Acute Liver Failure 2017

William M. Lee, MD, FAASLD, FACP
Meredith Mosle Chair in Liver Diseases
UT Southwestern Medical Center at Dallas

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Disclosures

Research Support:

Consulting:

I may discuss off-label uses during this presentation!

Three Pre-test Questions

1. A 23 year old had a fight with her boyfriend and is found two days later confused and somnolent. In the Emergency Department 4 hours later, she is unarousable. Initial laboratory findings include: acetaminophen level 10.3 µg/L, AST 10,300 IU/L, ALT 8,500 IU/L, Alk Phos 145 IU/L, T Bilirubin 3.4 mg/dL. INR 4.8. Next steps should include:

   a. Fresh frozen plasma to correct the INR
   b. *N*-acetylcysteine 140 mg/kg/hr intravenous infusion
   c. I mg Haldol q 4 hr
   d. Frequent EKGs
   e. Seizure precautions

2. Idiosyncratic DILI reaching the point of acute liver failure (choose all that apply):
   a) Has poor overall outcome without transplantation
   b) Outcome in part depends on coma grade on admission
   c) NAC may be of some value in these patients
   d) May occur with weight loss herbal products

3. A 22 yr old college student is admitted to hospital with rapid onset of severe jaundice. She was undergoing work up for abnormal liver enzyme elevations, thought to be autoimmune hepatitis, when she deteriorated and was admitted with confusion and somnolence. Her family denies that she took any recent medications including acetaminophen or herbal supplements.

On exam, vital signs stable, deeply icteric, had asterixis and a spleen tip was palpable.

Labs disclosed WBC 4.5, Hgb 7.5, platelets 53,000; Bilirubin 65 mg/dL, Alk phos 23, AST 145/ALT 33. Albumin 2.3, globulin 1.8, ANA negative, ASMA 1:20, Cr 3.4 mg/dL.

Select the correct diagnosis:

a. Autoimmune hepatitis.
b. Drug-induced liver injury
c. Unintentional acetaminophen toxicity
d. Wilson disease

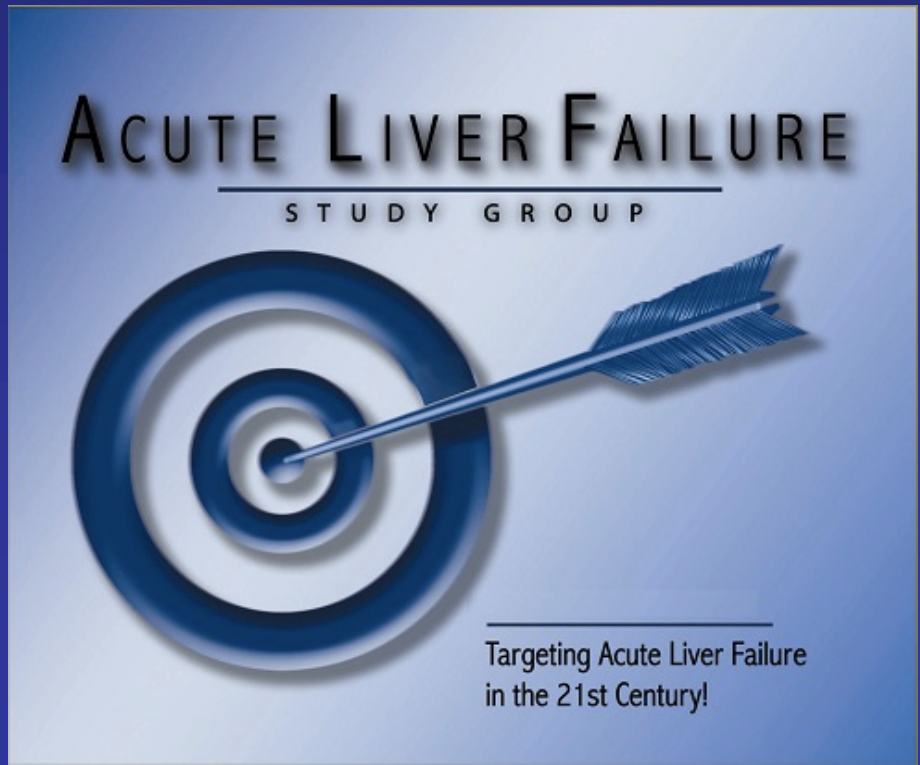
Acute Liver Failure: A 'Super Orphan' Disease

~~Fulminant Hepatic Failure~~

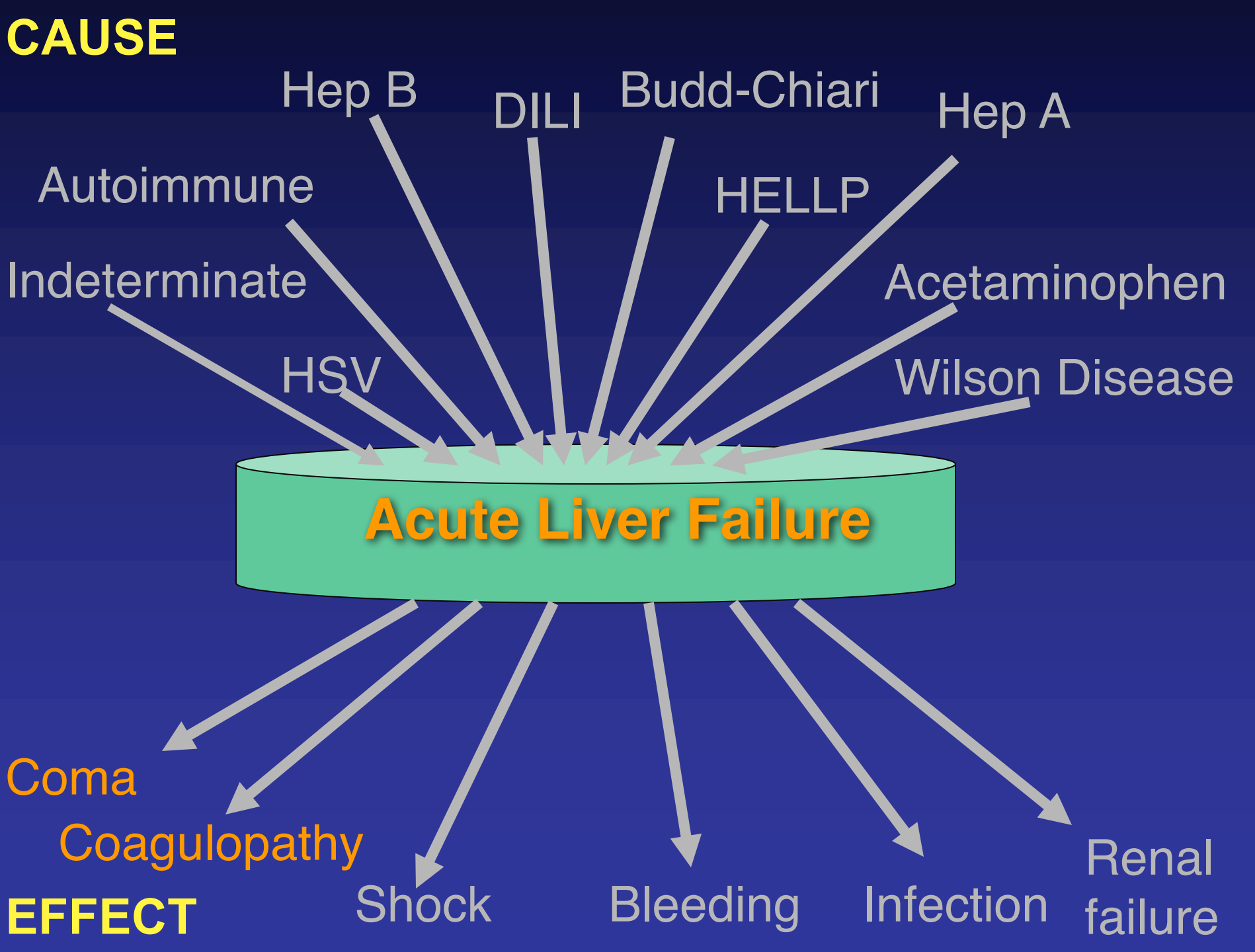
- Most severe form of liver injury but rare, 2,000/yr
- Devastating: survival <10% in earlier era
- Definition: INR ≥ 1.5, any grade enceph, acute illness
- UNOS Status 1a
- Fascinating
- Frustrating
- Hard to treat
- Difficult to study

ALF 2017
AIMS for this talk:

- Review criteria and clinical scenario
- Etiologies including APAP and others
- Intensive care issues
- Clinical Trials
- Prognosis



Supported by U-01 58369
from NIDDK 1997-2020


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


CAUSE
Apoptosis
Loss of oval cells
Innate immunity
Adaptive immunity
Necrosis
Local factors
DIC
Cytokines
Acute Liver Failure
Cerebral edema
Toxic cellular debris
Poor synthetic fxn
No regeneration
Poor toxin clearance
Increased infection risk
EFFECT

Acute Liver Failure Study Group: based at UTSW

Rationale: Network to study a rare disease

- **Began in 1998, currently 12 adult sites**
- **2,500+ cases in adult, ~1,100 in PALF registry**
- **Plus ~770 ALI, defined as: INR >2.0/no enceph**
- **Three directions:**
  - **Prospective clinical data, sera, urine, plasma, DNA, Numerous ancillary studies in progress: 100 ms.!**
  - **Therapy trials: NAC, STOP-ALF done; MBT and ROTEM**

Funding: NIDDK U-01 through 2020

Etiology of Acute Liver Failure in the USA Adult Registry (n = 2,436)

Acetaminophen (Paracetamol) Hepatotoxicity

- Popular (mild) pain reliever
- Dose-related toxin for all mammalian species
- Dwarfs all other forms of drug-related liver injury
- Largest selling OTC product/largest Rx generic
- Multi-billion dollar product/well-protected brand
- >100,000 calls annually to poison control centers
- 400+ deaths annually in the US, similar in EU
- Iconic model for studying liver injury
- Keeps basic scientists and clinicians employed!

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 FV et al., NEJM 1997:337:1112-17

Only 9 of 71 had ALF, nearly all were unintentional

‘Suicidal’ vs. ‘Accidental’ APAP cases

N=606 (56=unk)	Intentional (n=251)	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
Antidepress’t (%)	39	34	NS
History of depression (%)	45	24	< 0.001
Opioid cpd (%)	18	63	< 0.001
Multiple preps (%)	5	38	< 0.001
Spont surv (%)	70	65	NS

Comparison of Different ALF Etiology Groups

N = 2,436

	APAP N=1115	Drug n=261	Indeterminate n=282	HepA/HepB n=38/173	All Others N=560
Age (median)	37	46	40	50/43	45
Sex (% F)	76	69	61	45/46	70
Jaundice to coma (Days)	1	12	10	4/8	7
Coma ≥3 (%)	53	36	47	53/50	40
ALT (median IU)	3798.5	648	870	2316.5/1415	774
Bili (median)	4.3	19.2	20.1	12.3/18.8	12.7
Tx (%)	8.6	38	42	34/39	29
Spontaneous Survival (%)	64.4	25	23	50/19	31
Overall Survival (%)	71.5	59	61	74/53	55

The Conundrum of Idiosyncracy: Why are just a few patients susceptible?

"idio-sug-krasia" (Hippocrates, ~ 400 B.C.)

idios (ιδιος) - one's own, self

syn (συν) - together

crasis (κρασις) - mixing, mixture

a person's own individual mixture of characteristics, factors; uniqueness

It does NOT mean rare, unexpected, unexplained, although it may or may not be any or all of them!

Features of Idiosyncratic Drug Reactions

1. Occur rarely, not really dose related
2. Similar consistent pattern for each drug
3. Similar drugs exhibit similar features, “class effects”
4. Individual drugs in a class still vary considerably
5. Reactions occur at varying time intervals after ingestion (3 days to one year)
6. Reactions vary in severity, but typically severe and fatal if drug continued
7. Mild injury often disappears with continued use (adaptation)
8. Rarity of most reactions suggests multiple hits
9. Re-challenge is virtually always met with greater severity, shorter latency
10. Most drugs causing idiosyncrasy are at doses >100 mg/day

Clinical DILI: Basic points

- Most reactions are hepatocellular, some cholestatic
- Hard to distinguish from viral hep on biochem or biopsy
- Common drugs cause more than 50% of reactions
- Frequency of DILI depends on intrinsic toxicity and number of uses (e.g., Augmentin is extremely popular)
- Continued use of a product after becoming ill is strongly associated with bad outcome.

Most frequent DILI agents in adults

	ALFSG	DILIN
	N=137	N=899
Antibiotics		408
Amox/Clavulanate	0	91
INH (w/wo rif/pyraz)	25	28
Nitrofurantoin	11	42
Sulfa (TMP/SMX, sulfasalazine	12	31
Minocycline	6	28
Cefazolin	0	20
Others	13	115
Herbal and Dietary Supplements	14	145
CNS	18	82

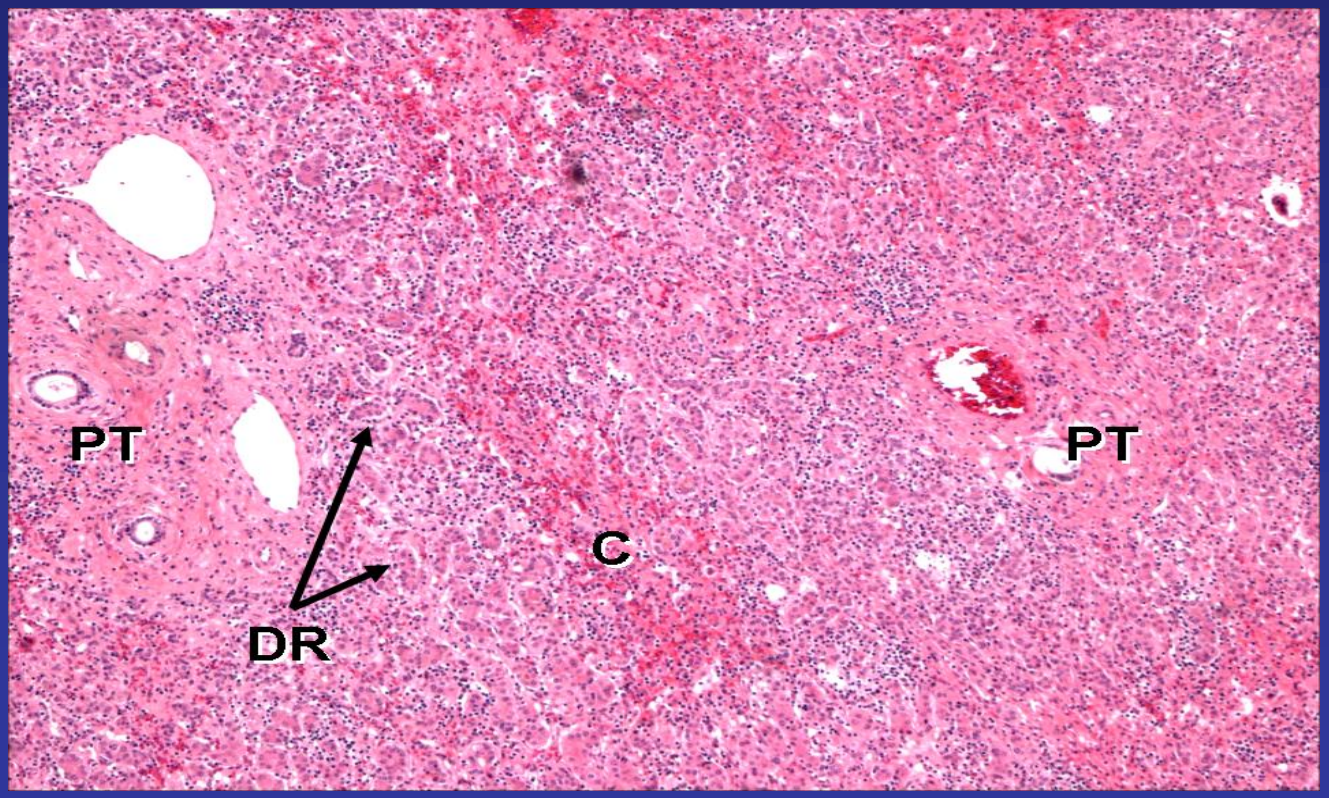
Black cohosh hepatotoxicity: autoimmune hepatitis

35 yo woman, began a mail order pill one/day.

Admitted 4 wks later with coma.

TB 19.3, AST 835/ALT 674, INR 3.9, ANA 1:640.

Transplantation required.



Basic Steps in Causality

Most injury is to hepatocytes: determine is it 'hepatitis?'

- Measure aminotransferases and are they new?
- Assess severity: level of ALT, INR, encephalopathy
- What are other possible causes? Alcohol, Viral, Ischemia, (gall)Stones = "AVIS."
- What (other) drugs are being taken?
- What is likelihood of each drug? This is now outlined on livertox.nih.gov

Wilson disease

- Autosomal recessive, present in all populations at about 1/30,000
- Still need combination of clinical and biochemical studies to characterize phenotype and establish diagnosis
- Better availability of genetic testing for ATP7B mutations now makes this first line for family screening and for indeterminate cases
- Medical therapy is lifelong; transplant is curative

What establishes the diagnosis of Wilson's disease?

- Low ceruloplasmin and KF rings
- Low ceruloplasmin and elevated liver copper (>250 ug/g dry wt)
- Histology/histochemistry/ultrastructure and elevated liver copper >250 ug/g dry wt
- evidence for homozygosity or compound heterozygosity for known ATP7B mutation
- evidence of common haplotype with proband

What about ALF due to Wilson disease?

- Uniformly fatal: but how to diagnose?
- Low ceruloplasmin in >50% of ALF patients
- No time to get send out tests
- Classic features are: massive hemolysis, AKI
- Aberrant labs: Low Alk P, very high bilirubin
- Low Hgb, AST/ALT ratio, so:
  - AlkP/Bili ratio < 4.0 and AST/ALT ratio > 2.2

Korman JD, et al. Hepatology 2008;48:1167-1174

Initial Management ALF

- Must have high index of suspicion at time of admission
- Condition progresses rapidly
- Changes in consciousness occur hour-by-hour
- Admission or early transfer to ICU warranted
- Use an app or order set: ALFSG has app

History: ALF

- Often provided by family or friends due to altered level of consciousness
- Focus should be on possible exposures to drugs (prescription medications, OTC analgesics, herbal supplements or CAM) or viral infection

Principles of care

- Intensive care management of severe, rapidly progressive multi-organ system failure
- Only effective treatment: **emergent liver transplant**
  - Rapid psycho-social evaluation critical
  - Move quickly whatever the diagnosis
- Don't transfuse for INR alone
- Intubate for Grade 2-3 coma
- No substitute for experience

Disease-specific treatments

- N-acetylcysteine (NAC)
  - Acetaminophen overdose
  - ?Non-acetaminophen ALF?
- Nucleos(t)ide analogues
  - Acute hepatitis B
- Acyclovir
  - Acute HSV
- Steroids
  - AIH
- Plasmapheresis/ exchange transfusion
  - Wilson's
- Penicillin G and silymarin (milk thistle)
  - Mushroom poisoning (Amanita phalloides)
  - Outcome benefit not established, data scarce

Treatment for APAP Overdose
N-acetylcysteine (NAC) is an effective antidote!

- **IV NAC will totally prevent toxicity if given < 12 hrs**
- **Uncertain benefit after 30 hours**
- **Supportive care in ICU: may develop fatal complications: brain edema.**
- **Initial evaluation: is it ALF? If so, is he/she a LT candidate? If so, consider early transfer to OSU.**

TREATMENT

NAC is the accepted standard of care antidote worldwide—should be used even when uncertain

THE LANCET

Volume 310, Issue 8035, 27 August 1977, Pages 432–434

Originally published as Volume 2, Issue 8035

Preliminary Communications

1977

TREATMENT OF PARACETAMOL (ACETAMINOPHEN) POISONING WITH N-ACETYLCYSTEINE

L.F. Prescott, A. Ballantyne, A.T. Proudfoot, J. Park, P. Adri

Therapeutics

Abstract

Fifteen pat
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admission
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ingestion.
three in wh
ingestion.
tolerated a
preparatio

Paracetamol (acetaminophen) poisoning

1995

J A Vale, A T Proudfoot

Few physicians can have escaped the impact of paracetamol (acetaminophen) overdosage since the first reports of hepatotoxicity in 1966.[1,2] In 1993, for exampl concern about paracetamol prompted about 10% of inquiries to the UK National Poisons Information Servi and over 40 000 reports to the Toxic Exposu Surveillance Scheme of the American Association Poison Control Centres.[3] Over the past 30 years o understanding of paracetamol poisoning and of how manage it has improved. The mechanism of the toxicity known, effective antidotes have been developed, and liv transplantation has been introduced for patients for who no other therapeutic option is available. Nonetheles there remains confusion about several aspects management. Which is the antidote of choice, and what route and for how long? Who should recei treatment? What is the value of late acetylcysteine (NA administration and what are the risk implications of liv enzyme induction? Are the adverse effects of NAC due idiosyncrasy or are they dose-related?

of 200 mg/L at 4 h and 30 mg/L at 15 h (the "200 line") on a semilogarithmic graph. A similar nomogram, but

Nomograms

Although hepatotoxicity is very unlikely if less th 150 mg paracetamol per kg body weight has be

THE LANCET

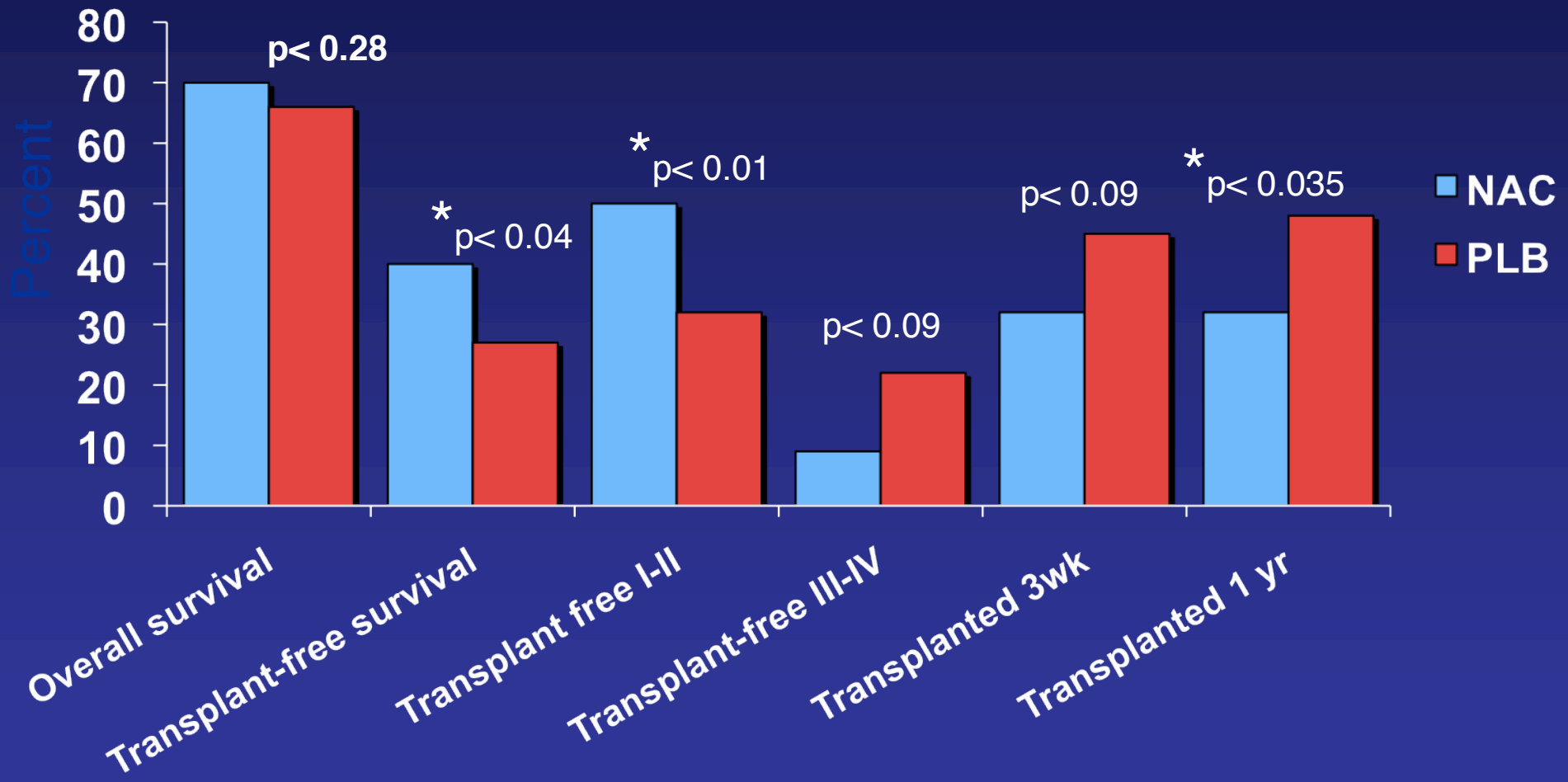
1990

Volume 335, Issue 8705, 30 June 1990, Pages 1572–1573

Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine

P.M. Harrison, MRCP, R. Keays, MRCP, G.P. Bray, MRCP, G.J.M. Alexander, MRCP, R. Williams, MD Liver Unit, King's College Hospital and School of Medicine and Dentistry, London SE5 9RS, UK

Primary/secondary outcomes in the NAC trial



The most impressive difference was in transplant free survival in coma grades I-II. * = statistically significant

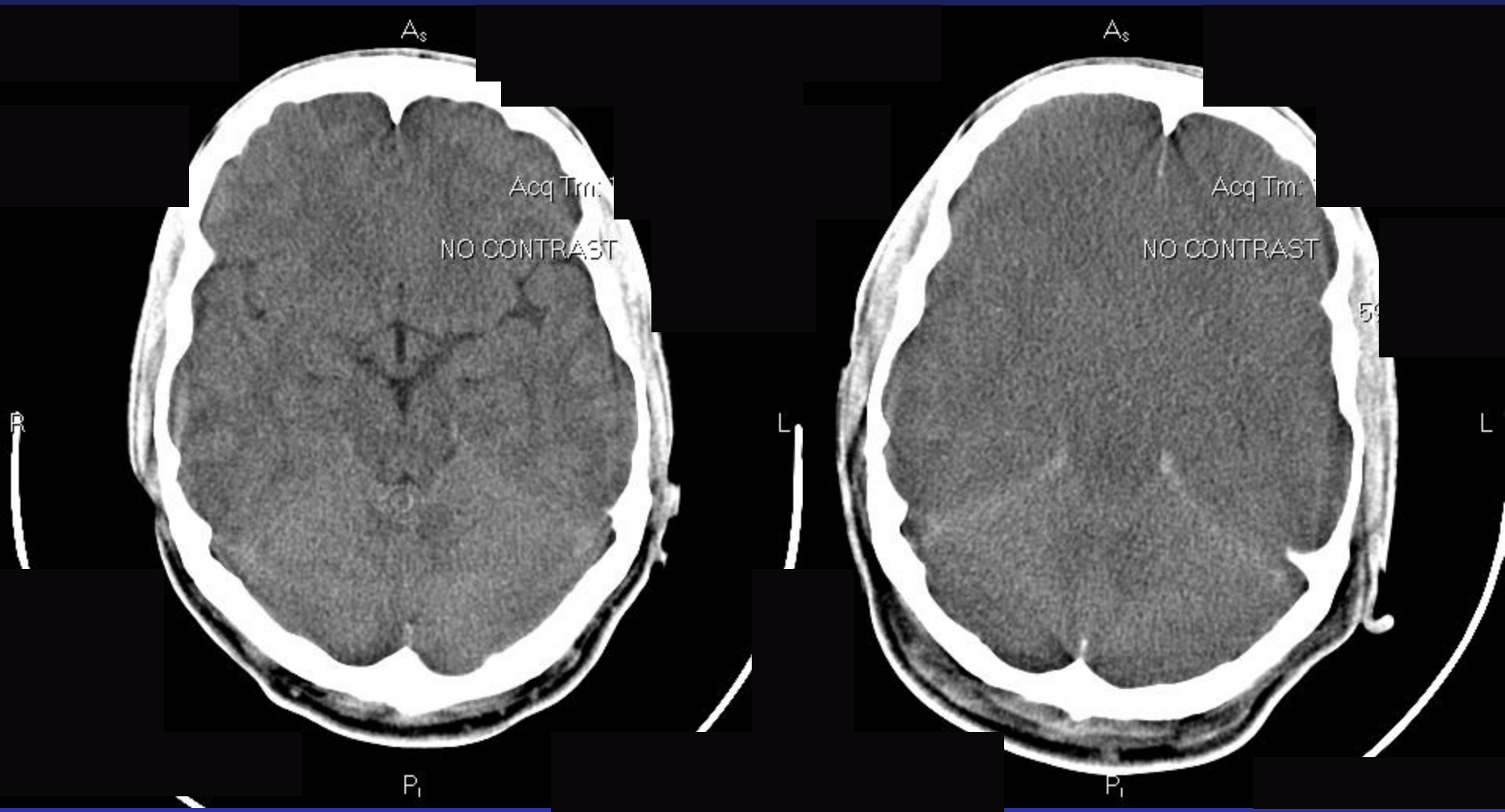
NAC Results by Etiology

	Overall survival		Transplant free survival	
	PLB	NAC	PLB	NAC
DILI N=45	17/26 65%	15/19 79%	7/26 27%	11/19 58%
AIH N=26	10/15 67%	7/11 64%	4/15 27%	1/11 9%
HBV N=37	6/12 50%	19/25 76%	2/12 17%	10/25 40%
Indeterm N=41	18/26 69%	9/15 60%	6/26 23%	6/15 40%

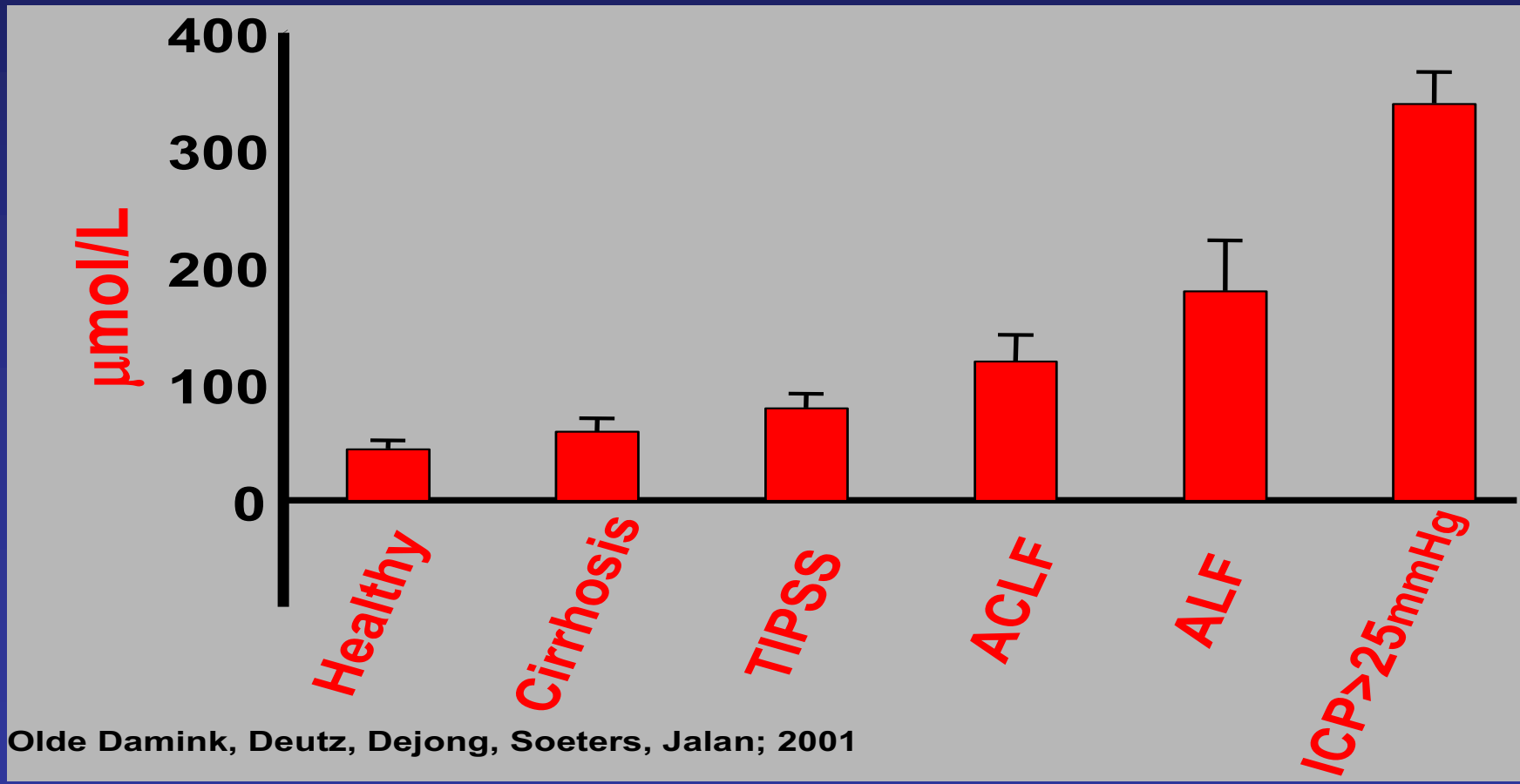
32 year-old male with ALF of indeterminate etiology

Admission head CT

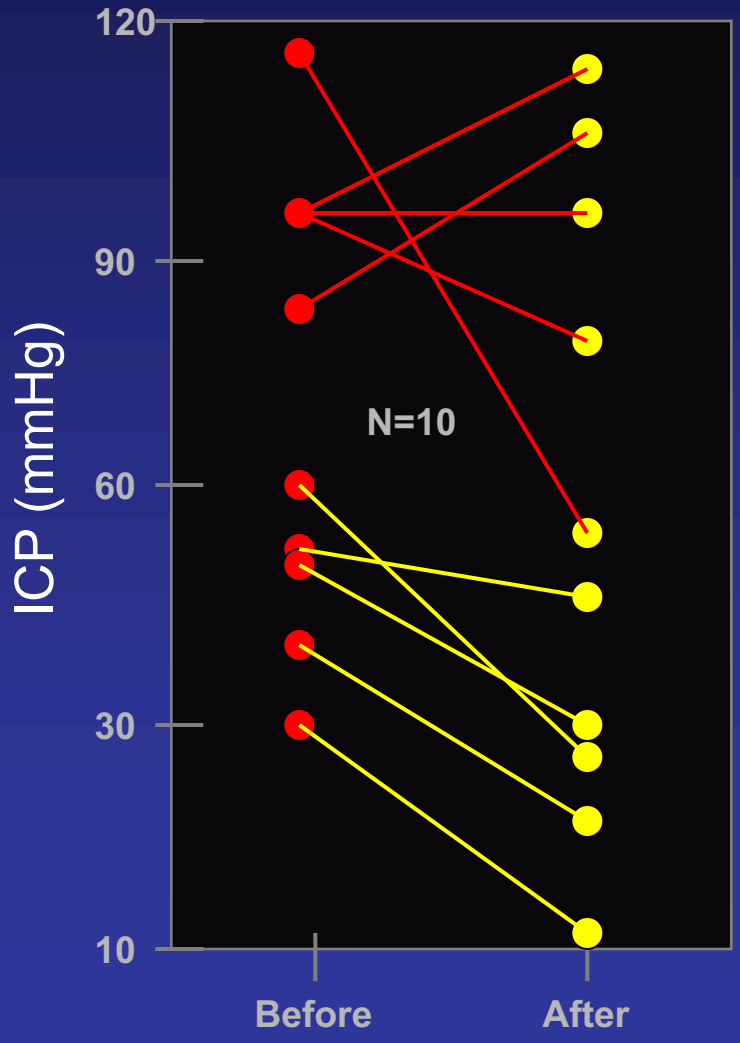
48 h after admission



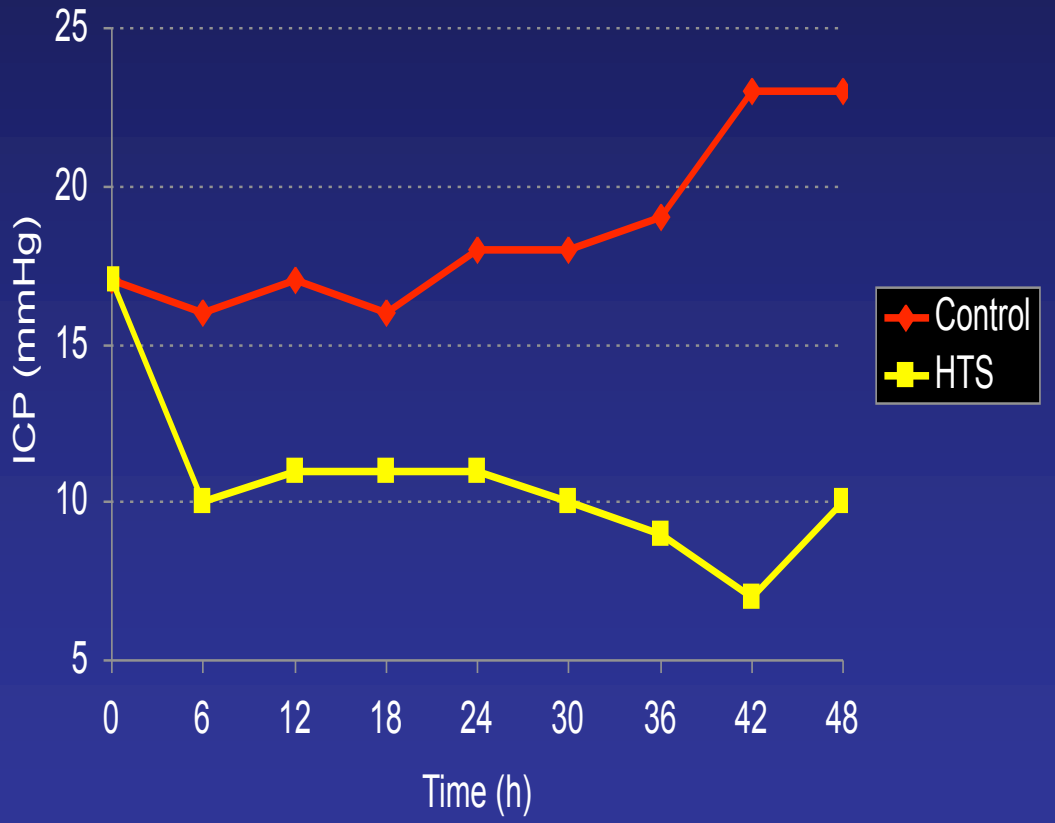
Increased ammonia closely associated with ALF



Effects of Mannitol or Induced Hypernatremia on Intracranial Hypertension in Patients with ALF

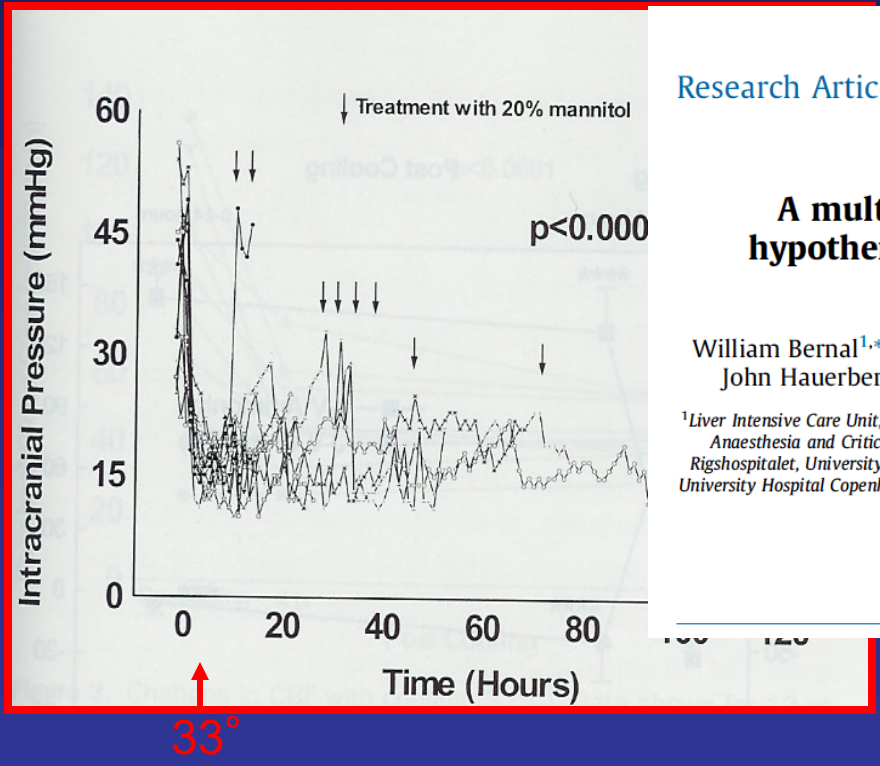


Hanid, et al. Gut 1980;21:866.



Murphy, et al. Hepatology. 2004; 39: 464.

Hypothermia in patients with ALF and intracranial hypertension: Not clinically effective



Jalan, et al. Gastroenterology. 2004; 127:1338.

Research Article

CrossMark

EASL | JOURNAL OF HEPATOLOGY

A multicentre randomized controlled trial of moderate hypothermia to prevent intracranial hypertension in acute liver failure

William Bernal[1,*], Nicholas Murphy[2], Sarah Brown[1], Tony Whitehouse[2], Peter Nissen Bjerring[3], John Hauerberg[4], Hans J. Frederiksen[5], Georg Auzinger[1], Julia Wendon[1], Fin Stolze Larsen[3]

[1]Liver Intensive Care Unit, Institute of Liver Studies, Kings College Hospital, Denmark Hill, London SE5 9RS, United Kingdom; [2]Department of Anaesthesia and Critical Care, University Hospital Birmingham, Birmingham B15 2GW, United Kingdom; [3]Department of Hepatology, Rigshospitalet, University Hospital Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark; [4]Department of Neurosurgery, Rigshospitalet, University Hospital Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark; [5]Department of Anaesthesia, Rigshospitalet, University Hospital Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark

See Editorial, pages 240–242

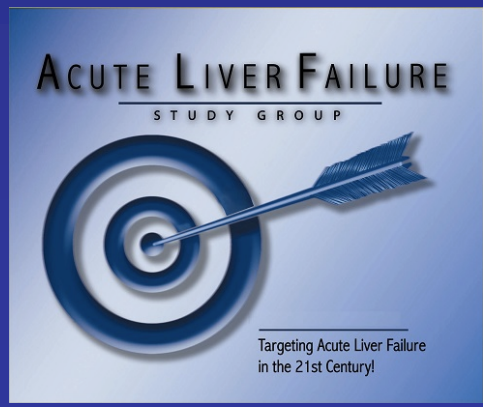
Bernal W, et al J. Hepatol. 2016;65:273-79.

Conclusions: In patients with ALF at high risk of ICH, MH at 33–34 °C did not confer a benefit above management at 36 °C in prevention of ICH or in overall survival. This study did not confirm

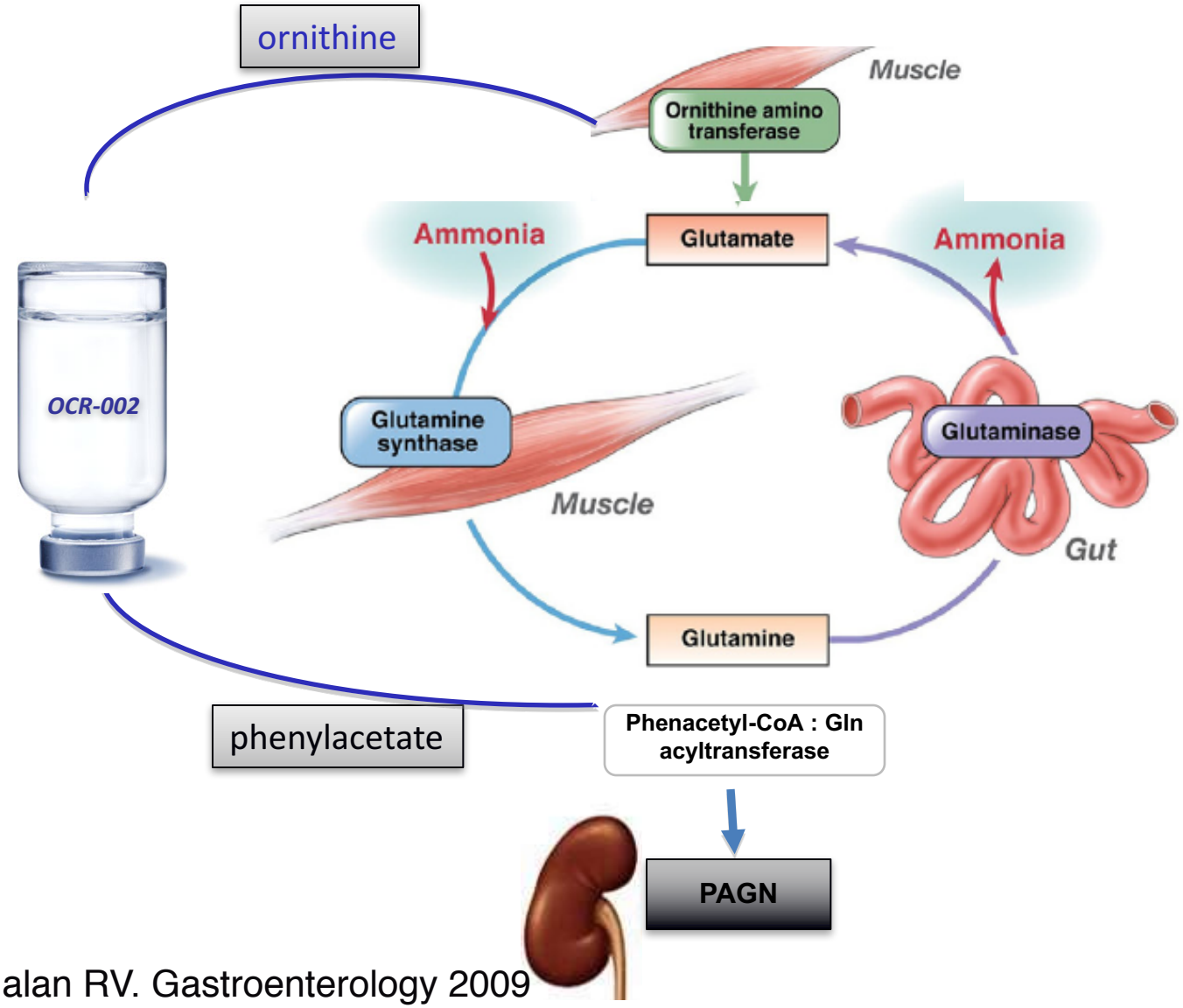
Ornithine Phenyl Acetate (OPA): STOP-ALF Trial

Lower ammonia to manage cerebral edema

- **Ammonia is the putative cause for cerebral edema**
- **OPA traps ammonia and allows renal excretion**
- **Could be used prophylactically or as treatment**
- **IV, few side effects, might work in cirrhosis also**
- **ALFSG is studying the acetaminophen ALF/ALI group since July 2012—to be completed 2016.**



OCR-002 Uses Physiological Pathways to Eliminate Nitrogen

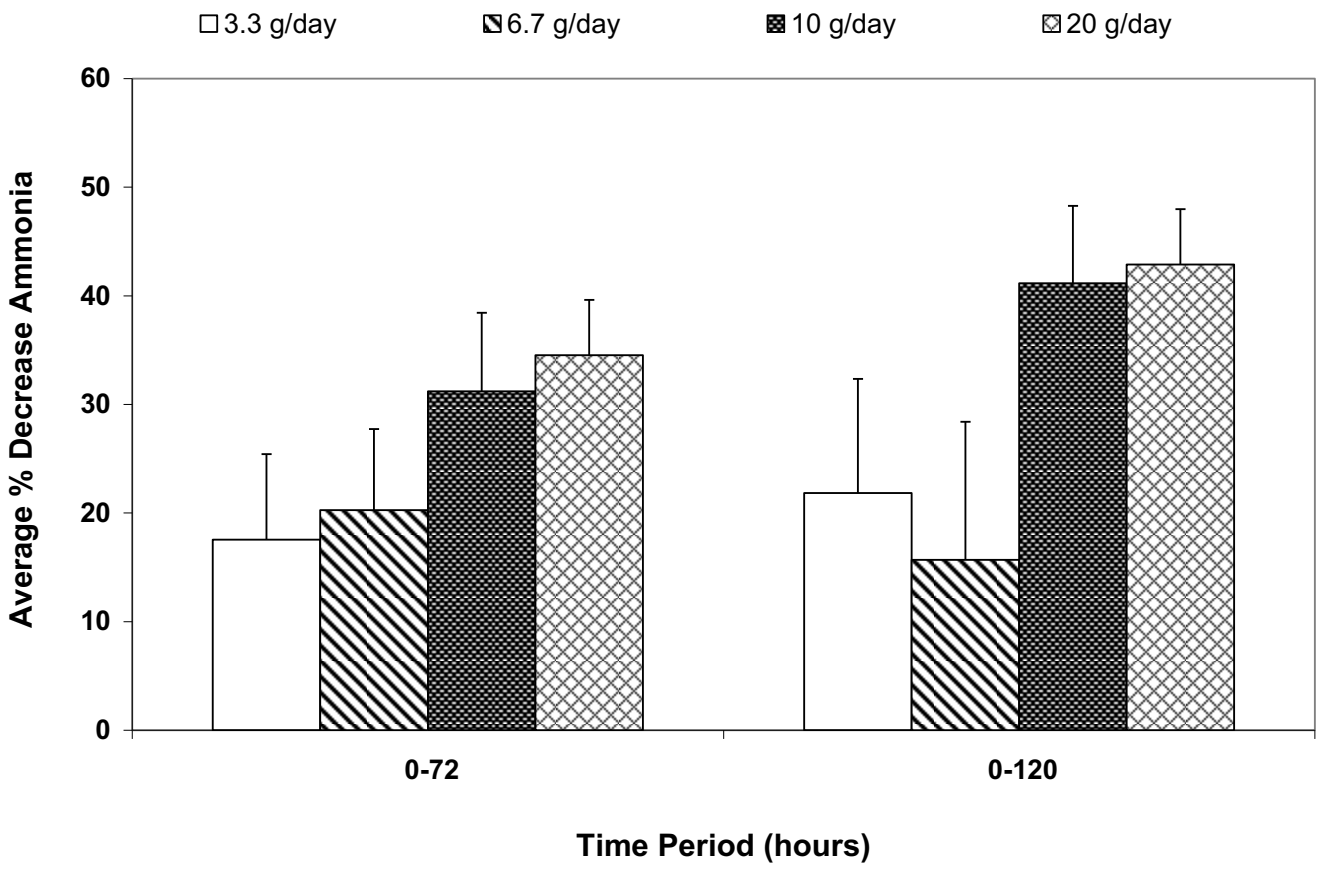


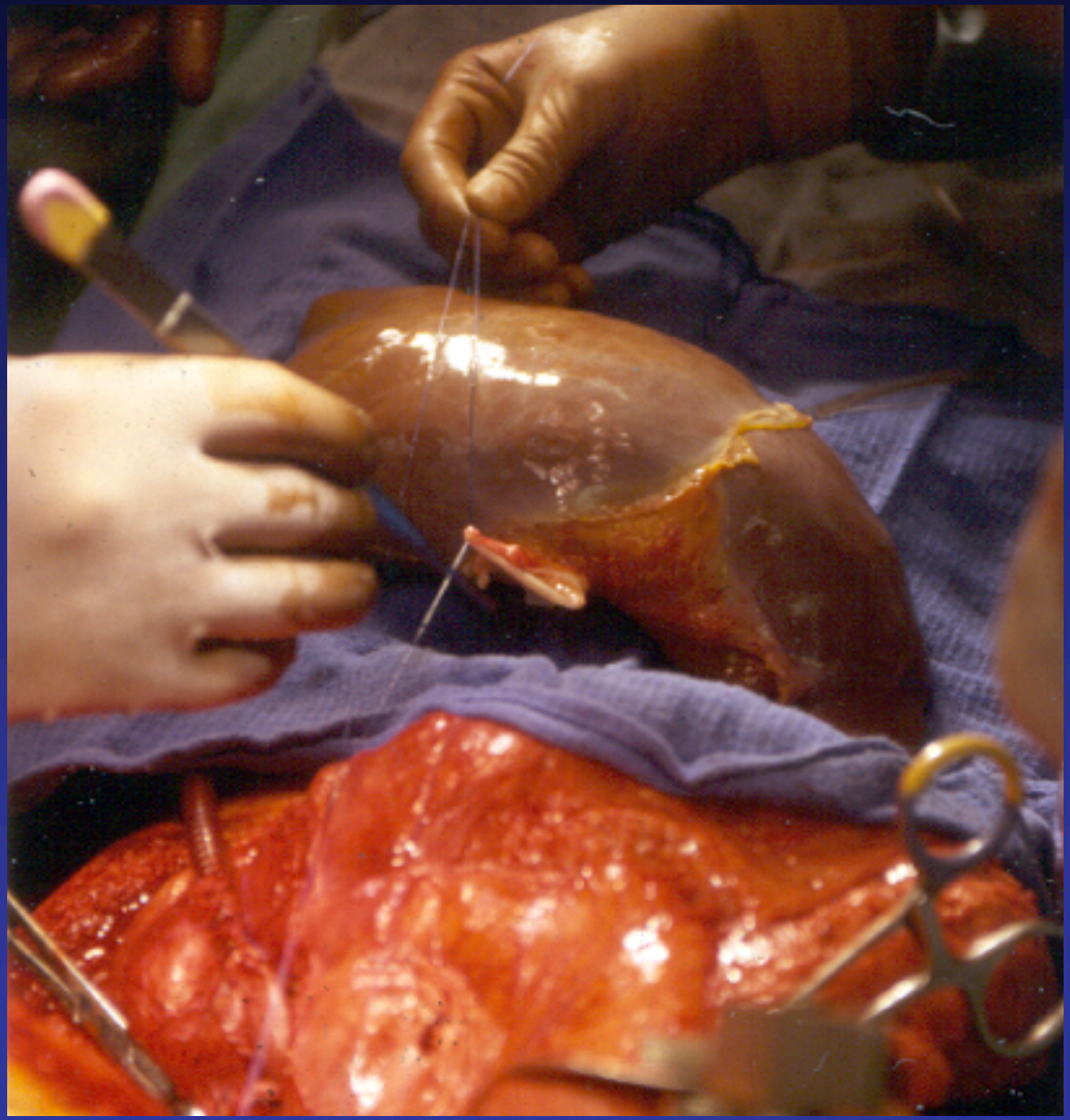
Lee WM, Jalan RV. Gastroenterology 2009

Safety and Tolerability of OPA for ALF
Results of STOP-ALF Phase IIa Trial

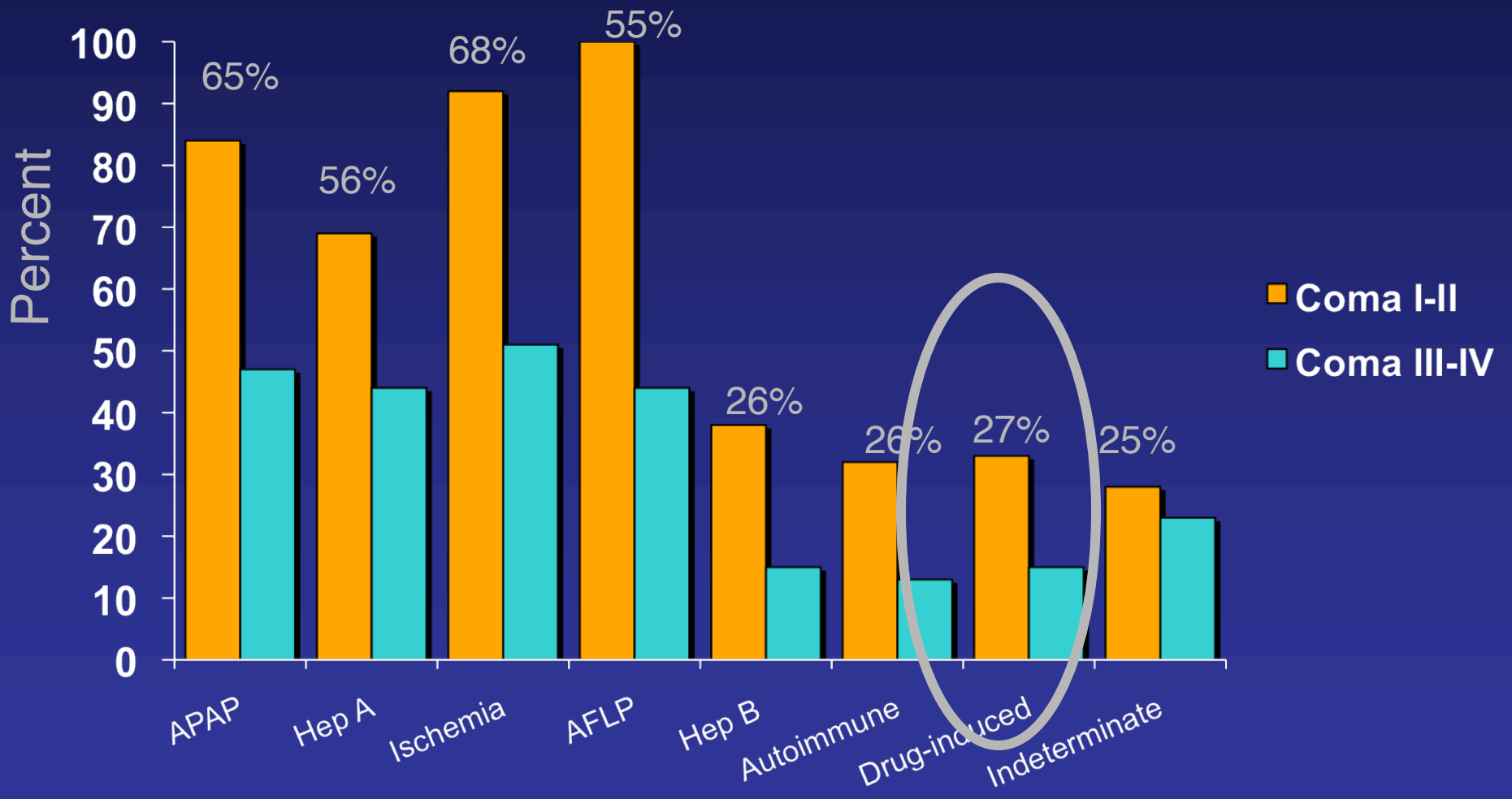
- Study completed 47 patients, no safety signals
- OPA likely under-dosed in the early phase
- Mild nausea/HA only apparent symptoms
- 20 gm/day dose associated with improved NH_3
- Parallel trial has been completed for management of HE in patients with cirrhosis: STOP-HE

Percent Change in NH_3 Over Time





Transplant-free survival by etiology and coma grade



Coma grade I-II patients had ~50% better survival than III-IV

Prognosis in ALF: Etiology is a Main Determinant

Transplant free survival rates differ greatly

Good prognosis:

- APAP 66%
- Ischemia 66%
- Pregnancy 55%
- Hepatitis A 56%

Bad prognosis:

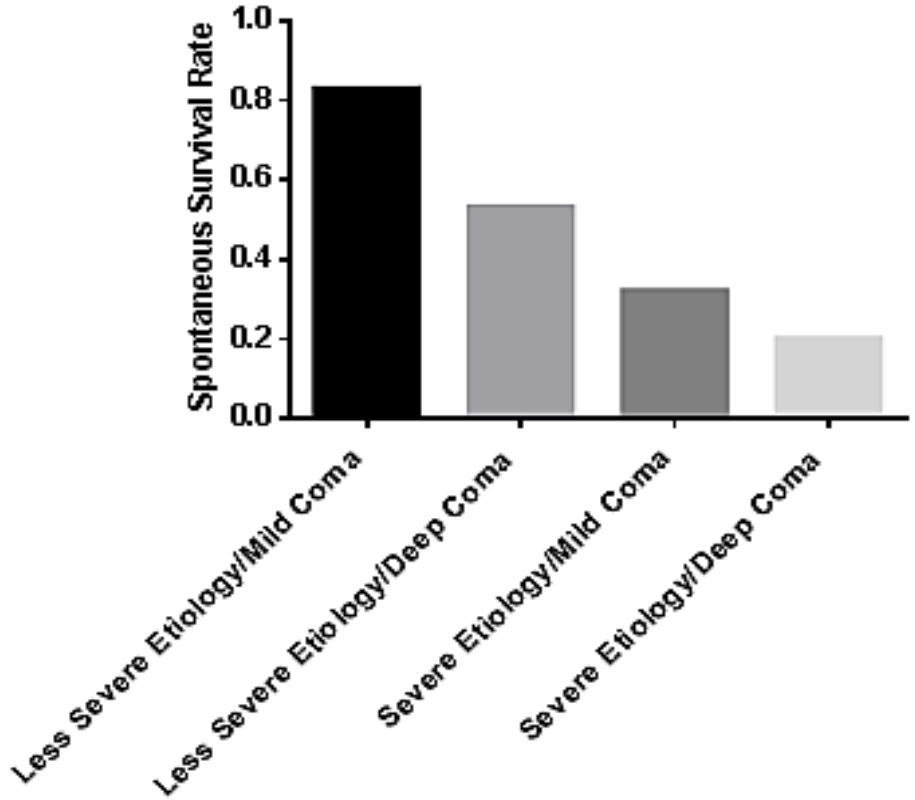
- Drugs 27%
- Indeterminate 25%
- Autoimmune 26%
- Hepatitis B 26%
- Wilson Disease 0%

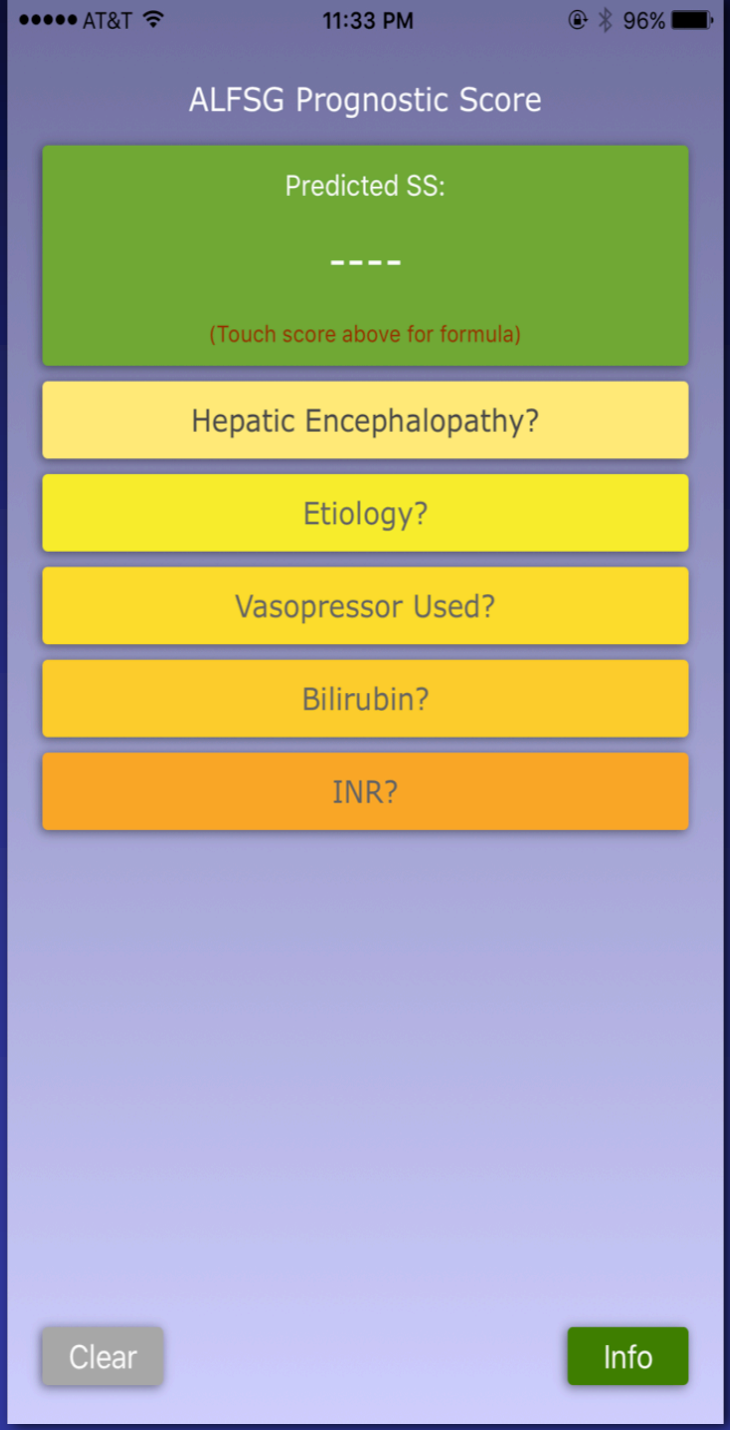
(Age is NOT an important determinant)*

**Schiødt FV, et al., Liver Transplant 2009*

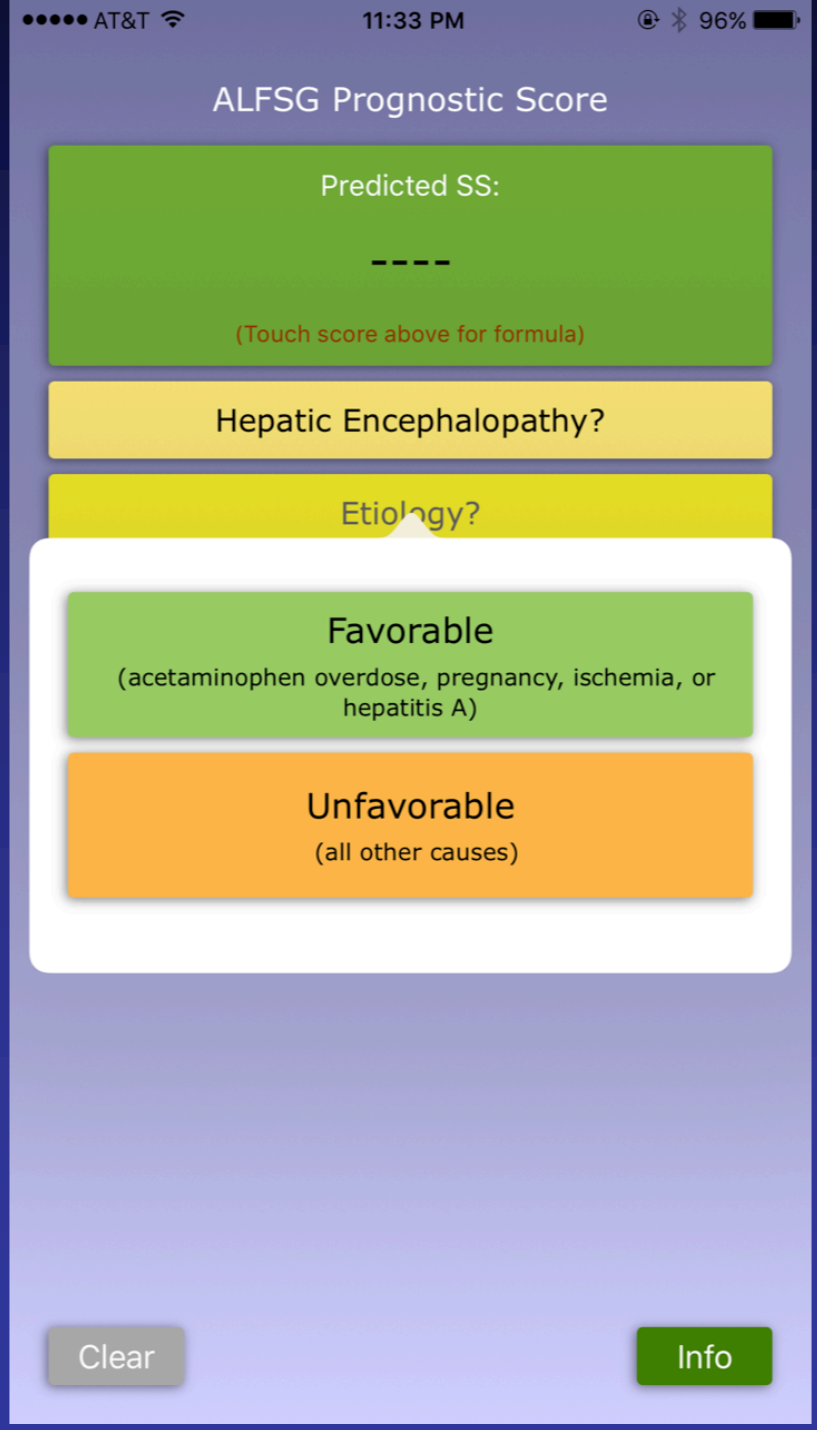
ALFSG Prognostic Score

Significance of Etiology and Coma Grade




AT&T
11:33 PM
96%
ALFSG Prognostic Score
Predicted SS:

(Touch score above for formula)
Hepatic Encephalopathy?
Etiology?
Vasopressor Used?
Bilirubin?
INR?
Clear
Info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11:33 PM
96%
ALFSG Prognostic Score
Predicted SS:

(Touch score above for formula)
Hepatic Encephalopathy?
Etiology?
Favorable
(acetaminophen overdose, pregnancy, ischemia, or hepatitis A)
Unfavorable
(all other causes)
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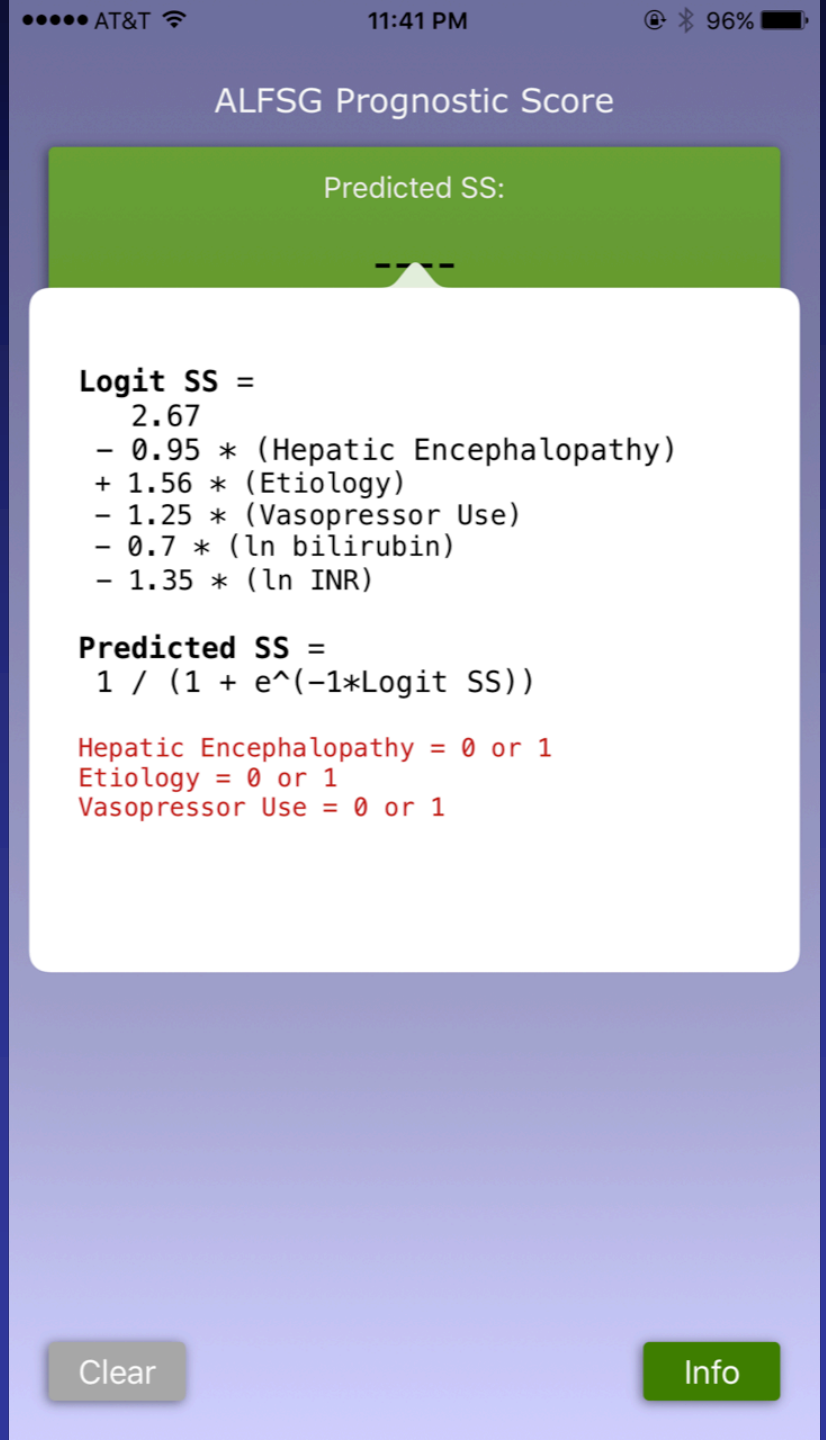
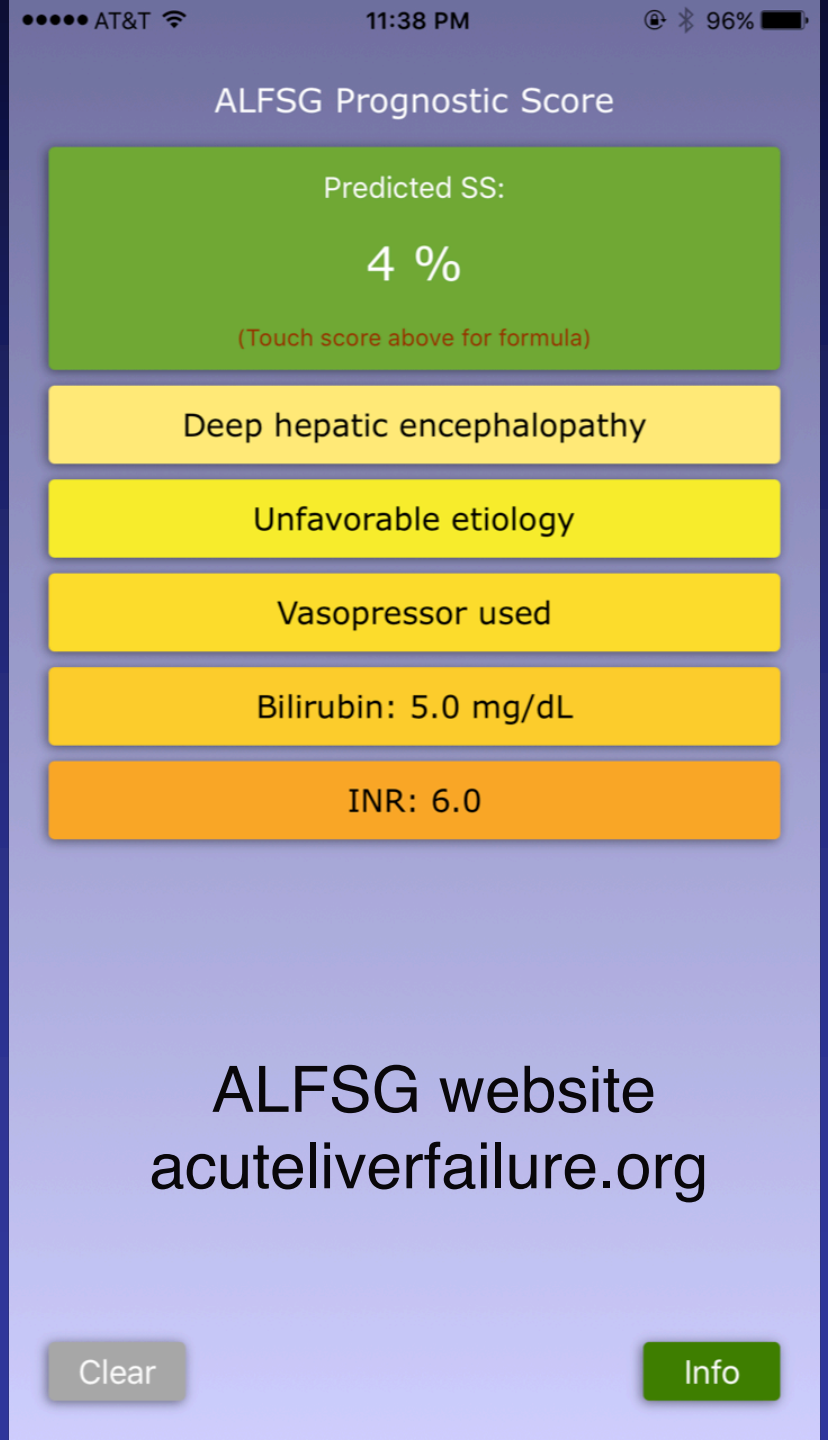




ALFSG website
acuteliverfailure.org

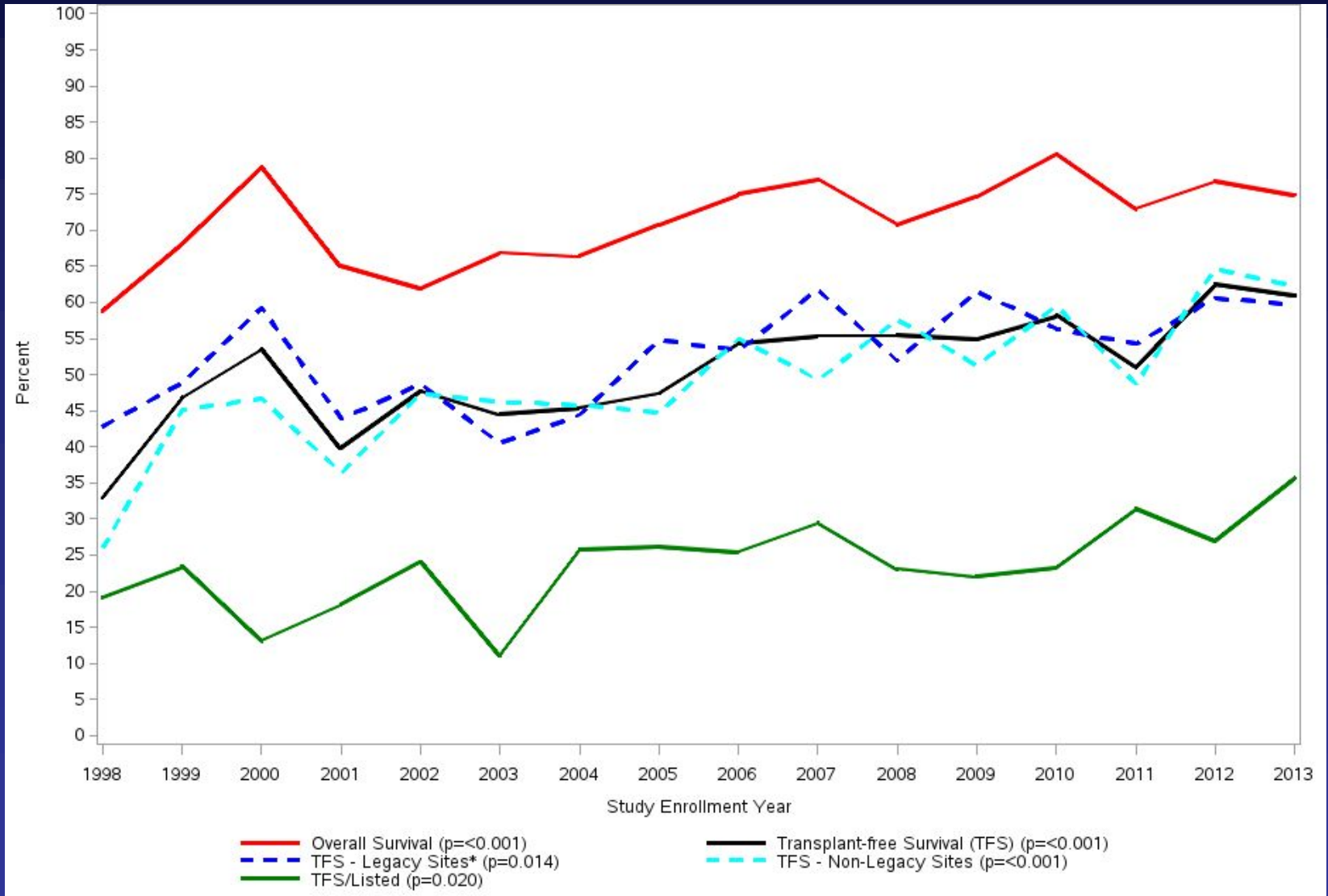
Outcomes in Adults with Acute Liver Failure from 1998-2013: An Observational Cohort Study

Have changes in management/outcomes occurred?

- 2070 patients in 16 yrs, with 21 day outcomes known
- No differences in etiologies or disease severity, referral patterns or time to referral
- Results: decline in:
  - Listing, deaths, transplantation
  - Use of vasopressors, ventilation, blood products
- Overall and transplant-free survival improved.

Reuben A et al: Ann Intern Med April 2016

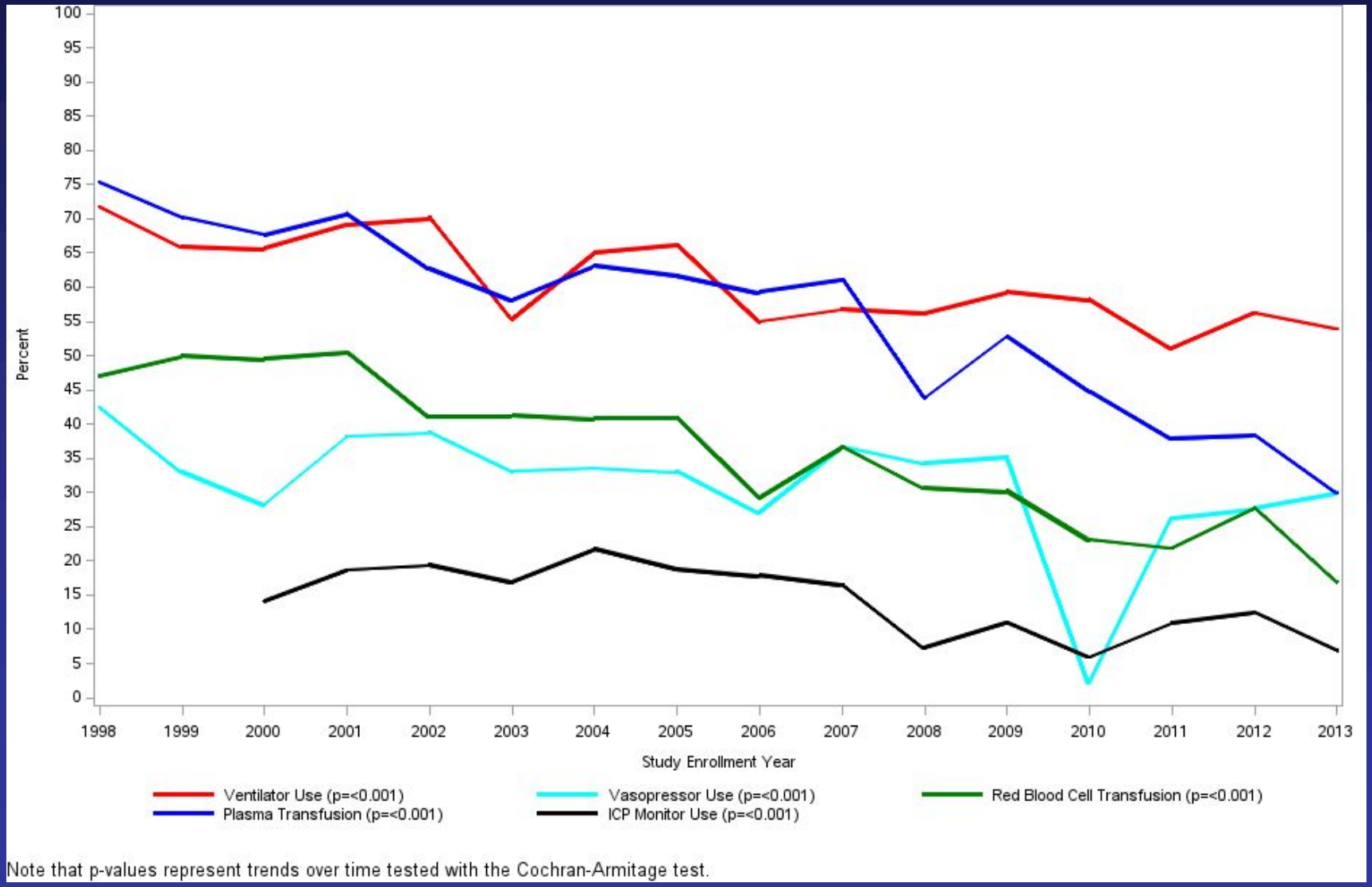
Overall and transplant-free survival over time: 1998-2013



*Legacy sites have enrolled at least one subject in each of the 16 years of the registry. They include: Northwestern University, University of California at San Francisco, University of Michigan, University of Washington, and the University of Texas Southwestern Medical Center.
Note that p-values represent trends over time tested with the Cochran-Armitage test.

Reuben A et al: Ann Intern Med April 2016

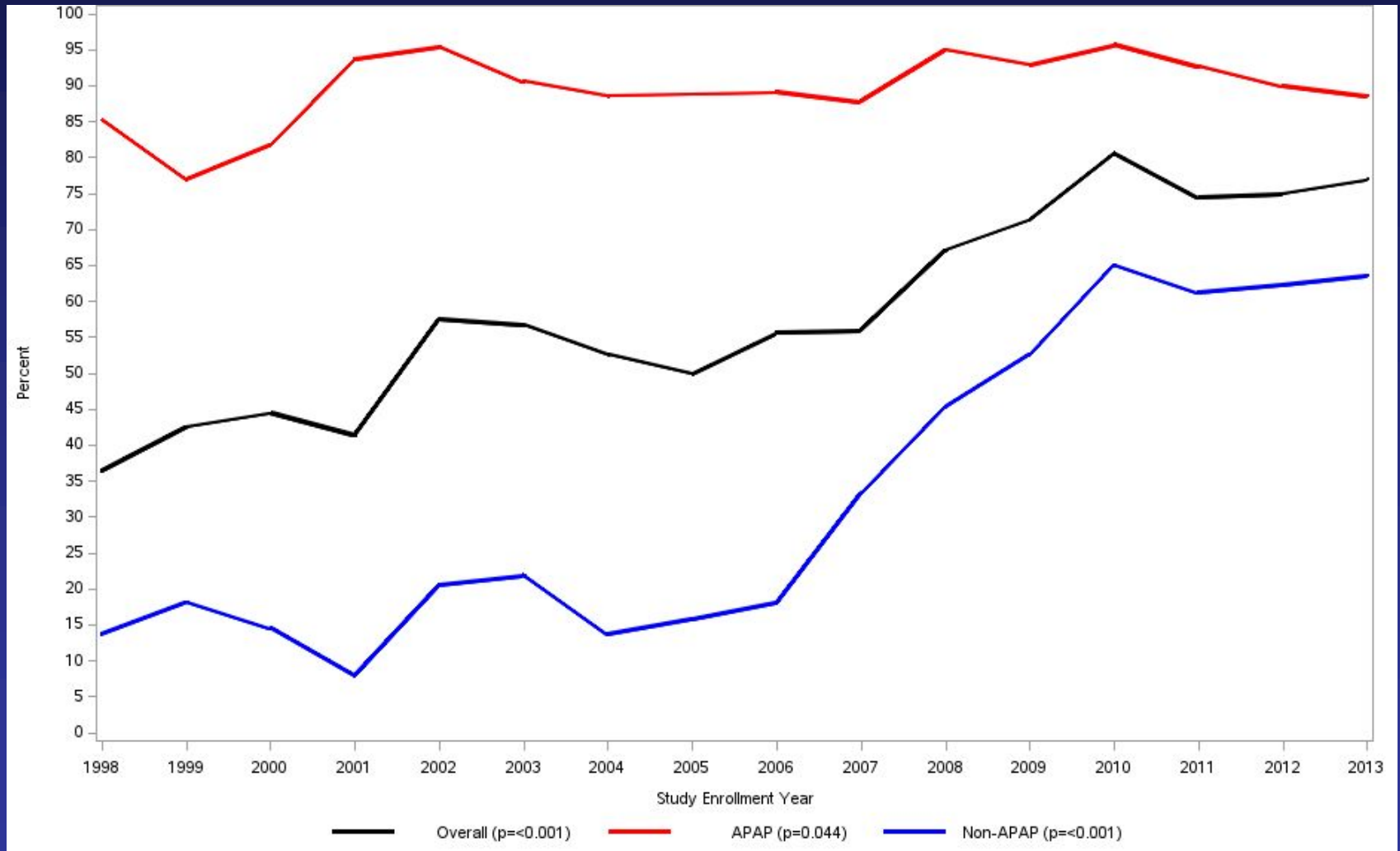
Treatment modalities over time



Note that p-values represent trends over time tested with the Cochran-Armitage test.

Reuben A et al. Ann Intern Med 2016;164:724-732

Use of N-acetylcysteine over 16 years: 1998-2013



Note that p-values represent trends over time tested with the Cochran-Armitage test.

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Acute Liver Failure

OK, you get the call from the ED…

A 22 yo has arrived with abdominal pain and is found to have acute liver injury with an INR of 3.2, ALT >6500 and AST >3700. Initial exam virtually normal. Labs: WBC 14, Hgb 14, plts 75k; Bili 2.2, Ammonia 135, INR 5.2. APAP level is undetectable. Tox screen positive for opioids, cannabis.

What should you do?

Acute Liver Failure

OK, you get the call from the ED…

- She has no encephalopathy. Wants to sign out, seems hyper.
- Admit?
- NAC?
- ICU?
- Etiology?
- Prognosis?
- Other things to rule out?

Acute Liver Failure

OK, you get the call from the ED…

- She has no encephalopathy. Wants to sign out, seems hyper.
- Admit? YES
- NAC? YES
- ICU? YES
- Etiology? APAP
- Prognosis? Consult the App: 81% likelihood of spont survival
- Other things to rule out? Ischemia, HSV

Acute Liver Failure: A 'Super Orphan' Disease

Overall lessons

- Act quickly, acute patients evolve over hours
- Etiology is tied to prognosis and treatment options/antidotes
- Consider transplant option early, safer to travel before Gr 3-4
- Good intensive care with attention to:
  - CNS: Neuro checks, no sedation, watch for deterioration
  - Renal: Consider CRRT early
  - Pulmonary: intubate for Gr III-IV coma
  - Infection: frequent cultures, no empiric antibiotics
  - May need volume but not too much, pressor support
  - Don't correct coagulopathy, little FFP needed

Acute Liver Failure: A 'Super Orphan' Disease

Still very rare but interesting!

- Requires expert specialty care
- Outcomes are tied closely to etiology which has not changed over time; differences in pathogenesis based on etiology
- Outcomes have improved in recent years
- Transplantation still the centerpiece of care, but not for all.
- Treatment trials underway; NAC for all, not FDA approved
- Extremely hard to conduct clinical trials in this space!
- More accurate prognostic tools would help!
- ALF is best studied with a multi-center network.

Adult Study Sites in the ALFSG 2017

• UT Southwestern	Lee/Tujios/Rule/Rowan
• U Washington	Liou/Kim
• UCSF	Hameed/Dobai
• Northwestern University	Ganger/Gottstein
• Michigan	Fontana/
• Univ Alabama Birmingham	McGuire/Williams
• VCU	Stravitz/Taylor
• MUSC Charleston	Koch/Crolley
• Yale University	Schilsky/Stavris
• University of Kansas	Olson/Taylor
• The Ohio State University	Hanje/Nava
• University of Alberta	Karvellas/Baig

UTSW: Admin Center

Angela Bowling
Nahid Attar
Rehana Mohammed
Sycil Mathew
Debra Rowan
Jody Rule, PhD

MUSC: Data Coordinating Center

Valerie Durkalski, PhD
Caitlyn Ellerbe, PhD
Evan Tomaszek
Kristen Clasen
Michelle Gottfried

1. A 23 year old had a fight with her boyfriend and is found two days later confused and somnolent. In the Emergency Department 4 hours later, she is unarousable. Initial laboratory findings include: acetaminophen level 10.3 µg/L, AST 10,300 IU/L, ALT 8,500 IU/L, Alk Phos 145 IU/L, T Bilirubin 3.4 mg/dL. INR 4.8. Next steps should include:

   a. Fresh frozen plasma to correct the INR
   b. **N-acetylcysteine 140 mg/kg/hr intravenous infusion**
   c. I mg Haldol q 4 hr
   d. Frequent EKGs
   e. Seizure precautions

2. Idiosyncratic DILI reaching the point of acute liver failure (choose all that apply):
   a) **Has poor overall outcome without transplantation**
   b) **Outcome in part depends on coma grade on admission**
   c) **NAC may be of some value in these patients**
   d) **May occur with weight loss herbal products**

3. A 22 yr old college student is admitted to hospital with rapid onset of severe jaundice. She was undergoing work up for abnormal liver enzyme elevations, thought to be autoimmune hepatitis, when she deteriorated and was admitted with confusion and somnolence. Her family denies that she took any recent medications including acetaminophen or herbal supplements.

On exam, vital signs stable, deeply icteric, had asterixis and a spleen tip was palpable.

Labs disclosed WBC 4.5, Hgb 7.5, platelets 53,000; Bilirubin 65 mg/dL, Alk phos 23, AST 145/ALT 33. Albumin 2.3, globulin 1.8, ANA negative, ASMA 1:20.

Select the correct diagnosis:

a. Autoimmune hepatitis.
b. Drug-induced liver injury
c. Unintentional acetaminophen toxicity
d. Wilson disease

ACUTE LIVER FAILURE

STUDY GROUP

Targeting Acute Liver Failure
in the 21st Century!

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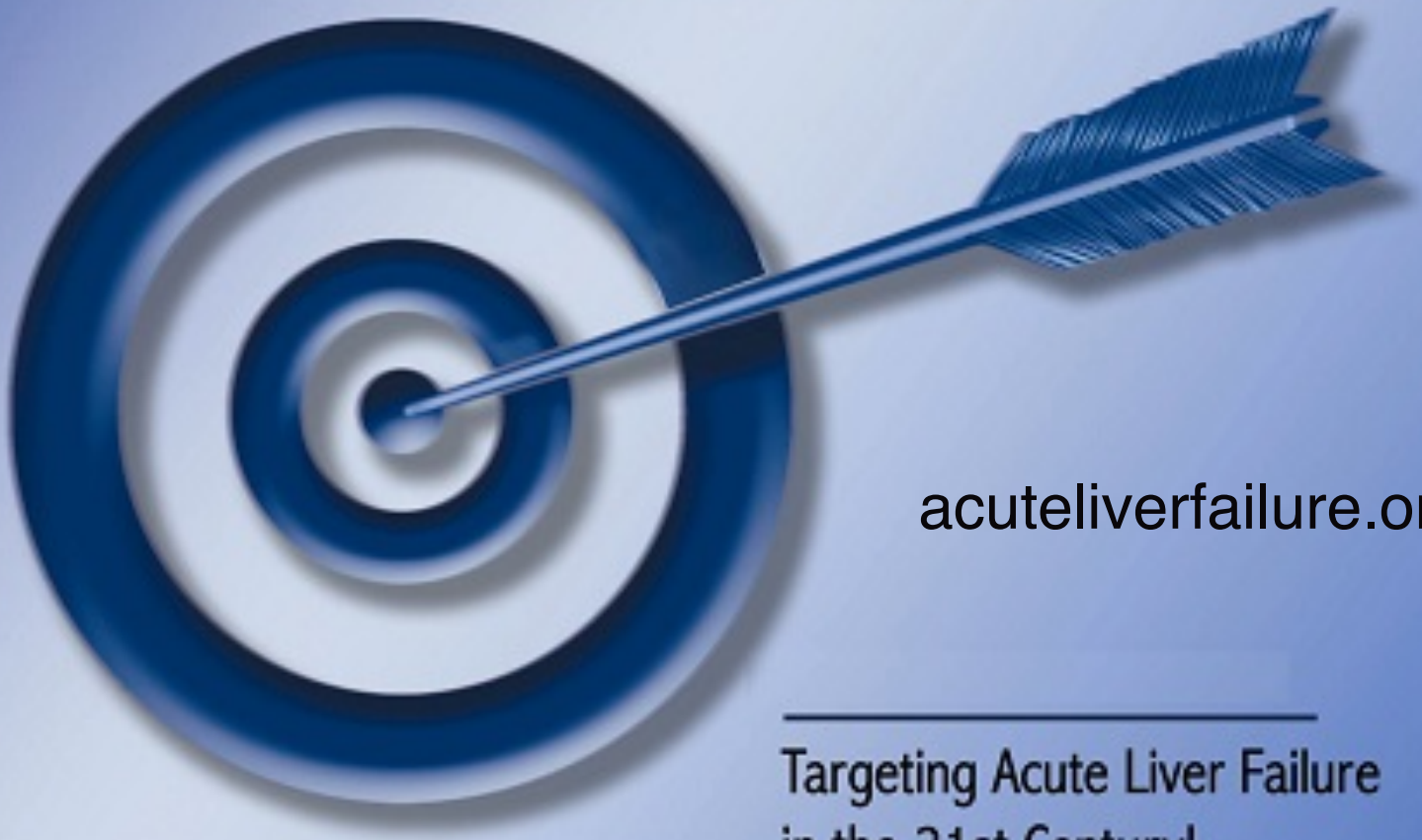

acuteliverfailure.org

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