

Approach to Acute Liver Failure 2011

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ACG Postgraduate Course 10/30/2011

www.acuteliverfailure.org



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Acute Liver Failure: An Orphan Disease

Fulminant Hepatic Failure

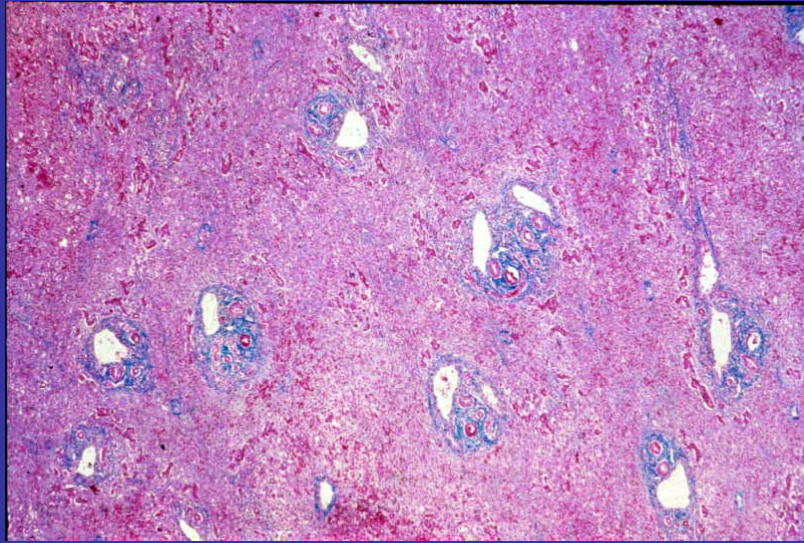
- Most severe form of liver injury but rare, 2000/yr
- Devastating: survival <10% in earlier era
- Definition: INR \geq 1.5, any grade enceph, acute illness
- UNOS Status 1a
- Fascinating
- Frustrating
- Hard to treat
- Difficult to study



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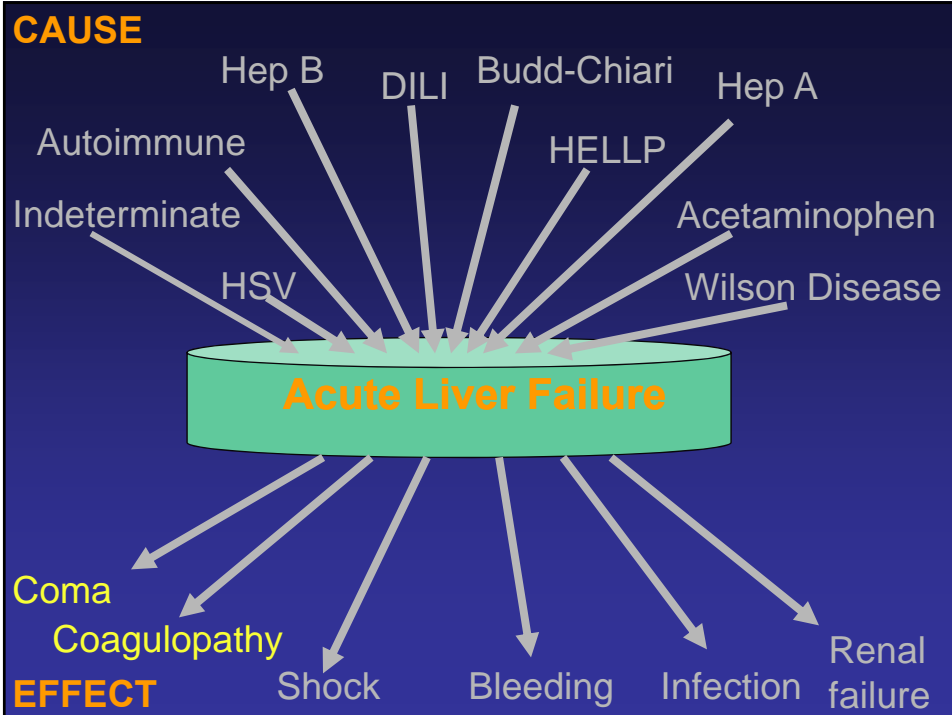
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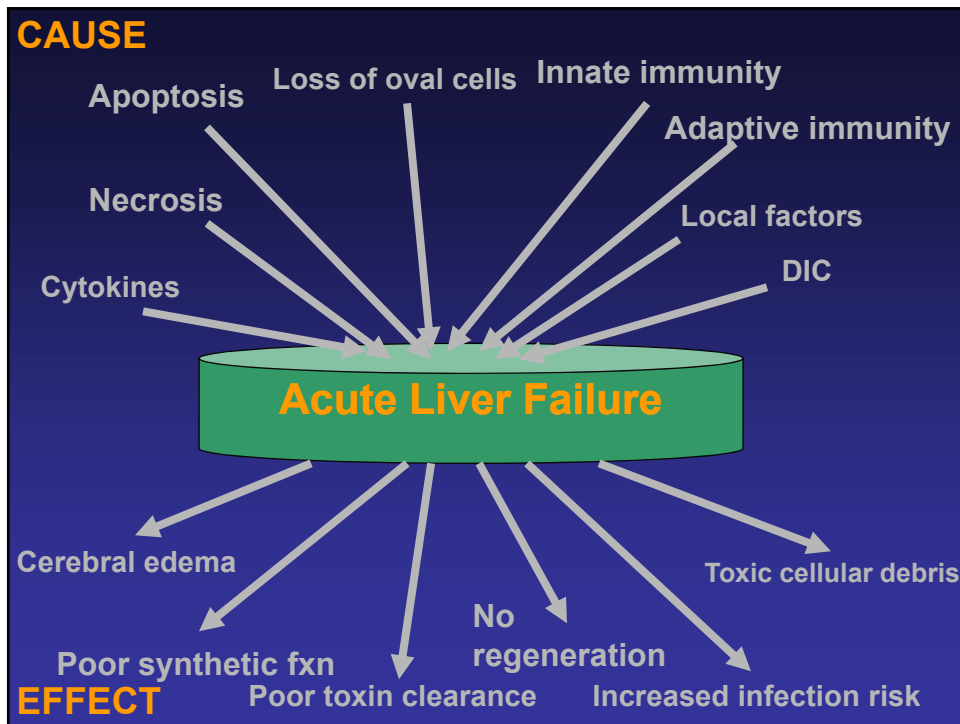
Fulminant hepatic failure due to halothane



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Acute Liver Failure Study Group

Rationale: Network to study a rare disease

- Began in 1998, 13 adult, 15 pediatric sites
- 1,850 cases in adult, ~1,100 in pediatric registry
- New added definition: ALI—INR > 2.0/no enceph
- Three directions:
 - Prospective clinical data, sera, plasma, DNA, tissue
 - Numerous ancillary studies in progress
 - Therapy trials: NAC trial done, others on the way

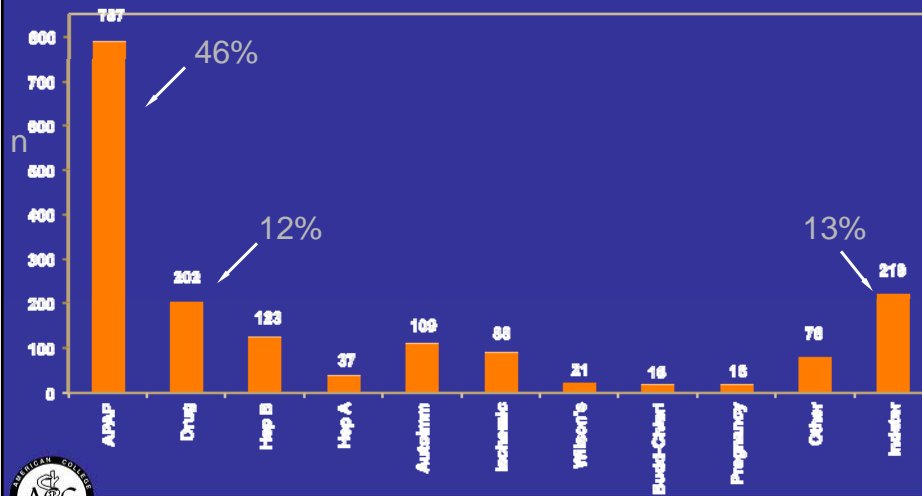


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Funding: NIDDK U-01 through 2015

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Etiology of Acute Liver Failure in the USA Adult Registry (n = 1,696)



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Comparison of Different ALF Etiology Groups

N = 1,696

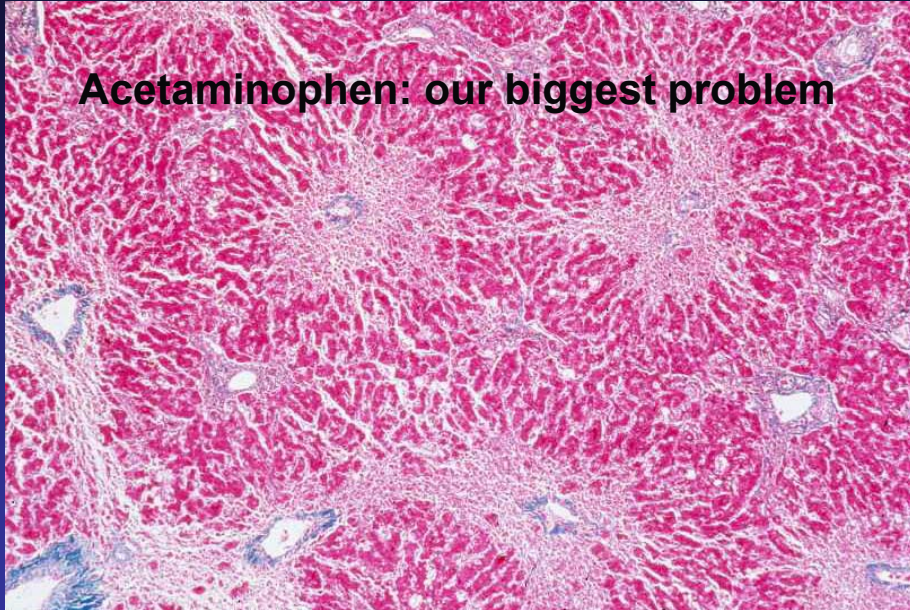
	APAP n=787	Drug n=202	Indeterminate n=219	HepA/HepB n=37/123	All Others N=328
Age (median)	37	47	38	48/43	45
Sex (% F)	76	66	60	46/45	73
Jaundice (Days) (median)	0	8	8	3/5	4
Coma ≥3 (%)	53	37	50	51/55	43
ALT (median)	3846	685	849	2124/1702	677
Bili (median)	4.4	19.8	22.0	12.5/19.1	14.6
Tx (%)	9	40	45	32/41	30
Spontaneous Survival (%)	67	31	27	54/24	38
Overall Survival (%)	75	68	69	84/61	65



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Acetaminophen: our biggest problem



'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
Narcotic cpd (%)	18	63	< 0.001
Multiple preps	5	38	< 0.001
Spont surv (%)	70	65	NS



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Acetaminophen (APAP) adducts assay

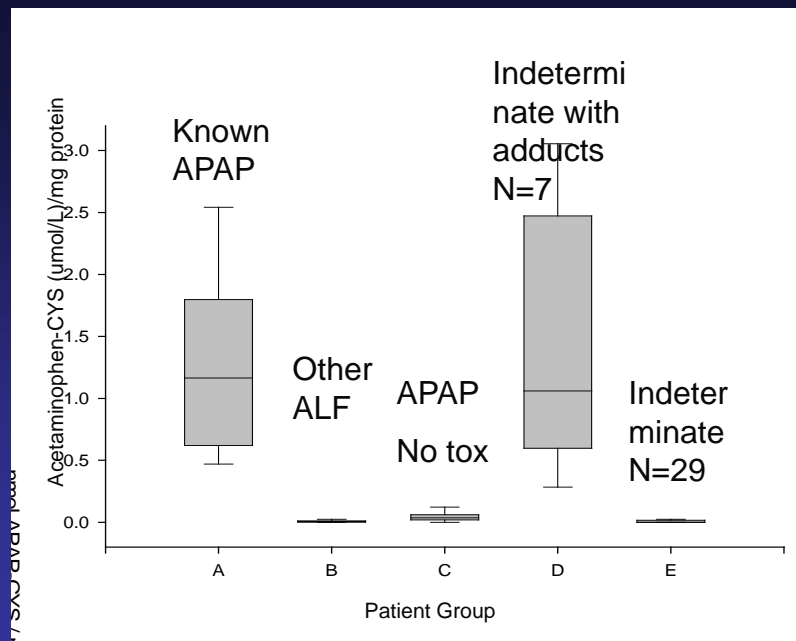
- HPLC-EC detects APAP-cysteine residues (smoking gun)
- Highly sensitive and specific
- Excellent correlation with AST
- Remains positive up to 9 days after ingestion
- Present in 20% of indeterminate cases, peds and adults

Davern TJ, et al. *Gastroenterology* 2006;130:687-94
James LP, et al. *Pediatrics* 2006;118:e676-681.



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Davern TJ, et al. *Gastroenterology* 2006;130:687-94

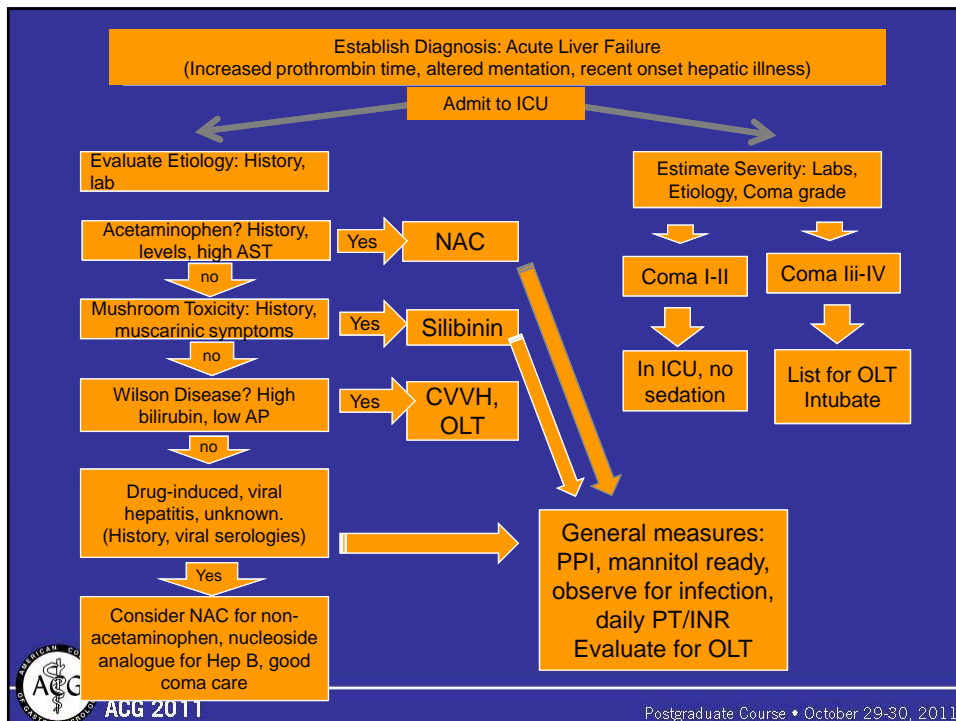
Multi-organ Failure in ALF

- Cerebral edema: 10-30%
- Circulatory abnormality with shock
- Renal dysfunction: 55%
- Coagulopathy: 100% but is it real?
- Infection: 20%
- ARDS: <10%
- Cardiac abnormalities (rare)



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Management of cerebral edema

US ALFSG: Management Strategies in Use

Most use:

- ↑ Head of bed
- quiet room
- brain imaging with CT
- intubation for gr III/IV HE
- mannitol for ICH
- CVVHD if dialysis needed
- careful hemodynamic monitoring (art line, CVP, PA cath)

Many use:

- hyperventilation (ICH)
- antibiotic prophylaxis

*Widely variable use of lactulose

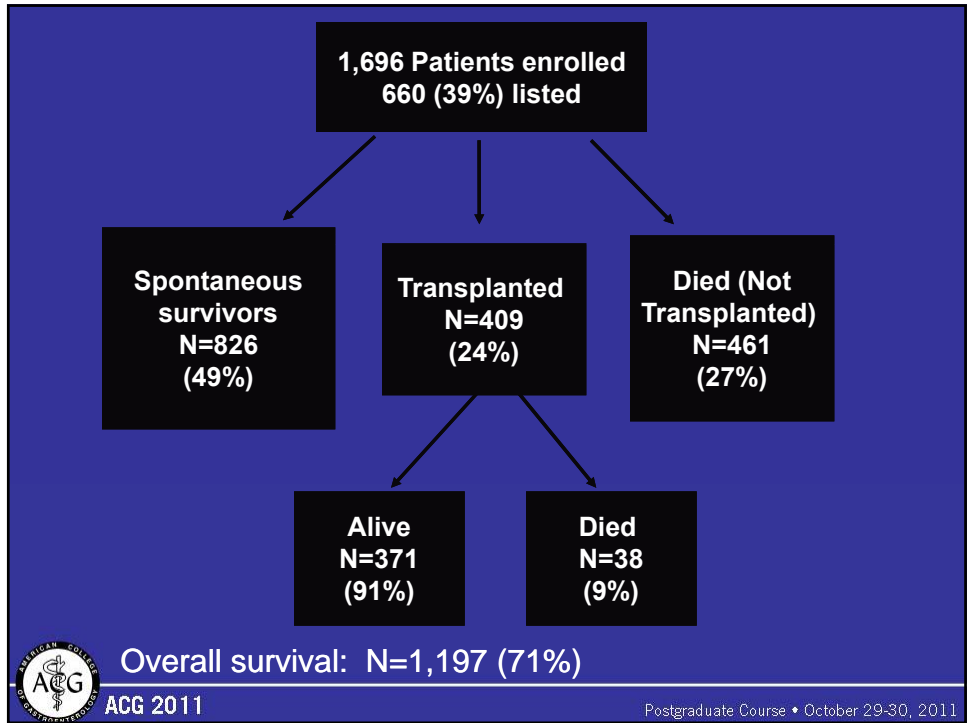
- ? Hypothermia?
- ? Seizure prophylaxis?
- ? Continuous EEG?
- ? Hypertonic saline

➤ Approx 1/2 centers using ICP monitoring



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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%

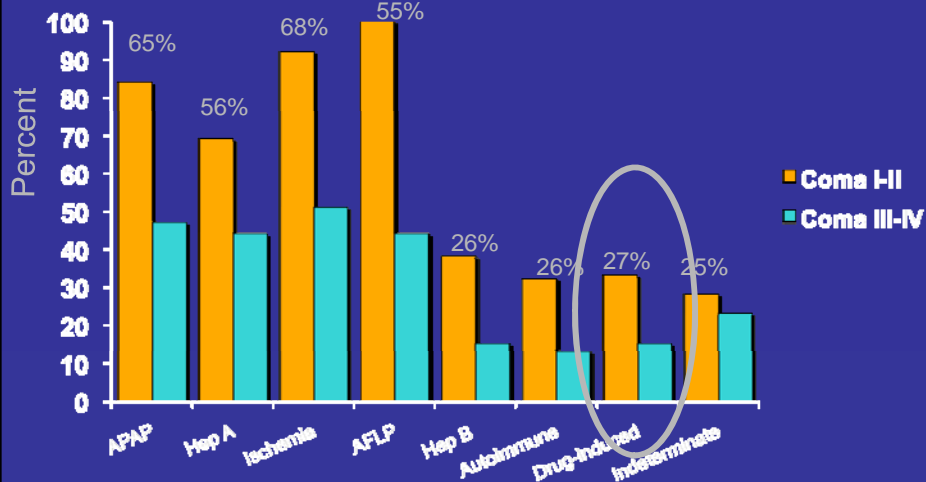
Bad prognosis:

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

(Age is NOT an important determinant)*

*Schldt FV, et al. Liver Transplant 2009

Transplant-free survival by etiology and coma grade



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



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Therapies for the overall condition ALF

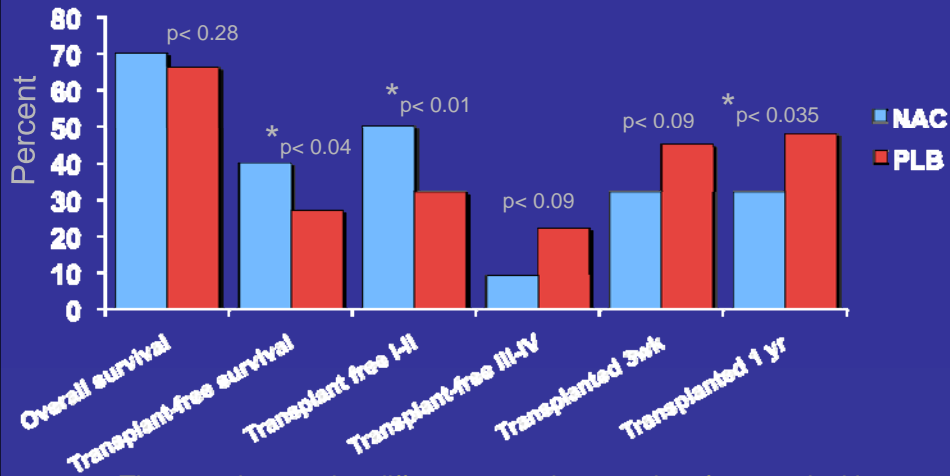
Therapy	Rationale	Result
Total body washout	Detoxify	No help; harmful
Heparin	DIC	No help; harmful
Steroids	Inflammation	No help
Prostaglandins	Cytoprotection	No help
Activated charcoal	Clear toxins	No help
Plasmapheresis	Clear toxins	Possible
Cell systems	Replace liver	May improve coma
Cell transplants	Replace liver	Not enough data
NAC	GSH donor	Positive trial



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Primary/secondary outcomes in the NAC trial



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



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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%



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Ornithine Phenyl Acetate: 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 will study in APAP patient group beginning in 12/11



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Determine quickly the diagnosis/etiology/severity

- Acetaminophen most common etiology, good prognosis, hyperacute features: 2/3 will survive
- DILI, Hep B, Autoimmune, Indeterminate poor prognosis, slower evolution: 1 in 4 will survive
- NAC appears effective for non-acetaminophen with early coma grade
- Prognosis depends on coma grade and etiology
- When in doubt, assume the worst



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“Dos and Don’ts—if you don’t have to”

- **Do: Quiet room, head up 30°, monitor closely for CNS change, replete volume, consider intubation at coma grade 2-3**
- **Don’t:**
 - Sedate unless agitated
 - Give FFP unless bleeding
 - Give antibiotics without cause
 - Give lactulose if planning OLT



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Summary/Conclusions

- **Evaluate quickly, take these cases seriously**
- **Refer to a transplant center if likelihood of OLT**
 - Subacute etiologies, advanced coma grades
- **Good coma care**
 - Attention to volume, replace glucose, phosphate, vigilance for infection, bleeding, consider CVVH
 - Give specific antidotes: err on side of giving NAC



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Study Sites (Adult) in the ALFSG 2009

- UT Southwestern
 - U Washington
 - UCSF
 - Mt. Sinai NYC
 - Univ Nebraska Omaha
 - Baylor Dallas
 - Univ Pittsburgh
 - Northwestern Univ
 - OHSU, Portland
 - UCLA
 - Michigan
 - Univ Alabama Birmingham
 - Mass General
 - Columbia/Cornell NYC
 - VCU
 - Mayo Clinic: Rochester, Jax
 - UC Davis
 - Einstein Philadelphia
 - MUSC Charleston
 - Pennsylvania
 - Yale University
- Lee/Larson/Sanders
 - Liou
 - Fix
 - Liu/Zuniga
 - McCashland/Teten
 - Murray/Coultrup
 - Shakil/Gooch
 - Ganger/Gottstein
 - Zaman/Ingram/Wilson
 - McClune/Peacock/Melgoza
 - Fontana/Welch
 - McGuire/Hogue
 - Chung/Rutherford/Lundmark/Gustafson
 - Brown/Odeh-Ramadan
 - Stravitz/White/Topaz
 - Hay, Raj, Kramer: Groettum/Kontras
 - Rossaro/Dhaliwal
 - Munoz/Riera/Carmody
 - Reuben/Minshall
 - Reddy/Wirjosemito
 - Schilsky/Emre/Engle/Snyder



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ACUTE LIVER FAILURE

STUDY GROUP



www3.utsouthwestern.edu/liver

Targeting Acute Liver Failure
in the 21st Century!