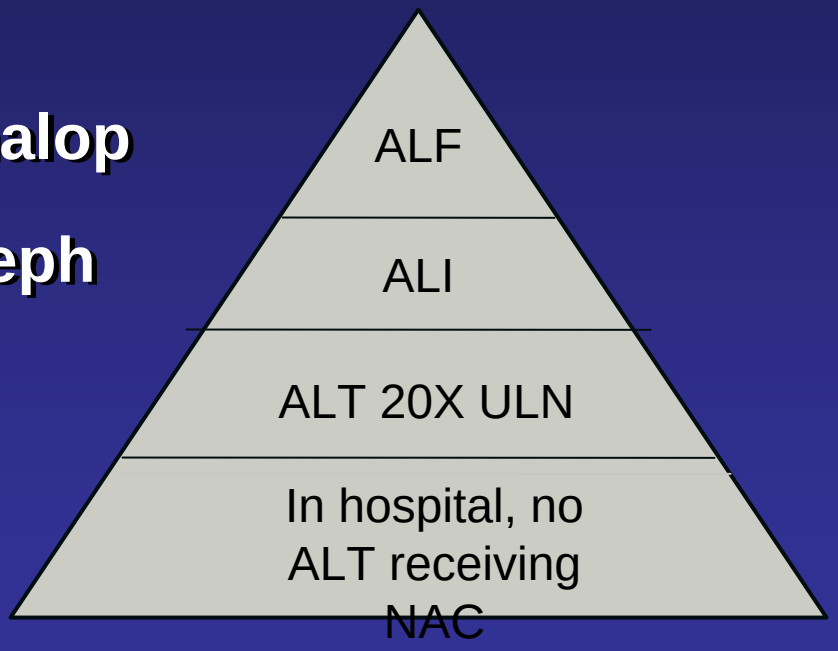
Only a fraction of cases make criteria of ALF

INR 1.5/Encephalop

INR 2.0/No enceph

Liver injury

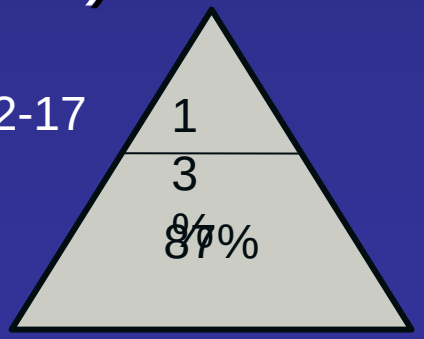
Risk of toxicity



Parkland Hospital study of APAP overdoses

Suicidal: n=50	Unintentional: n=21
• Suicide admitted	• Suicide denied
• Single time point	• Several days' use
• No cause of pain	• Reason for pain
• Early presentation	• Late presentation
• 20% ALT > 1,000	• Virtually all high ALT
• 1 ALF/death in 50 (2%)	• 8 ALF; 6 (29%) died

Schiødt et al., NEJM 1997:337:1112-17



Difference betw. Parkland study & ALFSG: ALFSG is all ALF, Parkland study was all patients admitted.

Background on ALF:

- **Relatively rare disease: ca. 2,000 cases/yr**
- **No one center can study the condition**
- **No viable treatment for all patients**
- **High mortality/morbidity (94% p.t. OLTx)**
- **Hep B the predominant dx, p.t. 1980, no APAP**
- **Transplantation has helped – but how much?**

Acute Liver Failure Study Group

Rationale: Network to study a rare disease

- **Over 1,400 cases enrolled over 10+ years at 23 sites**
- **37 original articles**
- **Clinical trial of NAC for non-APAP ALF**
- **Standardized protocol for treatment of ALF**
- **APAP adducts assay**
- **80 other ancillary studies**

Funding: NIDDK R-03/R-01/U-01: 1997-2010

Case Report Form

Acute Liver Failure Study Group
William M. Lee M.D.

Study Form A

Admission to Study Pg 1

Center No.	Patient Study No.	Date Initial Hospital Admission:	Time Admitted:	Hospital Transfer?: ◯ Yes ◯ No
		month day year	hr min	If Yes, date: month day year

1. Meets ALF Criteria?

Jaundice/Illness:	Yes	No	Altered mental status?	Yes	No	INR ≥ 1.5?	Yes	No
< 8 wks	◯	◯		◯	◯		◯	◯
OR								
≥ 8 weeks and < 26 wks	◯	◯						

2. Consent obtained?	Yes	No	3. Date of Admission to Study:	4. Time:	5. Previous:	Yes	No
	◯	◯	month day year	hr min	Sedatives	◯	◯
					FFP	◯	◯

6. Date of birth: month day year

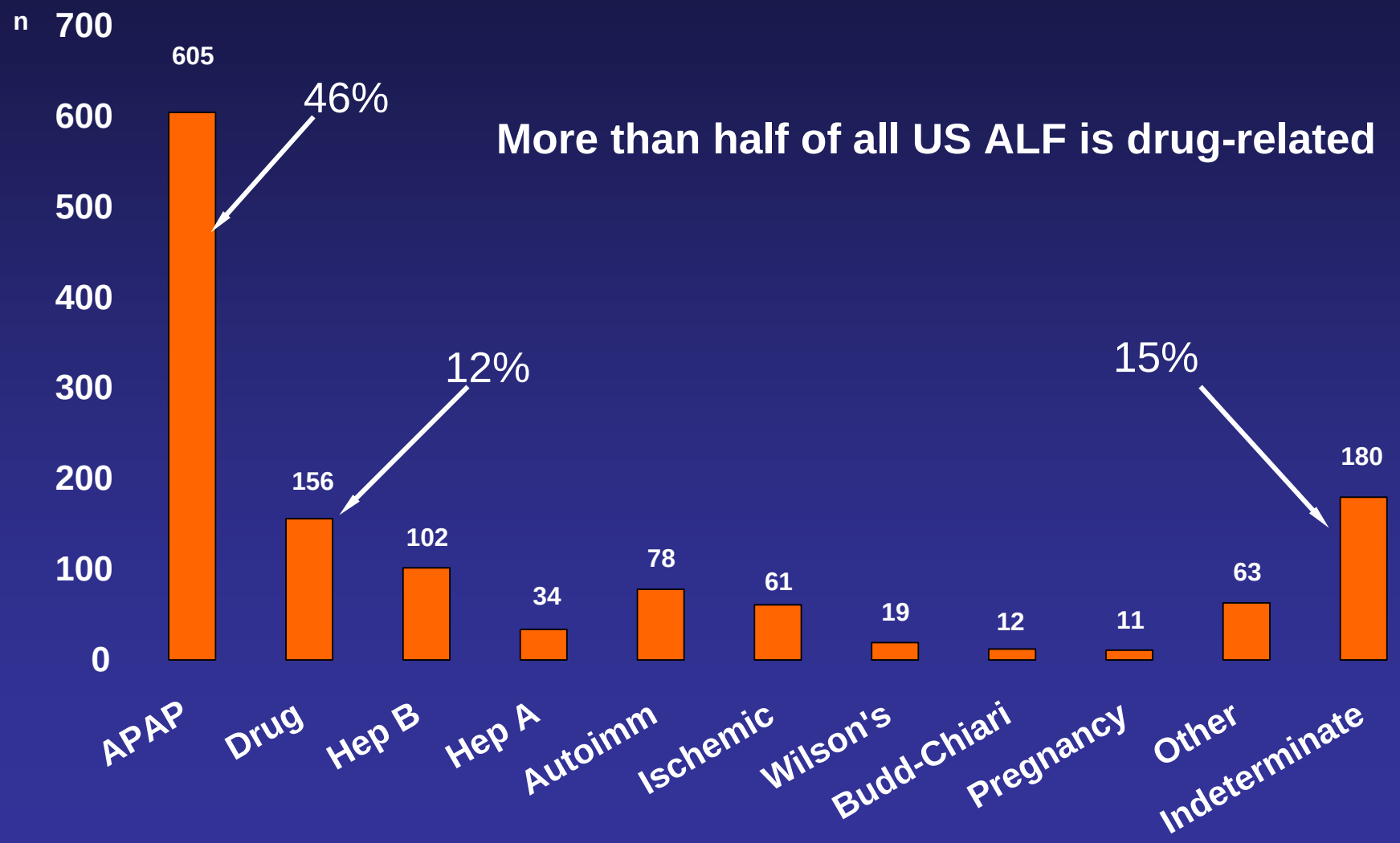
7. Age:

8. Sex: ◯ Male ◯ Female

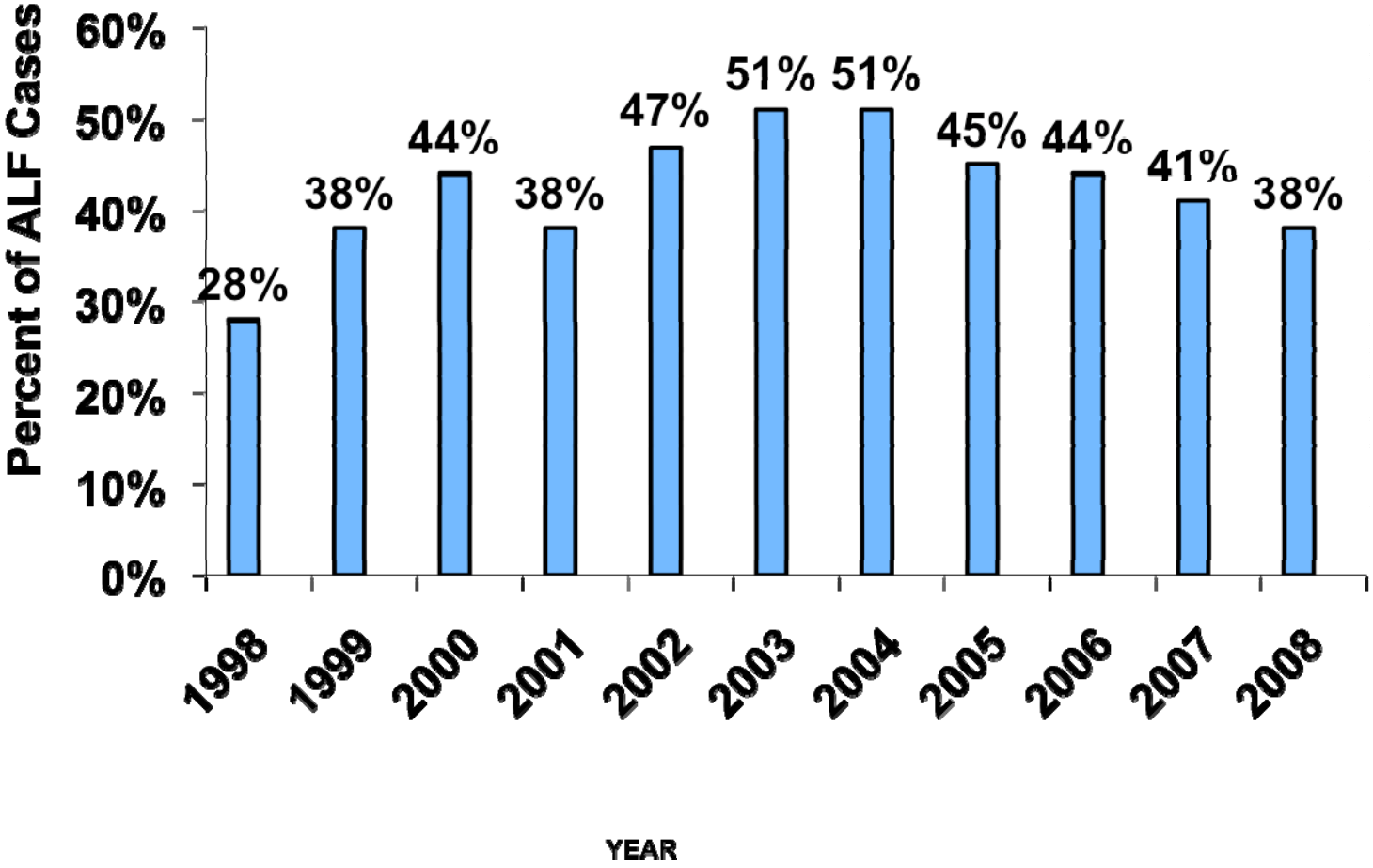
9. Years of Education Completed: ◯ Unknown

Etiology of ALF in the USA

Adult Registry (n = 1,321)



Acetaminophen cases as % of all ALF per year



‘Suicidal’ vs. ‘Accidental’ APAP cases ♬ N=275

N=253 22 unk	Intentional (n=122)	Unintentional (n=131)	p-value
Female (%)	74	73	NS
ACM dose (g)	25	20	NS
Dose per day	25	7.5	0.001
Coma (%≥3)	39	55	0.026
ALT (IU/L)	5,326	3,129	0.001
Spont surv (%)	66	64	NS
Antidepressant use	38	37	NS
History of depression	45	24	0.001
Narcotic cpd (%)	18	63	0.001
Multiple preps	5	38	0.001

Larson AM et al. Hepatology 2005; 42:1367-72

‘Suicidal’ vs. ‘Accidental’ APAP cases

N=606 (56=unk)	Intentional (n=254)	Unintentional (n=296)	p-value
Female (%)	77	71	NS
Age	35	39	< 0.001
ACM dose(g)	38/38	47/7.5	NS
Coma (% ≥3)	39	55	< 0.026
ALT (IU/L)	6053	4207	< 0.0001
Alcohol use/abuse (%)	50/18	50/17	NS
Antidepressant	39	34	NS
Used only OTC APAP	49	32	< 0.001
Narcotic Cpd only (%)	42	41	0.85
APAP + Narc Cpd	8	27	< 0.001
Spont surv (%)	70	65	NS

Comparison of males vs. females

N=606	Males (n=149)	Females (n=457)	p-value
Age	35	36	0.03
Percent suicide	49	39	0.019
Chronic EtOH (%)	68	45	< 0.001
Antidepressant (%)	20	41	< 0.001
Used only OTC APAP	55	31	< 0.001
Narcotic cpd only (%)	29	46	0.11
APAP + Cpd	16	22	< 0.001
ALT (IU/L)	5,618	4,647	< 0.01
Coma grade adm	2	3	< 0.001
Spont surv (%)	68	66	NS

Comparison of early vs. recent years

N=606	1998-2003 (n=275)	2004-2009 (n=331)	p-value
Age	37	36	NS
Percent suicide	44	40	0.019
Chronic EtOH (%)	55	49	0.04
Antidepress't (%)	20	41	<0.001
History of psych illness	42	59	<0.001
History of drug abuse	35	41	<0.01
Only one OTC product	54	20	<0.001
Narcotic Cpd only (%)	29	46	0.11
APAP + Narc Cpd	16	22	< 0.001
ALT (IU/L)	5,618	4,647	<0.01
Coma grade adm	2	3	<0.001
Spont surv (%)	65	68	NS

Reasons for APAP Use: Usually Pain!

Complaint	Early ('98-'03)	Late ('04-'09)
Chronic pain NOS	32	37
Back pain	24	20
Abdominal pain	9	14
Headache/migraine	23	14
Viral illness	7	10
Suicide	122	132
Unknown	27	71

Update of Larson Paper: 606 cases of ALF due to APAP

- Overall pattern is similar between early and late period
- More unintentional cases, ? better outcomes
- Slight decline in overall percent of ALF
- However, 71% of ALI cases were APAP
- 40% of suicidal/unintentional cases used Cpd
- More unintentional cases used additional APAP
- 50% increase in Cpd use in recent time period

Current Data APAP ALF: N=606

- Still comprises nearly 50% of all ALF
- 75% female
- Alcohol: some 50%; abuse 17%
- Suicide 42%; Unintentional 49%
- Seasonal? No, 25% each quarter
- Overall survival: 74%, died/transplanted 26%
- Spontaneous survival 66%
- 156 died or were transplanted!

Pediatric Acute Liver Failure Group (PALF)
NIDDK Funded Network begun in 2000

- **Over 800 cases enrolled over 9 years at 20 sites**
- **2 sites in UK, one in Canada**
- **Similar registry of data and biosamples**
- **Clinical trial of NAC for non-APAP ALF**
- **Rob Squires, Univ Pittsburgh, PI**

Funding: NIDDK R-03/R-01/U-01: 1997-2010

Pediatric ALF Registry Principal Investigators and Sites

Rob Squires-U Pittsburgh
Norberto Rodriguez-UTSW Dallas
Karen Murray-UW Seattle
Phil Rosenthal-UCSF San Francisco
Nanda Kerkar-New York (Mt. Sinai)
Estella Alonso-Chicago (Northwestern)
Jim Lopez-U Mich Ann Arbor
Mike Narkewicz-U Colo Denver
Scott Elisofon-Boston (Harvard)
Girish Subbarao- IU Indianapolis

NIH-NIDDK
Pat Robuck, PhD, MPH
Edward Doo, MD
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David Rudnick-Wash U St. Louis
Kathy Schwarz-JHMS Baltimore
Steve Lobritto-Columbia NYC
Liz Rand-Philadelphia (CHOP)
Saul Karpen-Baylor Houston
Rene Romero-Emory Atlanta
Vicky Ng-U Toronto, Canada
Anil Dhawan-Kings London, UK
Deirdre Kelly-U Birminghan, UK

ALF in Infants

Final Diagnosis*	< 4 weeks,	4-8 weeks	9 weeks - <1 year
Indeterminate	32 (34.4)	18 (51.4)	42 (43.3)
APAP	0 (0)	1 (2.9)	4 (4.1)
Metabolic	13 (14.0)	7 (20.0)	19 (19.6)
Autoimmune	0 (0)	0 (0)	5 (5.2)
Viral Hepatitis	22 (23.7)	0 (0)	3 (3.1)
Shock/Ischemia	3 (3.2)	2 (5.7)	5 (5.2)
Drug-induced	0 (0)	0 (0)	1 (1.0)
Neonatal iron storage dis.	13 (14.0)	3 (8.6)	2 (2.1)
Veno-occlusive disease	0 (0)	0 (0)	4 (4.1)
Hemophagocytic Syndrome	1 (1.1)	0 (0)	6 (6.2)
Budd-Chiari	0 (0)	0 (0)	0 (0)
Other diagnosis	7 (7.5)	3 (8.6)	3 (3.1)
Multiple diagnosis	2 (2.2)	1 (2.9)	2 (2.1)
Total	93	35	96

* Final diagnosis pending for 1 participant

ALF in Older Children

Final Diagnosis	1 - 5 years	6-10 years	> 10 years
Indeterminate	138 (63.6)	52 (55.9)	85 (31.0)
APAP	9 (4.2)	4 (4.3)	85 (31.0)
Metabolic	10 (4.6)	8 (8.6)	22 (8.0)
Autoimmune	16 (7.4)	6 (6.5)	28 (10.2)
Viral Hepatitis	13 (6.0)	3 (3.2)	13 (4.7)
Shock/Ischemia	4 (1.8)	5 (5.4)	7 (2.6)
Drug-induced	3 (1.4)	3 (3.2)	17 (6.2)
Neonatal iron storage dis.	0 (0.0)	0 (0.0)	0 (0.0)
Veno-occlusive disease	2 (0.9)	1 (1.1)	4 (1.5)
Hemophagocytic Syndrome	5 (2.3)	0 (0)	1 (0.4)
Budd-Chiari	0 (0)	1 (1.1)	2 (0.7)
Other diagnosis	13 (6.0)	4 (4.3)	5 (1.8)
Multiple diagnosis	4 (1.8)	6 (6.5)	5 (1.8)
Total	217	93	274

Pediatric ALF: Role of APAP

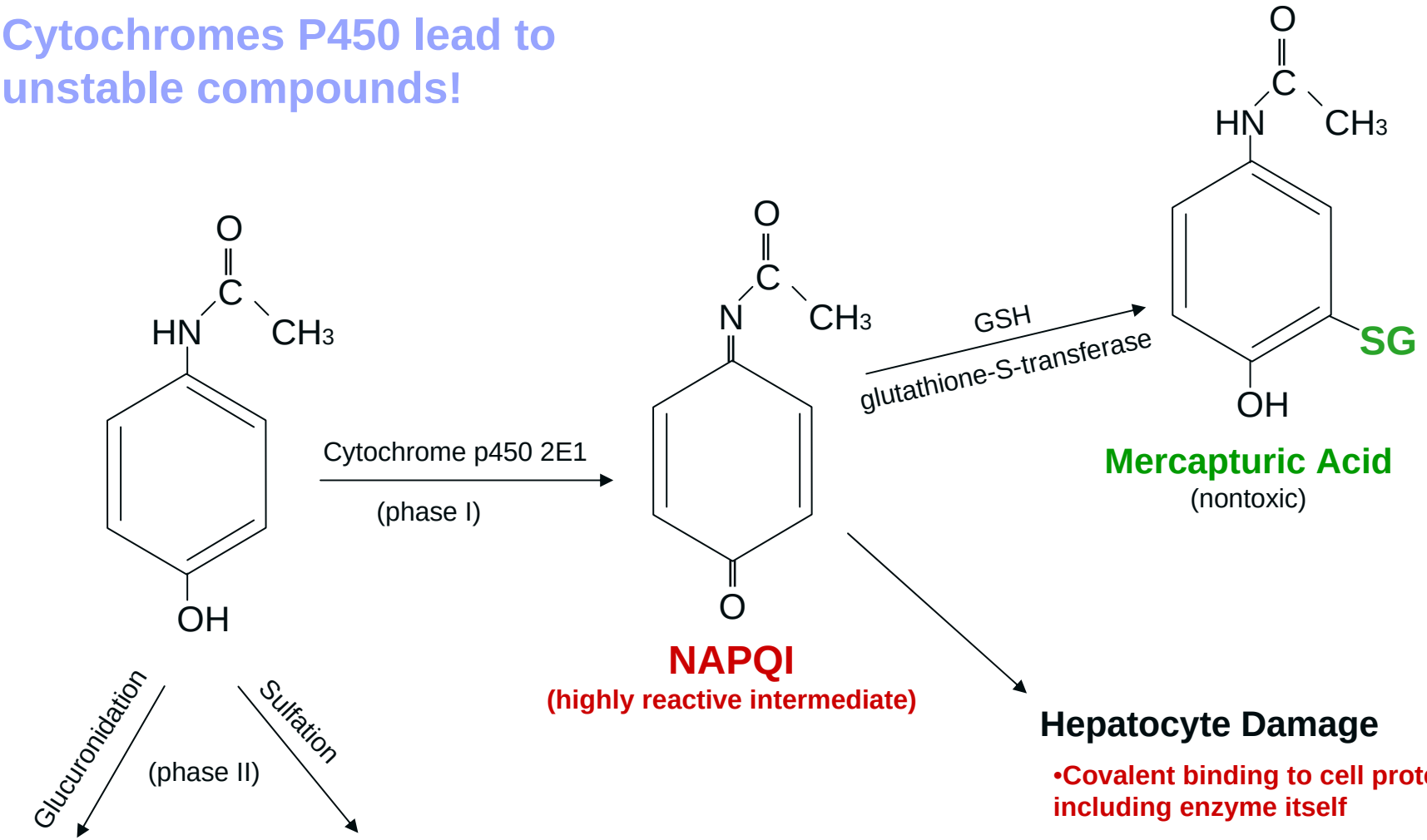
- 13% (103/808) are APAP-related toxicity
  One third are *chronic* exposures in young children
  - Care givers failed to realize they were giving too much drug (unintentional).
  - Chronic patients are: < 10 yrs, have normal APAP levels on admission and worse encephalopathy, similar outcomes
- Overall, ~5% die and ~5% are transplanted
- Among age > 10, APAP is the most common cause of ALF (31%), mostly adolescent suicide attempts

Acetaminophen: our biggest problem

Comparison of Different ALF Etiology Groups

	ACM n=407	Drug n=111	Indeterminate n=131	HepA/HepB n=29/69	All Others n=159
Age (median)	36.0	42.0	38.0	48.0/41.0	42.0
Sex (% F)	74	67	57	48/48	78
Jaundice (Days) (median)	0.0	8.0	8.0	3.0/6.0	6.0
Coma ¾ (%)	52	39	49	52/50	42
ALT (median)	4248	586	899	2622/1740	674
Bili (median)	4.5	20.9	22.7	11.8/19.7	15.8
Transplant (%)	9	42	41	31/49	35
Spontaneous Survival (%)	63	25	26	55/26	30
Overall Survival (%)	71	64	63	83/68	60

Cytochromes P450 lead to unstable compounds!



Hepatocyte Damage

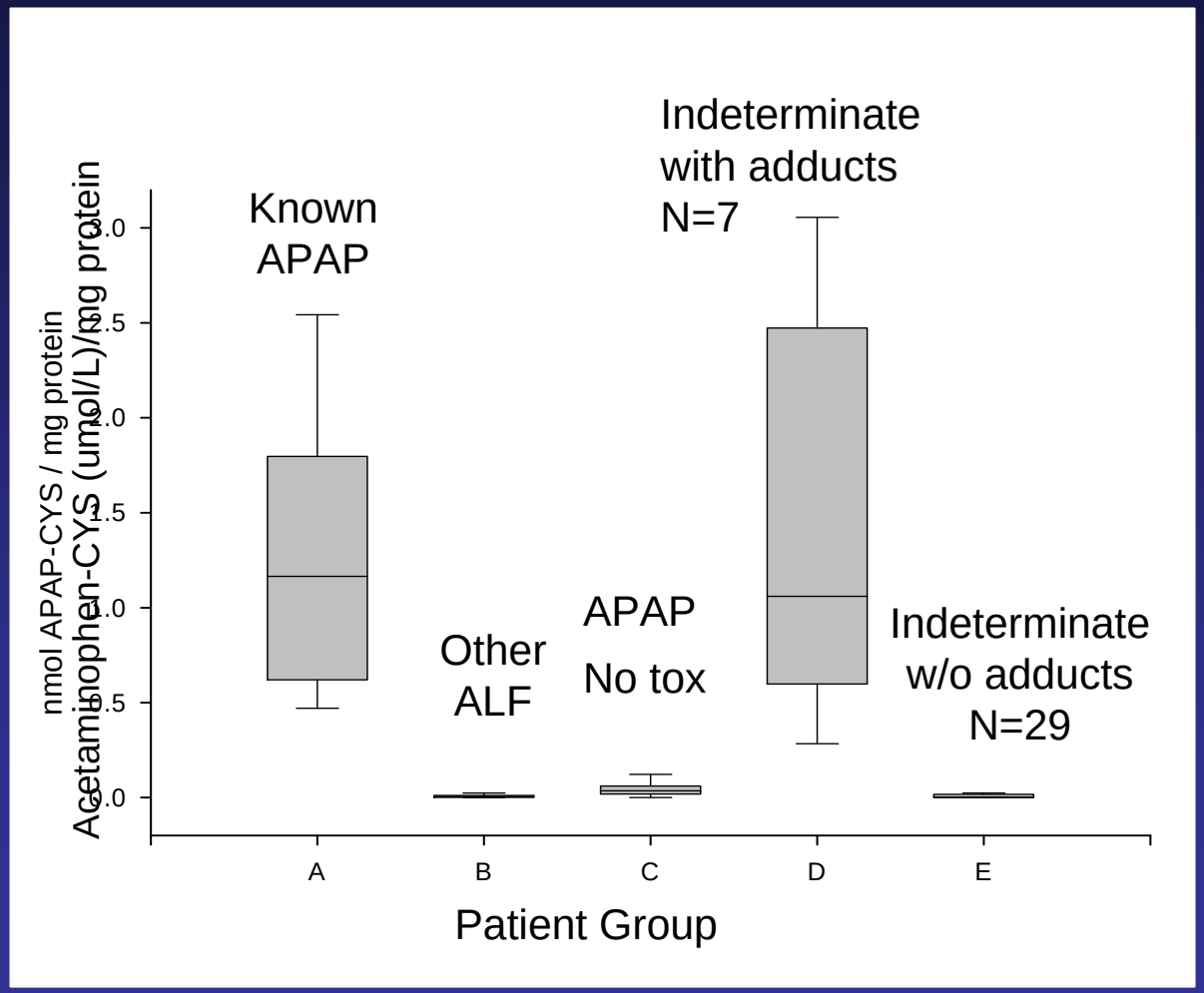
- **Covalent binding to cell proteins, including enzyme itself**
- **ADDUCTS**
- **Derangement of apoptosis?**
- **CAR?**

APAP adduct assay correctly identifies 100% of overdoses

HPLC-ED assay, specific for APAP-cys.

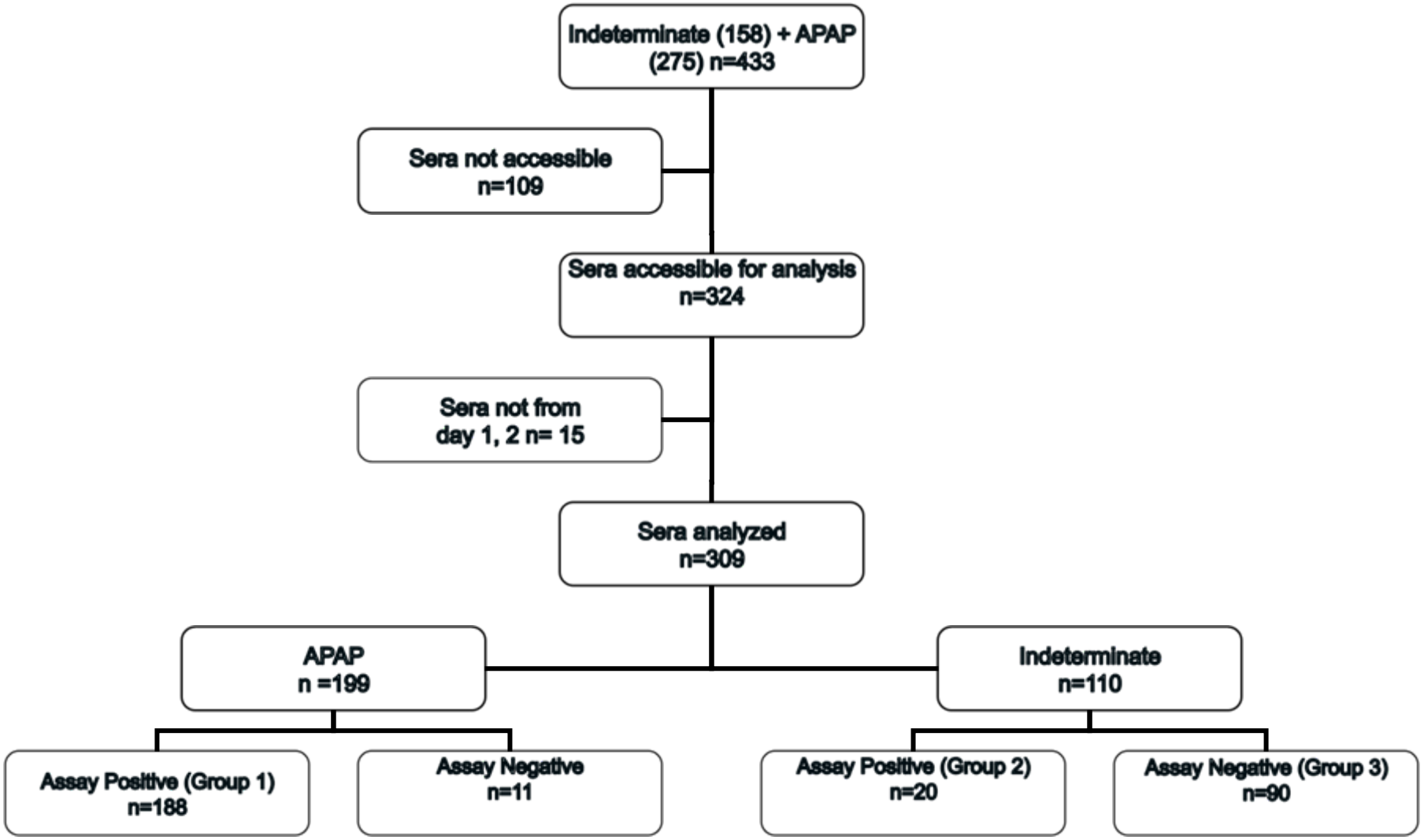
Remains positive for 12 days following overdose

Assay effectively identifies 'occult' cases.



Davern TJ, et al. Gastroenterology 2006;130:687

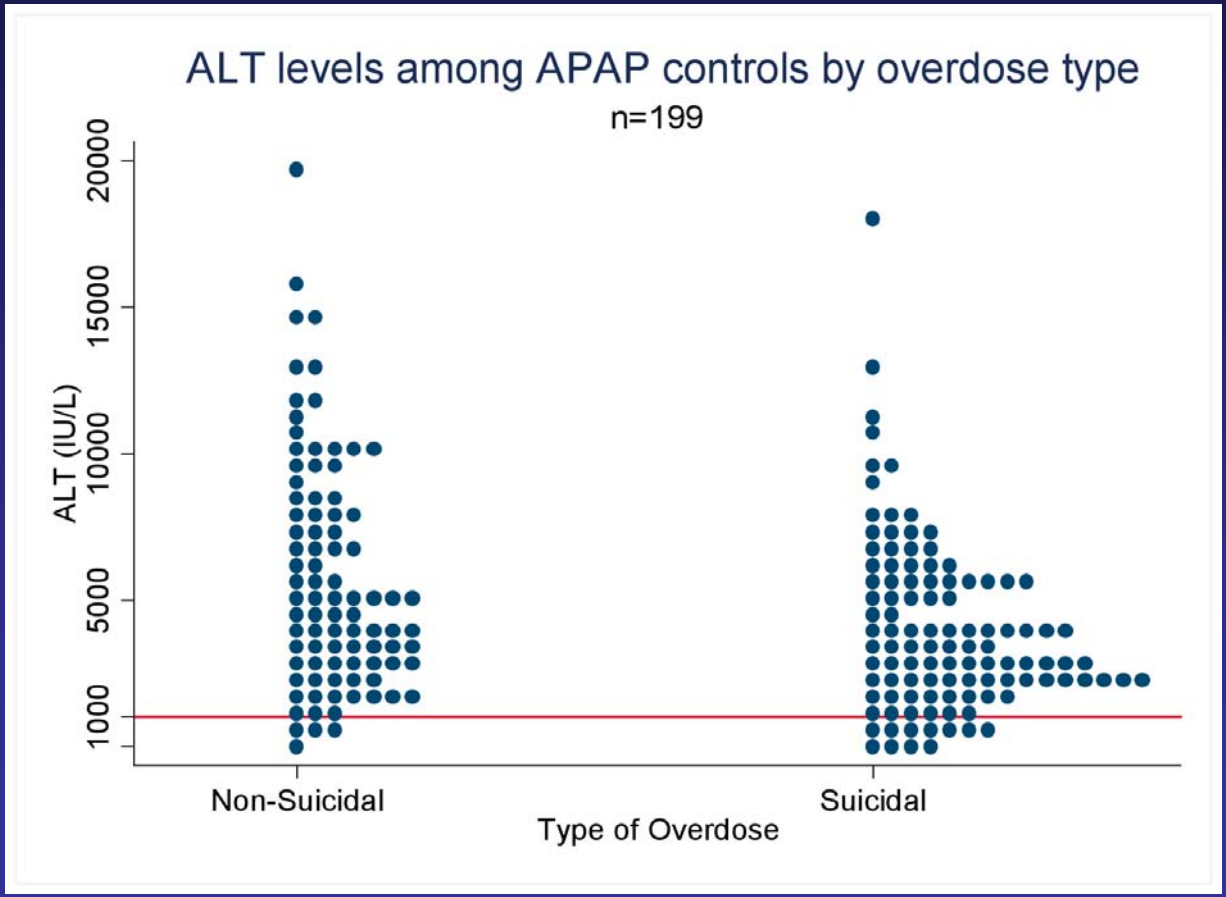
Scheme for evaluating APAP adduct assay



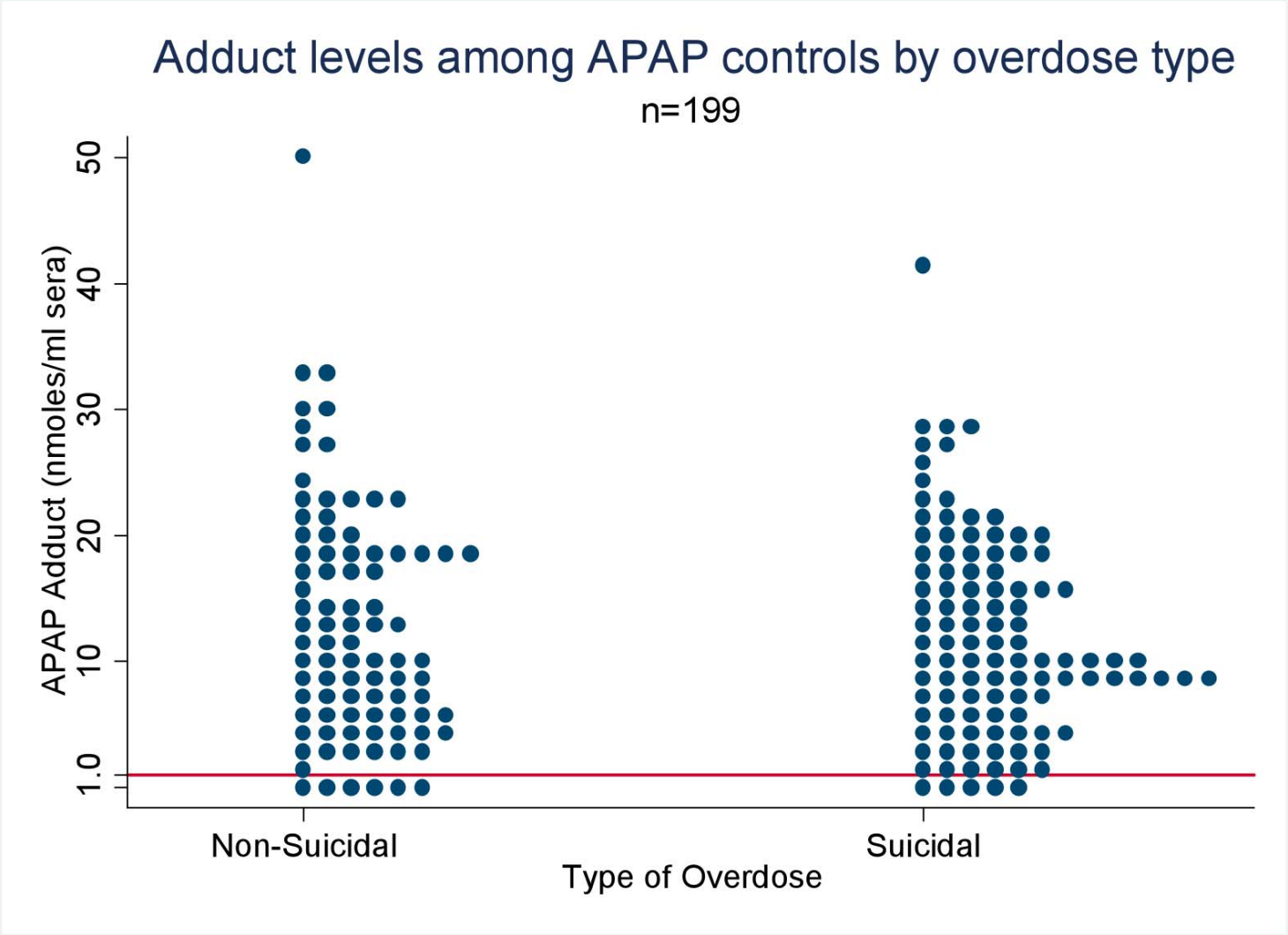
Examination of adducts in ALF

		Indeterminate patients		
	Grp 1 (APAP) N=188	Grp 2 (Adduct pos) N=20	Grp 3 (Adduct neg) N=190	p value
Age	37	33	39	NS
Gender % fem	75	80	48	< 0/001
ALT (IU/L)	4,025	5,156	811	< 0.001
Adduct levels	11.1	9.2	0	< 0.001
Bilirubin (mg/dl)	4.1	5.1	24.3	< 0.001
NAC Rec'd (%)	94	40	18	< 0.001
Spont survival	64	55	21	< 0.001

Aminotransferase levels in APAP overdoses



Adduct levels in APAP overdoses



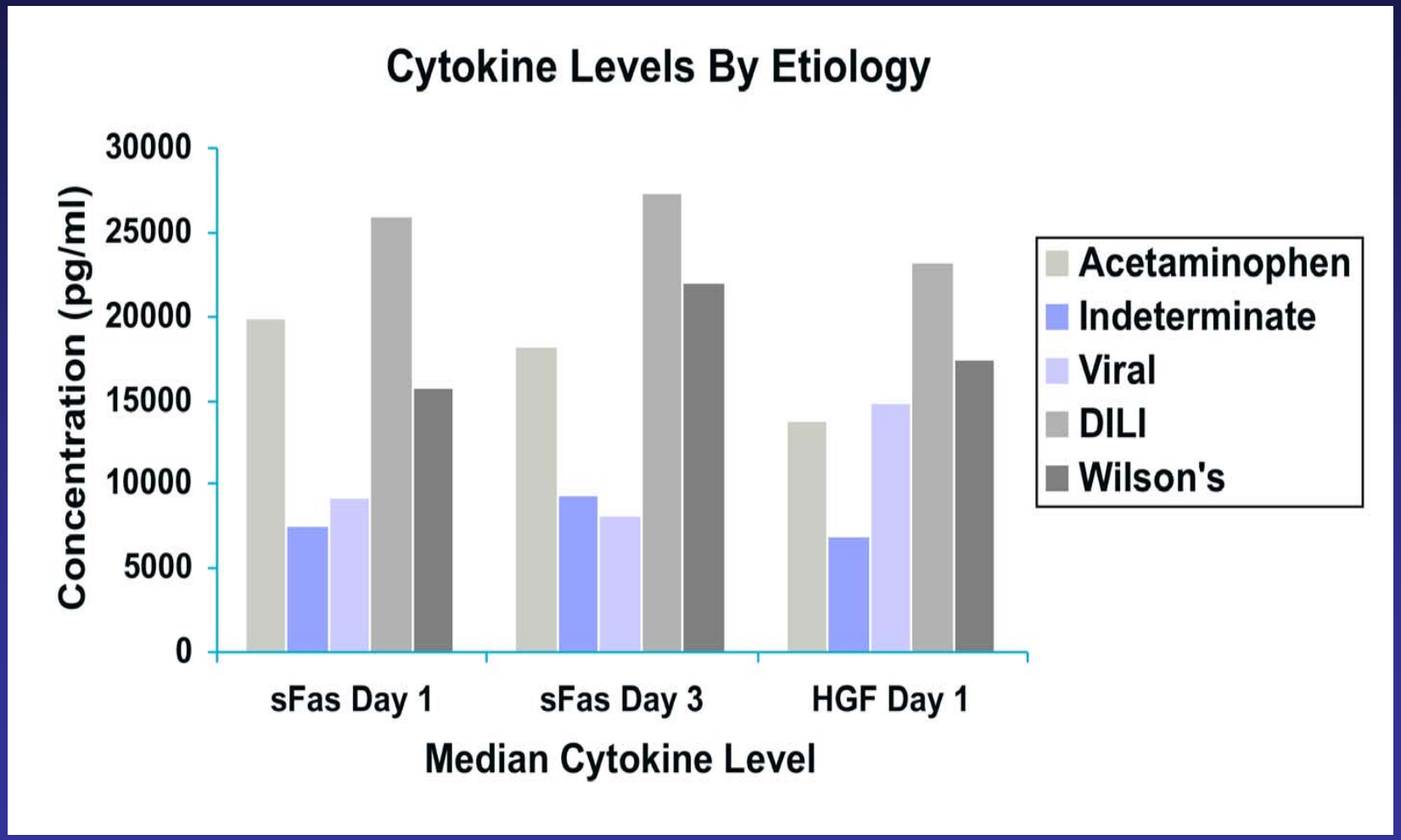
Pathogenesis of APAP Toxicity

- Direct necrosis due to NAPQI binding to cell proteins
- May lead to dysfunction of calcium homeostasis?
- Or does covalent binding begin an innate immune process?
  - Mitochondrial involvement/ROS/peroxynitrite
  - Glutathione reverses oxidative stress
  - Neutrophils/Kuppfer cells/lymphocytes all involved

Masson MJ et al. Hepatology 2008;48:889.

Jaeschke HJ. Hepatology 2008;48:899.

Role of cytokines in APAP ALF



Results AKI in ALF

	APAP	Shock	Other	Total
Cr < 1.3	169 (27.3%)	6 (9.5%)	225 (33.7%)	400 (29.7%)
Cr ≥ 1.3	164 (26.5%)	27 (42.8%)	163 (24.4%)	354 (26.2%)
Stage 1	21 (3.4%)	2 (3.2%)	28 (4.2%)	51 (3.8%)
Stage 2	24 (3.8%)	1 (1.6%)	47 (7.0%)	72 (5.3%)
Stage 3	28 (4.5%)	0	39 (5.8%)	67 (4.9%)
RRT	212 (34.3%)	27 (42.9%)	166 (24.9%)	405 (30%)
	618	63	688	1349

$p < 0.05$

AKI and Spontaneous Survival

- Need for RRT negatively impacted spontaneous survival in APAP, shock and others (53% vs 73%; 59% vs 72%; 17% vs 31%, $p<0.05$)
- AKI did not correlate with severity of liver injury
- Only coma grade and presence of AKI affected spontaneous survival in APAP ALF

- After adjusting for etiology and coma grade, AKI remained an independent risk factor negatively impacting spontaneous survival ($p<0.001$)

APAP Hepatotoxicity: Summary

- Still an important problem dwarfing DILI!
- Narcotic compounds involved in 40+%
- Comprises 18% of indeterminate ALF
- Frequent psych and drug abuse in both groups
- Multiple products important in at least 20%, more in pain patients.
- Renal injury is common in APAP
- Injury enhanced or ameliorated by con meds
- Incidence may be declining slightly
- Still the largest cause of death from ALF in US

APAP Hepatotoxicity: Current Plans

- Continue registry, we plan a ‘Larson II’ paper
- Use follow-up questionnaires
- Alert clinicians about ‘acute indeterminate’ ALF
  - Considering NAC for ALFs with unclear history
- Further studies relate to cytokine markers
  - Study osteopontin, M-30 antigen, IL-17
- What are the regulatory issues?
  - Not likely to be withdrawn
  - Limit dose or package size, blister packs, unbundle cpds.

ACUTE LIVER FAILURE

STUDY GROUP

www3.utsouthwestern.edu/liver

Targeting Acute Liver Failure
in the 21st Century!

Study Sites (Adult) in the ALFSG 2009

• UT Southwestern	Lee/Larson/Sanders
• U Washington	Liou/Strom
• UCSF	Fix
• Mt. Sinai NYC	Liu/Zuniga
• Univ Nebraska Omaha	McCashland/Bernard
• Baylor Dallas	Murray/Coultrup
• Univ Pittsburgh	Shakil/Gooch
• Northwestern Univ	Ganger/Gottstein
• OHSU, Portland	Zaman/Ingram/Wilson
• UCLA	Han/Kim/Peacock
• Michigan	Fontana/Welch
• Univ Alabama Birmingham	McGuire/Eddleman
• Mass General	Chung/Rutherford/Chen
• Columbia/Cornell, NYC	Brown/Odeh-Ramadan
• VCU	Stravitz/White
• Mayo Clinic: Rochester, Jax	Hay, Raj, Kramer/Groettum
• UC Davis	Rossaro/Dhaliwal
• Einstein Philadelphia	Munoz/Riera/Carmody
• MUSC Charleston	Reuben/Minshall
• Pennsylvania	Reddy/Blonski
• Yale	Schilsky/
• CPMC, San Francisco	Davern/

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- NIDDK Staff: Pat Robuck, Pat Lake, Ed Doo, Jay Hoofnagle, Len Seeff, Sharon Bourque, Becky Torrance
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