Acute Hepatitis

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Acute Hepatitis Overview

- **Viral hepatitis – Hepatitis A-E and EBV**
- **DILI – Acetaminophen, Augmentin and more!**
- **Alcohol and Biliary stones**
- **Ischemia**
- **Autoimmune hepatitis**
- **Remaining causes**

Acute hepatitis vs. ALF

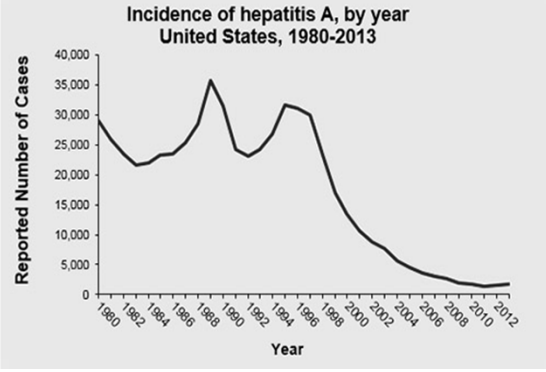
- **Management is very different**

	Acute hepatitis	ALF
AST and/or ALT > 400	Yes	Yes
INR	< 1.5	≥ 1.5
Any Encephalopathy	No	Yes
Pre-existing liver disease	Possibly	No

HAV

- **Most common form of acute viral hepatitis worldwide**
- **Fecal-oral transmission, contaminated food/water**

- **Typically self-limited, no chronic form**
- **May have prolonged or relapsing course**
- **Incubation 2-4 wks, rarely up to 6 wks**



www.cdc.gov

HBV

- 350-400 million people worldwide have chronic HBV; 75% in Asia and western Pacific
- 1.25 million Hep B carriers in US – HBsAg positive > 6 months
  - 15-40% will develop serious sequelae
  - Increased risk of cirrhosis and hepatocellular carcinoma (HCC)
- Chronic HBV causes 1 million deaths worldwide – chief cause of cirrhosis and HCC

Wells, J and Perrillo R. Hepatitis B. Gastrointestinal and Liver Disease. 2016 Vol 2, 10th Edition. 1309-1321

HBV

- 100 x more virulent that HIV, 10 x more virulent than HCV
- Most infections worldwide – transmission from mother to neonate
  - 60-90% of HBsAg and HBeAg positive mothers transmit infection to offspring
  - 15-20% transmission among mothers with anti-Hbe (envelope protein)
- CDC reported cases – 40% intimate contact among heterosexuals, 15-20% IV drug use, 12% MSM

Wells, J and Perrillo R. Hepatitis B. Gastrointestinal and Liver Disease. 2016 Vol 2, 10th Edition. 1309-1321

HBV

- **Horizontal spread among children in high-prevalence areas**
- **Risk of chronic HBV**
  - **90% in newborns of HBeAg positive mothers**
  - **25-30% in infants and children under 5**
  - **Less than 5% in adult**
- **Age at time of infection is main determinant of clinical outcome**
- **Progressive liver disease seen in 1/4-1/3 of pts with chronic HBV**

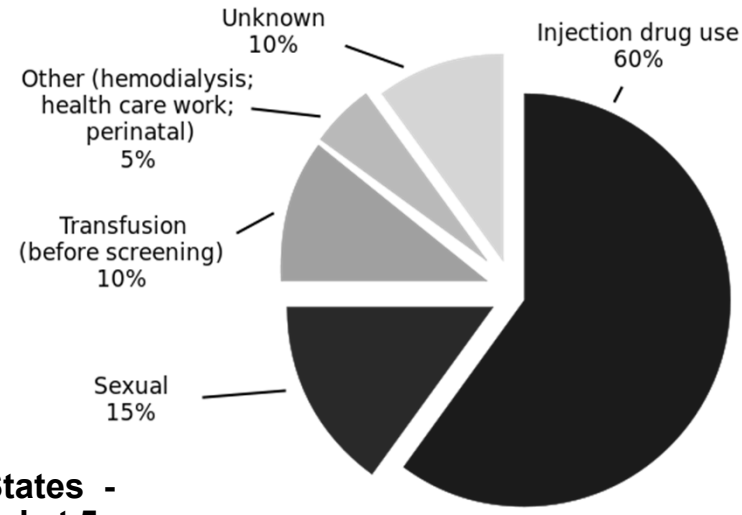
Wells, J and Perrillo R. Hepatitis B. Gastrointestinal and Liver Disease. 2016 Vol 2, 10th Edition. 1309-1321

HBV labs: Antigen = Disease

	Surface Antigen	Surface Antibody	Core Ab	DNA
Acute	Pos or neg	Neg	Pos or Neg	Pos
Chronic	Pos	Neg	Pos	Pos
Exposed only	Neg	Neg	Pos	Neg
Exposed + immune	Neg	Pos	Pos	Neg
Immunized	Neg	Pos	Neg	Neg

Wells, J and Perrillo R. Hepatitis B. Gastrointestinal and Liver Disease. 2016 Vol 2, 10th Edition. 1309-1321

HCV



- **United States - Estimated at 5 million people**

Sources of Infection for Persons with Hepatitis C (CDC) US.png

HCV

- Slow progression ≥ 30 years with female gender, early age of infection

Normal Liver ⇨ **Acute infection** ➡ **Chronic infection develops in ~ 80%** ➡ **Chronic hepatitis** ➡ **Cirrhosis develops in 20%** ➡ **HCC risk 3-5% yearly**

- Fast progression ≤ 20 years with alcohol use, coinfection

Wedemeyer, H. Hepatitis C. Gastrointestinal and Liver Disease. 2016 Vol 2, 10th Edition. 1309-1321

HCV testing

- One-time HCV testing is recommended for persons born between 1945 and 1965
- Positive HCV Ab should be confirmed by HCV quant RNA test
- Those with anti-HCV test and negative results for HCV RNA PCR do not have current HCV infection. Class I, Level A

AASLD-IDSA. Recommendations for testing, managing, and treating HCV. http://www.hcvguidelines.org. Accessed 9/6/2016.

HCV

- Treat all patients with chronic HCV except those with short life expectancies that cannot be remediated by treating HCV, transplantation or other directed therapy. Class I, Level A
- Acute HCV – may clear spontaneously
- Chronic hepatitis develops in 50-90% of patients with acute HCV infection

AASLD-IDSA. Recommendations for testing, managing, and treating HCV. http://www.hcvguidelines.org. Accessed 9/6/2016.

HDV and HEV

- **HDV – coinfection with hepatitis B**
- **HEV – Acute HEV: similar to acute HAV or HBV, most asymptomatic**
  - **Pregnancy (2nd/3rd trimester) → ALF with mortality 5-25%**
  - **Increased rates of infection in pregnancy ~ 9-19%**
  - **Week 1: malaise, fever, chills, abdominal pain, anorexia, aversion to smoking, vomiting, diarrhea, arthralgias, transient macular rash**
  - **Weeks 2-4: jaundice, pruritus, dark urine/clay colored stools**
  - **Weeks 4-8: spontaneous resolution**

Behrendt et al, 2014 J of Hepatology

EBV

- **Infants / Children typically asymptomatic or mild disease**
- **Adolescents / Adults: Pharyngitis, fever, lymphadenopathy**
  - **EBV hepatitis more severe in adults > 30 years**
  - **Splenomegaly is common**
- **Liver involvement is nearly universal:**
  - ✓ **90% have AST/ ALT / LDH elevations 2-3x ULN.**
    - **Rise over 1-2 wks, peak < 5x ULN (lower than acute HAV, HBV or HEV)**
    - **45% with high alk phos and mildly elevated bilirubin, LFTs typically normal in 1 month**

EBV Diagnosis

- Monospot positive after ~10 days after infection
  - Anti-EBV IgM peaks early, persists for months
  - EBV serum PCR
- Treatment is supportive: No benefit from Acyclovir; Ganciclovir not well studied

DILI

- Most common reason for post-marketing drug withdrawals
- 10% overall mortality for patients hospitalized with DILI, varies greatly
- Accounts for > 50% of ALF cases in U.S.
- Only serious events require report to FDA, but less than 10% of adverse reactions reported by physicians and pharmacists to MedWatch

http://www.livertox.nih.gov/

DILI

- Necrosis – Acetaminophen, isoniazid
- Cholestasis - Augmentin (clavulanic acid), anabolic steroids, sulfonamides, anti-fungals, warfarin, ibuprofen, rarely OCPs
- Steatosis – Methotrexate, amiodarone
- Mixed – Tamoxifen, nitrofurantoin, tetracycline, phenytoin

Biliary stones (Choledocholithiasis)

- Risk assessment per 2010 ASGE Guideline —

Very strong predictors
- Common bile duct (CBD) stone on abdominal ultrasound
- Clinical acute cholangitis
- Serum bilirubin > 4

Strong predictors – CBD > 6 mm on US in patient with a gallbladder in situ
- Serum bilirubin 1.8 - 4

Alcoholic hepatitis

- Occurs after decades of alcohol abuse, typical age 40-60, female gender is independent risk factor
- Cardinal sign – rapid onset of jaundice
- Other common signs - fever, ascites and proximal muscle loss, hepatomegaly, RUQ pain, encephalopathy
- AST > twice ULN, but rarely over 300, AST / ALT > 2; elevated WBC and INR, total bili > 5

Lucey MR. *NEJM* 2009; 360: 2758-2769.

Ischemia

- Labs similar to acetaminophen overdose with towering AST and ALT, high INR, mild elevation of bilirubin; LDH especially high
- Seen in patients with risk factors, including CAD, PAD, Afib who experience sepsis, arrhythmia or other hemodynamic event
- Supportive care, circumstances calling for transplant are rare

Autoimmune hepatitis

- Markedly elevated aminotransferases
- Most patients have positive ANA and anti-smooth muscle antibody with high titers, elevated IgG level; liver biopsy to confirm
- Typically have other autoimmune conditions and family history of autoimmune disease
- Prednisone and azathioprine are cornerstones of treatment

Manns MP, et al. Diagnosis and management of autoimmune hepatitis. Hepatology 2010; 51; 2193.

Remaining causes

- Wilson's disease: copper metabolism disorder, hemolytic anemia, Kayser-Fleischer rings, may present with ALF
- Budd-Chiari: thrombosis of the hepatic veins (outflow of liver)
- Disorders specific to pregnancy: Hyperemesis gravidarum - 1st trimester

HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) and
Acute fatty liver of pregnancy – 3rd Trimester

Hay JE. Liver Disease in Pregnancy. *Hepatology.* 2008; 47 (3): 1067-1076.

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Approach to Acute Liver Failure

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Educational Objectives

Understand common etiologies and prognosis

Execute early management steps

Discuss management of late complications

Disclosure

Salix pharmaceuticals

King's College Criteria

GASTROENTEROLOGY 1989;97:439–45

Early Indicators of Prognosis in Fulminant Hepatic Failure

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ALFSG

Definition

Definition

- **“ACUTE LIVER FAILURE” (no longer referred to as Fulminant)**
- **Rare disease**
- **Life threatening**
- **Rapidly progressive**
- **Requires sub-specialized, multidisciplinary care**
- **Requires prompt recognition and early referral to tertiary care center with liver transplant program**

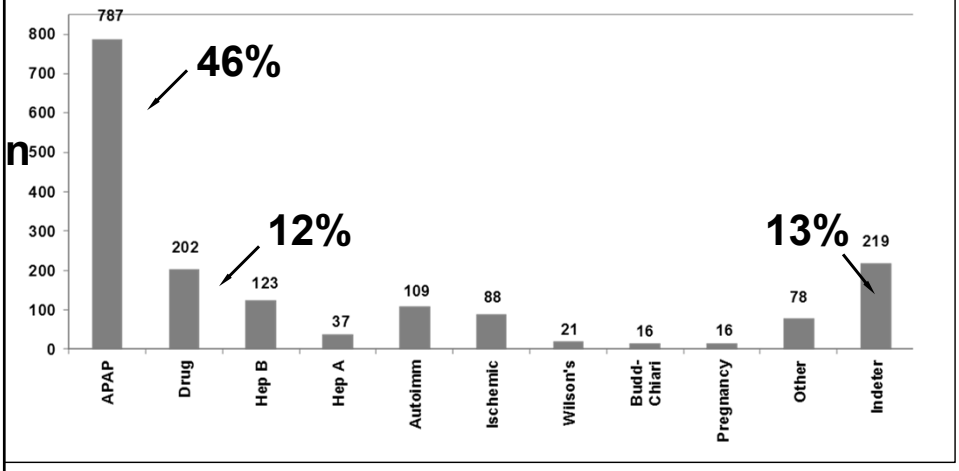
Definition

- **Biochemical evidence of moderate to severe acute hepatitis (AST/ALT > 5x ULN)**
- **Evidence of coagulopathy (INR ≥ 1.5) AND encephalopathy**
- **No pre-existing cirrhosis**
- **Duration of illness < 26 weeks**
- **Wilson's disease, HBV, and AIH may be included if disease recognized for < 26 weeks**

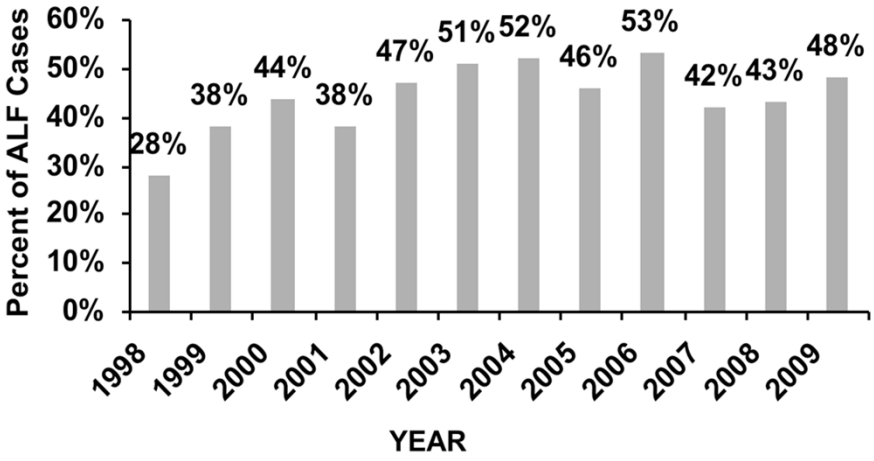
Etiology and prognosis

Etiology of Acute Liver Failure in the USA

Adult Registry (n = 1,696)



Acetaminophen cases as % of all cases



'Suicidal' vs. 'Accidental' APAP cases

N=606 (56=unk)	Intentional (n=251)	Unintentional (n=296)	p-value
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

Comparison of Different ALF Etiology Groups

	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

"Hyperacute Phenomenon" in APAP Cases

	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
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Tx (%)	9	40	45	32/41	30
Spontaneous Survival (%)	67	31	27	54/24	38
Overall Survival (%)	75	68	69	84/61	65

"Subacute Phenomenon" in DILI Cases

	APAP n=787	Drug n=202	Indeterminate n=219	HepA/Hep B 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
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Tx (%)	9	40	45	32/41	30
Spontaneous Survival (%)	67	31	27	54/24	38
Overall Survival (%)	75	68	69	84/61	65

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%**

*Schiødt FV, et al., Liver Transplant 2009

Prognosis models

- **King's College Criteria for predicting poor prognosis**
  - **High positive predictive value (70-100%)**
  - **Low sensitivity**
- **ALFSG for predicting good prognosis**
  - **Based on bilirubin, INR, etiology, pressor use, coma grade**
- **All prognostic scoring systems inaccurate**
- **Predicting prognosis requires a case-by-case, multidisciplinary approach**

Initial Management

Initial Management

- 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

History

- 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

Exam

- Careful documentation of neurologic status (hyperreflexia, mental status)
  - Can change rapidly, need frequent neuro checks
- Jaundice often (but not always) present
- Need careful evaluation of stigmata of chronic liver disease
  - Spider nevi, palmar erythema

Principals of Care

- Intensive care management of severe, rapidly progressive multi-organ system failure
- Only effective treatment: emergent liver transplant
  - Rapid psycho-social evaluation critical
- Clinical course requires managing both aspects simultaneously

Treatment

Treatment

- N-acetylcysteine (NAC)
  - Acetaminophen and 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)
- <u>Outcome benefit not established, data scarce</u>

GASTROENTEROLOGY 2009;137:856–864

Intravenous *N*-Acetylcysteine Improves Transplant-Free Survival in Early Stage Non-Acetaminophen Acute Liver Failure

WILLIAM M. LEE,* LINDA S. HYNAN,‡ LORENZO ROSSARO,§ ROBERT J. FONTANA,‖ R. TODD STRAVITZ,¶ ANNE M. LARSON,# TIMOTHY J. DAVERN II,** NATALIE G. MURRAY,‡‡ TIMOTHY McCASHLAND,§§ JOAN S. REISCH,* PATRICIA R. ROBUCK,‖‖ and the Acute Liver Failure Study Group

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CLINICAL ADVANCES IN LIVER, PANCREAS,

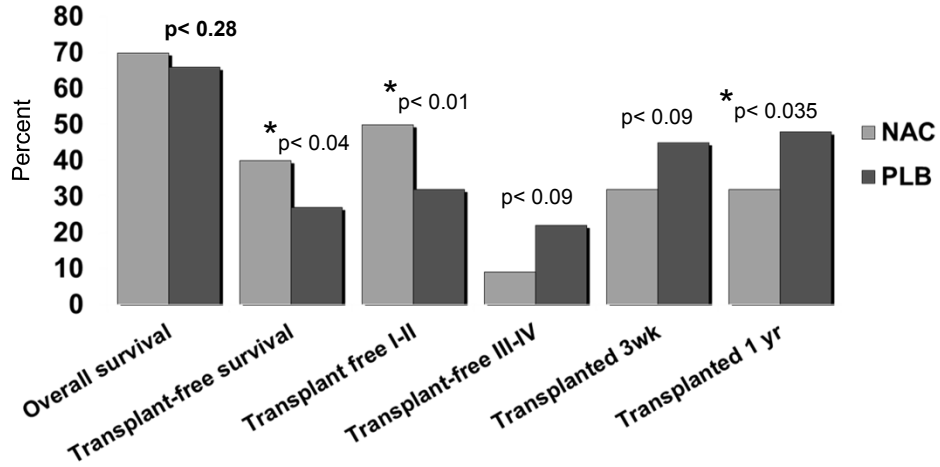
See related article, Kitzberger R et al, on page 1000 in *CGH*; see CME quiz on page 1162.

To view this article's video abstract, go to the AGA's YouTube Channel.

BACKGROUND & AIMS: *N*-acetylcysteine (NAC), an antidote for acetaminophen poisoning, might benefit patients with non–acetaminophen-related acute liver failure. **METHODS:** In a prospective, double-blind

Acute liver failure is a relatively rare syndrome associated with a high mortality rate and frequent need for liver transplantation. Since the 1950s, trials of therapies to limit further damage or improve hepatic regeneration have failed to show evidence of benefit.[1–6] In

Primary/secondary outcomes in the NAC trial



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

Central Nervous System

- **Cerebral edema and intracranial hypertension (ICH) leading cause of death[1]**
- **Herniation, ischemic, and hypoxic injury all potential contributors to CNS injury**
- **Pathophysiology poorly understood, likely involving multiple factors, including ammonia**

1. Stravitz RT, et al. Crit Care Med 2009;37:S258.

Incidence

- **Incidence of cerebral edema increases with worsening grade of encephalopathy[1]**
  - **Grade I – II: rare**
  - **Grade III: 25 – 35%**
  - **Grade IV: 65 – 75%**
- **Close monitoring warranted with emphasis on early identification, prevention and treatment**

1. Munoz SJ, et al. Semin Liver Disease 1993;13:395.

Grading of Encephalopathy

	Cognitive symptoms	**Muscular symptoms**
Grade I	Awake, with slight disorientation, forgetfulness, slow in answering questions	Muscular incoordination, tremors, insomnia
Grade II	Decreased level of consciousness, opens eyes spontaneously, confusion	Hyporeflexia, ataxia asterixis, slurred speech
Grade III	Somnolent, arousable to verbal and painful stimuli, does not open eyes spontaneously	Unable to cooperate with exam, nystagmus
Grade IV	Comatose, no response	Seizures, rigidity, dilated pupils

Prevention and Treatment of Encephalopathy

- Grade I – II
  - Avoid all sedating, centrally acting medications
    - Benzodiazepines, narcotics, anti-histamines
  - Avoid overstimulation
  - Lactulose, Rifaxamin
  - Head CT to rule out alternate explanations
    - Not sensitive in detection of cerebral edema

Prevention and Treatment of Encephalopathy

- Grade III – IV
  - Transfer to ICU, intubation for airway protection
  - Propofol recommended as sedation agent
    - May reduce cerebral blood flow[1]
  - Elevate HOB to 30, avoid suctioning
  - Prophylactic use of phenytoin not recommended[2,3]

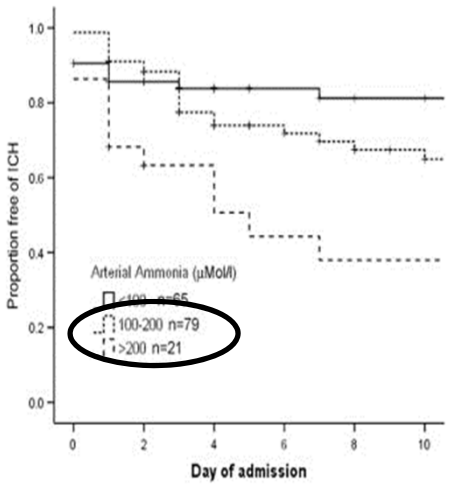
1. Wijkicks EFM, et al. Transplant Proc 2002; 34:1220
2. Ellis AJ, et al. Hepatology 2000;32:536
3. Bhatia V, et al. J Hepatol2004;41:89

Management of Intracranial Hypertension

- <u>Avoid over-resuscitation with fluids</u>
  - Minimize any fluids given, especially blood products
- Goal:
  - Intracranial pressure (ICP) < 20 mmHg
  - Cerebral perfusion pressure (CPP) 60 – 80 mmHg
    - CPP = MAP - ICP

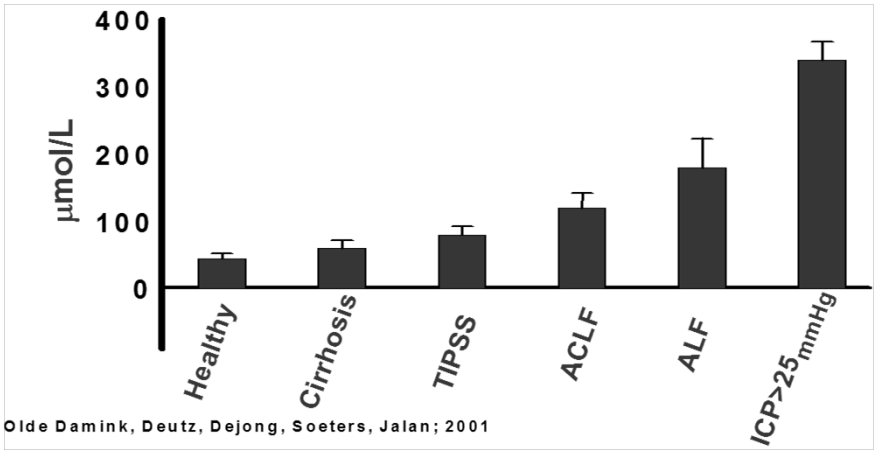
Arterial ammonia and encephalopathy and intracranial hypertension in ALF

- Elevated arterial ammonia thought to cause astrocyte swelling
- Increased arterial ammonia levels > 100 associated with worsening grade of encephalopathy and ICH



Bernal W, et al. Hepatology 2007;46:1844
http://onlinelibrary.wiley.com/doi/10.1002/hep.21838/full#fig4

Increased arterial ammonia closely associated with ALF



Management of Intracranial Hypertension

- Low systemic vascular resistance common
- Systemic vasopressors frequently required to maintain Mean Arterial Pressure (MAP) > 75 mmHg and CPP to 60 - 80 mmHg
- Norepinephrine used as first line agent
  - Vasopressin often added if second agent required

1. Clemmesen JO, et al. Scand J Gastroenterol 199;34:9

Management of Intracranial Hypertension

- Hypertonic saline[1]
  - Goal is induction and maintenance of serum sodium between 145 – 155 mmol/L
  - Decreased ICP and intracranial hypertension in treatment group
- Mannitol[2, 3]
  - Short term benefit for acute increase in ICP
  - 0.5 – 1 g/kg; dose repeated 1-2 times as needed
  - Risks: volume overload, hyperosmolality (keep serum osmolality < 320 mosm/L), hypernatremia

1. Murphy N, et al. Hepatology 2004;39:464
2. Nath F, et al. J Neurosurg 1986;65:41
3. Canalese J, et al. Gut 1982;23:625

New updates on older recommendations

- NO LONGER RECOMMENDED:
- Placement of intracranial pressure monitor (ICP)
- Mild hypothermia
- Prophylactic hyperventilation
- Prophylactic antibiotics
- Barbiturate coma

Current Acute Liver Failure Trials at OSU

- ALFSG Registry (OPEN)
- STOP-ALF: OPA infusion for encephalopathy and hyperammonemia (CLOSED)
- Methacetin Breath Test (OPEN)
- ROTEM (OPEN)

Summary

- Definition of ALF requires COAGULOPATHY and/or encephalopathy in the patient with acute hepatitis
- Acetaminophen still the most common cause (intentional and unintentional use)
- Successful management of ALF requires early recognition and rapid transfer to a Transplant Center
  - NAC indicated for ALL causes of ALF